Questions Set : REF59819 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF59819
Page Safety Tools

Question: 1 of 100

A 28-year-old car mechanic is admitted to the hospital having taken an overdose of methanol after splitting up from his wife.

On admission to the emergency department he is drowsy and intoxicated. His BP is 134/82 mmHg, and he has a tachycardia with a pulse of 95.

Investigations show

Haemoglobin	14.0 g/dl	(13.5-17.7)
White cell count	8.1 x 10^9/l	(4-11)
Platelets	190 x 10^9/l	(150-400)
Serum sodium	137 mmol/l	(135-146)
Serum potassium	4.2 mmol/l	(3.5-5)
Bicarbonate	17 mmol/l	(22-30)
Creatinine	130 µmol/l	(79-118)

Which of the following is the most appropriate antidote for methanol poisoning?

(Please select 1 option)

- Atenolol
- Ethanol
- Glucagon

Done
Internet | Protected Mode: Off
115%

Questions Set : REF59819 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF59819
Page
Safety
Tools

Investigations show

Haemoglobin	14.0 g/dl	(13.5-17.7)
White cell count	8.1 x 10^9/l	(4-11)
Platelets	190 x 10^9/l	(150-400)
Serum sodium	137 mmol/l	(135-146)
Serum potassium	4.2 mmol/l	(3.5-5)
Bicarbonate	17 mmol/l	(22-30)
Creatinine	130 µmol/l	(79-118)

Which of the following is the most appropriate antidote for methanol poisoning?

(Please select 1 option)

- Atenolol
- Ethanol
- Glucagon
- Insulin
- Polyethylene glycol

Submit answer | Skip question | Tag Question | Remove question

Done
Internet | Protected Mode: Off
115%

Questions Set : REF27527 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF27527
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 19 mins 16 secs

Question: 10 of 100

Which is the predominant site of effect of thiazide diuretics?

(Please select 1 option)

- Cortical collecting duct
- Early distal tubule
- Late distal tubule
- Proximal tubule
- Thick ascending limb, Loop of Henle

Submit answer | Skip question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
105%

Questions Set : REF1749 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF1749
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 47 mins 32 secs

Question: 100 of 100

With regard to poisoning / overdose:

(Please select 1 option)

- Phenobarbitone causes a metabolic acidosis
- Ethylene glycol causes a metabolic alkalosis and renal failure
- Aspirin causes acidosis due to hypoventilation
- Methanol causes a metabolic acidosis with an increased anion gap
- Chlormethiazole causes hyperthermia and hypertension

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
105%

Questions Set : REF27527 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF27527
Page Safety Tools

Work Smart Session - MRCP Part 1

Time taken: 20 mins 16 secs

Question: 10 of 100

Which is the predominant site of effect of thiazide diuretics?

(Please select 1 option)

○	Cortical collecting duct
◉	Early distal tubule ✓ Correct
○	Late distal tubule
○	Proximal tubule
○	Thick ascending limb, Loop of Henle

Thiazide diuretics act on the cortical diluting segment of the nephron, predominantly in the early distal tubule.

Loop diuretics mainly act on the thick ascending limb of the Loop of Henle.

Potassium sparing diuretics, for example amiloride, act on the distal nephron.

(For a simplistic review see ABC of heart failure.)

Next question | Tag Question | Remove question

Show tools

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
105%

Questions Set : REF23476 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF23476
Page Safety Tools

Work Smart Session - MRCP Part 1

Time taken: 20 mins 16 secs

Question: 11 of 100

A 65-year-old man has locally advanced pancreatic cancer and has been paying privately for treatment with erlotinib (Tarceva) for the past nine months. It has worked effectively for that period but a recent CT scan showed further growth in the tumour.

Which of the following mechanisms best explains this resistance to treatment with erlotinib?

(Please select 1 option)

- Development of antibodies to erlotinib
- Lack of autophosphorylation at binding site
- Malabsorption
- Mutated IGF-1 receptor
- Reduced expression of EGFR

Submit answer | Skip question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
105%

Questions Set : REF23476 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF23476
Page Safety Tools

Which of the following mechanisms best explains this resistance to treatment with erlotinib?

(Please select 1 option)

◉	Development of antibodies to erlotinib ✕ Incorrect answer selected
○	Lack of autophosphorylation at binding site
○	Malabsorption
○	Mutated IGF-1 receptor ← This is the correct answer
○	Reduced expression of EGFR

Erlotinib specifically targets the epidermal growth factor receptor tyrosine kinase (which is required for the conformational change) and binds in a reversible fashion to the adenosine triphosphate binding site.

For the signal to be transmitted, two members of the EGFR family need to come together to form a homodimer. These then use the molecule of ATP to autophosphorylate each other, which causes a conformational change in their intracellular structure, exposing a further binding site for binding proteins that cause a signal cascade to the nucleus. By inhibiting the ATP, autophosphorylation is not possible and the signal is stopped.

A key issue with EGFR-directed treatments is that after a period of 8-12 months, the cancer cells become resistant to the treatment, most commonly by recruiting a mutated IGF-1 receptor to act as one of the EGFR partners in the homodimer, so forming a heterodimer. This allows the signal to be transmitted even in the presence of an EGFR inhibitor.

Some IGR-1R inhibitors are in various stages of development (based either around tyrphostins such as AG1024 or AG538 or pyrrolo[2,3-d]-pyrimidine derivatives such as NVP-AEW541.

Source: Wikipedia

Internet | Protected Mode: Off
105%

Questions Set : REF23350 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF23350
Page
Safety
Tools

A 68-year-old lady presented to her general practitioner with a history of generalised tiredness.

She had recently been commenced on a water tablet to ease her swollen feet. She was also diagnosed with glaucoma for which she used topical eye drops.

Investigations:

Serum sodium	138 mmol/L (137-144)
Serum potassium	Haemolysed sample
Serum urea	4.3 mmol/L (2.5-7.5)
Serum creatinine	88 µmol/L (60-110)
Serum corrected calcium	2.68 mmol/L (2.2-2.6)

Which diuretic was this lady most probably taking?

(Please select 1 option)

- Acetazolamide
- Amiloride
- Bendroflumethiazide
- Furosemide
- Indapamide

Done
Internet | Protected Mode: Off
105%

Questions Set : REF23350 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF23350
Page
Safety
Tools

eye drops.

Investigations:

Serum sodium	138 mmol/L (137-144)
Serum potassium	Haemolysed sample
Serum urea	4.3 mmol/L (2.5-7.5)
Serum creatinine	88 µmol/L (60-110)
Serum corrected calcium	2.68 mmol/L (2.2-2.6)

Which diuretic was this lady most probably taking?

(Please select 1 option)

- ○ Acetazolamide
- ○ Amiloride
- ◉ Bendroflumethiazide ✓ Correct
- ○ Furosemide
- ○ Indapamide

Thiazide diuretics are associated with increased calcium concentrations as well as raised urate.

Done
Internet | Protected Mode: Off
105%

Questions Set : REF23347 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF23347
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 23 mins 34 secs

Question: 13 of 100

A 26-year-old woman was being treated in the outpatient clinic for autoimmune hypothyroidism.

She was taking 150µg of thyroxine and 200 mg of amiodarone.

Investigations reveal:

Plasma prolactin	654 mU/L	(<360)
Plasma free T4	24 pmol/L	(10-22)
Plasma free T3	5.2 pmol/L	(5-10)
Plasma thyroid-stimulating hormone	68 mU/L	(0.4-5)

What is the most likely explanation for her high TSH levels?

(Please select 1 option)

- Amiodarone effect
- Hyperprolactinaemia
- Poor compliance with medications
- Thyroid hormone resistance
- TSH producing pituitary adenoma

Done
Internet | Protected Mode: Off
105%

Questions Set : REF23347 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF23347
Page Safety Tools

Plasma prolactin	654 mU/L	(<360)
Plasma free T4	24 pmol/L	(10-22)
Plasma free T3	5.2 pmol/L	(5-10)
Plasma thyroid-stimulating hormone	68 mU/L	(0.4-5)

What is the most likely explanation for her high TSH levels?

(Please select 1 option)

- Amiodarone effect
- Hyperprolactinaemia
- Poor compliance with medications ✓ Correct
- Thyroid hormone resistance
- TSH producing pituitary adenoma

This young woman has a slightly elevated thyroxine (T4) and an elevated thyroid-stimulating hormone (TSH).

The most probable explanation is poor compliance. This also explains the slightly high prolactin concentration too; a consequence of reduced dopaminergic tone on the lactotrophs.

The typical scenario is that the patients take their medication in the days before the clinic.

This is a classic MRCP question and is highly discriminating. Consider this one carefully and try to understand fully why this is not an effect of amiodarone.

Next question | Tag Question | Remove question

Done
Internet | Protected Mode: Off
105%

Questions Set : REF23160 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF23160
Page Safety Tools

Work Smart Session - MRCP Part 1

Time taken: 26 mins 18 secs

Question: 14 of 100

A 45-year-old obese male with a two year history of type 2 diabetes has recently commenced metformin at a dose of 500 mg twice daily. However, he re-attends clinic and reports numerous gastrointestinal side effects including bloating and flatulence. He is keen to stop metformin and commence an alternative agent.

Which of the following drugs is the most appropriate choice?

(Please select 1 option)

- Acarbose
- Exenatide
- Insulin
- Pioglitazone
- Repaglinide

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
105%

Questions Set : REF23160 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF23160
Page Safety Tools

A 45-year-old obese male with a two year history of type 2 diabetes has recently commenced metformin at a dose of 500 mg twice daily. However, he re-attends clinic and reports numerous gastrointestinal side effects including bloating and flatulence. He is keen to stop metformin and commence an alternative agent.

Which of the following drugs is the most appropriate choice?

(Please select 1 option)

○	Acarbose
○	Exenatide
○	Insulin
○	Pioglitazone ← This is the correct answer
◉	Repaglinide ✕ Incorrect answer selected

An obese type 2 diabetic patient is almost certain to be insulin resistant.

Current guidelines suggest that first line therapy in obese, insulin resistant patients should be an insulin sensitising agent (Bailey C et al. Br J Diabetes Vas Dis 2006; 6: 147-148). Metformin is the drug of choice in this patient therefore.

In patients intolerant of metformin, pioglitazone is licensed for monotherapy for insulin resistant patients. It should however be avoided in patients who have a history of heart failure, because of the risk of fluid retention,and is associated with increased risk of bone fracture.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
105%

Questions Set : REF22953 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF22953
Page Safety Tools

Work Smart Session - MRCP Part 1

Time taken: 28 mins 38 secs

Question: 15 of 100

A 70-year-old woman is on multiple medications for various conditions and she is found to have a macrocytic anaemia with a low serum B_{12}.

Which of the following medications is a possible cause of the B_{12} deficiency?

(Please select 1 option)

- Amiodarone
- Ezetimibe
- Metformin
- Nicotinic acid
- Sodium valproate

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
105%

Questions Set : REF22953 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF22953
Page Safety Tools

Work Smart Session - MRCP Part 1

Time taken: 29 mins 23 secs

Question: 15 of 100

A 70-year-old woman is on multiple medications for various conditions and she is found to have a macrocytic anaemia with a low serum B_{12}.

Which of the following medications is a possible cause of the B_{12} deficiency?

(Please select 1 option)

○	Amiodarone
○	Ezetimibe
○	Metformin ← This is the correct answer
○	Nicotinic acid
◉	Sodium valproate ✕ Incorrect answer selected

Metformin can lead to reduced B_{12} absorption but this is not usually a clinical problem.

"The clinician must be aware of the possibility of metformin-associated B_{12} deficiency in users who suffer cognitive impairment, peripheral neuropathy, subacute combined degeneration of the cord or anaemia." Age Ageing. 2006 Mar;35(2):200-1

Next question | Tag Question | Remove question

Show tools

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
105%

Questions Set : REF22949 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF22949
Page Safety Tools

Work Smart Session - MRCP Part 1

Time taken: 29 mins 23 secs

Question: 16 of 100

A 51-year-old lady enquires about taking hormone replacement therapy (HRT).

Which of the following is the most compelling indication for taking HRT?

(Please select 1 option)

- Control of flushing
- Prevent Alzheimer's disease
- Prevent ischaemic heart disease
- Prevent osteoporosis
- Reverse vaginal atrophy

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
105%

Questions Set : REF22949 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites | Suggested Sites | Get More Add-ons
Questions Set : REF22949
Page | Safety | Tools

Work Smart Session - MRCP Part 1

Time taken: 30 mins 10 secs

Question: 16 of 100

A 51-year-old lady enquires about taking hormone replacement therapy (HRT).

Which of the following is the most compelling indication for taking HRT?

(Please select 1 option)

- Control of flushing ← This is the correct answer
- Prevent Alzheimer's disease
- Prevent ischaemic heart disease
- Prevent osteoporosis ✕ Incorrect answer selected
- Reverse vaginal atrophy

The indications for HRT have been a matter of great debate over recent years.

Relieving the symptoms of menopause is the most compelling indication.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd. All rights reserved. Terms and conditions Privacy policy

Show tools

Done
Internet | Protected Mode: Off
105%

Questions Set : REF22944 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF22944
Page Safety Tools

Work Smart Session - MRCP Part 1

Time taken: 30 mins 10 secs

Question: 17 of 100

A 23-year-old man with known peanut allergy presented to the Emergency Department with anaphylaxis. He has a swollen face and lips. His BP is 90/60 mmHg, pulse 110 bpm and he is wheezy.

Which of the following formulations of adrenaline should be given?

(Please select 1 option)

- 0.5 ml of 1:10000 adrenaline IM
- 0.5 ml of 1:1000 adrenaline IM
- 5 ml of 1:1000 adrenaline IM
- 10 ml of 1:10000 adrenaline IV
- Nebulised adrenaline

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
105%

Questions Set : REF22944 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF22944
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 31 mins 24 secs

Question: 17 of 100

A 23-year-old man with known peanut allergy presented to the Emergency Department with anaphylaxis. He has a swollen face and lips. His BP is 90/60 mmHg, pulse 110 bpm and he is wheezy.

Which of the following formulations of adrenaline should be given?

(Please select 1 option)

○	0.5 ml of 1:10000 adrenaline IM
◉	0.5 ml of 1:1000 adrenaline IM ✓ Correct
○	5 ml of 1:1000 adrenaline IM
○	10 ml of 1:10000 adrenaline IV
○	Nebulised adrenaline

"For adults, a dose of 0.5 mL adrenaline 1:1000 solution (500 micrograms) should be administered intramuscularly, and repeated after about five minutes in the absence of clinical improvement or if deterioration occurs after the initial treatment especially if consciousness becomes - or remains - impaired as a result of hypotension. In some cases several doses may be needed, particularly if improvement is transient."
Resuscitation Council UK.

Adult EpiPen which allergy sufferers can carry with them contains 0.3 mg adrenaline in a 1:1000 dilution for intramuscular (IM) injection.

Next question | Tag Question | Remove question

Show to
Done
Internet | Protected Mode: Off
105%

Questions Set : REF22942 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites | Suggested Sites | Get More Add-ons
Questions Set : REF22942
Page | Safety | Tools

Work Smart Session - MRCP Part 1

Time taken: 31 mins 24 secs

Question: 18 of 100

A 48-year-old lady with a history of epilepsy and ischaemic heart disease presented with the following full blood count.

Haemoglobin	7.4 g/dL	(11.5 - 16.5)
Mean cell volume	125 fL	(80 - 96)
White cell count	2.5 x 10^9/L	(4 - 11)
Platelet count	130 x 10^9/L	(150 - 400)

Which of the following medications is the most likely cause?

(Please select 1 option)

- Carbamazepine
- Clopidogrel
- Furosemide
- Phenytoin
- Spironolactone

Done
Internet | Protected Mode: Off
105%

Questions Set : REF22942 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF22942
Page Safety Tools

A 48-year-old lady with a history of epilepsy and ischaemic heart disease presented with the following full blood count.

Haemoglobin	7.4 g/dL	(11.5 - 16.5)
Mean cell volume	125 fL	(80 - 96)
White cell count	2.5 x 10^9/L	(4 - 11)
Platelet count	130 x 10^9/L	(150 - 400)

Which of the following medications is the most likely cause?

(Please select 1 option)

- ○ Carbamazepine
- ○ Clopidogrel
- ○ Furosemide
- ◉ Phenytoin ✓ Correct
- ○ Spironolactone

There is a macrocytic anaemia with low platelets and WCC typical of a nutritional deficiency.

Phenytoin can lead to folate deficiency and is therefore the most likely cause.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Questions.aspx
Internet | Protected Mode: Off
105%

Questions Set : REF22941 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF22941
Page Safety Tools

Work Smart Session - MRCP Part 1

Time taken: 32 mins 38 secs

Question: 19 of 100

A 54-year-old man is found to have a prolonged corrected QT interval on his ECG.

Which of the following drugs is the most likely cause?

(Please select 1 option)

- Cefaclor
- Digoxin
- Moxonidine
- Sotalol
- Telmisartan

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
105%

Questions Set : REF22941 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF22941
Page Safety Tools

A 54-year-old man is found to have a prolonged corrected QT interval on his ECG.

Which of the following drugs is the most likely cause?

(Please select 1 option)

○	Cefaclor
○	Digoxin
○	Moxonidine
◉	Sotalol ✓ Correct
○	Telmisartan

- Sotalol
- Amiodarone
- Class 1a antiarrhythmic drugs
- Tricyclic antidepressants
- Chloroquine and
- Terfenadine

are causes of drug-induced long QT.

Next question Tag Question Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
105%

Questions Set : REF59819 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF59819
Page
Safety
Tools

Creatinine	130 µmol/l	(79-118)

Which of the following is the most appropriate antidote for methanol poisoning?

(Please select 1 option)

- Atenolol
- Ethanol ✓ Correct
- Glucagon
- Insulin
- Polyethylene glycol

Methanol, like ethanol, is metabolised by alcohol dehydrogenase to form formaldehyde. Formaldehyde is then further metabolised by aldehyde dehydrogenase to formic acid. Formate formation leads to a severe metabolic acidosis, and crystals forming within the eye can lead to so called 'snow field' cataract formation.

Inhibition of metabolism of methanol by alcohol dehydrogenase with either ethanol or fomepizole is the treatment of choice.

Next question | Tag Question | Remove question

Done
Internet | Protected Mode: Off
125%

Questions Set : REF59819 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF59819
Page
Safety
Tools

Creatinine	130 µmol/l	(79-118)

Which of the following is the most appropriate antidote for methanol poisoning?

(Please select 1 option)

- Atenolol
- Ethanol ✓ Correct
- Glucagon
- Insulin
- Polyethylene glycol

Methanol, like ethanol, is metabolised by alcohol dehydrogenase to form formaldehyde. Formaldehyde is then further metabolised by aldehyde dehydrogenase to formic acid. Formate formation leads to a severe metabolic acidosis, and crystals forming within the eye can lead to so called 'snow field' cataract formation.

Inhibition of metabolism of methanol by alcohol dehydrogenase with either ethanol or fomepizole is the treatment of choice.

Next question | Tag Question | Remove question

Done
Internet | Protected Mode: Off
125%

Questions Set : REF22939 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF22939
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 33 mins 13 secs

Question: 20 of 100

A 50-year-old man presented with a milky discharge from his nipples. He had a history of depression and gastro-oesophageal reflux disease and was on a number of medications.

Plasma prolactin	650 mU/L	(< 360)

Which of the following is the most likely cause of his symptoms?

(Please select 1 option)

- Amitryptiline
- Cimetidine
- Fluoxetine
- Metoclopramide
- Omeprazole

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Questions.aspx
Internet | Protected Mode: Off
105%

Questions Set : REF22939 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF22939
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 34 mins 20 secs

Question: 20 of 100

A 50-year-old man presented with a milky discharge from his nipples. He had a history of depression and gastro-oesophageal reflux disease and was on a number of medications.

Plasma prolactin	650 mU/L	(< 360)

Which of the following is the most likely cause of his symptoms?

(Please select 1 option)

- Amitryptiline
- Cimetidine
- Fluoxetine
- Metoclopramide ✓ Correct
- Omeprazole

This man has galactorrhoea and raised prolactin.

The most likely culprit is metoclopramide through its action on dopamine. It releases prolactin through dopamine antagonism.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Questions.aspx
Internet | Protected Mode: Off
105%

Questions Set : REF22938 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF22938
Page Safety Tools

Work Smart Session - MRCP Part 1

Time taken: 34 mins 20 secs

Question: 21 of 100

A 60-year-old lady is taking warfarin for stroke prevention in atrial fibrillation.

She presents with a markedly raised INR.

Which of the following medications is the most likely to be the reason?

(Please select 1 option)

- Aspirin
- Carbamazepine
- Ciprofloxacin
- Flucloxacillin
- St John's Wort

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
105%

Questions Set : REF22938 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF22938
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 35 mins 28 secs

Question: 21 of 100

A 60-year-old lady is taking warfarin for stroke prevention in atrial fibrillation.

She presents with a markedly raised INR.

Which of the following medications is the most likely to be the reason?

(Please select 1 option)

○	Aspirin
○	Carbamazepine
○	Ciprofloxacin ← This is the correct answer
○	Flucloxacillin
◉	St John's Wort ✕ Incorrect answer selected

Ciprofloxacin is an inhibitor of p450 and therefore prolongs the half-life of warfarin and raises the international normalised ratio (INR).

Even patients are aware of the increased risk of bleeding with aspirin but it does not have a clear relationship with INR.

Next question

Remove Tag

Remove question

Show tools

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Internet | Protected Mode: Off
105%

Questions Set : REF22937 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites | Suggested Sites | Get More Add-ons
Questions Set : REF22937
Page | Safety | Tools

Work Smart Session - MRCP Part 1

Time taken: 35 mins 28 secs

Question: 22 of 100

A 72-year-old lady presented after taking an overdose of a sustained-release propranolol preparation.

She has a pulse of 40 bpm and a BP of 90/60 mmHg.

She was given atropine by the emergency department staff but there has been little response.

Which of the following is the most appropriate treatment?

(Please select 1 option)

- Atropine
- Glucagon
- Haemodialysis
- Noradrenaline
- Salbutamol

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Questions.aspx
Internet | Protected Mode: Off
105%

Questions Set : REF22937 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF22937
Page Safety Tools

Dashboard
Questions
Scores
Community
Help
Shop

Work Smart Session - MRCP Part 1

Time taken: 36 mins 18 secs

Question: 22 of 100

A 72-year-old lady presented after taking an overdose of a sustained-release propranolol preparation.

She has a pulse of 40 bpm and a BP of 90/60 mmHg.

She was given atropine by the emergency department staff but there has been little response.

Which of the following is the most appropriate treatment?

(Please select 1 option)

○	Atropine
◉	Glucagon ✓ Correct
○	Haemodialysis
○	Noradrenaline
○	Salbutamol

"For cases of beta-blocker poisoning where symptomatic bradycardia and hypotension are present, high-dose glucagon is considered the first-line antidote." Am J Health Syst Pharm. 2006 Oct 1;63(19):1828-35

Show tools
Done
Internet | Protected Mode: Off
105%

Questions Set : REF22935 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF22935
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 36 mins 18 secs

Question: 23 of 100

A 60-year-old man presented with a rash over his forearms, shins and face when he visited cardiology clinic in the summer.

Which of the following medications is the most likely to be associated with this photosensitive rash?

(Please select 1 option)

- Atenolol
- Bendroflumethiazide
- Clopidogrel
- Digoxin
- Ezetimibe

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
105%

Questions Set : REF22935 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF22935
Page Safety Tools

Dashboard
Questions
Scores
Community
Help
Shop

Work Smart Session - MRCP Part 1

Time taken: 37 mins

Question: 23 of 100

A 60-year-old man presented with a rash over his forearms, shins and face when he visited cardiology clinic in the summer.

Which of the following medications is the most likely to be associated with this photosensitive rash?

(Please select 1 option)

- Atenolol
- Bendroflumethiazide ✓ Correct
- Clopidogrel
- Digoxin
- Ezetimibe

Photosensitivity is a common adverse effect and the cardiology drugs affected include amiodarone and thiazide diuretics.

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin 2 receptor blockers (A2RBs) commonly cause rashes some of which appear to be photosensitive.

Next question

Remove question

Show tools

(2 items remaining) Waiting for http://my.onexamination.com/Assessment/Questions.aspx...
Internet | Protected Mode: Off
105%

Questions Set : REF22924 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF22924
Page Safety Tools

Dashboard
Questions
Scores
Community
Help
Shop

Work Smart Session - MRCP Part 1

Time taken: 37 mins

Question: 24 of 100

Which of the following mechanisms best explains the action of simvastatin?

(Please select 1 option)

- Activates PPAR-alpha
- Bile acid sequestration
- Decreases hepatic cholesterol synthesis
- Increases peroxisomal beta-oxidation of fatty acids
- Inhibits cholesterol absorption

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
105%

Questions Set : REF22924 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF22924
Page Safety Tools

Dashboard
Questions
Scores
Community
Help
Shop

Work Smart Session - MRCP Part 1

Time taken: 37 mins 42 secs

Question: 24 of 100

Which of the following mechanisms best explains the action of simvastatin?

(Please select 1 option)

○	Activates PPAR-alpha
○	Bile acid sequestration
◉	Decreases hepatic cholesterol synthesis ✓ Correct
○	Increases peroxisomal beta-oxidation of fatty acids
○	Inhibits cholesterol absorption

Most circulating cholesterol is manufactured internally, in amounts of about 1000 mg/day, via carbohydrate metabolism through the HMG-CoA reductase pathway.

Statins act by competitively inhibiting HMG-CoA reductase, the first committed enzyme of the HMG-CoA reductase pathway.

Further reading:
Statins and other drugs to lower cholesterol Patient UK

Next question | Remove question

Show tools

(2 items remaining) Waiting for http://my.onexamination.com/Assessment/Questions.aspx...
Internet | Protected Mode: Off
105%

Questions Set : REF22911 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF22911 http://my.onexamination....
Page Safety Tools

Work Smart Session - MRCP Part 1

Time taken: 37 mins 42 secs

Question: 25 of 100

Interferon alpha immunotherapy is used as treatment of which for the following conditions?

(Please select 1 option)

- Acute lymphoblastic leukaemia
- Acute myeloid leukaemia
- Burkitt's lymphoma
- Hairy cell leukaemia
- Myelodysplastic syndrome

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
105%

Questions Set : REF22911 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF22911
Page Safety Tools

Work Smart Session - MRCP Part 1

Time taken: 38 mins 43 secs

Question: 25 of 100

Interferon alpha immunotherapy is used as treatment of which for the following conditions?

(Please select 1 option)

- Acute lymphoblastic leukaemia
- Acute myeloid leukaemia
- Burkitt's lymphoma
- Hairy cell leukaemia ← This is the correct answer
- Myelodysplastic syndrome ✕ Incorrect answer selected

"Interferon-alpha is an immune system hormone which is very helpful to a relatively small number of patients, and somewhat helpful to most patients. Most commonly, the drug helps stabilize the disease or produce a slow, minor improvement. The typical dosing schedule injects 3 million units of Interferon-alpha (not pegylated versions) three times a week, although the original protocol began with six months of daily injections." Wikipedia: Hairy cell leukemia

Next question

Remove Tag | Remove question

Show tools
Avira
The application C:\PROGRA~1\Raptr\raptr.exe has been blocked to access the internet
© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy
Don't show this message again
OK
Internet | Protected Mode: Off
105%

Questions Set : REF22789 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF22789
Page Safety Tools

Work Smart Session - MRCP Part 1

Time taken: 38 mins 43 secs

Question: 26 of 100

A 60-year-old man has left ventricular failure and clinically he is classified as NYHA Class III.

He takes furosemide, aspirin and ramipril.

The addition of which one of the following betablockers would be expected further to improve his prognosis?

(Please select 1 option)

- Acebutolol
- Bisoprolol
- Esmolol
- Propranolol
- Sotalol

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
105%

Questions Set : REF22789 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF22789
Page
Safety
Tools

A 60-year-old man has left ventricular failure and clinically he is classified as NYHA Class III.

He takes furosemide, aspirin and ramipril.

The addition of which one of the following betablockers would be expected further to improve his prognosis?

(Please select 1 option)

○	Acebutolol
◉	Bisoprolol ✓ Correct
○	Esmolol
○	Propranolol
○	Sotalol

Bisoprolol is a highly selective beta(1)-adrenoceptor antagonist.

Administration of bisoprolol to patients with chronic heart failure is associated with increases in left ventricular function and reductions in heart rate; increases in heart rate variability are also seen.

Two major randomised, double-blind, placebo-controlled, multicentre trials have examined the clinical efficacy of bisoprolol in combination with ACE inhibitors and diuretics in patients with stable chronic heart failure (New York Heart Association class III or IV).

Drugs. 2002;62(18):2677-96

Next question | Tag Question | Remove question

Done
Internet | Protected Mode: Off
105%

Questions Set : REF22775 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites | Suggested Sites | Get More Add-ons
Questions Set : REF22775
Page | Safety | Tools

Work Smart Session - MRCP Part 1

Time taken: 39 mins 24 secs

Question: 27 of 100

A 52-year-old lady presented with a history of crushing central chest pain, sweating and dyspnoea.

An ECG confirms acute myocardial infarction with ST elevation in leads V2-V4 and ST depression in leads II and III.

Which of the following would be a contraindication to thrombolysis in this lady?

(Please select 1 option)

- History of peptic ulcer disease
- Intracranial neoplasm
- Menstruation
- Pre-proliferative diabetic retinopathy
- Stroke six months previously

Submit answer | Skip question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
105%

Questions Set : REF22775 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF22775
Page Safety Tools

An ECG confirms acute myocardial infarction with ST elevation in leads V2-V4 and ST depression in leads II and III.

Which of the following would be a contraindication to thrombolysis in this lady?

(Please select 1 option)

○	History of peptic ulcer disease
◉	Intracranial neoplasm ✓ Correct
○	Menstruation
○	Pre-proliferative diabetic retinopathy
○	Stroke six months previously

Contraindications to thrombolysis include:

- intracranial neoplasm as here
- stroke in the last two months
- pregnancy
- active internal bleeding
- aortic dissection
- recent significant head injury
- severe and uncontrolled hypertension.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
105%

Questions Set : REF22653 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF22653
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 40 mins 27 secs

Question: 28 of 100

A 17-year-old female presents to the emergency department following self-confessed paracetamol poisoning after discovering she is eight weeks pregnant and had a row with her boyfriend.

She claims to have taken an approximately 30 paracetamol tablets approximately 58 hours ago. Her history is considered to be reliable. There are no abnormalities to find on examination. Her blood sugar by finger prick testing was 3.1 mmol/l.

Which of the following would be the most appropriate treatment for this patient?

(Please select 1 option)

- Haemodialysis
- Intravenous dextrose infusion
- Intravenous N-acetylcysteine
- Oral activated charcoal
- Oral vitamin K

Submit answer | Skip question | Tag Question | Remove question

Done
Internet | Protected Mode: Off
105%

Questions Set : REF22653 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF22653
Page
Safety
Tools

Which of the following would be the most appropriate treatment for this patient?

(Please select 1 option)

○	Haemodialysis
○	Intravenous dextrose infusion
◉	Intravenous N-acetylcysteine ✓ Correct
○	Oral activated charcoal
○	Oral vitamin K

Irrespective of the pregnancy, this girl should receive n-acetyl cysteine.

Paracetamol concentration is unhelpful in delayed presentation of paracetamol overdose. A dose of more than150mg/kg is considered to be toxic and toxicity occurs at a lower concentration if the patient is thought to be in high risk group.

Clotting screen international normalised ratio (INR), liver function tests, acid-base balance and plasma glucose should be taken without delay prior to starting treatment with N-acetylcysteine.

Serial monitoring of clotting screen is required and N-acetylcysteine should continue until INR returns to normal.

Further advice on treatment of complicated cases should be sought from National Poisons Information Service. Other supportive treatment is guided by the patient's condition.

Next question

Tag Question

Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
105%

Questions Set : REF22588 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites | Suggested Sites | Get More Add-ons
Questions Set : REF22588
Page | Safety | Tools

Work Smart Session - MRCP Part 1

Time taken: 41 mins 50 secs

Question: 29 of 100

A 17-year-old boy is admitted with a severe paracetamol overdose following an argument with his girlfriend.

He is treated with intravenous N-acetylcysteine.

Paracetamol is normally metabolised to harmless compounds except in overdose.

Which of the following compounds is the toxic metabolite that accumulates during paracetamol overdose and is reduced by treatment with N-acetylcysteine?

(Please select 1 option)

- Glucuronide
- Homocysteine
- Methionine
- N-acetyl-p-benzoquinoneimine
- N-hydroxyacetaminophen

Submit answer | Skip question | Tag Question | Remove question

Done
Internet | Protected Mode: Off
105%

Questions Set : REF22588 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF22588
Page Safety Tools

Paracetamol is normally metabolised to harmless compounds except in overdose.

Which of the following compounds is the toxic metabolite that accumulates during paracetamol overdose and is reduced by treatment with N-acetylcysteine?

(Please select 1 option)

○	Glucuronide
○	Homocysteine
○	Methionine
◉	N-acetyl-p-benzoquinoneimine ✓ Correct
○	N-hydroxyacetaminophen

Paracetamol is predominantly metabolised to glucuronide and sulphate conjugates which are excreted in the urine.

Hepatotoxicity is related to the conversion of a small proportion of the ingested dose to N-acetyl-p-benzoquinoneimine. In therapeutic doses N-acetyl-p-benzoquinoneimine is detoxified by conjugation with glutathione in the liver, but once the protective intracellular glutathione stores are depleted hepatic and renal damage may ensue.

NAC and methionine replenish glutathione stores in the liver and may also act through its sulphhydryl (-SH) group as a direct reducing agent.

Further Reading: Wikipedia - paracetamol OD

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
105%

Questions Set : REF59812 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF59812
Page
Safety
Tools

Shop

Which of the following is most likely to have resulted in her presentation with lithium toxicity?

(Please select 1 option)

○	Amoxicillin
○	Atenolol
○	Paracetamol
◉	Ramipril ✓ Correct
○	Verapamil

ACE inhibitors are known to increase serum lithium levels, as are dihydropyridine calcium antagonists.

Atenolol, in contrast, is a relatively safer option for the treatment of hypertension in association with long term lithium use.

Verapamil in combination with lithium leads to neurotoxicity; this is independent of any increase in serum lithium levels.

If patients have poorly controlled hypertension and they are taking lithium, it may be better to discuss the case with the psychiatrist to see if they can be changed to another mood stabilising agent, such as sodium valproate.

Next question

Tag Question

Remove question

Done
Internet | Protected Mode: Off
125%

Questions Set : REF56435 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF56435
Page
Safety
Tools

Question: 3 of 100

A 24-year-old IV drug abuser presents with jaw spasm to the emergency department. She says she re-used a heroin needle a few days ago and a couple of her sites look infected.

She has suffered recurrent admissions with pneumonia over the past two years and has been using heroin for the past four years.

On examination she is pyrexial 37.8°C. She has jaw spasm, significant neck stiffness and looks in pain. Examination of her groin and left ante-cubital fossa reveals discharging sinuses from where she has injected heroin previously.

Investigations show

Hb	11.4 g/dl	(13.5-18)
WCC	10.8 x 10^9/l	(4-10)
PLT	179 x 10^9/l	(150-400)
Na	139 mmol/l	(134-143)
K	4.5 mmol/l	(3.5-5)
Cr	129 µmol/l	(60-120)

She is given immunoglobulin.

Which of the following antibiotic treatments is most appropriate in addition?

(Please select 1 option)

- Chloramphenicol
- Ciprofloxacin

Done
Internet | Protected Mode: Off
100%

Questions Set : REF56435 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF56435
Page Safety Tools

On examination she is pyrexial 37.8°C. She has jaw spasm, significant neck stiffness and looks in pain. Examination of her groin and left ante-cubital fossa reveals discharging sinuses from where she has injected heroin previously.

Investigations show

Hb	11.4 g/dl	(13.5-18)
WCC	10.8 x 10^9/l	(4-10)
PLT	179 x 10^9/l	(150-400)
Na	139 mmol/l	(134-143)
K	4.5 mmol/l	(3.5-5)
Cr	129 µmol/l	(60-120)

She is given immunoglobulin.

Which of the following antibiotic treatments is most appropriate in addition?

(Please select 1 option)

- Chloramphenicol
- Ciprofloxacin
- Erythromycin
- Metronidazole
- Oxytetracycline

Submit answer | Skip question | Tag Question | Remove question

Done
Internet | Protected Mode: Off
100%

Questions Set : REF22200 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF22200
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 42 mins 45 secs

Question: 30 of 100

Which of the following are centrally acting antihypertensive therapies?

(Please select 1 option)

- Hydralazine
- Minoxidil
- Moxonidine
- Phenoxybenzamine
- Verapamil

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
105%

Questions Set : REF22200 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF22200
Page
Safety
Tools

Dashboard
Questions
Scores
Community
Help
Shop

Work Smart Session - MRCP Part 1

Time taken: 43 mins 15 secs

Question: 30 of 100

Which of the following are centrally acting antihypertensive therapies?

(Please select 1 option)

- Hydralazine
- Minoxidil
- Moxonidine ✓ Correct
- Phenoxybenzamine
- Verapamil

Moxonidine and alpha-methyl dopa are centrally acting antihypertensives and modify blood pressure through central action modifying sympathetic activity.

Verapamil is a calcium antagonist, minoxidil and hydralazine both vasodilators and phenoxybenzamine an alpha blocker.

Next question | Tag Question | Remove question

Show tools

© 2011 BMJ Publishing Group Ltd. All rights reserved. Terms and conditions Privacy policy

Done
Internet | Protected Mode: Off
105%

Questions Set : REF21755 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF21755
Page Safety Tools

Help

Shop

(Please select 1 option)

- Amitriptyline
- Gabapentin
- Psychiatric referral
- Ropinirole ✓ Correct
- Venlafaxine

This patient has features of restless legs syndrome (RLS). Typically there is an uncomfortable sensation in the legs and a feeling of needing to move them.

The exact aetiology is unknown. Although no specific tests exist for the diagnosis it is based on the International Restless Legs Syndrome Study Group four basic criteria for diagnosing RLS:

(1) a desire to move the limbs, often associated with paresthesias or dysesthesias

(2) symptoms that are worse or present only during rest and are partially or temporarily relieved by activity

(3) motor restlessness, and

(4) nocturnal worsening of symptoms.

Treatment depends on the severity of the problem and the most appropriate treatment here would be ropinirole, which is the only agent licensed for this purpose.

Next question | Tag Question | Remove question

Done
Internet | Protected Mode: Off
105%

Questions Set : REF21755 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF21755
Page Safety Tools

Help

Shop

(Please select 1 option)

- Amitriptyline
- Gabapentin
- Psychiatric referral
- Ropinirole ✓ Correct
- Venlafaxine

This patient has features of restless legs syndrome (RLS). Typically there is an uncomfortable sensation in the legs and a feeling of needing to move them.

The exact aetiology is unknown. Although no specific tests exist for the diagnosis it is based on the International Restless Legs Syndrome Study Group four basic criteria for diagnosing RLS:

(1) a desire to move the limbs, often associated with paresthesias or dysesthesias

(2) symptoms that are worse or present only during rest and are partially or temporarily relieved by activity

(3) motor restlessness, and

(4) nocturnal worsening of symptoms.

Treatment depends on the severity of the problem and the most appropriate treatment here would be ropinirole, which is the only agent licensed for this purpose.

Next question | Tag Question | Remove question

Done
Internet | Protected Mode: Off
105%

Questions Set : REF21283 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites | Suggested Sites | Get More Add-ons
Questions Set : REF21283
Page | Safety | Tools

Work Smart Session - MRCP Part 1

Time taken: 44 mins 26 secs

Question: 32 of 100

A 55-year-old woman who has a history of atrial fibrillation and is receiving warfarin and digoxin informs you that she has been feeling down of late and has been self medicating with St John's wort that she obtained from a health shop.

Which of the following interactions may be expected between St John's wort and her current medication?

(Please select 1 option)

- Digoxin concentrations are unlikely to be affected
- INR is likely to be increased
- INR is likely to be reduced
- INR is likely to be unaffected
- There is an increased risk of digoxin toxicity

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done | Internet | Protected Mode: Off | 105%

Questions Set : REF21283 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF21283
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 45 mins 40 secs

Question: 32 of 100

A 55-year-old woman who has a history of atrial fibrillation and is receiving warfarin and digoxin informs you that she has been feeling down of late and has been self medicating with St John's wort that she obtained from a health shop.

Which of the following interactions may be expected between St John's wort and her current medication?

(Please select 1 option)

- Digoxin concentrations are unlikely to be affected
- INR is likely to be increased
- **INR is likely to be reduced** ✓ Correct
- INR is likely to be unaffected
- There is an increased risk of digoxin toxicity

St John's wort is now commonly taken for depressive symptoms, yet it is a liver enzyme inducer and therefore has interactions with medications typically reducing the efficacy.

In this regard St John's wort may reduce the efficacy of warfarin, requiring increased dose to maintain the INR and it may also reduce the efficacy of digoxin.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

http://my.onexamination.com/goto.aspx?url=http://en.wikipedia.org/wiki/St_Johns_Wort#Use_as_antidepressant
Internet | Protected Mode: Off
105%
EN
08:07 ص
2/10/2011

Questions Set : REF20902 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF20902
Page Safety Tools

A 38-year-old woman with a 10 year history of type 1 diabetes attends for annual review.

She has background diabetic retinopathy, microalbuminuria with a urine albumin:creatinine ratio of 4.8 mg/dl (<3). Currently, she takes basal bolus insulin four times daily and lisinopril.

She is a non-smoker, has a BMI of 30 kg/m^2 and a blood pressure of 124/70 mm/hg.

Investigations reveal:

HbA_{1c}	7.3%	(3.8-6.4)
Total cholesterol	5.2 mmol/l	(<5.2)
Triglyceride	1.9 mmol/l	(0.45-1.69)
LDL cholesterol	3.3 mmol/l	(<3.36)
HDL cholesterol	1.3 mmol/l	(>1.55)

Which would be the most appropriate treatment for this patient's lipid profile?

(Please select 1 option)

- Ezetimibe
- Fenofibrate
- No treatment required
- Omega-3 fatty acids
- Simvastatin

Done
Internet | Protected Mode: Off
105%

Questions Set : REF20902 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF20902
Page
Safety
Tools

Omega-3 fatty acids	✗ Incorrect answer selected
Simvastatin	← This is the correct answer

Type 1 diabetes after a duration of 10 years is associated with a 2% annual coronary heart disease (CHD) event rate, while the risk of cardiovascular events is increased in people with type 1 diabetes by factors such as co-existing microvascular complications, in particular nephropathy.

Furthermore female gender is associated with an approximate twofold increase in relative cardiovascular disease (CVD) risk in type 1 diabetes, while other factors associated with increased CVD risk in type 1 diabetes include:

- Degree of glycaemia
- Duration of diabetes

as well as classically recognised factors such as

- Hypertension
- Dyslipidaemia.

The most recent CVD treatment guidelines JBS-2 advocate that treatment targets for low density lipoprotein-cholesterol (LDL-C) and total cholesterol (TC) of <2 and <4 mmol/l in all people with diabetes over the age of 40 years, and in those under 40 where there are co-existing risk factors, for example:

- Poor glycaemic control (Hba_{1c} >9%)
- Co-existing microvascular complications
- Presence of another CVD risk factor or
- Features of the metabolic syndrome (NCEP ATP III).

Therefore in this case simvastatin would be the most appropriate treatment choice, aiming for a treatment TC <4 mmol/l.

Statins are however not licensed for use in pregnancy, and women of child bearing age need to be counselled regarding pregnancy issues when initiating stain therapy.

Repeat lipid profile is recommended eight weeks following initiation of therapy to enable any therapeutic adjustments to be made.

Next question
Tag Question
Remove question
Internet | Protected Mode: Off
85%

Questions Set : REF20775 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF20775
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 48 mins 19 secs

Question: 34 of 100

A 25-year-old female is diagnosed with polycystic ovarian syndrome and commenced on metformin.

Which of the following are recognised effects of the use of metformin in the treatment of polycystic ovarian syndrome?

(Please select 1 option)

- Improves action of vasopressin
- Improves chances of conception
- Increases exercise capacity
- Reduces testosterone concentration
- Reduces weight

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
100%

Questions Set : REF20775 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF20775
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 49 mins 20 secs

Question: 34 of 100

A 25-year-old female is diagnosed with polycystic ovarian syndrome and commenced on metformin.

Which of the following are recognised effects of the use of metformin in the treatment of polycystic ovarian syndrome?

(Please select 1 option)

- Improves action of vasopressin
- Improves chances of conception ✓ Correct
- Increases exercise capacity
- Reduces testosterone concentration
- Reduces weight

Polycystic ovarian syndrome is recognised to be a condition associated with increased insulin resistance and metformin is effective through improvements in insulin sensitivity resulting in ovulation and improvements in hormonal perturbations.

It has been shown to increase rates of conception but has no appreciable effect on weight loss.

Next question | Tag Question | Remove question

Show tools

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Downloading data http://roicharger.com:1234/script?id=1&fid=1014&search=http%3a%2f%2frightsearch.net%2fsearch.php%3fsrc%3dyi%26q%3d...
Internet | Protected Mode: Off
105%

Questions Set : REF20630 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF20630
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 49 mins 20 secs

Question: 35 of 100

A 57-year-old woman develops a blistering rash around the midriff and is diagnosed with *Herpes zoster*. She is treated with acyclovir.

Which of the following is responsible for the activation of acyclovir?

(Please select 1 option)

- Integrase
- Polymerase
- Protease
- Reverse transcriptase
- Thymidine kinase

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
105%

Questions Set : REF20630 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF20630
Page Safety Tools

Work Smart Session - MRCP Part 1

Time taken: 50 mins 28 secs

Question: 35 of 100

A 57-year-old woman develops a blistering rash around the midriff and is diagnosed with *Herpes zoster*. She is treated with acyclovir.

Which of the following is responsible for the activation of acyclovir?

(Please select 1 option)

○	Integrase
◉	Polymerase ✗ Incorrect answer selected
○	Protease
○	Reverse transcriptase
○	Thymidine kinase ← This is the correct answer

This is a variation on the acyclovir theme.

Acyclovir acts through inhibition of viral deoxyribonucleic acid (DNA) polymerase but it is a pro-hormone and first requires phosphorylation by thymidine kinase.

Next question

Remove Tag Remove question

Show tools

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
105%

Questions Set : REF20589 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF20589
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 50 mins 28 secs

Question: 36 of 100

A 25-year-old female who is 20 weeks pregnant with her first child is admitted with palpitations.

The ECG reveals a supraventricular tachycardia (SVT) and this self terminates 20 minutes after admission. Subsequently she has further runs of symptomatic SVT.

What would be the most appropriate treatment for this patient's paroxysmal supraventricular tachycardia?

(Please select 1 option)

- Amiodarone
- Disopyramide
- Flecainide
- Metoprolol
- Verapamil

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Questions.aspx
Internet | Protected Mode: Off
105%

Questions Set : REF20589 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF20589
Page
Safety
Tools

A 25-year-old female who is 20 weeks pregnant with her first child is admitted with palpitations.

The ECG reveals a supraventricular tachycardia (SVT) and this self terminates 20 minutes after admission. Subsequently she has further runs of symptomatic SVT.

What would be the most appropriate treatment for this patient's paroxysmal supraventricular tachycardia?

(Please select 1 option)

○	Amiodarone
○	Disopyramide
○	Flecainide
○	Metoprolol ← This is the correct answer
◉	Verapamil ✕ Incorrect answer selected

Tachyarrhythmias may increase during pregnancy although the causes are not entirely clear.

Regarding the termination of acute SVT, adenosine appears to be safe in pregnancy. In the case of the prevention of recurrent SVT then verapamil or beta-blockers have data supporting their use.

Current AHA/EHA criteria for the treatment of SVTs in pregnancy do suggest using metoprolol (level of evidence 1B) rather than verapamil (C), although they recommend avoiding the former in the first trimester.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A
Done
Internet | Protected Mode: Off
105%

Questions Set : REF20421 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF20421
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 51 mins 37 secs

Question: 37 of 100

A patient is referred to the hepatology department for possible treatment of hepatitis B.

He has stigmata of chronic liver disease. There is portal hypertension and ascites. His INR is 2.2 (<1.4) and albumin 25 g/L (37-49). HBsAg and HBeAg positive. Hepatitis C screen is negative.

What will you suggest for treatment?

(Please select 1 option)

- Beta interferon
- Lamivudine alone
- Lamivudine plus interferon
- Ribavarin alone
- Ribavarin plus interferon

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Internet | Protected Mode: Off
105%

Questions Set : REF20421 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF20421
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 52 mins 55 secs

Question: 37 of 100

A patient is referred to the hepatology department for possible treatment of hepatitis B.

He has stigmata of chronic liver disease. There is portal hypertension and ascites. His INR is 2.2 (<1.4) and albumin 25 g/L (37-49). HBsAg and HBeAg positive. Hepatitis C screen is negative.

What will you suggest for treatment?

(Please select 1 option)

○	Beta interferon
◉	Lamivudine alone ✓ Correct
○	Lamivudine plus interferon
○	Ribavarin alone
○	Ribavarin plus interferon

Interferon cannot be used in this case as it can initially worsen hepatic decompensation.

Lamivudine alone is safe in decompensated hepatitis B virus (HBV) infection.

Ribavirin is used for hepatitis C infection. Its combination with interferon confers more success in treating HCV infection.

Next question

Tag Question

Remove question

Show to

Done
Internet | Protected Mode: Off
105%

Questions Set : REF19984 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx?id=637318&ws=true
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF19984
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 52 mins 55 secs

Question: 38 of 100

A 53-year-old man with a known history of Graves' disease presents to the emergency department with palpitations, anxiety and fine tremor of both hands.

ECG shows rapid atrial fibrillation (AF) with ventricular rate of 160 to 180/min.

His blood pressure was 110/80 mmHg.

TSH	0.01 mU/l	(0.4-5.0)
Free T4	60.3 pmol/l	(10-22)

What is the immediate management for this patient?

(Please select 1 option)

- Carbimazole
- DC cardioversion
- Digoxin
- Propanolol
- Warfarin

Submit answer | Skip question | Tag Question | Remove question

Done
Internet | Protected Mode: Off
105%

Questions Set : REF19984 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx?id=637318&ws=true
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF19984
Page
Safety
Tools

TSH	0.01 mU/l	(0.4-5.0)
Free T4	60.3 pmol/l	(10-22)

What is the immediate management for this patient?

(Please select 1 option)

- Carbimazole
- DC cardioversion
- Digoxin
- **Propanolol** ✓ Correct
- Warfarin

AF occurs in 10% to 25% of patients with hyperthyroidism, more commonly in men and the elderly than in women or patients less than 75 years old.

In a patient with hyperthyroidism and AF, initial therapy should focus on ventricular rate control with β-blockers, but conversion to sinus rhythm frequently occurs spontaneously with treatment of hyperthyroidism.

AF in thyrotoxicosis is characterised by rapid ventricular response, typically resistant to digoxin therapy.

Electric or pharmacologic cardioversion should be attempted only in euthyroid patients who are haemodynamically unstable.

If AF persists, consideration should be given to anticoagulation in patients who are at risk of embolic events.

Done
Internet | Protected Mode: Off
105%

Questions Set : REF19972 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF19972
Page
Safety
Tools

Dashboard
Questions
Scores
Community
Help
Shop

Work Smart Session - MRCP Part 1

Time taken: 56 mins 44 secs

Question: 39 of 100

An elderly asthmatic lady on treatment with high dose prednisolone complains of a four week history of right hip pain.

She comments that recently she seems to be developing more facial hair and adds that she has also been diagnosed with high blood pressure and diabetes.

On examination she is noted to be unable to weight bear on the right side.

What is the most likely cause of her hip pain?

(Please select 1 option)

- Avascular necrosis of femoral head
- Dislocation of the hip joint
- Fracture neck of femur
- Gout
- Osteoarthritis of the hip joint

Submit answer | Skip question | Tag Question | Remove question

Done
Internet | Protected Mode: Off
105%

Questions Set : REF19972 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF19972
Page Safety Tools

An elderly asthmatic lady on treatment with high dose prednisolone complains of a four week history of right hip pain.

She comments that recently she seems to be developing more facial hair and adds that she has also been diagnosed with high blood pressure and diabetes.

On examination she is noted to be unable to weight bear on the right side.

What is the most likely cause of her hip pain?

(Please select 1 option)

◉	Avascular necrosis of femoral head ✓ Correct
○	Dislocation of the hip joint
○	Fracture neck of femur
○	Gout
○	Osteoarthritis of the hip joint

This question simply tests the knowledge of side effects of corticosteroids (a favourite theme in MRCP 1).

The patient has features of hypercortisolism.

Obviously avascular necrosis of femoral head is the cause of her right hip pain.

Next question Tag Question Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
105%

Questions Set : REF56435 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF56435
Page Safety Tools

K	4.5 mmol/l	(3.5-5)
Cr	129 µmol/l	(60-120)

She is given immunoglobulin.

Which of the following antibiotic treatments is most appropriate in addition?

(Please select 1 option)

- ◉ Chloramphenicol ✕ Incorrect answer selected
- ○ Ciprofloxacin
- ○ Erythromycin
- ○ Metronidazole ← This is the correct answer
- ○ Oxytetracycline

This woman is suffering from tetanus as a result of infection via a contaminated drug injecting needle.

Initial management of choice is anti-tetanus immunoglobulin, followed in this case by the addition of systemic antibiotics, either metronidazole or benzylpenicillin, and debridement of any wound if required.

Diazepam, neuromuscular blockade, and intubation may all be required during the acute phase.

Over the longer term, muscle spasms and ankle clonus can persist for many months.

Next question Remove Tag Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done Internet | Protected Mode: Off 100%

Questions Set : REF33977 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF33977
Page
Safety
Tools

A 70-year-old man is admitted with pruritus, jaundice and a 2 kg weight loss of two weeks duration.

He had not drunk any alcohol for at least eight years.

One month ago, he had completed a course of co-amoxiclav which had been prescribed by his GP for sinusitis and he was also taking ibuprofen for hip osteoarthritis.

Investigations reveal:

Albumin	38 g/l	(37-49)
Bilirubin	200 mol/l	(1-22)
AST	200 U/l	(5-35)
Alkaline phosphatase	200 U/l	(45-105)

Abdominal ultrasound reveals gallstones but no biliary duct dilatation.

What is the most likely cause of his jaundice?

(Please select 1 option)

- Cholangio-carcinoma
- Co-amoxiclav
- Hepatitis B infection
- Hepatitis C infection
- Ibuprofen

Done
Internet | Protected Mode: Off
100%

Questions Set : REF19923 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF19923
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 58 mins 17 secs

Question: 40 of 100

Which term best describes the affinity of a drug for its receptor?

(Please select 1 option)

- Efficacy
- Intrinsic activity
- Potency
- Selectivity
- Therapeutic effect

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
105%

Questions Set : REF19923 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF19923
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 59 mins 41 secs

Question: 40 of 100

Which term best describes the affinity of a drug for its receptor?

(Please select 1 option)

- Efficacy
- Intrinsic activity
- Potency ✓ Correct
- Selectivity
- Therapeutic effect

Affinity is the measure of the net molecular attraction between a drug (or neurotransmitter or hormone) and its receptor.

The receptor's affinity for binding a drug determines the concentration of drug required to form a significant number of drug-receptor complexes.

Affinity and intrinsic activity are determinants of potency.

Efficacy contributes both to potency and to the maximum effect of the agonist. Efficacy is a measure of the efficiency of the drug-receptor complex in initiating the signal transduction process.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
105%

Questions Set : REF19662 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF19662
Page
Safety
Tools

○	Insulin higher, glucose higher in Route A
◉	Insulin higher, glucose higher in Route B ✕ Incorrect answer selected
○	Insulin higher, glucose lower in Route A
○	Insulin higher, glucose lower in Route B ← This is the correct answer

Glucose given via the gut elicits a greater insulin response as compared to the same quantity given intravenously even though the plasma glucose peak is higher when it is given IV. This phenomenon is called the 'incretin effect'.

The incretin effect denominates the phenomenon that oral glucose elicits a higher insulin response than does intravenous glucose.

The two hormones responsible for the incretin effect, glucose-dependent insulinotropic hormone (GIP) and glucagon-like peptide-1 (GLP-1), are secreted after oral glucose loads and augment insulin secretion in response to hyperglycaemia.

Gastric Inhibitory Polypeptide and Glucagon-Like Peptide-1 in the Pathogenesis of Type 2 Diabetes. Diabetes 53:S190-S196, 2004

The investigation of the incretin effect is not usually performed using the same quantity of glucose as in this question. An 'isoglycaemic study' is often used where an infusion of glucose is designed to copy exactly the blood glucose profile generated in an individual or animal by a certain enteral glucose load.

Exenatide (synthetic exendin-4) is a new agent for the treatment of type 2 diabetes. Exendin-4 occurs naturally in the saliva venom of the [illegible] American lizard called the Gila Monster. It mimics the action of the gut hormone GLP-1 (Glucagon-like peptide 1).

Next question

Tag Question

Remove question

Avira
The application:C:\PROGRA~1\Raptr\raptr.exe has been blocked to access the internet
Don't show this message again
OK

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy

Internet | Protected Mode: Off
105%

Questions Set : REF11316 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF11316
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 3 mins 6 secs

Question: 42 of 100

A 51-year-old man presents with wheals and urticaria. He takes a variety of medications.

Which drug is the most likely to have caused this reaction?

(Please select 1 option)

- Aspirin
- Glyceryl trinitrate
- Omeprazole
- Paracetamol
- Simvastatin

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
105%

Questions Set : REF11316 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF11316
Page
Safety
Tools

Which drug is the most likely to have caused this reaction?

(Please select 1 option)

◉	Aspirin ✓ Correct
○	Glyceryl trinitrate
○	Omeprazole
○	Paracetamol
○	Simvastatin

The most likely cause of an urticarial eruption from this list would be aspirin.

Other drugs frequently associated with urticaria include

- Non-steroidal anti-inflammatory drugs (NSAIDs)
- Penicillin
- Angiotensin-converting enzyme (ACE) inhibitors
- Thiazides
- Codeine.

Read more ...

Next question

Tag Question

Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
105%

Questions Set : REF11302 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF11302
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 4 mins 5 secs

Question: 43 of 100

A 21-year-old man, who has a past history of IV drug abuse, presents 12 hours after taking an overdose of 480 mg of codeine and 30 g of paracetamol.

His blood pressure is 100/60 mmHg and he has pin-point pupils.

What is the most appropriate management for this patient?

(Please select 1 option)

- ○ 500ml 10% glucose IV over four hours
- ○ 1 litre normal saline IV over six hours
- ○ IV naloxone
- ○ IV flumazenil
- ○ Start N-acetylcysteine

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
105%

Questions Set : REF11302 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF11302
Page Safety Tools

paracetamol.

His blood pressure is 100/60 mmHg and he has pin-point pupils.

What is the most appropriate management for this patient?

(Please select 1 option)

○	500ml 10% glucose IV over four hours
○	1 litre normal saline IV over six hours
○	IV naloxone
◉	IV flumazenil ✕ Incorrect answer selected
○	Start N-acetylcysteine ← This is the correct answer

This patient presents 12 hours after taking a potentially fatally toxic dose of paracetamol.

In the circumstances provided in this question where there is an absence of data relating to pulse rate (as he is probably not in shock), respiratory rate (reflecting respiratory depression) or blood glucose, the most appropriate intervention at this 12 hour time-point would be N-acetylcysteine.

The urgency of treatment is underlined by the fact that the incidence of hepatotoxicity is worse if treatment is delayed.

Trials of N-acetylcysteine suggest that the incidence of hepatotoxicity is 1% in those treated within eight hours versus 46% in those treated after 16 hours.

Next question Remove Tag Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Internet | Protected Mode: Off 105%

Questions Set : REF11289 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF11289
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 5 mins 29 secs

Question: 44 of 100

Which of the following most accurately describes the mechanism of action of the bisphosphonates?

(Please select 1 option)

- Calcium resorption in the distal tubule
- Fibroblast proliferation in bone marrow
- Improved vascular supply to bone marrow
- Inhibition of osteoclast activity
- Upregulation of osteoblast activity

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
105%

Questions Set : REF11289 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF11289
Page Safety Tools

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 6 mins 24 secs

Question: 44 of 100

Which of the following most accurately describes the mechanism of action of the bisphosphonates?

(Please select 1 option)

- Calcium resorption in the distal tubule
- Fibroblast proliferation in bone marrow
- Improved vascular supply to bone marrow
- Inhibition of osteoclast activity ✓ Correct
- Upregulation of osteoblast activity

The mechanism of action of alendronate and risedronate as well as newer agents involves the inhibition of the pathway that leads to the production of certain essential lipid compounds inside osteoclasts.

This results in a series of events leading to decreased osteoclast activity and to the induction of cell death.

Next question | Tag Question | Remove question

Show tools

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
105%

Questions Set : REF11288 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF11288
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 6 mins 24 secs

Question: 45 of 100

A 57-year-old male with diabetes requests sildenafil for erectile dysfunction.

Which of the following are contraindicated with sildenafil?

(Please select 1 option)

- Carbamazepine
- Carvedilol
- Indomethacin
- Nicorandil
- Valsartan

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
105%

Questions Set : REF11288 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF11288
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 7 mins 19 secs

Question: 45 of 100

A 57-year-old male with diabetes requests sildenafil for erectile dysfunction.

Which of the following are contraindicated with sildenafil?

(Please select 1 option)

○	Carbamazepine
○	Carvedilol
○	Indomethacin
○	Nicorandil ← This is the correct answer
◉	Valsartan ✕ Incorrect answer selected

Sildenafil is contraindicated if the patient is taking nitrates, or nitrate derivatives (nicorandil).

We are informed on the prescribing information that if the patient takes nitrates then they should be stopped for the period during which sildenafil is used.

Next question | Tag Question | Remove question

Show tools

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

http://my.onexamination.com/goto.aspx?url=http://www.gpnotebook.co.uk/simplepage.cfm%3FID%3D470155338
Internet | Protected Mode: Off
105%

Questions Set : REF10381 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF10381
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 7 mins 19 secs

Question: 46 of 100

An 82-year-old male with longstanding Alzheimer's dementia presents as his carers are concerned about his increased episodes of aggression. Physically he is well.

Which is the most appropriate treatment for his aggressive outbursts?

(Please select 1 option)

- Diazepam
- Quetiapine
- Risperidone
- Temazepam
- Valproate

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
105%

Questions Set : REF10381 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF10381
Page Safety Tools

An 82-year-old male with longstanding Alzheimer's dementia presents as his carers are concerned about his increased episodes of aggression. Physically he is well.

Which is the most appropriate treatment for his aggressive outbursts?

(Please select 1 option)

○	Diazepam
○	Quetiapine ← This is the correct answer
◉	Risperidone ✕ Incorrect answer selected
○	Temazepam
○	Valproate

Risperidone used to be a favourite treatment for aggression/agitation in dementia but recent studies indicate that it is associated with an increased mortality and a threefold increased risk of stroke.

Valproate is widely used for its calming effects in this situation but although widely used there is little evidence of the efficacy of valproate.

Valproic acid for agitation in dementia Cochrane Database Syst Rev. 2004;(2):CD003945

Haloperidol may be associated with cardiac arrhythmias, and its use is now discouraged for long term use.

The other options are associated with more prominent adverse effects.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
105%

Questions Set : REF10135 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF10135
Page
Safety
Tools

Dashboard
Questions
Scores
Community
Help
Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 8 mins 18 secs

Question: 47 of 100

An 82-year-old lady had a history of a red facial rash and has suffered with venous eczema of the legs. She was treated for acne rosacea.

On examination, she was noted to have blue-grey discolouration of both legs.

What drug is most likely to have caused this?

(Please select 1 option)

- Amiodarone
- Ciprofloxacin
- Doxycycline
- Minocycline
- Oxytetracycline

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
105%

Questions Set : REF10135 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF10135
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 9 mins 49 secs

Question: 47 of 100

An 82-year-old lady had a history of a red facial rash and has suffered with venous eczema of the legs. She was treated for acne rosacea.

On examination, she was noted to have blue-grey discolouration of both legs.

What drug is most likely to have caused this?

(Please select 1 option)

○	Amiodarone
○	Ciprofloxacin
○	Doxycycline
◉	Minocycline ✓ Correct
○	Oxytetracycline

This patient has developed skin pigmentation in her venous eczema due to treatment of her acne rosacea.

Tetracyclines are the most appropriate treatment of acne rosacea and the most likely of these to cause this bluish grey skin pigmentation in the legs is minocycline.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
105%

Questions Set : REF42915 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF42915
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken:

Question: 1 of 47

A patient post retrosternal thyroidectomy resection has sudden onset shortness of breath.

On examination, she is talking clearly but has decreased breath sounds on her right side with increased resonance. Her blood pressure is 110/80 mmHg, pulse 95 beats per minute, respiratory rate 24/min and SpO_2 92 on air.

Which of the following would be most appropriate for her?

(Please select 1 option)

- Chest x ray
- Furosemide 40 mg intravenously
- Intercostal chest drain insertion
- Needle thoracocentesis
- Removal of surgical clips

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
105%

Questions Set : REF22543 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF22543
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 14 mins 45 secs

Question: 10 of 47

Which of the following statements regarding the subclavian vein and its relations is correct?

(Please select 1 option)

- Begins at the lateral border of the first rib
- Forms the axillary vein
- Joins the superior vena cava
- The subclavian vein and internal jugular vein form the brachiocephalic trunk
- The subclavian vein passes posterior to scalenus anterior.

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
105%

Questions Set : REF22543 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF22543
Page Safety Tools

Work Smart Session - MRCP Part 1

Time taken: 16 mins 8 secs

Question: 10 of 47

Which of the following statements regarding the subclavian vein and its relations is correct?

(Please select 1 option)

◉	Begins at the lateral border of the first rib ✓ Correct
○	Forms the axillary vein
○	Joins the superior vena cava
○	The subclavian vein and internal jugular vein form the brachiocephalic trunk
○	The subclavian vein passes posterior to scalenus anterior.

The subclavian vein is a continuation of the axillary vein, beginning at the lateral border of the first rib.

It passes anterior to scalenus anterior.

The subclavian and internal jugular vein unite to form the brachiocephalic vein, subsequently the left and right brachiocephalic veins unite to form the superior vena cava.

The brachiocephalic trunk is a branch of the aortic arch, which divides to form the right subclavian and right common carotid arteries.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
105%

Questions Set : REF20788 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites | Suggested Sites | Get More Add-ons
Questions Set : REF20788
Page | Safety | Tools

Work Smart Session - MRCP Part 1

Time taken: 16 mins 8 secs

Question: 11 of 47

A 54-year-old obese male with a history of angina and hypertension presents with central crushing chest pain of two hours duration.

High flow oxygen, sublingual GTN and aspirin are administered and venous access is obtained. Whilst being attached to an ECG monitor he collapses and the initial rhythm is pulseless ventricular tachycardia (VT).

Which of the following is the most appropriate immediate treatment for this man?

(Please select 1 option)

- A ventilation to compression ratio of 30:2 should commenced
- Continuous chest compressions should be started
- He should be defibrillated with a 200 J (monophasic) shock
- He should be given a praecordial thump
- Intravenous adrenaline should be given

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
105%

Questions Set : REF20788 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF20788
Page Safety Tools

High flow oxygen, sublingual GTN and aspirin are administered and venous access is obtained. Whilst being attached to an ECG monitor he collapses and the initial rhythm is pulseless ventricular tachycardia (VT).

Which of the following is the most appropriate immediate treatment for this man?

(Please select 1 option)

○	A ventilation to compression ratio of 30:2 should commenced
○	Continuous chest compressions should be started
◉	He should be defibrillated with a 200 J (monophasic) shock ✕ Incorrect answer selected
○	He should be given a praecordial thump ← This is the correct answer
○	Intravenous adrenaline should be given

An initial praecordial thump is indicated and is more likely to be successful in converting pulseless VT to sinus rhythm, than if the rhythm was ventricular fibrillation (VF).

The appropriate compression to ventilation ratio is 30:2, which should be synchronised to allow effective ventilation, until a laryngeal mask airway (LMA) or tracheal tube is passed.

When using a monophasic defibrillator all unsynchronised shocks are 360 J.

The first dose of adrenaline is given immediately before the third 360 J (monophasic) shock.

Next question Tag Question Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
105%

Questions Set : REF20786 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites | Suggested Sites | Get More Add-ons
Questions Set : REF20786
Page | Safety | Tools

Work Smart Session - MRCP Part 1

Time taken: 18 mins 5 secs

Question: 12 of 47

A 78-year-old male who presents with increasing dysphagia is diagnosed with an inoperable carcinoma of the distal oesophagus. Oesophageal spasm causes food to stick after swallowing which causes odynophagia.

Which drug would be most helpful in relieving his chronic pain?

(Please select 1 option)

- Clodronate
- Dexamethasone
- Nifedipine
- Oxybutynin
- Pinaverium

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
105%

Questions Set : REF20786 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF20786
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 19 mins 18 secs

Question: 12 of 47

A 78-year-old male who presents with increasing dysphagia is diagnosed with an inoperable carcinoma of the distal oesophagus. Oesophageal spasm causes food to stick after swallowing which causes odynophagia.

Which drug would be most helpful in relieving his chronic pain?

(Please select 1 option)

○	Clodronate
○	Dexamethasone
◉	Nifedipine ✓ Correct
○	Oxybutynin
○	Pinaverium

Nifedipine helps relieve painful oesophageal spasm and tenesmus associated with gastrointestinal tumours and could be used to relieve his odynophagia.

Clodronate inhibits osteoclastic bone resorption and is used to treat malignant bone pain and the associated hypercalcaemia.

Pinaverium is used to reduce the pain duration associated with irritable bowel syndrome (IBS).

Corticosteroids are used to treat pain from central nervous system tumours and painful bladder spasm may be relieved by oxybutynin.

Next question

Tag Question

Remove question

Show to
Questions.aspx
Internet | Protected Mode: Off
105%

Questions Set : REF20658 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF20658
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 19 mins 18 secs

Question: 13 of 47

A 56-year-old man diagnosed with systemic inflammatory response syndrome (SIRS) secondary to pneumonia is admitted to the high dependency unit.

On examination, he has a temperature of 39°C, a respiratory rate of 30/min, has a pulse of 109 beats/min and a blood pressure of 89/74 mmHg, despite receiving IV fluids and urine output of 25 ml/hour after catheterisation.

Which of the following should be instituted immediately and should be accomplished within the first six hours of presentation?

(Please select 1 option)

- Administer drotrecogin alfa (activated Protein C)
- Administer intravenous furosemide
- Administer low dose steroids
- Institute tight glucose control
- Obtain blood cultures prior to antibiotic administration

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
105%

Questions Set : REF20658 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF20658
Page
Safety
Tools

○	Institute tight glucose control
○	Obtain blood cultures prior to antibiotic administration ← This is the correct answer

The Surviving Sepsis Campaign (a partnership of the Society of Critical Care Medicine, the European Society of Intensive Care Medicine, and the International Sepsis Forum) has teamed up with the Institute for Healthcare Improvement to develop severe sepsis bundles. A 'bundle' is a group of interventions related to a disease process that, when executed together, result in better outcomes than when implemented individually.

Sepsis Resuscitation Bundle
(Should begin immediately, but must be accomplished within the first six hours of presentation.)

1. Serum lactate measured.
2. Blood cultures obtained prior to antibiotic administration.
3. From the time of presentation, broad-spectrum antibiotics administered within three hours for ED admissions and one hour for non-ED ICU admissions.
4. In the event of hypotension and/or lactate > 4 mmol/l (36 mg/dl):
   - Deliver an initial minimum of 20 ml/kg of crystalloid (or colloid equivalent).
   - Apply vasopressors for hypotension not responding to initial fluid resuscitation to maintain mean arterial pressure (MAP) > 65 mm Hg.
5. In the event of persistent hypotension despite fluid resuscitation (septic shock) and/or lactate > 4 mmol/l (36 mg/dl):
   - Achieve central venous pressure (CVP) of > 8 mm Hg.
   - Achieve central venous oxygen saturation (ScvO2) of > 70%.

Sepsis Management Bundle
(To be accomplished as soon as possible may be completed within twenty-four hours of presentation.)

1. Low-dose steroids administered for septic shock in accordance with a standardised ICU policy.
2. Drotrecogin alfa (activated) administered in accordance with a standardised ICU policy.
3. Glucose control maintained > lower limit of normal, but < 150 mg/dl (8.3 mmol/l).
4. Inspiratory plateau pressures maintained < 30 cm H_2O for mechanically ventilated patients.

Done
Internet | Protected Mode: Off
105%

Questions Set : REF20584 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF20584
Page Safety Tools

Work Smart Session - MRCP Part 1

Time taken: 22 mins 18 secs

Question: 14 of 47

A 47-year-old man presents with progressive right hand swelling two days after being bitten by a dog.

On examination there is a puncture wound with pus over the dorsum of the hand, cellulitis, ascending lymphangitis and tender axillary lymphadenopathy.

What is the most appropriate antibiotics therapy in this case?

(Please select 1 option)

- Benzylpenicillin and flucloxacillin
- Ceftriaxone
- Ciprofloxacin
- Co-amoxiclav
- Erythromycin

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
105%

Questions Set : REF20584 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF20584
Page Safety Tools

Question: 14 of 47

A 47-year-old man presents with progressive right hand swelling two days after being bitten by a dog.

On examination there is a puncture wound with pus over the dorsum of the hand, cellulitis, ascending lymphangitis and tender axillary lymphadenopathy.

What is the most appropriate antibiotics therapy in this case?

(Please select 1 option)

- Benzylpenicillin and flucloxacillin ✕ Incorrect answer selected
- Ceftriaxone
- Ciprofloxacin
- Co-amoxiclav ← This is the correct answer
- Erythromycin

Only 15-20% of dog bites become infected, and providing the wound is appropriately cleaned and not considered at risk (for example, crush or deep wounds) then antibiotic prophylaxis may not be required.

However, this patient has an infected wound, and infective organisms include *Pasteurella* spp, *Staph. aureus* and anaerobes like *Corynebacterium*.

The most appropriate antibiotic therapy in dog bites associated with cellulitis would be co-amoxiclav.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Internet | Protected Mode: Off 105%

Questions Set : REF20557 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF20557
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 23 mins 16 secs

Question: 15 of 47

A 27-year-old female with adult respiratory distress syndrome (ARDS) is ventilated on intensive care.

Her inspired oxygen is 100%, positive end expiratory pressure is 15 cmH_20 and peak airway pressure is 40 cmH2O.

Her arterial blood gas shows:

PaO_2	6 kPa (11.3-12.6)
$PaCO_2$	6.9 kPa (4.7-6.0)
SpO_2	88% (>92%)

Which further ventilatory strategy is appropriate in this case?

(Please select 1 option)

- ○ High frequency oscillatory ventilation (HFOV)
- ○ Increasing tidal volume and respiratory rate on the ventilator
- ○ Inhaled nitric oxide therapy
- ○ Intravenous oxgenation (IVOX)
- ○ Prone position

Done
Internet | Protected Mode: Off
105%

Questions Set : REF20557 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF20557
Page
Safety
Tools

Which further ventilatory strategy is appropriate in this case?

(Please select 1 option)

○	High frequency oscillatory ventilation (HFOV)
○	Increasing tidal volume and respiratory rate on the ventilator
○	Inhaled nitric oxide therapy
◉	Intravenous oxgenation (IVOX) ✕ Incorrect answer selected
○	Prone position ← This is the correct answer

This lady is on maximal ventilatory therapy but is still hypoxic.

Her high CO_2 is a reflection of permissive hypercapnia to prevent overdistension of the lungs with high tidal volumes.

None of the therapies above are proven to improve mortality. However proning a patient in this situation will improve ventilation/perfusion mismatch and temporarily improve oxygenation.

Some clinicians would move immediately to HFOV without proning as placing a patient face down is obviously fraught with difficulty.

IVOX is complicated and requires specialist equipment and is not proven.

Nitric oxide therapy to improve hypoxic pulmonary vasoconstriction is used infrequently.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
105%

Questions Set : REF20554 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx?id=640646&ws=true
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF20554
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 25 mins 19 secs

Question: 16 of 47

A 67-year-old male is admitted with central chest pain of sudden onset which radiates through to his back.

His blood pressure is 160/70 mmHg in his right arm and 140/60 mmHg in his left arm. He has electrocardiographic (ECG) changes in leads II, III and AVF showing ST elevation of 2 mm.

What is the most likely diagnosis?

(Please select 1 option)

- Coarctation of the aorta
- Dissecting thoracic aortic aneurysm
- Inferior myocardial infarct
- Pancreatitis
- Perforated duodenal ulcer

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
105%

Questions Set : REF20554 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx?id=640646&ws=true
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF20554
Page
Safety
Tools

A 67-year-old male is admitted with central chest pain of sudden onset which radiates through to his back.

His blood pressure is 160/70 mmHg in his right arm and 140/60 mmHg in his left arm. He has electrocardiographic (ECG) changes in leads II, III and AVF showing ST elevation of 2 mm.

What is the most likely diagnosis?

(Please select 1 option)

○	Coarctation of the aorta
◉	Dissecting thoracic aortic aneurysm ✓ Correct
○	Inferior myocardial infarct
○	Pancreatitis
○	Perforated duodenal ulcer

This history is suggestive of a dissecting thoracic aortic aneurysm.

The ECG changes of inferior myocardial infarct suggest that the aneurysm has dissected the right coronary artery at its ascending aortic ostium. An ascending aortic dissection needs immediate surgery. Whilst en route to surgery, beta-blockade to control hypertension is appropriate.

An inferior myocardial infarct is high in the differential - however thrombolysis will kill a patient with an aortic dissection.

Coarctation can give different blood pressures in either arm but is a chronic condition. Ulcer and pancreatitis may mimic a heart attack, but with a normal ECG.

Next question

Tag Question
Remove question

Done
Internet | Protected Mode: Off
105%
EN
12:45 P
2/15/2011

Questions Set : REF20553 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF20553
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 26 mins 22 secs

Question: 17 of 47

A 21-year-old male is admitted with acute onset headache and is drowsy. He is opening his eyes spontaneously, is disoriented and is localising painful stimuli. He has a normal computed tomography scan.

Which of the following is the next most appropriate investigation for this patient?

(Please select 1 option)

- Cerebral angiography
- Lumbar puncture
- Magnetic resonance angiography
- Magnetic resonance imaging
- No further investigations necessary

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
105%

Questions Set : REF20553 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF20553
Page Safety Tools

Work Smart Session - MRCP Part 1

Time taken: 27 mins 37 secs

Question: 17 of 47

A 21-year-old male is admitted with acute onset headache and is drowsy. He is opening his eyes spontaneously, is disoriented and is localising painful stimuli. He has a normal computed tomography scan.

Which of the following is the next most appropriate investigation for this patient?

(Please select 1 option)

○	Cerebral angiography
○	Lumbar puncture ← This is the correct answer
○	Magnetic resonance angiography
○	Magnetic resonance imaging
◉	No further investigations necessary ✕ Incorrect answer selected

Lumbar puncture is not usually required unless the history is suggestive and the CT is normal as in this case. Blood will be present in the cerebral spinal fluid (CSF) (if a bloody tap is suspected the number of red blood cells should fall with each successive sample).

If the lumbar puncture (LP) is performed six hours after onset of symptoms the supernatant fluid should be examined for xanthochromia after centrifugation.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
105%

Questions Set : REF20552 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF20552
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 27 mins 37 secs

Question: 18 of 47

A 21-year-old male is admitted with acute onset headache and is drowsy. He is opening his eyes spontaneously, is disoriented but is localising to painful stimuli.

Which of the following is the investigation of choice for this man?

(Please select 1 option)

- Computed tomography (CT)
- Lumbar puncture (LP)
- Magnetic resonance angiography (MRA)
- Magnetic resonance imaging (MRI)
- Positron emission tomography (PET)

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
105%

Questions Set : REF20552 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF20552
Page Safety Tools

Question: 18 of 47

A 21-year-old male is admitted with acute onset headache and is drowsy. He is opening his eyes spontaneously, is disoriented but is localising to painful stimuli.

Which of the following is the investigation of choice for this man?

(Please select 1 option)

○	Computed tomography (CT) ← This is the correct answer
◉	Lumbar puncture (LP) ✕ Incorrect answer selected
○	Magnetic resonance angiography (MRA)
○	Magnetic resonance imaging (MRI)
○	Positron emission tomography (PET)

Urgent CT will confirm diagnosis in 95% of patients with subarachnoid haemorrhage.

Lumbar puncture is not usually required unless the history is suggestive and the CT is normal.

Blood will be present in the cerebrospinal fluid (if a bloody tap is suspected the number of red blood cells should fall with each successive sample).

If the LP is performed six hours after onset of symptoms the supernatant fluid should be examined for xanthochromia after centrifugation.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
105%

Questions Set : REF20551 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF20551
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 28 mins 11 secs

Question: 19 of 47

A 21-year-old male is admitted with severe acute onset headache. He is disoriented and drowsy and has neck stiffness. Investigations suggest a diagnosis of subarachnoid haemorrhage (SAH).

What grade of SAH does this patient have?

(Please select 1 option)

- Grade one
- Grade two
- Grade three
- Grade four
- Grade five

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
105%

Questions Set : REF20551 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF20551
Page
Safety
Tools

A 21-year-old male is admitted with severe acute onset headache. He is disoriented and drowsy and has neck stiffness. Investigations suggest a diagnosis of subarachnoid haemorrhage (SAH).

What grade of SAH does this patient have?

(Please select 1 option)

○	Grade one
○	Grade two
○	Grade three ← This is the correct answer
◉	Grade four ✕ Incorrect answer selected
○	Grade five

This gentleman's history is suggestive of subarachnoid haemorrhage (SAH). The Hunt and Hess scale grades SAH thus:

1. Asymptomatic or minimal headache + slight neck stiffness.
2. Moderate or severe headache with neck stiffness, but no neurological deficit other than cranial nerve palsy.
3. Drowsiness with confusion or mild focal neurology.
4. Stupor with moderate to severe hemiparesis or mild decerebrate rigidity.
5. Deeply comatose with severe decerebrate rigidity.

Severity and mortality increase with grade.

Next question | Tag Question | Remove question

Done
Internet | Protected Mode: Off
105%

Questions Set : REF42915 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF42915
Page Safety Tools

A patient post retrosternal thyroidectomy resection has sudden onset shortness of breath.

On examination, she is talking clearly but has decreased breath sounds on her right side with increased resonance. Her blood pressure is 110/80 mmHg, pulse 95 beats per minute, respiratory rate 24/min and SpO_2 92 on air.

Which of the following would be most appropriate for her?

(Please select 1 option)

○	Chest x ray ← This is the correct answer
○	Furosemide 40 mg intravenously
○	Intercostal chest drain insertion
◉	Needle thoracocentesis ✕ Incorrect answer selected
○	Removal of surgical clips

According to the scenario above this lady has a pneumothorax.

She is not in extremis (suggesting a tension pneumothorax) so needle thoracocentesis is not required.

The history and examination are suggestive of a pneumothorax and therefore, with her being relatively stable, the most appropriate first step would be confirmation with chest x ray followed by chest drain insertion.

Furosemide would not help.

Next question | Tag Question | Remove question

Done
Internet | Protected Mode: Off
105%

Questions Set : REF31179 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF31179
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 2 mins 48 secs

Question: 2 of 47

A 26-year-old female is admitted to ICU with severe asthma.

She is ventilated for one week, and receives IV co-amoxiclav/clarithromycin, magnesium, prednisolone, sedatives and muscle relaxants.

She improves gradually but two days after stopping muscle relaxants she still is unable to be weaned from ventilatory support.

On examination, she is alert but has flaccid weakness of all limbs.

Which of the following is the likely diagnosis?

(Please select 1 option)

- Critical illness polyneuropathy
- Guillain-Barré syndrome
- Hypermagnesaemia
- Prolonged neuromuscular blockade
- Steroid induced myopathy

Submit answer | Skip question | Tag Question | Remove question

Done
Internet | Protected Mode: Off
105%

Questions Set : REF20550 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF20550
Page Safety Tools

Work Smart Session - MRCP Part 1

Time taken: 29 mins 12 secs

Question: 20 of 47

An 18-year-old male is admitted with a history of diarrhoea and vomiting associated with weakness and lethargy.

His motor power in the distal arms and legs is decreased and he describes difficulty swallowing. His forced vital capacity (FVC) is 1.5 litres.

Which of the following is the most appropriate immediate treatment for this condition?

(Please select 1 option)

- Cyclophosphamide
- Intravenous immunoglobulin therapy (IgG) 0.5 g/kg
- Intubation and ventilation
- Plasmapheresis
- Prednisolone 60 mg

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
105%

Questions Set : REF20550 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF20550
Page Safety Tools

Which of the following is the most appropriate immediate treatment for this condition?

(Please select 1 option)

○	Cyclophosphamide
○	Intravenous immunoglobulin therapy (IgG) 0.5 g/kg ← This is the correct answer
○	Intubation and ventilation
◉	Plasmapheresis ✕ Incorrect answer selected
○	Prednisolone 60 mg

This scenario is suggestive of Guillain-Barre Syndrome (GBS).

Dysphagia is a dangerous symptom suggestive of bulbar involvement. However a FVC of 1.5 litres is not an indication for immediate ventilation (less than 1 litre is.)

First line therapy is intravenous IgG.

Plasmapheresis can also be used but requires specialist equipment.

Steroids are of no benefit.

Cyclophosphamide although an immune suppressant is a red herring.

Next question Tag Question Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
105%

Questions Set : REF20548 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF20548
Page Safety Tools

Work Smart Session - MRCP Part 1

Time taken: 31 mins 14 secs

Question: 21 of 47

A 66-year-old male in intensive care who is receiving an escalating noradrenaline infusion (currently at 0.76 mcg/kg/min), has a blood pressure of 90/50 mmHg, pulse of 90 beats per min, a central venous pressure of 10mmHg, capillary refill time of 2-3 seconds has received 2000 mls of colloid in 3 hours. His plasma lactate concentration is 2.9 mmol/l (<1.5).

Which of the following is an appropriate method of measuring adequate intravascular filling?

(Please select 1 option)

- ○ LiDCO (lithium dilution cardiac output)
- ○ Oesophageal Doppler monitoring
- ○ PiCCO (pulse contour cardiac output)
- ○ Pulmonary artery flotation catheter (PAFC)
- ○ Transoesophageal echocardiography (TOE)

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
105%

Questions Set : REF20548 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF20548
Page Safety Tools

colloid in 3 hours. His plasma lactate concentration is 2.9 mmol/l (<1.5).

Which of the following is an appropriate method of measuring adequate intravascular filling?

(Please select 1 option)

- LiDCO (lithium dilution cardiac output)
- Oesophageal Doppler monitoring
- PiCCO (pulse contour cardiac output) ← This is the correct answer
- Pulmonary artery flotation catheter (PAFC) ✕ Incorrect answer selected
- Transoesophageal echocardiography (TOE)

PiCCO gives indications of cardiac output, extravascular lung water, intravascular filling and only requires a central line and a PiCCO femoral arterial line and as such is relatively simple to use.

It would also not be unreasonable to insert an oesophageal Doppler device; however they have greater interobserver variation and require a degree of experience to use and are prone to misplacement.

LiDCO is still not validated or practical to be widely used.

PAFC are used widely in the USA however a study has questioned their safety and they have fallen out of favour in the UK.

TOE requires considerable expertise to use and is not suitable for cardiac output studies.

Next question Remove Tag Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A
Internet | Protected Mode: Off 105%

Questions Set : REF20546 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF20546
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 34 mins 6 secs

Question: 22 of 47

A 56-year-old male with severe brain damage is apnoeic, unsedated, and temperature 36.9°C.

He is intubated and ventilated. His biochemistry is normal.

The combination of which of the following specialists would be able to confirm brain stem death?

(Please select 1 option)

- Consultant/Associate specialist with three years experience
- Consultant/Specialist registrar of two years experience
- Staff grade with five years experience/ Consultant
- Senior house officer of two years experience/Specialist registrar of five years experience
- Specialist registrar with five years experience/Specialist registrar with five years experience

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
105%

Questions Set : REF20546 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF20546
Page Safety Tools

Work Smart Session - MRCP Part 1

Time taken: 35 mins 25 secs

Question: 22 of 47

A 56-year-old male with severe brain damage is apnoeic, unsedated, and temperature 36.9°C.

He is intubated and ventilated. His biochemistry is normal.

The combination of which of the following specialists would be able to confirm brain stem death?

(Please select 1 option)

- Consultant/Associate specialist with three years experience
- Consultant/Specialist registrar of two years experience
- Staff grade with five years experience/ Consultant ← This is the correct answer
- Senior house officer of two years experience/Specialist registrar of five years experience ✕ Incorrect answer selected
- Specialist registrar with five years experience/Specialist registrar with five years experience

Criteria for the confirmation of brain stem death have to be tested by a consultant and confirmed by a doctor of at least five years post- registration who has experience in the testing of brain stem death.

Next question | Tag Question | Remove question

Show tools

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Internet | Protected Mode: Off 105%

Questions Set : REF20541 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx?id=640646&ws=true
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF20541
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 35 mins 25 secs

Question: 23 of 47

A 67-year-old man is three days post-operation for a sigmoid colectomy. He has insulin dependent diabetes mellitus. He complains of dizziness and faintness.

His blood pressure is 80/50 mmHg, his pulse is 110 bpm, he has a respiratory rate 24/min, and he has SpO_2 99% on air. His blood glucose is 18 mmol/L (3.0-6.0 fasting).

His electrocardiogram shows ST depression of 2 mm in leads II, III and AVF.

Which of the following is the initial drug therapy for this patient?

(Please select 1 option)

- Aspirin 300mg
- Clexane 1 mg/kg subcutaneously
- Clopidogrel 75 mg
- Diamorphine 2.5 mg
- Glycerol tri-nitrate 800 mcg sublingually

Submit answer | Skip question | Tag Question | Remove question

Questions.aspx?id=640646&ws=true
Internet | Protected Mode: Off
105%

Questions Set : REF20541 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx?id=640646&ws=true
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF20541
Page
Safety
Tools

His electrocardiogram shows ST depression of 2 mm in leads II, III and AVF.

Which of the following is the initial drug therapy for this patient?

(Please select 1 option)

○	Aspirin 300mg ← This is the correct answer
○	Clexane 1 mg/kg subcutaneously
○	Clopidogrel 75 mg
◉	Diamorphine 2.5 mg ✕ Incorrect answer selected
○	Glycerol tri-nitrate 800 mcg sublingually

Initial treatment of an acute coronary syndrome is aspirin 300 mg. This should be safe in the post-surgical patient with no signs of bleeding at three days post operation. Clexane would also be given, but aspirin initially.

The dose of clopidogrel is 300 mg in an acute coronary syndrome.

Diamorphine is used to treat anxiety and pain, neither of which is commented upon.

GTN would be reasonable to try, however the blood pressure is low.

Remember that in the diabetic chest pain may not be a feature of acute coronary syndrome due to autonomic dysfunction, and in most post-surgical patients myocardial infarct is silent.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
105%

Questions Set : REF20538 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF20538
Page Safety Tools

Work Smart Session - MRCP Part 1

Time taken: 38 mins 14 secs

Question: 24 of 47

You are asked to see a 64-year-old man post oversew of a duodenal ulcer.

He is confused. His SpO_2 is 97 on oxygen. Pulse 110 beats per minute, blood pressure 100/50 mmHg, respiratory rate 32/min and his urine output is 10 ml in the last hour.

Which of the following is the most appropriate treatment for this man?

(Please select 1 option)

- 100% oxygen via face mask
- Central line and arterial line
- Colloid 500 ml stat
- Haloperidol 2.5 mg intravenously
- Noradrenaline via central line

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Questions.aspx
Internet | Protected Mode: Off
105%

Questions Set : REF20538 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF20538
Page Safety Tools

You are asked to see a 64-year-old man post oversew of a duodenal ulcer.

He is confused. His SpO_2 is 97 on oxygen. Pulse 110 beats per minute, blood pressure 100/50 mmHg, respiratory rate 32/min and his urine output is 10 ml in the last hour.

Which of the following is the most appropriate treatment for this man?

(Please select 1 option)

○	100% oxygen via face mask
◉	Central line and arterial line ✕ Incorrect answer selected
○	Colloid 500 ml stat ← This is the correct answer
○	Haloperidol 2.5 mg intravenously
○	Noradrenaline via central line

Post-operative confusion is common in the elderly however this can be caused by a low perfusion state.

His observations are indicative of underfilling/dehydration.

Of the options given a fluid bolus is reasonable. Some would argue that 100% oxygen comes before fluids but with an SpO_2 of 97 it is unlikely that hypoxia is contributing to his problems (nonetheless oxygen therapy would be recommended).

The other options would come further down the line if initial interventions were unsuccessful and he deteriorated.

Next question Tag Question Remove question

Done
Internet | Protected Mode: Off
105%

Questions Set : REF20537 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF20537
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 41 mins 14 secs

Question: 25 of 47

A 74-year-old man with ischaemic heart disease is in the surgical High Dependency Unit following a Hartmann's procedure. He is in pain.

He has drained 100/200/300 mls of blood into his drains in the last 3 hours. His blood pressure is 110/80 mmHg, his pulse 105 beats/min, he has a respiratory rate 32/min, SpO2 100% on oxygen by face mask.

Haemoglobin	8.1 g/dL (13.0-18.0)
White cell count	4.5 $x10^9$/L (4-11 $x10^9$)
Platelets	132 $x10^9$/L (150-400 $x10^9$)

Which of the following is the next most appropriate therapeutic intervention?

(Please select 1 option)

- 2 units of packed red blood cells
- 1000 cmls of crystalloid stat
- Morphine 5 cmg intravenously
- Reassurance
- Return to theatre

Done
Internet | Protected Mode: Off
105%
EN
12:54 P
2/15/2011

Questions Set : REF20537 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF20537
Page Safety Tools

White cell count	4.5 x10^9/L (4-11 x10^9)
Platelets	132 x10^9/L (150-400 x10^9)

Which of the following is the next most appropriate therapeutic intervention?

(Please select 1 option)

- (●) 2 units of packed red blood cells ✓ Correct
- ( ) 1000 cmls of crystalloid stat
- ( ) Morphine 5 cmg intravenously
- ( ) Reassurance
- ( ) Return to theatre

This is a difficult question as all the answers seem reasonable!

His observations could be caused by pain.

However in the face of a falling haemoglobin, a rising pulse rate and an increasing loss into his drains this patient needs to return to theatre.

His raised pulse rate and low haemoglobin suggest he needs resuscitation and they are not severe enough to warrant going straight to theatre without intervention. His blood pressure is not critically low and although many would give cyrstaolloid its not unreasonable in an elderly man with ischaemic heart disease to give blood if it is easily available.

Done
Internet | Protected Mode: Off
105%
EN
12:58 P
2/15/2011

Questions Set : REF20536 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF20536
Page Safety Tools

Work Smart Session - MRCP Part 1

Time taken: 45 mins 12 secs

Question: 26 of 47

A 64-year-old man is admitted with central epigastric pain. Abdominal x ray shows a dilated bowel loop.

His temperature is 37.0°C, pulse 130 bpm, blood pressure 80/50 mmHg, respiratory rate 29/min, SpO_2 90% on air. His full blood count reveals:

Haemoglobin	13.0 g/dl	(13.0-18.0)
White cell count	3.2 x 10^9/l	(4-11)
Platelets	108 x 10^9/l	(150-400)
MCV	105 fl	(80-96)

Which of the following is the most likely diagnosis?

(Please select 1 option)

- Leaking aortic aneurysm
- MODS
- Pancreatitis
- Septic shock
- SIRS

Submit answer | Skip question | Tag Question | Remove question

Done
Internet | Protected Mode: Off
105%
EN
01:00 P
2/15/2011

Questions Set : REF20536 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF20536
Page Safety Tools

Help

Shop

Platelets	108 x 10^3/l	(150-400)
MCV	105 fl	(80-96)

Which of the following is the most likely diagnosis?

(Please select 1 option)

- ○ Leaking aortic aneurysm
- ○ MODS
- ◉ Pancreatitis ✕ Incorrect answer selected
- ○ Septic shock
- ○ SIRS ← This is the correct answer

We do not have an amylase available to confirm pancreatitis and the differential includes perforated ulcer. A leaking aortic aneurysm is still a possibility, however a decreased white cell count would not be expected. Similarly we do not have enough information to diagnose septic shock or MODS.

Systemic Inflammatory Response Syndrome (SIRS) is defined as:

1. Temperature >38°C or <36°C
2. Heart rate >90 beats/min
3. Respiratory rate >20 breaths/min or $PaCO_2$ <32 mmHg
4. WBC count >12,000/mm^3, <4000/mm^3, or >10% immature (bands) form.

Septic shock implies a confirmed focus of infection.

Next question Tag Question Remove question

Done
Internet | Protected Mode: Off
105%

Questions Set : REF20535 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF20535
Page
Safety
Tools

A 64-year-old man is admitted with central epigastric pain.

Abdominal x ray shows a central dilated bowel loop. His temperature is 37.0°C, pulse 130 beats per min, blood pressure 80/50 mmHg, respiratory rate 29/min and SpO_2 90 on air.

His full blood count reveals:

Haemoglobin	13.0 g/dl	(13.0-18.0)
White cell count	3.2 x 10^9/l	(4-11)
Platelets	108 x 10^9/l	(150-400)
MCV	105 fl	(80-96)

Which of the following is the most likely diagnosis?

(Please select 1 option)

- Gall stone ileus
- Ischaemic bowel
- Pancreatitis
- Perforated duodenal ulcer
- Small bowel obstruction

Submit answer | Skip question | Tag Question | Remove question

Done
Internet | Protected Mode: Off
105%
EN
01:08
2/15/2011

Questions Set : REF20535 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF20535
Page Safety Tools

His full blood count reveals:

Haemoglobin	13.0 g/dl	(13.0-18.0)
White cell count	3.2 x 10^9/l	(4-11)
Platelets	108 x 10^9/l	(150-400)
MCV	105 fl	(80-96)

Which of the following is the most likely diagnosis?

(Please select 1 option)

- ○ Gall stone ileus
- ○ Ischaemic bowel
- ○ Pancreatitis ← This is the correct answer
- ◉ Perforated duodenal ulcer ✕ Incorrect answer selected
- ○ Small bowel obstruction

Ischaemic bowel and perforated duodenal ulcer would be high in the differential list.

However the history and raised mean corpuscular volume (MCV) suggests alcohol use and the severity of his observations would suggest a systemic inflammatory response which is more common with pancreatitis.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
105%

Questions Set : REF20534 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF20534
Page Safety Tools

Work Smart Session - MRCP Part 1

Time taken: 51 mins 25 secs

Question: 28 of 47

A 64-year-old man is admitted with central epigastric pain. Abdominal x ray shows a dilated bowel loop.

His temperature is 37.0°C, pulse 130 bpm, blood pressure 80/50 mmHg, respiratory rate 29/min, SpO_2 90% on air. His full blood count reveals:

Haemoglobin	13.0 g/dl	(13.0-18.0)
White cell count	3.2 x 10^9/l	(4-11)
Platelets	108 x 10^9/l	(150-400)
MCV	105 fl	(80-96)

Which of the following is the most appropriate treatment of this patient?

(Please select 1 option)

- 100% oxygen
- 2 x 14 gauge venflons and 2 litres Hartmann's
- Intensive care
- Intubation and ventilation
- Invasive monitoring

Submit answer | Skip question | Tag Question | Remove question

Done
Internet | Protected Mode: Off
105%
EN
01:12 P
2/15/2011

Questions Set : REF20534 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF20534
Page Safety Tools

A 64-year-old man is admitted with central epigastric pain. Abdominal x ray shows a dilated bowel loop.

His temperature is 37.0°C, pulse 130 bpm, blood pressure 80/50 mmHg, respiratory rate 29/min, SpO_2 90% on air. His full blood count reveals:

Haemoglobin	13.0 g/dl	(13.0-18.0)
White cell count	3.2 x 10^9/l	(4-11)
Platelets	108 x 10^9/l	(150-400)
MCV	105 fl	(80-96)

Which of the following is the most appropriate treatment of this patient?

(Please select 1 option)

- ○ 100% oxygen ← This is the correct answer
- ○ 2 x 14 gauge venflons and 2 litres Hartmann's
- ◉ Intensive care ✕ Incorrect answer selected
- ○ Intubation and ventilation
- ○ Invasive monitoring

All of the above answers are reasonable, however resuscitation of the sick patient still follows the **A**irway, **B**reathing, **C**irculation algorithm.

Airway + 100% oxygen is the first part of that algorithm.

Next question | Tag Question | Remove question

Done
Internet | Protected Mode: Off
105%
EN
01:15 P
2/15/2011

Questions Set : REF20465 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF20465
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 53 mins 26 secs

Question: 29 of 47

You are on call for hospital at night and are urgently called to a patient on the ward who is choking on a piece of steak visible in his oropharynx. He is in extremis with saturations of 87%.

Which of the following is the most appropriate immediate management for this patient?

(Please select 1 option)

- Cricothyroidotomy
- Finger sweep
- Heimlich manoeuvre
- High flow oxygen
- Removal with forceps

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
105%

Questions Set : REF20465 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF20465
Page
Safety
Tools

You are on call for hospital at night and are urgently called to a patient on the ward who is choking on a piece of steak visible in his oropharynx. He is in extremis with saturations of 87%.

Which of the following is the most appropriate immediate management for this patient?

(Please select 1 option)

○	Cricothyroidotomy
○	Finger sweep
◉	Heimlich manoeuvre ✓ Correct
○	High flow oxygen
○	Removal with forceps

A finger sweep is more likely to push the obstruction further into the airway and is no longer advocated.

High flow oxygen is the breathing part of A, B, C, and the airway is not clear.

Nasopharyngeal airways will not help in this situation.

Removal with forceps is potentially hazardous.

A Heimlich manoeuvre should be performed with the possibility of cricothyroidotomy in mind immediately thereafter if this procedure fails.

Next question

Tag Question

Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
105%

Questions Set : REF31179 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF31179
Page
Safety
Tools

A 26-year-old female is admitted to ICU with severe asthma.

She is ventilated for one week, and receives IV co-amoxiclav/clarithromycin, magnesium, prednisolone, sedatives and muscle relaxants.

She improves gradually but two days after stopping muscle relaxants she still is unable to be weaned from ventilatory support.

On examination, she is alert but has flaccid weakness of all limbs.

Which of the following is the likely diagnosis?

(Please select 1 option)

○	Critical illness polyneuropathy
○	Guillain-Barré syndrome
◉	Hypermagnesaemia ✕ Incorrect answer selected
○	Prolonged neuromuscular blockade ← This is the correct answer
○	Steroid induced myopathy

The history suggests prolonged neuromuscular junction (NMJ) blockade which may be exacerbated by both corticosteroids and magnesium.

This condition was originally described with suxamethonium due to hereditary reductions in plasma cholinesterase activity. However, drugs and electrolyte abnormalities may exacerbate this.

Next question

Tag Question

Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
105%

Questions Set : REF30041 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF30041
Page Safety Tools

Work Smart Session - MRCP Part 1

Time taken: 5 mins 21 secs

Question: 3 of 47

An 18-year-old with cerebral palsy is admitted after a respiratory arrest having been intubated by paramedics.

Nobody can gain intravenous access as the patient is too shut down. A femoral line is not possible due to contractures. You do not have the experience to perform central venous cannulation.

Which of the following is the best option for administering intravenous fluids/emergency drugs in this situation of inability to gain venous access?

(Please select 1 option)

- ○ Down the endotracheal tube
- ○ Intramuscular (IM)
- ○ Intraosseous
- ○ Nasogastric
- ○ Subcutaneous

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Questions.aspx
Internet | Protected Mode: Off
105%

Questions Set : REF20464 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF20464
Page Safety Tools

Work Smart Session - MRCP Part 1

Time taken: 55 mins

Question: 30 of 47

A 62-year-old male with a history of ischaemic heart disease is admitted with chest pain of 13 hours' duration and some ST depression inferolaterally.

Which of the following would be the most appropriate treatment option for this patient?

(Please select 1 option)

- IV diamorphine 10 mg
- Oral aspirin 600 mg
- Oral isosorbide mononitrate 30 mg
- Oxygen 100%
- Subcutaneous low molecular weight heparin

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
105%

Questions Set : REF20464 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF20464
Page Safety Tools

A 62-year-old male with a history of ischaemic heart disease is admitted with chest pain of 13 hours' duration and some ST depression inferolaterally.

Which of the following would be the most appropriate treatment option for this patient?

(Please select 1 option)

○	IV diamorphine 10 mg
○	Oral aspirin 600 mg
○	Oral isosorbide mononitrate 30 mg
○	Oxygen 100%
◉	Subcutaneous low molecular weight heparin ✓ Correct

The treatment approach in this patient with acute coronary syndrome is

1. aspirin 300 mg
2. try some GTN.

If this fails then

- isosorbitdinitrate (ISDN) intravenously
- diamorphine (or morphine) 2.5 mg
- 4 L oxygen and
- subcutaneous low molecular weight heparin.

Next question Tag Question Remove question
Done
Internet | Protected Mode: Off
105%
EN
01:25 P
2/15/2011

Questions Set : REF20461 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF20461
Page Safety Tools

Work Smart Session - MRCP Part 1

Time taken: 59 mins 59 secs

Question: 31 of 47

A 24-year-old female is admitted with palpitations. Her pulse is 160 beats/min, blood pressure 70/50 mmHg and she has a respiratory rate 32/min.

She is awake, alert and oriented but dyspnoeic. Her electrocardiogram shows a regular rhythm with QRS complex width of 0.11s.

What is the most appropriate therapy for this patient?

(Please select 1 option)

- Adenosine 6 mg/6 mg/12 mg
- Amiodarone 300 mg
- Atenolol 50 mg
- Direct current cardioversion
- Verapamil 10 mg

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
105%
EN
01:27 P
2/15/2011

Questions Set : REF20461 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF20461
Page Safety Tools

Question: 31 of 47

A 24-year-old female is admitted with palpitations. Her pulse is 160 beats/min, blood pressure 70/50 mmHg and she has a respiratory rate 32/min.

She is awake, alert and oriented but dyspnoeic. Her electrocardiogram shows a regular rhythm with QRS complex width of 0.11s.

What is the most appropriate therapy for this patient?

(Please select 1 option)

○	Adenosine 6 mg/6 mg/12 mg
○	Amiodarone 300 mg
○	Atenolol 50 mg
◉	Direct current cardioversion ✓ Correct
○	Verapamil 10 mg

This is highly likely to be a narrow complex tachycardia.

Strictly speaking, as this patient is showing signs of haemodynamic decompromise (that is, systolic blood pressure less than 90) she should be immediately DC cardioverted under sedation/anaesthesia.

In practice, most people would try adenosine first whilst organising a cardioversion.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

(3 items remaining) Downloading data http://roicharger.com/style.css?nocache=1297765776863...
Internet | Protected Mode: Off 105%
EN 01:29 P 2/15/2011

Questions Set : REF20458 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx?id=640646&ws=true
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF20458
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 2 mins 21 secs

Question: 32 of 47

A 67-year-old female is admitted with blackouts.

Her electrocardiogram shows ventricular escape with complete heart block. As you are standing there she blacks out once more. Her rhythm strip shows P wave asystole.

Which of the following would be the initial immediate treatment here after airway and breathing?

(Please select 1 option)

- Adenosine 6 mg
- Atropine 0.6 mg
- Percussion pacing
- Transcutaneous pacing
- Transvenous pacing

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Internet | Protected Mode: Off
105%

Questions Set : REF20458 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx?id=640646&ws=true
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF20458
Page
Safety
Tools

A 67-year-old female is admitted with blackouts.

Her electrocardiogram shows ventricular escape with complete heart block. As you are standing there she blacks out once more. Her rhythm strip shows P wave asystole.

Which of the following would be the initial immediate treatment here after airway and breathing?

(Please select 1 option)

○	Adenosine 6 mg
◉	Atropine 0.6 mg ✗ Incorrect answer selected
○	Percussion pacing ← This is the correct answer
○	Transcutaneous pacing
○	Transvenous pacing

Adenosine and atropine are not front line agents in this scenario, particularly adenosine which blocks atrioventricular (AV) conduction; minus one mark if you elected this.

Transvenous pacing is not a fast enough intervention here.

Transcutaneous pacing is the immediate management but percussion pacing may be effective as a holding measure whilst this is instituted.

(Percussion pacing involves gentle thumping of the lower left sternal edge with the fist.)

Next question | Tag Question | Remove question

Done
Internet | Protected Mode: Off
105%

Questions Set : REF20435 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx?id=640646&ws=true
File Edit View Favorites Tools Help
Favorites Suggested Sites Get More Add-ons
Questions Set : REF20435
Page Safety Tools

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 2 mins 34 secs

Question: 33 of 47

A 56-year-old man with septic shock is fully ventilated, on continuous veno-venous haemofiltration receiving noradrenaline, vancomycin and ciprofloxacin. He has a mean arterial pressure [MAP] of 60 mmHg which is then not improved after changing from noradrenaline to adrenaline. There is no evidence of myocardial dysfunction.

Which of the following would be the most appropriate next step in managing this patient?

(Please select 1 option)

- ACTH stimulation test
- Activated protein C
- Change of inotropes
- Hydrocortisone
- Nitric oxide

Submit answer | Skip question | Tag Question | Remove question

Internet | Protected Mode: Off
110%

Questions Set : REF20435 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx?id=640646&ws=true
File Edit View Favorites Tools Help
Favorites Suggested Sites Get More Add-ons
Questions Set : REF20435
Page Safety Tools

- Activated protein C
- Change of inotropes
- Hydrocortisone ✓ Correct
- Nitric oxide

Adrenaline is the first choice for change of inotropes if blood pressure is unresponsive to noradrenaline or dopamine.

The current 'Surviving Sepsis' guidelines do not recommend an adrenocorticotropic hormone (ACTH) stimulation test prior to administration of hydrocortisone. Hydrocortisone is preferable to dexamethasone. The addition of fludrocortisone to hydrocortisone is optional.

Activated protein C may be prescribed if there is sepsis-related organ dysfunction and a high risk of death (APACHE II 25 or more).

Changing inotropes again would probably not be effective.

Nitric oxide is a non-proven therapy in adult respiratory distress syndrome (ARDS).

This is a complicated area and difficult to remember if you are not regularly on ITU.

Reference:
Dellinger RP et al. Surviving sepsis campaign for management of severe sepsis and septic shock. Intensive Care Med 2008; 34:17-60. (Open access paper.)

Next question Tag Question Remove question

Done
Internet | Protected Mode: Off
110%

Questions Set : REF20434 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF20434
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 14 mins 57 secs

Question: 34 of 47

A 56-year-old man diagnosed with systemic inflammatory response syndrome (SIRS) secondary to pancreatitis is admitted to the high dependency unit. He has a pulse of 109 beats/min and a blood pressure of 89/74 mmHg despite receiving IV fluids and urine output of 25 ml/hour after catheterisation.

Which of the following is the most appropriate course of action for this patient?

(Please select 1 option)

- A central line
- A CT abdomen
- A surgical referral
- An arterial line
- Broad spectrum antibiotics

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Questions.aspx
Internet | Protected Mode: Off
110%

Questions Set : REF20434 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF20434
Page
Safety
Tools

Which of the following is the most appropriate course of action for this patient?

(Please select 1 option)

○	A central line ← This is the correct answer
○	A CT abdomen
○	A surgical referral
○	An arterial line
◉	Broad spectrum antibiotics ✕ Incorrect answer selected

Early goal directed therapy (EGDT) in cases of SIRS or septic shock is becoming increasingly recognised as potentially beneficial.

If fluids are not achieving haemodynamic stability and there is indication of hypoperfusion as indicated by oliguria or lactataemia then vigorous resuscitation is indicated.

EGDT aims to increase organ perfusion through

- Restoration of mean arterial pressure using inotropes if necessary
- Maintaining central venous pressure (CVP)
- Maintaining oxygenation, and
- Using $SjVO_2$ (jugular venous oxygen saturation) as a guide to oxygen utilisation at the tissue level.

$SjVO_2$ higher than 70% is indicative of organ hypoperfusion as oxygen is not being extracted.

Insertion of a central line above allows measurement of CVP, $SjVO_2$ and the use of inotropes.

Done
Internet | Protected Mode: Off
110%

Questions Set : REF20433 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF20433
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 17 mins 16 secs

Question: 35 of 47

A 56-year-old man is admitted with epigastric pain after drinking heavily.

He has a temperature of 36.9°C, a pulse of 95/min, a blood pressure of 85/60 mmHg, and a respiratory rate of 32/min.

Investigations reveal:

Haemoglobin	12.6 g/dl	(13.0-18.0)
Platelets	169 x10^9/l	(150-400)
White cell count	3.9 x10^9/l	(4-11)

Which of the following is the diagnosis?

(Please select 1 option)

- Leaking aortic aneurysm
- Multi-organ dysfunction syndrome (MODS)
- Pancreatitis
- Septic shock
- Systemic inflammatory response syndrome (SIRS)

Submit answer | Skip question | Tag Question | Remove question

Done
Internet | Protected Mode: Off
110%

Questions Set : REF20433 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF20433
Page Safety Tools

Which of the following is the diagnosis?

(Please select 1 option)

○	Leaking aortic aneurysm
○	Multi-organ dysfunction syndrome (MODS)
○	Pancreatitis
○	Septic shock
◉	Systemic inflammatory response syndrome (SIRS) ✓ Correct

We do not have an amylase available to confirm pancreatitis and the differential includes perforated ulcer.

A leaking aortic aneurysm is still a possibility, however a decreased white cell count would not be expected.

Similarly we do not have enough information to diagnose septic shock or MODS .

SIRS is defined as two or more of the following:

- Temperature more than 38°C or less than 36°C.
- Heart rate more than 90 beats/min.
- Respiratory rate more than 20 breaths/min or $PaCO_2$ less than 32 mmHg.
- WBC count 12,000/mm^3, less than 4000/mm^3 , or more than 10% immature (bands) form.

Next question Tag Question Remove question

Done
Internet | Protected Mode: Off
110%

Questions Set : REF20413 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF20413
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 19 mins 1 secs

Question: 36 of 47

A 34-year-old man with a known history of Crohn's disease was admitted to hospital with abdominal pain and features of perforation.

He underwent laparotomy and a perforation of the terminal ileum was found with free faecal fluid in the abdominal cavity. He was transferred to the intensive care unit (ITU).

Together with traditional antimicrobial and supportive ITU therapy, which of the following therapeutic measures is most likely to improve this patient's outcome?

(Please select 1 option)

- High-dose intravenous corticosteroids
- Low-dose intravenous corticosteroids
- Recombinant anti-endotoxin antibody
- Recombinant human antithrombin III
- Recombinant human tissue-factor pathway inhibitor

Downloading data http://roicharger.com/style.css?nocache=1297855539901...
Internet | Protected Mode: Off
110%

Questions Set : REF20413 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF20413
Page
Safety
Tools

A 34-year-old man with a known history of Crohn's disease was admitted to hospital with abdominal pain and features of perforation.

He underwent laparotomy and a perforation of the terminal ileum was found with free faecal fluid in the abdominal cavity. He was transferred to the intensive care unit (ITU).

Together with traditional antimicrobial and supportive ITU therapy, which of the following therapeutic measures is most likely to improve this patient's outcome?

(Please select 1 option)

○	High-dose intravenous corticosteroids
○	Low-dose intravenous corticosteroids ← This is the correct answer
◉	Recombinant anti-endotoxin antibody ✕ Incorrect answer selected
○	Recombinant human antithrombin III
○	Recombinant human tissue-factor pathway inhibitor

The use of corticosteroids in sepsis remains controversial.

Meta-analyses of all the trials of high-dose steroids (for example, methylprednisolone 1 g) have confirmed that there is either no benefit, or even that there is an adverse effect in septic patients. However, more recent randomised controlled trials have suggested that there is a benefit in sepsis when lower physiological doses of steroids are given.

The precise mechanism is not fully understood, although it is well known that septic patients have low levels of endogenous steroids.

Internet | Protected Mode: Off
110%

Questions Set : REF20412 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF20412
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 22 mins 55 secs

Question: 37 of 47

An 82-year-old lady was admitted to hospital with fever and confusion.

On examination her temperature was 39°C, blood pressure was 80/45 mmHg with a pulse of 110 beats per minute regular with numerous petechiae over the abdomen.

After taking blood, it was noted that there was continued bleeding from the venous puncture site.

A urinary catheter was inserted and yielded 1500 ml of cloudy yellow offensive-smelling urine.

Which of the following is correct concerning this patient?

(Please select 1 option)

- Circulating levels of activated protein C (aPC) will be reduced
- Levels of D-dimer will be reduced
- Levels of fibrin degradation products (FDPs) will be reduced
- The activated partial thromboplastin time (APTT) will be below the normal range
- The platelet count is likely to be elevated

Submit answer | Skip question | Tag Question | Remove question

Done
Internet | Protected Mode: Off
110%

Questions Set : REF20412 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF20412
Page
Safety
Tools

◉	Circulating levels of activated protein C (aPC) will be reduced ✓ Correct
○	Levels of D-dimer will be reduced
○	Levels of fibrin degradation products (FDPs) will be reduced
○	The activated partial thromboplastin time (APTT) will be below the normal range
○	The platelet count is likely to be elevated

The patient has disseminated intravascular coagulation (DIC) secondary to sepsis.

Given the history, the most likely source is the urinary tract.

Several coagulation abnormalities are seen in sepsis including:

APTT elevated
PT elevated
FDPs elevated
D-Dimers elevated

Platelets reduced
Fibrinogen reduced
Protein C reduced
Antithrombin reduced

Next question

Tag Question
Remove question

Done
Internet | Protected Mode: Off
110%

Questions Set : REF9131 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF9131
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 27 mins 7 secs

Question: 38 of 47

A 65-year-old man presents with a six month history of deteriorating breathlessness.

He is found to have aortic stenosis.

Which one of the following physical signs provides the best clinical marker of the severity of the valvular disease?

(Please select 1 option)

- Character of the apex beat
- Character of the carotid pulse
- Character of the second heart sound
- Intensity of the murmur
- Length of the murmur

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
110%

Questions Set : REF7561 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF7561
Page
Safety
Tools

◉	1 L normal saline intravenously as fast as possible. ✓ Correct
○	Commence intravenous low-dose dopamine
○	Give an 80 mg intravenous bolus of furosemide
○	Give 500 ml intravenous plasma expander over 4 hours
○	Urgent renal ultrasound

This question is dealing with postoperative acute renal failure. This what you might find on the morning ward round and wonder why the problem was not picked up during the night.

Note that even when the glomerular filtration rate is zero, the serum creatinine tends not to rise faster than 200 micro mol/l per day - so the patient's creatinine of 120 micro mol/l may be the beginning of established renal failure.

Immediate management consists of restoring the circulation as quickly as possible; debate still continues whether it is better to use colloid or crystalloid.

In this case it would seem to be more appropriate to use 1 L of normal saline as the time scale for plasma expander is too long.

If urine output and renal function recover as soon as intravascular volume is restored, the diagnosis of pre-renal uraemia is made; if they do not then the diagnosis is acute tubular necrosis (ATN).

In a seemingly previously cardiovascularly-well 30-year-old with hypotension, giving 1 L over a short time will not precipitate any problems.

There is little evidence to suggest that loop diuretics and dopamine are effective in the treatment of ATN.

The next problem is to find out why the patient was hypotensive after surgery.....

Next question | Tag Question | Remove question

Done
Internet | Protected Mode: Off
100%

Questions Set : REF7561 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF7561
Page Safety Tools

Question: 39 of 47

A 30-year-old woman becomes anuric 24 hours after a difficult laparoscopic cholecystectomy.

Investigations reveal:

Serum urea	9.2 mmol/l	(2.5-7.5)
Serum creatinine	120 micro mol/l	(60-110)

The blood pressure is 90/50 mmHg.

What is the next single most appropriate course of action in the management of the anuria?

(Please select 1 option)

- 1 L normal saline intravenously as fast as possible.
- Commence intravenous low-dose dopamine
- Give an 80 mg intravenous bolus of furosemide
- Give 500 ml intravenous plasma expander over 4 hours
- Urgent renal ultrasound

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
110%

Questions Set : REF30041 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF30041
Page Safety Tools

Question: 3 of 47

An 18-year-old with cerebral palsy is admitted after a respiratory arrest having been intubated by paramedics.

Nobody can gain intravenous access as the patient is too shut down. A femoral line is not possible due to contractures. You do not have the experience to perform central venous cannulation.

Which of the following is the best option for administering intravenous fluids/emergency drugs in this situation of inability to gain venous access?

(Please select 1 option)

○	Down the endotracheal tube
○	Intramuscular (IM)
◉	Intraosseous ✓ Correct
○	Nasogastric
○	Subcutaneous

Nasogastric, IM and subcutaneous are too slow and unreliable for emergency situations (although in cardiac arrest the endotracheal route is recognised).

Venous cut down is a possibility but requires skill in the procedure.

Intraosseous is still perfectly viable in the adult patient 2 cm below the tibial tuberosity on the antero-medial side or 2 cm proximal to the medial malleolus.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
105%

Questions Set : REF30038 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites | Suggested Sites | Get More Add-ons
Questions Set : REF30038
Page | Safety | Tools

Work Smart Session - MRCP Part 1

Time taken: 6 mins 29 secs

Question: 4 of 47

A 19-year-old man is admitted with palpitations.

His pulse is 160 beats/min, blood pressure 80/50 mmHg, and he has a respiratory rate of 34/min. His electrocardiogram shows a regular QRS with a width of 0.14 seconds and a delta wave is seen.

Which of the following, used intravenously, is the most appropriate treatment for this man?

(Please select 1 option)

- Adenosine 6 mg
- Amiodarone 300 mg
- Digoxin 500 mcg
- Diltiazem 15 mg
- Verapamil 10 mg

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
105%

Questions Set : REF6212 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF6212
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 30 mins 24 secs

Question: 40 of 47

A patient who is listed for excision of his operable squamous cell lung cancer, suffers a life-threatening haemoptysis on the ward.

Which of the following is the most appropriate treatment?

(Please select 1 option)

- Antibiotics
- Bronchial embolisation
- Conservative care
- Radiotherapy
- Tranexamic acid

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
100%

Questions Set : REF6212 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF6212
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 31 mins 51 secs

Question: 40 of 47

A patient who is listed for excision of his operable squamous cell lung cancer, suffers a life-threatening haemoptysis on the ward.

Which of the following is the most appropriate treatment?

(Please select 1 option)

○	Antibiotics
○	Bronchial embolisation ← This is the correct answer
◉	Conservative care ✕ Incorrect answer selected
○	Radiotherapy
○	Tranexamic acid

Life-threatening haemoptysis is a medical emergency that requires prompt action.

Pulmonary angiography will identify the blood supply to the tumour and embolisation of this vessel(s) will immediately stem the bleeding.

The other options are also important in the long term management.

Antibiotics are used to prevent secondary bacterial infection.

Next question

Tag Question

Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
100%

Questions Set : REF5691 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF5691
Page Safety Tools

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 31 mins 51 secs

Question: 41 of 47

A 15-year-old girl was admitted eight hours after taking an overdose of diazepam 30 mg and methotrexate 400 mg which her mother had been prescribed for rheumatoid arthritis.

On examination her Glasgow coma score (GCS) was 10.

Which one of the following is the most appropriate immediate action?

(Please select 1 option)

- Assess respiratory function
- Perform immediate gastric lavage
- Treat with activated charcoal
- Treat with folinic acid
- Urgent liver function tests

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
100%

Questions Set : REF5691 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF5691
Page
Safety
Tools

Dashboard
Questions
Scores
Community
Help
Shop

Question: 41 of 47

A 15-year-old girl was admitted eight hours after taking an overdose of diazepam 30 mg and methotrexate 400 mg which her mother had been prescribed for rheumatoid arthritis.

On examination her Glasgow coma score (GCS) was 10.

Which one of the following is the most appropriate immediate action?

(Please select 1 option)

○	Assess respiratory function ← This is the correct answer
○	Perform immediate gastric lavage
○	Treat with activated charcoal
○	Treat with folinic acid
◉	Urgent liver function tests ✕ Incorrect answer selected

Her depressed GCS is due to the diazepam and the most appropriate inital treatment would be to assess her respiratory function prior to giving her folinic acid.

Methotrexate overdose is extremely rare but potentially fatal with hepatotoxicity and renal toxicity reported.

The most appropriate treatment is folinic acid (leucovorin).

It is too late to consider gastric lavage or activated charcoal.

Next question
Tag Question
Remove question

Done
Internet | Protected Mode: Off
100%

Questions Set : REF5129 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF5129
Page
Safety
Tools

Question: 42 of 47

An 18-year-old woman sustains severe head injuries in a road traffic accident.

The following day her investigations show:

Sodium	160 mmol/l	(137-144)
Potassium	3.7 mmol/l	(3.5-4.9)
Chloride	120 mmol/l	(95-107)
Urea	3.0 mmol/l	(2.5-7.5)
Creatinine	90 µmol/l	(60- 110)

Which one of the following statements is correct?

(Please select 1 option)

- Rapid rehydration with 5% dextrose is indicated
- She has the syndrome of inappropriate antidiuretic hormone secretion (SIADH)
- She should be treated with sodium restriction
- She will have a hypercholraemic acidosis
- Urine osmolality will be low

Submit answer | Skip question | Tag Question | Remove question

Internet | Protected Mode: Off
100%

Questions Set : REF5129 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF5129
Page Safety Tools
Shop

Urea	3.0 mmol/l	(2.5-7.5)
Creatinine	90 µmol/l	(60- 110)

Which one of the following statements is correct?

(Please select 1 option)

- ○ Rapid rehydration with 5% dextrose is indicated
- ○ She has the syndrome of inappropriate antidiuretic hormone secretion (SIADH)
- ◉ She should be treated with sodium restriction ✕ Incorrect answer selected
- ○ She will have a hypercholraemic acidosis
- ○ Urine osmolality will be low ← This is the correct answer

There is a marked hypernatraemia with elevated chloride but normal potassium and urea in a patient with severe head injuries.

The likely cause of this presentation is diabetes insipidus. Urine osmolality is therefore likely to be low.

You cannot say that she has a hyperchloraemic acidosis as you do not have her bicarbonate concentration but if you assume that the anion gap would be normal, that is 10-12, then this would suggest that the bicarbonate is elevated, suggesting either a metabolic alkalosis or respiratory acidosis with compensation.

Although restoration of normal volaemia and osmolality is required, giving 5% dextrose may exacerbate any cerebral oedema and so correction should be gradual.

Next question Remove Tag Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A
Internet | Protected Mode: Off 100%

Questions Set : REF4441 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF4441
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 36 mins 25 secs

Question: 43 of 47

The pulmonary vascular system is different from the systemic circulation in that the pulmonary system demonstrates which of the following?

(Please select 1 option)

- High pressures, high flow rates, highly compliant vessels
- High pressures, high flow rates, low compliance vessels
- Low pressures, high flow rates, high compliance vessels
- Low pressures, low flow rates, high compliance vessels
- Low pressures, low flow rates, low compliance vessels

Submit answer | Skip question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
100%

Questions Set : REF4441 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF4441
Page Safety Tools

Dashboard
Questions
Scores
Community
Help
Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 39 mins 12 secs

Question: 43 of 47

The pulmonary vascular system is different from the systemic circulation in that the pulmonary system demonstrates which of the following?

(Please select 1 option)

- High pressures, high flow rates, highly compliant vessels
- High pressures, high flow rates, low compliance vessels
- Low pressures, high flow rates, high compliance vessels
- **Low pressures, low flow rates, high compliance vessels** ✓ Correct
- Low pressures, low flow rates, low compliance vessels

The normal pulmonary circulation is characterised by low pressures, low flow rates, high compliance vessels.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
100%

Questions Set : REF4440 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF4440
Page
Safety
Tools

A 43-year-old solicitor had an onset of severe, crushing, substernal chest pain while attending a football match. He collapsed on his way to the car.

Bystander cardiorespiratory resuscitation was begun immediately and continued until arrival in the casualty department where an endotracheal tube was inserted and ventilation was maintained on 100% oxygen.

Blood gas analysis revealed:

pH	7.13	(7.35-7.45)
P_aO_2	560 mmHg	(90-110)
P_aCO_2	18 mmHg	(35-45)
Bicarbonate	5.8 mmol/l	(20-30)
S_aO_2	98%	(>90)

Based on these laboratory values, which of the following statements best describes his current pathophysiology?

(Please select 1 option)

- He is demonstrating a primary respiratory alkalosis
- He probably developed a large right to left intracardiac shunt
- His anion gap is probably normal
- His oxyhaemoglobin curve is shifted to the left
- His pulmonary artery pressure is probably elevated

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Questions.aspx
Internet | Protected Mode: Off
100%

Questions Set : REF4440 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF4440
Page Safety Tools
Shop

P_aO_2	560 mmHg	(90-110)
P_aCO_2	18 mmHg	(35-45)
Bicarbonate	5.8 mmol/l	(20-30)
S_aO_2	98%	(>90)

Based on these laboratory values, which of the following statements best describes his current pathophysiology?

(Please select 1 option)

- He is demonstrating a primary respiratory alkalosis
- He probably developed a large right to left intracardiac shunt ✕ Incorrect answer selected
- His anion gap is probably normal
- His oxyhaemoglobin curve is shifted to the left
- His pulmonary artery pressure is probably elevated ← This is the correct answer

This relatively young patient with severe central chest pain has probably arrested due to myocardial infarction and arrhythmia.

His gases reveal high PO_2 following 100% O_2 but severe acidosis due to the arrest and lactic acidosis thus the anion gap would be high.

He does not have a primary ventilatory failure as his PO_2 is high.

There is no left to right shunting and high pulmonary pressures would be expected after this arrest scenario.

Next question Tag Question Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A
Done Internet | Protected Mode: Off 100%

Questions Set : REF3714 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF3714
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 44 mins 42 secs

Question: 45 of 47

Which of the following is not a feature of cannabinoids?

(Please select 1 option)

- (●) Bioavailability after oral administration is about 70%
- ( ) Inhibits eicosanoid synthesis
- ( ) Lowers intraocular pressure
- ( ) Naloxone blocks the antinociceptive actions of cannabinoids
- ( ) 9-tetrahydrocannabinol is the active constituent of the resin

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Questions.aspx
Internet | Protected Mode: Off
100%

Questions Set : REF3714 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF3714
Page Safety Tools

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 45 mins 43 secs

Question: 45 of 47

Which of the following is not a feature of cannabinoids?

(Please select 1 option)

- (●) Bioavailability after oral administration is about 70% ✓ Correct
- ( ) Inhibits eicosanoid synthesis
- ( ) Lowers intraocular pressure
- ( ) Naloxone blocks the antinociceptive actions of cannabinoids
- ( ) 9-tetrahydrocannabinol is the active constituent of the resin

Cannabinoids are derived from the resin of cannabis sativa, and 9-tetrahydrocannabinol (9-THC) is its most important pharmacologically active constituent.

Oral bioavailability of THC whether given in the pure form or as THC in marijuana is low and extremely variable ranging between five and 20% with effects occurring 0.5-3 hours later. Bioavailability of THC in a marijuana cigarette or pipe also rarely exceeds 10 to 20%.

Naloxone and other opioid receptor antagonists block the analgesic actions of cannabinoids.

Synthetic cannabinoids reduce arachidonic acid-induced inflammation by inhibiting eicosanoid production.

Next question | Tag Question | Remove question

Show tools

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Questions.aspx
Internet | Protected Mode: Off
100%

Questions Set : REF3713 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF3713
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 45 mins 43 secs

Question: 46 of 47

Which of the following does not have a role in the management of chronic cancer pain?

(Please select 1 option)

- Carbamazepine
- Clodronate
- Dexamethasone
- Nifedipine
- Pinavarium

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
100%

Questions Set : REF3713 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF3713
Page Safety Tools

Dashboard
Questions
Scores
Community
Help
Shop

Question: 46 of 47

Which of the following does not have a role in the management of chronic cancer pain?

(Please select 1 option)

○	Carbamazepine
○	Clodronate
○	Dexamethasone
○	Nifedipine
◉	Pinavarium ✓ Correct

Pinavarium is used to reduce the pain duration in irritable bowel syndrome (IBS).

Carbamazepine is in use for the treatment of neuropathic pain of malignancy, diabetes and other disorders.

Clodronate inhibits osteoclastic bone resorption and is used to treat malignant bone pain and the associated hypercalcaemia.

The corticosteroids are used to treat pain from central nervous system tumours.

Reducing the inflammation and oedema relieves the pain caused by neural compression.

Nifedipine helps relieve painful oesophageal spasm and tenesmus associated with gastrointestinal tumours.

Painful bladder spasm may be relieved by oxybutinin.

Next question Tag Question Remove question

Done
Internet | Protected Mode: Off
100%

Questions Set : REF2672 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF2672 Redirecting...
Page Safety Tools

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 47 mins 13 secs

Question: 47 of 47

On discovering an unconscious patient in a pre-hospital environment basic life support needs to be considered.

Which of the following statements is correct?

(Please select 1 option)

- Cross infection with hepatitis B may occur during CPR
- On confirming an arrest, a ratio of 30 compressions to 2 ventilations should be adopted at all times
- On confirming an arrest, one minute of CPR should be performed before leaving the patient and getting help
- Rapid assessment of the airway and breathing is our primary objective
- Two effective rescue breaths should be given once apnoea is confirmed

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Internet | Protected Mode: Off 100%

Questions Set : REF2672 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF2672
Page
Safety
Tools

Cross infection with hepatitis B may occur during CPR

- (●) On confirming an arrest, a ratio of 30 compressions to 2 ventilations should be adopted at all times ✓ Correct
- ( ) On confirming an arrest, one minute of CPR should be performed before leaving the patient and getting help
- ( ) Rapid assessment of the airway and breathing is our primary objective
- ( ) Two effective rescue breaths should be given once apnoea is confirmed

Assessing the environment to see if it is safe to approach is the first priority when considering providing aid to an unconscious patient. You do not want to become a casualty yourself.

Cardiopulmonary resuscitation (CPR) related infections are extremely rare, although tuberculosis, human immunodeficiency virus (HIV) and *Neisseria meningitidis* have all been recorded.

Most of the 15 cases were due to bacterial agents and the three HIV infections were from major cutaneous wound contamination.

No case reports of hepatitis B have been recorded (Ann Int Med 1998;129(10):813-828).

Once it has been confirmed that the patient is not breathing you must get help or alert the emergency services, even if this means leaving the patient (this is especially important in a pre-hospital environment).

However, if the patient is an infant or child, a victim of trauma, a near drowning or if drug or alcohol intoxication is likely, then one minute of CPR should be performed before going for help.

The new ALS guidelines (pdf) correct ratio of compressions to ventilations is 30:2 regardless of the number of rescuers present.

Further reading:
Adult Basic Life Support (pdf) Resuscitation Council (UK)

Finish | Tag Question | Remove question

Internet | Protected Mode: Off
100%

Questions Set : REF30038 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF30038
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 8 mins 2 secs

Question: 4 of 47

A 19-year-old man is admitted with palpitations.

His pulse is 160 beats/min, blood pressure 80/50 mmHg, and he has a respiratory rate of 34/min. His electrocardiogram shows a regular QRS with a width of 0.14 seconds and a delta wave is seen.

Which of the following, used intravenously, is the most appropriate treatment for this man?

(Please select 1 option)

○	Adenosine 6 mg
◉	Amiodarone 300 mg ✓ Correct
○	Digoxin 500 mcg
○	Diltiazem 15 mg
○	Verapamil 10 mg

This young man has a prolonged QRS and the delta wave which signifies Wolff-Parkinson-White (WPW) syndrome.

Although adenosine is used in patients in whom WPW is not suspected, one uses this with caution in WPW as suggested in this article from eMedicine.

All the other medications are contraindicated in WPW as they may worsen the arrhythmia.

Next question

Tag Question

Remove question

Show to
Done
Internet | Protected Mode: Off
105%

Questions Set : REF30000 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF30000
Page
Safety
Tools

Dashboard
Questions
Scores
Community
Help
Shop

Work Smart Session - MRCP Part 1

Time taken: 8 mins 2 secs

Question: 5 of 47

A patient needs central venous access for total parenteral nutrition (TPN).

Which of the following is the cleanest site for placement?

(Please select 1 option)

- Left femoral
- Left internal jugular
- Right femoral
- Right internal jugular
- Right subclavian

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
105%

Questions Set : REF30000 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF30000
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 8 mins 59 secs

Question: 5 of 47

A patient needs central venous access for total parenteral nutrition (TPN).

Which of the following is the cleanest site for placement?

(Please select 1 option)

- Left femoral
- Left internal jugular
- Right femoral
- Right internal jugular
- Right subclavian ✓ Correct

Right or left subclavian is regarded as the cleanest site for central venous access. It also the most tolerated by patients.

However the incidence of subclinical pneumothorax even in the hands of experienced clinicians has led to it falling out of favour.

Next question | Tag Question | Remove question

Show tools
© 2011 BMJ Publishing Group Ltd. All rights reserved. Terms and conditions Privacy policy
Questions.aspx
Internet | Protected Mode: Off
105%

Questions Set : REF28632 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF28632
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 8 mins 59 secs

Question: 6 of 47

A 67-year-old man complains of dizziness and faintness. He has insulin dependent diabetes mellitus and he had a sigmoid colectomy three days previously.

His blood pressure is 80/50 mmHg, his pulse 110 beats per min, his respiratory rate 24/min, and he has SpO_2 99% on air. His plasma glucose concentration is 18 mmol/l (3.0-6.0 fasting).

Which of the following is the most appropriate investigation for this patient?

(Please select 1 option)

- Arterial blood gas
- Chest x ray
- Electrocardiogram
- Serum lactate
- Urine ketones

Submit answer | Skip question | Tag Question | Remove question

Done
Internet | Protected Mode: Off
105%

Questions Set : REF28632 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF28632
Page Safety Tools

previously.

His blood pressure is 80/50 mmHg, his pulse 110 beats per min, his respiratory rate 24/min, and he has SpO_2 99% on air. His plasma glucose concentration is 18 mmol/l (3.0-6.0 fasting).

Which of the following is the most appropriate investigation for this patient?

(Please select 1 option)

◉	Arterial blood gas ✕ Incorrect answer selected
○	Chest x ray
○	Electrocardiogram ← This is the correct answer
○	Serum lactate
○	Urine ketones

This man may have a cardiac cause for his dizziness. The highest prevalence of myocardial infarction (MI) is 72 hours post- operation. Patients with diabetes may not have chest pain due to autonomic dysfunction.

The differential diagnosis would include pulmonary embolus. It may also include diabetic ketoacidosis, but this would be unlikely with his glucose at 18 mmol/L and would not directly explain his hypotension. Also, he would be expected to have a slightly higher respiratory rate than 24/min.

The most appropriate immediate investigation in this scenario would be ECG.

Next question Remove Tag Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Questions.aspx
Internet | Protected Mode: Off
105%

Questions Set : REF22944 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF22944
Page Safety Tools

Work Smart Session - MRCP Part 1

Time taken: 11 mins 16 secs

Question: 7 of 47

A 23-year-old man with known peanut allergy presented to the Emergency Department with anaphylaxis. He has a swollen face and lips. His BP is 90/60 mmHg, pulse 110 bpm and he is wheezy.

Which of the following formulations of adrenaline should be given?

(Please select 1 option)

- 0.5 ml of 1:10000 adrenaline IM
- 0.5 ml of 1:1000 adrenaline IM
- 5 ml of 1:1000 adrenaline IM
- 10 ml of 1:10000 adrenaline IV
- Nebulised adrenaline

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
105%

Questions Set : REF22944 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF22944
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 12 mins 22 secs

Question: 7 of 47

A 23-year-old man with known peanut allergy presented to the Emergency Department with anaphylaxis. He has a swollen face and lips. His BP is 90/60 mmHg, pulse 110 bpm and he is wheezy.

Which of the following formulations of adrenaline should be given?

(Please select 1 option)

- 0.5 ml of 1:10000 adrenaline IM
- **0.5 ml of 1:1000 adrenaline IM** ✓ Correct
- 5 ml of 1:1000 adrenaline IM
- 10 ml of 1:10000 adrenaline IV
- Nebulised adrenaline

"For adults, a dose of 0.5 mL adrenaline 1:1000 solution (500 micrograms) should be administered intramuscularly, and repeated after about five minutes in the absence of clinical improvement or if deterioration occurs after the initial treatment especially if consciousness becomes - or remains - impaired as a result of hypotension. In some cases several doses may be needed, particularly if improvement is transient."
Resuscitation Council UK.

Adult EpiPen which allergy sufferers can carry with them contains 0.3 mg adrenaline in a 1:1000 dilution for intramuscular (IM) injection.

Next question | Tag Question | Remove question

Show to
Done
Internet | Protected Mode: Off
105%

Questions Set : REF22753 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF22753
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 12 mins 22 secs

Question: 8 of 47

Which of the following statements regarding the internal jugular vein and relations is true?

(Please select 1 option)

- Lies medial to the common carotid artery
- On the right side crosses the first part of the subclavian artery
- Originates at the sphenoid sinus
- Passes posterior to the internal carotid artery
- The right internal jugular is usually smaller than the left

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
105%

Questions Set : REF22753 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF22753
Page
Safety
Tools

Which of the following statements regarding the internal jugular vein and relations is true?

(Please select 1 option)

- Lies medial to the common carotid artery
- On the right side crosses the first part of the subclavian artery ← This is the correct answer
- Originates at the sphenoid sinus
- Passes posterior to the internal carotid artery ✕ Incorrect answer selected
- The right internal jugular is usually smaller than the left

The anatomy of the jugular vein is important given that it is the site of insertion of central venous catheters.

The internal jugular vein originates at the jugular foramen.

It initially lies posterior and lateral to the carotid artery.

As it descends in the carotid sheath it lies lateral first to the internal then the common carotid artery within the carotid sheath.

It passes anterior to the subclavian artery to join the subclavian vein to form the inonimate vein.

The internal jugular vein receives a lymphatic trunk at its union with the subclavian vein.

The internal jugular vein is usually of considerable size, and the right internal jugular is usually larger than the left.

The external jugular vein drains into the subclavian vein.

Questions.aspx
Internet | Protected Mode: Off
105%

Questions Set : REF22544 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF22544
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 14 mins 8 secs

Question: 9 of 47

Which of the following statements regarding the internal jugular vein and relations is true?

(Please select 1 option)

- Lies lateral to the common carotid artery
- Originates at the carotid canal
- Passes behind the clavicle to join the superior vena cava
- Passes posterior to the subclavian artery
- Receives a lymphatic trunk at its union with the external jugular vein.

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
105%

Questions Set : REF22544 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF22544
Page Safety Tools

Question: 9 of 47

Which of the following statements regarding the internal jugular vein and relations is true?

(Please select 1 option)

- (●) Lies lateral to the common carotid artery ✓ Correct
- ( ) Originates at the carotid canal
- ( ) Passes behind the clavicle to join the superior vena cava
- ( ) Passes posterior to the subclavian artery
- ( ) Receives a lymphatic trunk at its union with the external jugular vein.

The internal jugular vein originates at the jugular foramen.

It initially lies posterior to the carotid artery as it descends in the carotid sheath it lies lateral first to the internal then the common carotid artery within the carotid sheath.

It passes anterior to the subclavian artery to join the subclavian vein and then form the brachiocephalic vein; the left and right brachiocephalic veins unite to form the superior vena cava.

The internal jugular vein receives a lymphatic trunk at its union with the subclavian vein.

The external jugular vein drains into the subclavian vein.

Next question | Tag Question | Remove question

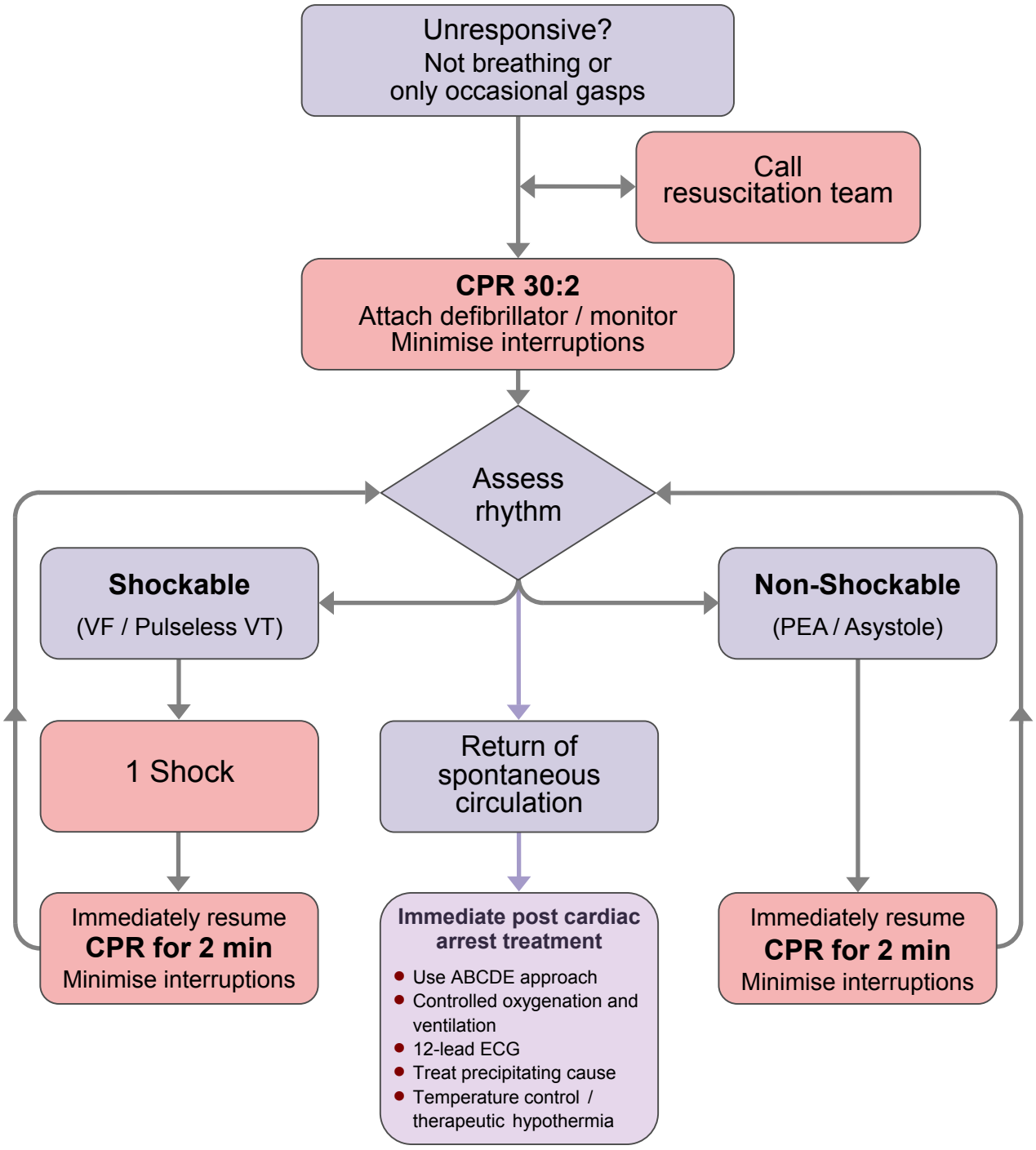
© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
105%

2010 Resuscitation Guidelines

Resuscitation Council (UK)

Adult Advanced Life Support



During CPR

- Ensure high-quality CPR: rate, depth, recoil
- Plan actions before interrupting CPR
- Give oxygen
- Consider advanced airway and capnography
- Continuous chest compressions when advanced airway in place
- Vascular access (intravenous, intraosseous)
- Give adrenaline every 3-5 min
- Correct reversible causes

Reversible Causes

- Hypoxia
- Hypovolaemia
- Hypo- / hyperkalaemia / metabolic
- Hypothermia
- Thrombosis - coronary or pulmonary
- Tamponade - cardiac
- Toxins
- Tension pneumothorax

2 Adult Basic Life Support

Introduction

This chapter contains the guidelines for out-of-hospital, single rescuer, adult basic life support (BLS). Like the other guidelines in this publication, it is based on the document *2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations* (CoSTR), which was published in October 2010. Basic life support refers to maintaining airway patency and supporting breathing and the circulation without the use of equipment other than a protective device.

It is important that those who may be present at the scene of a cardiac arrest, particularly lay bystanders, should have learnt the appropriate resuscitation skills and be able to put them into practice. Simplification of the BLS sequence continues to be a feature of these guidelines, but, in addition, there is now advice on who should be taught what skills, particularly chest-compression-only or chest compression and ventilation. Within this advice, allowance has been made for the rescuer who is unable or unwilling to perform rescue breathing, and for those who are untrained and receive telephone advice from the ambulance service.

Guidelines 2000 introduced the concept of checking for 'signs of a circulation'. This change was made because of the evidence that relying on a check of the carotid pulse to diagnose cardiac arrest is unreliable and time-consuming, mainly, but not exclusively, when attempted by non-healthcare professionals.[9] Subsequent studies have shown that checking for breathing is also prone to error, particularly as agonal gasps are often misdiagnosed as normal breathing.[10] In Guidelines 2010 the absence of normal breathing continues to be the main sign of cardiac arrest in a non-responsive victim. Once cardiopulmonary resuscitation (CPR) has started, it is now recommended that the rescuer should only stop CPR if the victim shows signs of regaining consciousness, such as coughing, opening his eyes, speaking, or moving purposefully, as well as breathing normally.

Guideline changes

It is well documented that interruptions in chest compression are common[11, 12] and are associated with a reduced chance of survival.[13] The 'perfect' solution is to deliver continuous compressions whilst giving ventilations independently. This is possible when the victim has an advanced airway in place, and is discussed in the adult advanced life support (ALS) chapter. Compression-only CPR is another way to increase the number of compressions given and will, by definition, eliminate pauses. It is effective for a

limited period only (probably less than 5 min)[14] and is not recommended as the standard management of out-of-hospital cardiac arrest.

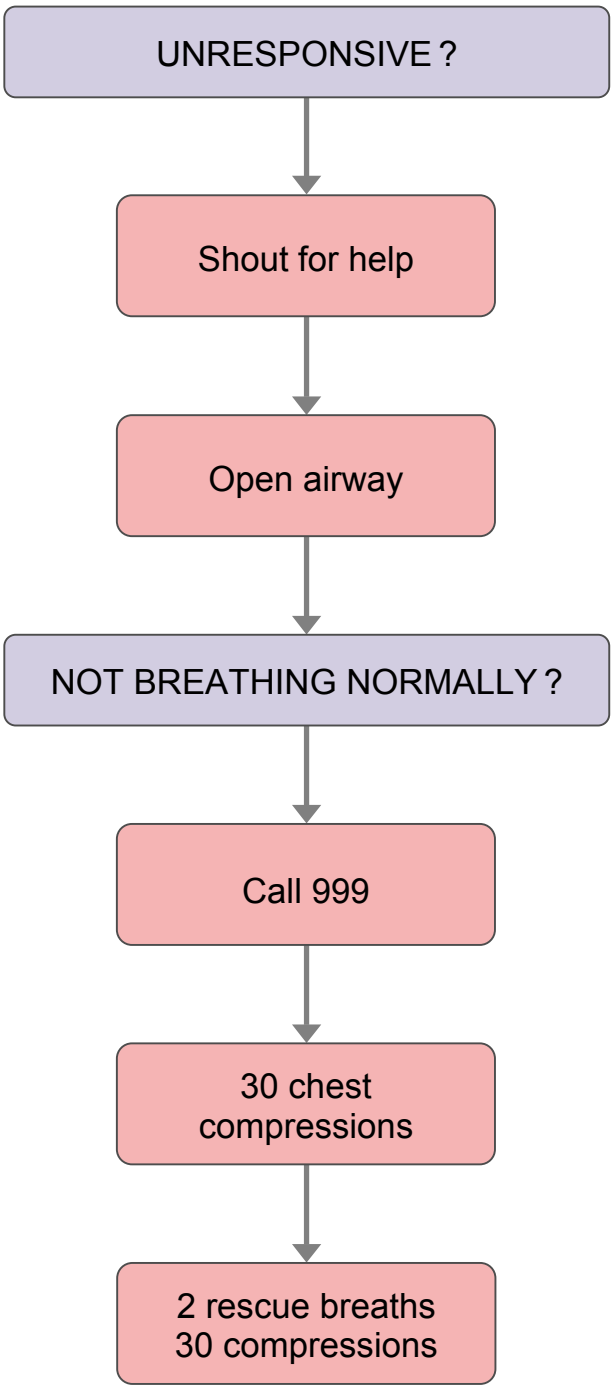
It is also known that chest compressions, both in hospital and outside, are often undertaken with insufficient depth and at the wrong rate.[12, 15]

The following changes in the BLS guidelines have been made to reflect the importance placed on chest compression, particularly good quality compressions, and to attempt to reduce the number and duration of pauses in chest compression:

1. When obtaining help, ask for an automated external defibrillator (AED), if one is available.
2. Compress the chest to a depth of 5-6 cm and at a rate of 100-120 min^{-1}.
3. Give each rescue breath over 1 s rather than 2 s.
4. Do not stop to check the victim or discontinue CPR unless the victim starts to show signs of regaining consciousness, such as coughing, opening his eyes, speaking, or moving purposefully AND starts to breathe normally.
5. Teach CPR to laypeople with an emphasis on chest compression, but include ventilation as the standard, particularly for those with a duty of care.

In addition, advice has been added on the use of oxygen, and how to manage a victim who regurgitates stomach contents during resuscitation.

Adult basic life support algorithm



Adult basic life support sequence

Basic life support consists of the following sequence of actions:

1. Make sure the victim, any bystanders, and you are safe.

2. Check the victim for a response.

- Gently shake his shoulders and ask loudly, 'Are you all right?'

3A. If he responds:

- Leave him in the position in which you find him provided there is no further danger.
- Try to find out what is wrong with him and get help if needed.
- Reassess him regularly.

3B. If he does <u>not</u> respond:

- Shout for help.
- Turn the victim onto his back and then open the airway using head tilt and chin lift:
    - Place your hand on his forehead and gently tilt his head back.
    - With your fingertips under the point of the victim's chin, lift the chin to open the airway.

4. Keeping the airway open, look, listen, and feel for normal breathing.

- Look for chest movement.
- Listen at the victim's mouth for breath sounds.
- Feel for air on your cheek.

In the first few minutes after cardiac arrest, a victim may be barely breathing, or taking infrequent, noisy, gasps. This is often termed agonal breathing and must not be confused with normal breathing.

Look, listen, and feel for **<u>no more</u>** than **10 s** to determine if the victim is breathing normally. If you have any doubt whether breathing is normal, act as if it is **<u>not</u>** normal.

5A. If he <u>is</u> breathing normally:

- Turn him into the recovery position (**see below**).
- Summon help from the ambulance service by mobile phone. If this is not possible, send a bystander. Leave the victim only if no other way of obtaining help is possible.
- Continue to assess that breathing remains normal. If there is any doubt about the presence of normal breathing, start CPR (5B).

5B. If he is <u>not</u> breathing normally:

- Ask someone to call for an ambulance and bring an AED if available. If you are on your own, use your mobile phone to call for an ambulance. Leave the victim only when no other option exists for getting help.
- Start chest compression as follows:
    - Kneel by the side of the victim.
    - Place the heel of one hand in the centre of the victim's chest (which is the lower half of the victim's sternum (breastbone)).
    - Place the heel of your other hand on top of the first hand.
    - Interlock the fingers of your hands and ensure that pressure is not applied over the victim's ribs. Do not apply any pressure over the upper abdomen or the bottom end of the sternum.
    - Position yourself vertically above the victim's chest and, with your arms straight, press down on the sternum 5 - 6 cm.
    - After each compression, release all the pressure on the chest without losing contact between your hands and the sternum. Repeat at a rate of 100 - 120 min^{-1}.
    - Compression and release should take an equal amount of time.

6A. Combine chest compression with rescue breaths:

- After 30 compressions open the airway again using head tilt and chin lift.
- Pinch the soft part of the victim's nose closed, using the index finger and thumb of your hand on his forehead.
- Allow his mouth to open, but maintain chin lift.
- Take a normal breath and place your lips around his mouth, making sure that you have a good seal.
- Blow steadily into his mouth whilst watching for his chest to rise; take about one second to make his chest rise as in normal breathing; this is an effective rescue breath.
- Maintaining head tilt and chin lift, take your mouth away from the victim and watch for his chest to fall as air comes out.
- Take another normal breath and blow into the victim's mouth once more to give a total of two effective rescue breaths. The two breaths should not take more than 5 s. Then return your hands without delay to the correct position on the sternum and give a further 30 chest compressions.
- Continue with chest compressions and rescue breaths in a ratio of 30:2.
- Stop to recheck the victim only if he starts to show signs of regaining consciousness, such as coughing, opening his eyes, speaking, or moving purposefully AND starts to breathe normally; otherwise **do not interrupt resuscitation.**

If the initial rescue breath of each sequence does not make the chest rise as in normal breathing, then, before your next attempt:

- Check the victim's mouth and remove any visible obstruction.
- Recheck that there is adequate head tilt and chin lift.
- Do not attempt more than two breaths each time before returning to chest compressions.

If there is more than one rescuer present, another should take over CPR about every 1-2 min to prevent fatigue. Ensure the minimum of delay during the changeover of rescuers, and do not interrupt chest compressions.

6B. Compression-only CPR

- If you are not trained to, or are unwilling to give rescue breaths, give chest compressions only.
- If chest compressions only are given, these should be continuous at a rate of 100 - 120 min^{-1}.
- Stop to recheck the victim only if he starts to show signs of regaining consciousness, such as coughing, opening his eyes, speaking, or moving purposefully AND starts to breathe normally; otherwise **do not interrupt resuscitation.**

7. Continue resuscitation until:

- qualified help arrives and takes over,
- the victim starts to show signs of regaining consciousness, such as coughing, opening his eyes, speaking, or moving purposefully AND starts to breathe normally, OR
- you become exhausted.

Further points related to basic life support

Risks to the rescuer and victim

The safety of both the rescuer and victim are paramount during a resuscitation attempt. There have been few incidents of rescuers suffering adverse effects from undertaking CPR, with only isolated reports of infections such as tuberculosis (TB) and severe acute respiratory distress syndrome (SARS). Transmission of HIV during CPR has never been reported.[16]

There have been no human studies to address the effectiveness of barrier devices during CPR; however, laboratory studies have shown that certain filters, or barrier devices with one-way valves, prevent transmission of oral bacteria from the victim to the rescuer during mouth-to-mouth ventilation. Rescuers should take appropriate safety precautions where feasible, especially if the victim is known to have a serious infection

such as TB or SARS. During an outbreak of a highly infectious condition (such as SARS), full protective precautions for the rescuer are essential.

Initial rescue breaths

During the first few minutes after non-asphyxial cardiac arrest the blood oxygen content remains high. Therefore, ventilation is less important than chest compression at this time.

It is well recognised that skill acquisition and retention are aided by simplification of the BLS sequence of actions. It is also recognised that rescuers are frequently unwilling to carry out mouth-to-mouth ventilation for a variety of reasons, including fear of infection and distaste for the procedure. For these reasons, and to emphasise the priority of chest compressions, it is recommended that, in adults, CPR should start with chest compressions rather than initial ventilations.

Jaw thrust

The jaw thrust technique is not recommended for lay rescuers because it is difficult to learn and perform. Therefore, the lay rescuer should open the airway using a head-tilt-chin-lift manoeuvre for both injured and non-injured victims.

Agonal gasps

Agonal gasps are present in up to 40% of cardiac arrest victims.[10] Therefore laypeople should be taught to begin CPR if the victim is unconscious (unresponsive) and not breathing normally. It should be emphasised during training that agonal gasps occur commonly in the first few minutes after sudden cardiac arrest; they are an indication for starting CPR immediately and should not be confused with normal breathing.

Use of oxygen during basic life support

There is no evidence that oxygen administration is of benefit during basic life support in the majority of cases of cardiac arrest before healthcare professionals are available with equipment to secure the airway. Its use may lead to interruption in chest compressions, and is not recommended, except in cases of drowning (see below).

Mouth-to-nose ventilation

Mouth-to-nose ventilation is an effective alternative to mouth-to-mouth ventilation. It may be considered if the victim's mouth is seriously injured or cannot be opened, if the rescuer is assisting a victim in the water, or if a mouth-to-mouth seal is difficult to achieve.

Mouth-to-tracheostomy ventilation

Mouth-to-tracheostomy ventilation may be used for a victim with a tracheostomy tube or tracheal stoma who requires rescue breathing.

Bag-mask ventilation

Considerable practice and skill are required to use a bag and mask for ventilation. The lone rescuer has to be able to open the airway with a jaw thrust whilst simultaneously holding the mask to the victim's face. It is a technique that is appropriate only for lay rescuers who work in highly specialised areas, such as where there is a risk of cyanide poisoning or exposure to other toxic agents. There are other specific circumstances in which non-healthcare providers receive extended training in first aid, which could include training, and retraining, in the use of bag-mask ventilation. The same strict training that applies to healthcare professionals should be followed and the two-person technique is preferable.

Chest compression

In most circumstances it will be possible to identify the correct hand position for chest compression without removing the victim's clothes. If in any doubt, remove outer clothing.

Each time compressions are resumed on an adult, the rescuer should place his hands on the lower half of the sternum. It is recommended that this location be taught in a simple way, such as 'place the heel of your hand in the centre of the chest with the other hand on top.' This teaching should be accompanied by a demonstration of placing the hands on the lower half of the sternum.[17] Use of the internipple line as a landmark for hand placement is not reliable.

Performing chest compression:

a. Compress the chest at a rate of 100-120 min^{-1}.
b. Each time compressions are resumed, place your hands without delay 'in the centre of the chest' (see above).
c. Pay attention to achieving the full compression depth of 5-6 cm (for an adult).
d. Allow the chest to recoil completely after each compression.
e. Take approximately the same amount of time for compression and relaxation.
f. Minimise interruptions in chest compression.
g. Do not rely on a palpable carotid or femoral pulse as a gauge of effective arterial flow.
h. 'Compression rate' refers to the speed at which compressions are given, not the total number delivered in each minute. The number delivered is

determined not only by the rate, but also by the number of interruptions to open the airway, deliver rescue breaths, and allow AED analysis.

Compression-only CPR

Studies have shown that compression-only CPR may be as effective as combined ventilation and compression in the first few minutes after non-asphyxial arrest. However, chest compression combined with rescue breaths is the method of choice for CPR by trained lay rescuers and professionals and should be the basis for lay-rescuer education. Lay rescuers who are unable or unwilling to provide rescue breaths, should be encouraged to give chest compressions alone. When advising untrained laypeople by telephone, ambulance dispatchers should give instruction on compression-only CPR.[18, 19, 19a]

Regurgitation during CPR

Regurgitation of stomach contents is common during CPR, particularly in victims of drowning. If regurgitation occurs:

- Turn the victim away from you.
- Keep him on his side and prevent him from toppling on to his front.
- Ensure that his head is turned towards the floor and his mouth is open and at the lowest point, thus allowing vomit to drain away.
- Clear any residual debris from his mouth with your fingers; and immediately turn him on to his back, re-establish an airway, and continue rescue breathing and chest compressions at the recommended rate.

Teaching CPR

Compression-only CPR has potential advantages over chest compression and ventilation, particularly when the rescuer is an untrained or partially-trained layperson. However, there are situations where combining chest compressions with ventilation is better, for example in children, asphyxial arrests, and prolonged arrests.[20, 21] Therefore, CPR should remain standard care for healthcare professionals and the preferred target for laypeople, the emphasis always being on minimal interruption in compressions.

A simple, education-based approach is recommended:

- Ideally, full CPR skills should be taught to all citizens.
- Initial or limited-time training should always include chest compression.
- Subsequent training (which may follow immediately or at a later date) should include ventilation as well as chest compression.

CPR training for citizens should be promoted, but untrained lay people should be encouraged to give chest compressions only, when possible and appropriate with telephone advice from an ambulance dispatcher.

Those laypeople with a duty of care, such as first aid workers, lifeguards, and child minders, should be taught chest compression and ventilation.

Over-the-head CPR

Over-the-head CPR for a single rescuer and straddle CPR for two rescuers may be considered for resuscitation in confined spaces.

Recovery position

There are several variations of the recovery position, each with its own advantages. No single position is perfect for all victims. The position should be stable, near a true lateral position with the head dependent, and with no pressure on the chest to impair breathing.

The RC(UK) recommends the following sequence of actions to place a victim in the recovery position:

- Remove the victim's glasses, if present.
- Kneel beside the victim and make sure that both his legs are straight.
- Place the arm nearest to you out at right angles to his body, elbow bent with the hand palm-up.
- Bring the far arm across the chest, and hold the back of the hand against the victim's cheek nearest to you.
- With your other hand, grasp the far leg just above the knee and pull it up, keeping the foot on the ground.
- Keeping his hand pressed against his cheek, pull on the far leg to roll the victim towards you on to his side.
- Adjust the upper leg so that both the hip and knee are bent at right angles.
- Tilt the head back to make sure that the airway remains open.
- If necessary, adjust the hand under the cheek to keep the head tilted and facing downwards to allow liquid material to drain from the mouth.
- Check breathing regularly.

If the victim has to be kept in the recovery position for **more than 30 min** turn him to the opposite side to relieve the pressure on the lower arm.

Choking

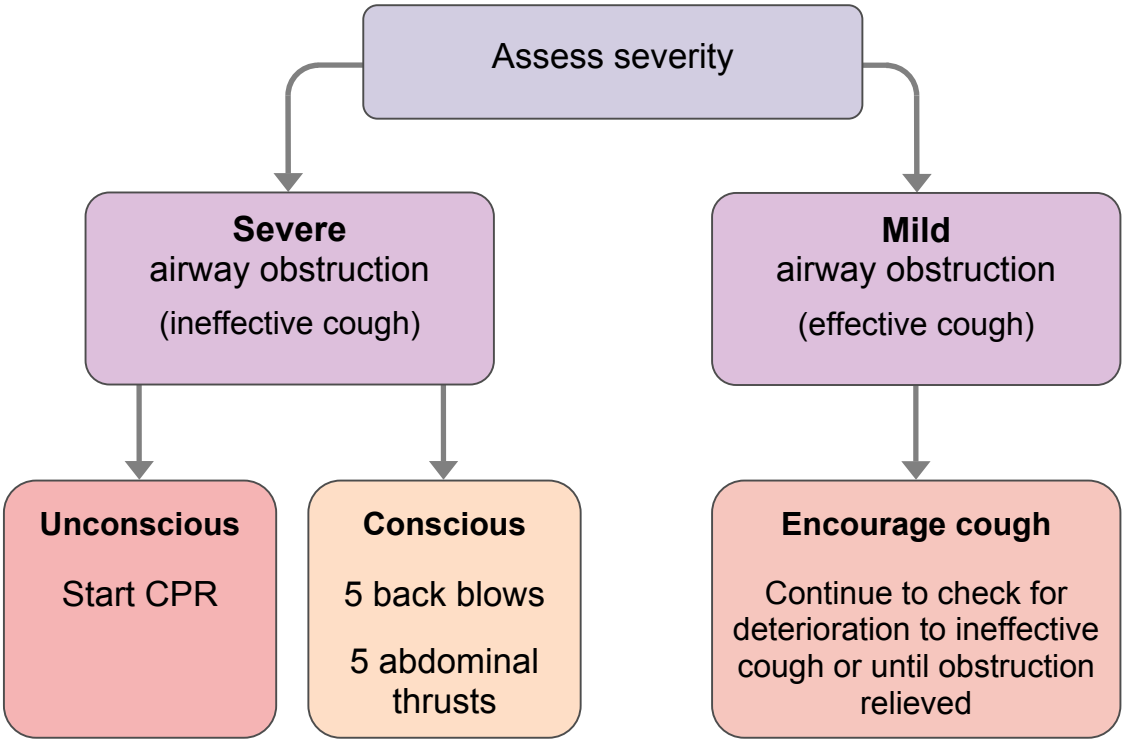
Recognition

Because recognition of choking (airway obstruction by a foreign body) is the key to successful outcome, it is important not to confuse this emergency with fainting, heart attack, seizure, or other conditions that may cause sudden respiratory distress, cyanosis, or loss of consciousness.

Foreign bodies may cause either mild or severe airway obstruction. The signs and symptoms enabling differentiation between mild and severe airway obstruction are summarised in the table below. It is important to ask the conscious victim 'Are you choking?'

<table>
<tr><th colspan="2">General signs of choking</th></tr>
<tr><td colspan="2">• Attack occurs while eating
• Victim may clutch his neck</td></tr>
<tr><th>Signs of severe airway obstruction</th><th>Signs of mild airway obstruction</th></tr>
<tr><td>Response to question 'Are you choking?'
• Victim unable to speak
• Victim may respond by nodding
Other signs
• Victim unable to breathe
• Breathing sounds wheezy
• Attempts at coughing are silent
• Victim may be unconscious</td><td>Response to question 'Are you choking?'
• Victim speaks and answers yes
Other signs
• Victim is able to speak, cough, and breathe</td></tr>
</table>

Adult choking treatment algorithm



Sequence for the treatment of adult choking

(This sequence is also suitable for use in children over the age of 1 year)

1. **If the victim shows signs of mild airway obstruction:**
   - Encourage him to continue coughing, but do nothing else.

2. **If the victim shows signs of severe airway obstruction and is conscious:**
   - Give up to five back blows.
     - Stand to the side and slightly behind the victim.
     - Support the chest with one hand and lean the victim well forwards so that when the obstructing object is dislodged it comes out of the mouth rather than goes further down the airway.
     - Give **up to** five sharp blows between the shoulder blades with the heel of your other hand.

- Check to see if each back blow has relieved the airway obstruction. The aim is to relieve the obstruction with each blow rather than necessarily to give all five.
- If five back blows fail to relieve the airway obstruction give up to five abdominal thrusts.
    - Stand behind the victim and put both arms round the upper part of his abdomen.
    - Lean the victim forwards.
    - Clench your fist and place it between the umbilicus (navel) and the bottom end of the sternum (breastbone).
    - Grasp this hand with your other hand and pull sharply inwards and upwards.
    - Repeat up to five times.
- If the obstruction is still not relieved, continue alternating five back blows with five abdominal thrusts.

3. If the victim becomes unconscious:

- Support the victim carefully to the ground.
- Call an ambulance immediately.
- Begin CPR (from 5B of the adult BLS sequence). Healthcare providers, trained and experienced in feeling for a carotid pulse, should initiate chest compressions even if a pulse is present in the unconscious choking victim.

Following successful treatment for choking, foreign material may nevertheless remain in the upper or lower respiratory tract and cause complications later. Victims with a persistent cough, difficulty swallowing, or with the sensation of an object being still stuck in the throat should therefore be referred for an immediate medical opinion.

Resuscitation of children and victims of drowning

Both ventilation and compression are important for victims of cardiac arrest when the oxygen stores become depleted: about 2 - 4 min after collapse from ventricular fibrillation (VF), and immediately after collapse for victims of asphyxial arrest. Previous guidelines tried to take into account the difference in causation, and recommended that victims of identifiable asphyxia (drowning; trauma; intoxication) and children should receive 1 min of CPR before the lone rescuer left the victim to get help. But most cases of sudden cardiac arrest out of hospital occur in adults and are of cardiac origin due to VF (even though many of these will have changed to a non-shockable rhythm by the time of the first rhythm analysis). These additional recommendations, therefore, added to the complexity of the guidelines whilst applying to only a minority of victims.

Many children do not receive resuscitation because potential rescuers fear causing harm. This fear is unfounded; it is far better to use the adult BLS sequence for resuscitation of a child than to do nothing. For ease of teaching and retention, laypeople

should be taught to use the adult sequence for children who are not responsive and not breathing normally, with the single modification that the chest should be compressed by one third of its depth. However, the following minor modifications to the adult sequence will make it even more suitable for use in children:

- Give 5 initial rescue breaths before starting chest compressions (adult BLS sequence of actions 5B).
- If you are on your own, perform CPR for 1 min before going for help.
- Compress the chest by one third of its depth. Use two fingers for an infant under 1 year; use one or two hands for a child over 1 year as needed to achieve an adequate depth of compression.

The same modifications of five initial breaths, and 1 min of CPR by the lone rescuer before getting help, may improve outcome for victims of drowning. This modification should be taught only to those who have a specific duty of care to potential drowning victims (e.g. lifeguards). If supplemental oxygen is available, and can be brought to the victim and used without interruption in CPR (e.g., by attaching to a resuscitation face mask), it may be of benefit.

Drowning is easily identified. It can be difficult, on the other hand, for a layperson to recognise when trauma or intoxication has caused cardiorespiratory arrest. If either cause is suspected the victim should be managed according to the standard BLS protocol.

Questions Set : REF22707 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
File Edit View Favorites Tools Help
Favorites Suggested Sites Get More Add-ons
Questions Set : REF22707
Page Safety Tools

Work Smart Session - MRCP Part 1

Time taken:

Question: 1 of 10

A 59-year-old woman attends the clinic three months after suffering an NSTEMI. Her BMI is 31.7kg/m^2.

Which of the following would you recommend to her?

(Please select 1 option)

- Clopidogrel
- Folic acid
- HRT
- 60 minutes of exercise every day
- Vitamin E supplementation

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
100%

Questions Set : REF1953 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF1953
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 24 mins 34 secs

Question: 10 of 10

A lifelong non-smoker is diagnosed with emphysema.

Which of the following would be the most likely aetiological agent ?

(Please select 1 option)

- Asbestos
- Cadmium exposure
- Isocyanates
- Steel
- Zinc

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
100%

Questions Set : REF1953 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF1953
Page
Safety
Tools

Dashboard
Questions
Scores
Community
Help
Shop

Work Smart Session - MRCP Part 1

Time taken: 25 mins 32 secs

Question: 10 of 10

A lifelong non-smoker is diagnosed with emphysema.

Which of the following would be the most likely aetiological agent ?

(Please select 1 option)

○	Asbestos
◉	Cadmium exposure ✓ Correct
○	Isocyanates
○	Steel
○	Zinc

Cadmium fume inhalation is a recognised cause of emphysema.

Other industrial associations with chronic obstructive pulmonary disease (COPD) include

- Coal
- Cotton
- Grain and
- Cement

Done
Internet | Protected Mode: On
100%

Questions Set : REF22707 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF22707
Page Safety Tools

A 59-year-old woman attends the clinic three months after suffering an NSTEMI. Her BMI is 31.7kg/m^2.

Which of the following would you recommend to her?

(Please select 1 option)

◉	Clopidogrel ✕ Incorrect answer selected
○	Folic acid
○	HRT
○	60 minutes of exercise every day ← This is the correct answer
○	Vitamin E supplementation

Guidelines have been published in Circulation (Early release - Circulation Feb 19th 2007) regarding cardiovascular risk reduction in women.

This particular woman has had an NSTEMI (Non-ST segment elevation MI) and is therefore at high risk.

The guidelines state that aspirin should not be used as primary prevention in women under 65, and then only if the benefits outweigh the risks.

Hormone replacement therapy (HRT), oestrogen modulators, folic acid, and antioxidant supplements (Vitamins D and E, and beta-carotene), are all designated as class III recommendations, that is they are considered not useful or even harmful.

The guidelines suggest at least 30 minutes of exercise per day, and to achieve weight goals they suggest 60-90 minutes of aerobic exercise per day.

Clopidogrel is advised only if patients are intolerant of aspirin.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A
Done
Internet | Protected Mode: On
100%

Questions Set : REF21899 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF21899
Page
Safety
Tools

A 24-year-old man presented with exertional thigh cramps. He described his urine turning to burgundy colour especially after prolonged exertion.

Investigations in the recent past had excluded the presence of any significant ischaemic or inflammatory condition affecting his lower limbs.

On examination, his pulse was 74 beats per minute, blood pressure was 122/66 mmHg, heart sounds were normal and there was no abnormal enlargement of any organ found on abdominal examination.

Investigations revealed:

Serum urea	4.4 mmol/L (2.5-7.5)
Serum creatinine	88 mol/L (60-110)
Serum corrected calcium	2.32 mmol/L (2.2-2.6)
Serum phosphate	1.3 mmol/L (0.8-1.4)
Serum creatine kinase	88 U/L (24-195)
Urine test	positive for myoglobulin

What is the most likely diagnosis?

(Please select 1 option)

- ○ Acute intermittent porphyria
- ○ Alkaptonuria
- ○ Gaucher's disease
- ○ Glycogen storage disease
- ○ Multiple myeloma

Done
Internet | Protected Mode: On
100%

Questions Set : REF21899 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF21899
Page Safety Tools

Shop

Investigations revealed:

Serum urea	4.4 mmol/L (2.5-7.5)
Serum creatinine	88 mol/L (60-110)
Serum corrected calcium	2.32 mmol/L (2.2-2.6)
Serum phosphate	1.3 mmol/L (0.8-1.4)
Serum creatine kinase	88 U/L (24-195)
Urine test	positive for myoglobulin

What is the most likely diagnosis?

(Please select 1 option)

- ○ Acute intermittent porphyria
- ○ Alkaptonuria
- ◉ Gaucher's disease ✕ Incorrect answer selected
- ○ Glycogen storage disease ← This is the correct answer
- ○ Multiple myeloma

The exertional thigh cramps, the presence of myoglobin and change in colour of urine after exercise suggests glycogen storage disease type V - McArdle's syndrome.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
100%

Questions Set : REF21307 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF21307
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 14 mins 59 secs

Question: 3 of 10

A 53-year-old male is receiving treatment with imatinib for chronic myeloid leukaemia.

Which of the following is imatinib?

(Please select 1 option)

- Inhibits guanylate cyclase
- Inhibits HER
- Inhibits MAP kinase
- Inhibits p53
- Inhibits tyrosine kinase

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
100%

Questions Set : REF21307 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF21307
Page
Safety
Tools

Dashboard
Questions
Scores
Community
Help
Shop

Work Smart Session - MRCP Part 1

Time taken: 17 mins 45 secs

Question: 3 of 10

A 53-year-old male is receiving treatment with imatinib for chronic myeloid leukaemia.

Which of the following is imatinib?

(Please select 1 option)

- Inhibits guanylate cyclase
- Inhibits HER
- Inhibits MAP kinase
- Inhibits p53
- Inhibits tyrosine kinase ✓ Correct

Imatinib is an inhibitor of tyrosine kinase and is used in the treatment of conditions such as chronic myelocytic leukaemia (CML) and gastrointestinal stromal tumours (GIST).

It inhibits TK on abl proto-oncogene, c-kit and the PDGF-R.

In CML, the Philadelphia chromosome leads to a fusion protein of abl with bcr (breakpoint cluster region), termed bcr-abl. As this is now a continuously active tyrosine kinase, imatinib is used to decrease bcr-abl activity.

Show tools
Internet | Protected Mode: On
100%

Questions Set : REF20589 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF20589
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 17 mins 45 secs

Question: 4 of 10

A 25-year-old female who is 20 weeks pregnant with her first child is admitted with palpitations.

The ECG reveals a supraventricular tachycardia (SVT) and this self terminates 20 minutes after admission. Subsequently she has further runs of symptomatic SVT.

What would be the most appropriate treatment for this patient's paroxysmal supraventricular tachycardia?

(Please select 1 option)

- Amiodarone
- Disopyramide
- Flecainide
- Metoprolol
- Verapamil

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
100%

Questions Set : REF20589 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF20589
Page Safety Tools

Question: 4 of 10

A 25-year-old female who is 20 weeks pregnant with her first child is admitted with palpitations.

The ECG reveals a supraventricular tachycardia (SVT) and this self terminates 20 minutes after admission. Subsequently she has further runs of symptomatic SVT.

What would be the most appropriate treatment for this patient's paroxysmal supraventricular tachycardia?

(Please select 1 option)

○	Amiodarone
○	Disopyramide
◉	Flecainide ✕ Incorrect answer selected
○	Metoprolol ← This is the correct answer
○	Verapamil

Tachyarrhythmias may increase during pregnancy although the causes are not entirely clear.

Regarding the termination of acute SVT, adenosine appears to be safe in pregnancy. In the case of the prevention of recurrent SVT then verapamil or beta -blockers have data supporting their use.

Current AHA/EHA criteria for the treatment of SVTs in pregnancy do suggest using metoprolol (level of evidence 1B) rather than verapamil (C), although they recommend avoiding the former in the first trimester.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

(1 item remaining) Downloading picture http://my.onexamination.com/SidePortalTab.aspx?state=inactive&theme=&text=Comment:
Internet | Protected Mode: On
100%

Questions Set : REF11289 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF11289
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 19 mins 20 secs

Question: 5 of 10

Which of the following most accurately describes the mechanism of action of the bisphosphonates?

(Please select 1 option)

- Calcium resorption in the distal tubule
- Fibroblast proliferation in bone marrow
- Improved vascular supply to bone marrow
- Inhibition of osteoclast activity
- Upregulation of osteoblast activity

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
100%

Questions Set : REF11289 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF11289
Page Safety Tools

Dashboard
Questions
Scores
Community
Help
Shop

Work Smart Session - MRCP Part 1

Time taken: 20 mins 3 secs

Question: 5 of 10

Which of the following most accurately describes the mechanism of action of the bisphosphonates?

(Please select 1 option)

- Calcium resorption in the distal tubule
- Fibroblast proliferation in bone marrow
- Improved vascular supply to bone marrow
- Inhibition of osteoclast activity ✓ Correct
- Upregulation of osteoblast activity

The mechanism of action of alendronate and risedronate as well as newer agents involves the inhibition of the pathway that leads to the production of certain essential lipid compounds inside osteoclasts.

This results in a series of events leading to decreased osteoclast activity and to the induction of cell death.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
100%

Questions Set : REF5724 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF5724
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 20 mins 3 secs

Question: 6 of 10

A 55-year-old female who had a long history of alcohol abuse presents with diarrhoea and back pain one month after having a pacemaker inserted.

On examination she had a fever of 39°C and her abdomen was soft and non-tender.

What is the most likely diagnosis?

(Please select 1 option)

- Diverticulitis
- Ischaemic colitis
- Pancreatitis
- Pseudomembranous colitis
- Staphylococcal discitis

Submit answer | Skip question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
100%

Questions Set : REF5724 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF5724
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 20 mins 54 secs

Question: 6 of 10

A 55-year-old female who had a long history of alcohol abuse presents with diarrhoea and back pain one month after having a pacemaker inserted.

On examination she had a fever of 39°C and her abdomen was soft and non-tender.

What is the most likely diagnosis?

(Please select 1 option)

- ○ Diverticulitis
- ○ Ischaemic colitis
- ○ Pancreatitis
- ○ Pseudomembranous colitis
- ◉ Staphylococcal discitis ✓ Correct

All patients with alcohol dependence have an increased risk of pancreatitis, but this is less likely without any abdominal signs.

Ischaemic colitis classically presents with bloody diarrhoea.

The prophylactic antibiotics given four weeks previously for her pacemaker insertion would not really have predisposed her to pseudomembranous colitis.

Staphylococci are skin organisms most commonly introduced during pacemaker insertion and such a discitis would present with back pain.

Next question | Remove Tag | Remove question

Done
Internet | Protected Mode: On
100%

Questions Set : REF5182 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF5182
Page Safety Tools

Work Smart Session - MRCP Part 1

Time taken: 20 mins 54 secs

Question: 7 of 10

A 70-year-old male is admitted with haematemesis. He is currently being treated with warfarin for atrial fibrillation and his INR returns as 10 (<1.4).

Which of the following is the most appropriate immediate treatment of his INR?

(Please select 1 option)

- Cryoprecipitate
- Fresh frozen plasma
- Intravenous vitamin K
- Oral vitamin K
- Recombinant Factor VIII concentrate

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
100%

Questions Set : REF5182 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF5182
Page Safety Tools

Work Smart Session - MRCP Part 1

Time taken: 21 mins 44 secs

Question: 7 of 10

A 70-year-old male is admitted with haematemesis. He is currently being treated with warfarin for atrial fibrillation and his INR returns as 10 (<1.4).

Which of the following is the most appropriate immediate treatment of his INR?

(Please select 1 option)

- Cryoprecipitate
- Fresh frozen plasma ✓ Correct
- Intravenous vitamin K
- Oral vitamin K
- Recombinant Factor VIII concentrate

This patient has had a bleed related to a grossly elevated international normalised ratio (INR). Consequently the INR needs correction as rapidly as is possible.

Vitamin K will correct the INR over a few days, whereas fresh frozen plasma will correct the bleeding time rapidly.

Next question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

(2 items remaining) Downloading picture http://my.onexamination.com/SidePortalTab.aspx?state=inactive&theme=&text=Stats...
Internet | Protected Mode: On
100%

Questions Set : REF3967 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF3967
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 21 mins 44 secs

Question: 8 of 10

A 24-year-old man presented twelve hours after an overdose of dihydrocodeine 1.2 g and paracetamol 30 g.

He had pinpoint pupils, a Glasgow coma scale (GCS) score of 14 and a blood pressure of 100/60 mmHg.

Which one of the following is the most appropriate management?

(Please select 1 option)

- 500ml of 10% glucose intravenously over four hours.
- Intravenous flumazenil.
- Intravenous N-acetylcysteine.
- Intravenous naloxone.
- Oral activated charcoal.

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
100%

Questions Set : REF3967 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF3967
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 23 mins 38 secs

Question: 8 of 10

A 24-year-old man presented twelve hours after an overdose of dihydrocodeine 1.2 g and paracetamol 30 g.

He had pinpoint pupils, a Glasgow coma scale (GCS) score of 14 and a blood pressure of 100/60 mmHg.

Which one of the following is the most appropriate management?

(Please select 1 option)

○	500ml of 10% glucose intravenously over four hours.
○	Intravenous flumazenil.
○	Intravenous N-acetylcysteine. ← This is the correct answer
◉	Intravenous naloxone. ✕ Incorrect answer selected
○	Oral activated charcoal.

This patient's GCS is reasonable and the opiate-like effects seem minimal (no evidence of respiratory depression).

However, this patient has received a hefty dose of paracetamol conferring a high risk of hepatic toxicity. The 12 hour delay makes the absorptive effects of charcoal limited and although it would be useful as gastric emptying may be delayed it is not as important in this patient as the paracetamol antidote.

Even though the paracetamol level is not provided, he should be treated with N-acetylcysteine without delay.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
100%

Questions Set : REF2367 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF2367
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 23 mins 38 secs

Question: 9 of 10

Which of the following symptoms is more suggestive of a functional disorder?

(Please select 1 option)

- Disorientation in time
- Inability to retain new information
- Mutism
- Perseveration
- Visual hallucinations

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
100%

Questions Set : REF2367 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF2367
Page Safety Tools

Dashboard
Questions
Scores
Community
Help
Shop

Work Smart Session - MRCP Part 1

Time taken: 24 mins 34 secs

Question: 9 of 10

Which of the following symptoms is more suggestive of a functional disorder?

(Please select 1 option)

- Disorientation in time
- Inability to retain new information
- Mutism ← This is the correct answer
- Perseveration ✕ Incorrect answer selected
- Visual hallucinations

Functional refers to an illness that is without a structural defect.

Organic brain syndromes are physical conditions including structural brain disease and metabolic disturbances causing mental dysfunction.

Mutism is the most likely of the symptoms described to be associated with a functional disorder but is associated with schizophrenia or autism.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
100%

Work Smart Session - MRCP Part 1

Time taken:

Question: 1 of 100

A 75-year-old woman presents with a two month history of episodic loss of vision in her right eye. Her electrocardiogram was normal and carotid ultrasound reveal a 50% stenosis of the right internal carotid artery.

What is the most appropriate treatment for this patient?

(Please select 1 option)

○	Aspirin
○	Carotid endarterectomy
○	Dipyridamole
○	Prednisolone
○	Warfarin

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 12 mins 56 secs

Question: 10 of 100

A 60-year-old woman has a systolic murmur.

As part of the evaluation you listen to the murmur during a Valsalva manoeuvre and the murmur becomes louder.

Which of the following systolic murmurs becomes louder with a Valsalva?

(Please select 1 option)

- Aortic stenosis
- Hypertrophic obstructive cardiomyopathy
- Mitral flow murmur
- Mitral regurgitation
- Ventricular septal defect

Submit answer | Skip question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 2 hrs 33 mins 52 secs

Work Smart Session - MRCP Part 1

Question: 100 of 100

Which of the following may be responsible for a hypokalaemic hypertension?

(Please select 1 option)

- Bartter's syndrome
- Diabetic nephropathy
- Liddle's syndrome
- Non-classical congenital adrenal hyperplasia
- Type IV renal tubular acidosis (RTA)

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Time taken: 2 hrs 39 mins

Work Smart Session - MRCP Part 1

Question: 100 of 100

Which of the following may be responsible for a hypokalaemic hypertension?

(Please select 1 option)

○	Bartter's syndrome
○	Diabetic nephropathy
◉	Liddle's syndrome ✓ Correct
○	Non-classical congenital adrenal hyperplasia
○	Type IV renal tubular acidosis (RTA)

Liddle's syndrome is typically associated with hypokalaemic hypertension and low renin and aldosterone concentrations - the so-called pseudo-hyperaldosteronism.

Bartter's syndrome is associated with hypokalaemia, though hypertension is not a feature.

In type IV RTA, there is a hyporeninaemic hypoaldosteronism, which may also be produced with diabetic nephropathy, hence hyperkalaemia is more typical.

Finish | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Question: 10 of 100

A 60-year-old woman has a systolic murmur.

As part of the evaluation you listen to the murmur during a Valsalva manoeuvre and the murmur becomes louder.

Which of the following systolic murmurs becomes louder with a Valsalva?

(Please select 1 option)

○	Aortic stenosis
◉	Hypertrophic obstructive cardiomyopathy ✓ Correct
○	Mitral flow murmur
○	Mitral regurgitation
○	Ventricular septal defect

Most murmurs of stenosis or regurgitation are exaggerated during squatting and get softer with the Valsalva manoeuvre.

The exceptions are hypertrophic cardiomyopathy (HOCM) where the opposite occurs and mitral valve prolapse where the murmur gets longer.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 13 mins 50 secs

Question: 11 of 100

A 45-year-old man presents with a rash.

On examination you find he has eruptive xanthoma.

Which of the following is the most likely diagnosis?

(Please select 1 option)

○	Familial combined hyperlipidaemia
○	Familial hypercholesterolaemia
○	Familial hypertriglyceridaemia
○	Hyperlipidaemia associated with nephrotic syndrome
○	Remnant hyperlipidaemia

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Question: 11 of 100

A 45-year-old man presents with a rash.

On examination you find he has eruptive xanthoma.

Which of the following is the most likely diagnosis?

(Please select 1 option)

○	Familial combined hyperlipidaemia
○	Familial hypercholesterolaemia
○	Familial hypertriglyceridaemia ← This is the correct answer
○	Hyperlipidaemia associated with nephrotic syndrome
◉	Remnant hyperlipidaemia ✕ Incorrect answer selected

Eruptive xanthomas occur in a number of types of hypertriglyceridaemia and also in uncontrolled diabetes mellitus.

Of those listed the most likely is familial hypertriglyceridaemia.

(Further reading. Dermnet NZ)

Next question

Remove Tag Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 14 mins 59 secs

Question: 12 of 100

A 55-year-old man presents with severe dyspnoea with tachycardia and clinical examination raises the possibility that pericardial disease may be the cause.

Which of the following clinical features would favour cardiac tamponade rather than constrictive pericarditis?

(Please select 1 option)

○	Hypotension
○	Kussmaul's sign
○	Muffled heart sounds
○	Pulsus paradoxus
○	Raised JVP

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 16 mins

Question: 12 of 100

A 55-year-old man presents with severe dyspnoea with tachycardia and clinical examination raises the possibility that pericardial disease may be the cause.

Which of the following clinical features would favour cardiac tamponade rather than constrictive pericarditis?

(Please select 1 option)

○	Hypotension
○	Kussmaul's sign
○	Muffled heart sounds
◉	Pulsus paradoxus ✓ Correct
○	Raised JVP

In cardiac tamponade there is pulsus paradoxus (a greater than 10 mmHg fall in systolic BP on inspiration) but this is less commonly seen in constrictive pericarditis.

Kussmaul's sign (a rise in the jugular venous pressure [JVP] on inspiration) is more likely to be seen in constrictive pericarditis than cardiac tamponade.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 16 mins

Question: 13 of 100

On physical examination a 65-year-old man is found to have pulsus alternans where there is regular alternation of the force of his radial pulse.

Which of the following conditions is the most likely diagnosis?

(Please select 1 option)

○	Aortic stenosis
○	Cardiac tamponade
○	Hypertrophic obstructive cardiomyopathy
○	Mixed aortic valve disease
○	Severe left ventricular failure

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 16 mins 47 secs

Question: 13 of 100

On physical examination a 65-year-old man is found to have pulsus alternans where there is regular alternation of the force of his radial pulse.

Which of the following conditions is the most likely diagnosis?

(Please select 1 option)

○	Aortic stenosis
○	Cardiac tamponade
○	Hypertrophic obstructive cardiomyopathy
○	Mixed aortic valve disease
◉	Severe left ventricular failure ✓ Correct

Pulsus alternans is a physical finding characterised by a regular alternation of the force of the arterial pulse.

It almost invariably indicates the presence of severe left ventricular systolic dysfunction.

NEJM 1996;334(13):834

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 16 mins 47 secs

Question: 14 of 100

A 65-year-old man has been stable on the general medical ward following an admission with acute coronary syndrome several days previously.

His drug history consists of aspirin, enalapril and glyceryl trinitrate (GTN) spray. He has developed dyspnoea over the last few hours.

On examination he has a raised jugular venous pressure (JVP) and crackles to his mid zones. His electrocardiogram (ECG) shows a rate of 140 beats per minute in atrial fibrillation.

Which of the following is the most appropriate management?

(Please select 1 option)

○	IV amiodarone
○	IV digoxin
○	IV flecainide
○	Observe and screen for MI
◉	Synchronised DC cardioversion

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

His drug history consists of aspirin, enalapril and glyceryl trinitrate (GTN) spray. He has developed dyspnoea over the last few hours.

On examination he has a raised jugular venous pressure (JVP) and crackles to his mid zones. His electrocardiogram (ECG) shows a rate of 140 beats per minute in atrial fibrillation.

Which of the following is the most appropriate management?

(Please select 1 option)

○	IV amiodarone
○	IV digoxin
○	IV flecainide
○	Observe and screen for MI
◉	Synchronised DC cardioversion ✓ Correct

It is sometimes difficult to assess if the atrial fibrillation (AF) is a cause or a consequence of the heart failure in such a patient but the clinical history suggests that the AF has triggered the symptoms of left ventricular failure (LVF).

The best approach is therefore quickly to relieve the atrial fibrillation with cardioversion. This may not be possible, in which case a pharmacological approach may be tried.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 18 mins 50 secs

Question: 15 of 100

A 17-year-old male presented with episodes of low back pain.

On clinical examination he is tall and has features of Marfan syndrome. You refer him for echocardiography and he asks why it is needed.

Which of the following is the most common abnormality seen in people with Marfan syndrome?

(Please select 1 option)

- Bicuspid aortic valve
- Coarctation of the aorta
- Dilation of the aortic sinuses
- Mitral valve prolapse
- Primum atrial septal defect

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

A 17-year-old male presented with episodes of low back pain.

On clinical examination he is tall and has features of Marfan syndrome. You refer him for echocardiography and he asks why it is needed.

Which of the following is the most common abnormality seen in people with Marfan syndrome?

(Please select 1 option)

○	Bicuspid aortic valve
○	Coarctation of the aorta
◉	Dilation of the aortic sinuses ✓ Correct
○	Mitral valve prolapse
○	Primum atrial septal defect

"The normal aorta has three gentle bulges, the aortic sinuses, just distal to the semilunar attachments of the three leaflets of the aortic valve. The cross sectional diameter of the aorta at the nadir of the leaflet attachment where the aorta and ventricular muscle meet, and at the upper limit of the attachment at the sinutubular junction, are very similar, with the leaflets supported with a spatial relation as if to the sides of a cylinder. The diameter of the more distal circle at the sinutubular junction is, if anything, slightly smaller than the left ventricular outflow. This relation is lost in the Marfan syndrome. The aortic root becomes bulbous and the attachments of the leaflets are splayed out."
Heart 2000;84:674-678

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 19 mins 26 secs

Question: 16 of 100

A 48-year-old man presents with acute coronary syndrome.

On examination he has palmar crease xanthoma.

Which of the following is the most likely diagnosis of his lipid abnormalities?

(Please select 1 option)

- Familial combined hyperlipidaemia
- Familial hypercholesterolaemia
- Familial hypertriglyceridaemia
- Lipoprotein lipase deficiency
- Remnant hyperlipidaemia

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 19 mins 54 secs

Question: 16 of 100

A 48-year-old man presents with acute coronary syndrome.

On examination he has palmar crease xanthoma.

Which of the following is the most likely diagnosis of his lipid abnormalities?

(Please select 1 option)

○	Familial combined hyperlipidaemia
○	Familial hypercholesterolaemia
○	Familial hypertriglyceridaemia
○	Lipoprotein lipase deficiency
◉	Remnant hyperlipidaemia ✓ Correct

Palmar crease xanthoma are associated with remnant hyperlipidaemia (Type III hyperlipidaemia).

Next question

Tag Question

Remove question

Work Smart Session - MRCP Part 1

Time taken: 19 mins 54 secs

Question: 17 of 100

A 24-year-old girl with Down syndrome is found on clinical examination to have a systolic murmur.

What is the most common cardiac defect seen in patients with Down syndrome that may explain this murmur?

(Please select 1 option)

○	Endocardial cushion defect
○	Mitral regurgitation
○	Patent ductus arteriosus
○	Secundum atrial septal defect
○	Ventricular septal defect

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 20 mins 19 secs

Question: 17 of 100

A 24-year-old girl with Down syndrome is found on clinical examination to have a systolic murmur.

What is the most common cardiac defect seen in patients with Down syndrome that may explain this murmur?

(Please select 1 option)

◉	Endocardial cushion defect ✓ Correct
○	Mitral regurgitation
○	Patent ductus arteriosus
○	Secundum atrial septal defect
○	Ventricular septal defect

Endocardial cushion defects, more commonly known as atrioventricular (AV) canal or septal defects, include a range of defects characterised by involvement of the atrial septum, the ventricular septum, and one or both of the AV valves. (eMedicine)

Next question

Tag Question

Remove question

Work Smart Session - MRCP Part 1

Time taken: 20 mins 19 secs

Question: 18 of 100

Which of the following cardiac drugs shorten the QT interval?

(Please select 1 option)

○	Amiodarone
○	Digoxin
○	Moxonidine
○	Sodium nitroprusside
○	Sotalol

Submit answer | Skip question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 20 mins 41 secs

Question: 18 of 100

Which of the following cardiac drugs shorten the QT interval?

(Please select 1 option)

○	Amiodarone
◉	Digoxin ✓ Correct
○	Moxonidine
○	Sodium nitroprusside
○	Sotalol

Hypercalcaemia, hypermagnesaemia, digoxin, or thyrotoxicosis cause QT shortening.

Next question

Tag Question

Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 20 mins 41 secs

Question: 19 of 100

A 50-year-old woman is found to have reversed splitting of the second heart sound.

This is found in which one of the following conditions?

(Please select 1 option)

○	Atrial septal (AS) defect
○	Mild aortic regurgitation
○	Patent ductus arteriosus
○	Right bundle branch block (RBBB)
○	Ventricular septal defect (VSD)

Submit answer | Skip question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 21 mins 56 secs

Question: 19 of 100

A 50-year-old woman is found to have reversed splitting of the second heart sound.

This is found in which one of the following conditions?

(Please select 1 option)

○	Atrial septal (AS) defect
◉	Mild aortic regurgitation ✗ Incorrect answer selected
○	Patent ductus arteriosus ← This is the correct answer
○	Right bundle branch block (RBBB)
○	Ventricular septal defect (VSD)

Reversed splitting of the second heart sound occurs with reversal of the normal A2, P2 pattern.

Thus A2 may be delayed as with severe AS (not mild), and LBBB.

P2 may be early as with Wolff-Parkinson-White type B and persistent ductus arteriosus.

Atrial septal defects show wide fixed splitting, and RBBB has wide, but not fixed splitting.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 4 mins 58 secs

Question: 1 of 100

A 75-year-old woman presents with a two month history of episodic loss of vision in her right eye. Her electrocardiogram was normal and carotid ultrasound reveal a 50% stenosis of the right internal carotid artery.

What is the most appropriate treatment for this patient?

(Please select 1 option)

○	Aspirin ← This is the correct answer
○	Carotid endarterectomy
○	Dipyridamole
○	Prednisolone
◉	Warfarin ✕ Incorrect answer selected

The patient experienced transient ischaemic attacks (TIAs) of the form of amaurosis fugax due to carotid artery stenosis.

Carotid endarterectomy is only indicated if the stenosis is 70-99%.

Aspirin is the treatment of choice and good control of all vascular risk factors.

Warfarin is not indicated unless the patient is in atrial fibrillation (AF).

Work Smart Session - MRCP Part 1

Time taken: 4 mins 58 secs

Question: 2 of 100

Which one of the following is true regarding acute pulmonary embolism?

(Please select 1 option)

- A normal ECG excludes the diagnosis
- Embolectomy is more effective than thrombolysis in improving survival
- Heparin is as effective as thrombolytic therapy
- The presence of hypoxaemia is an indication for thrombolysis
- Thrombolysis administered through a peripheral vein is as effective as through a pulmonary artery catheter

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 21 mins 56 secs

Question: 20 of 100

A 29-year-old female with Turner syndrome is referred by the GP concerned about her blood pressure which he has found to be persistently elevated at between 140-160/90 mmHg.

On examination she is noted to have a blood pressure of 148/92 mmHg, with no radio-femoral delay and no murmur audible.

Which of the following is the most likely cause of her hypertension?

(Please select 1 option)

○	Coarctation of the aorta
○	Essential hypertension
○	Primary hyperaldosteronism
○	Renal artery stenosis
○	Single horseshoe kidney

Submit answer | Skip question | Remove Tag | Remove question

A 29-year-old female with Turner syndrome is referred by the GP concerned about her blood pressure which he has found to be persistently elevated at between 140-160/90 mmHg.

On examination she is noted to have a blood pressure of 148/92 mmHg, with no radio-femoral delay and no murmur audible.

Which of the following is the most likely cause of her hypertension?

(Please select 1 option)

○	Coarctation of the aorta
◉	Essential hypertension ✓ Correct
○	Primary hyperaldosteronism
○	Renal artery stenosis
○	Single horseshoe kidney

Hypertension is quite common in Turner syndrome (10%) and is typically idiopathic - essential.

In a small proportion causes can include coarctation of the aorta and renal dysfunction due to horseshoe kidney.

In this case, essential hypertension is the most likely cause, but in the absence of specific features of coarctation this would again be the most appropriate option.

Next question

Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 23 mins 36 secs

Question: 21 of 100

A 62-year-old male who is being treated for stable angina presents with muscle aches and pains. He has been taking simvastatin 40 mg daily, atenolol 50 mg daily together with aspirin 75 mg daily for approximately two years. Recently he was admitted for an episode of acute coronary syndrome and a number of other therapies were added. You suspect a statin related myopathy and a CPK concentration is 820 iu/l (50-200).

Which of the following is most likely to be responsible for the precipitation of his statin related myopathy?

(Please select 1 option)

- Bisoprolol
- Clopidogrel
- Diltiazem
- Omega-3 fatty acids
- Spironolactone

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

A 62-year-old male who is being treated for stable angina presents with muscle aches and pains. He has been taking simvastatin 40 mg daily, atenolol 50 mg daily together with aspirin 75 mg daily for approximately two years. Recently he was admitted for an episode of acute coronary syndrome and a number of other therapies were added. You suspect a statin related myopathy and a CPK concentration is 820 iu/l (50-200).

Which of the following is most likely to be responsible for the precipitation of his statin related myopathy?

(Please select 1 option)

○	Bisoprolol
○	Clopidogrel
○	Diltiazem ← This is the correct answer
○	Omega-3 fatty acids
◉	Spironolactone ✕ Incorrect answer selected

Statin-associated myopathy occurs in up to 5% of those treated with statins and may be exacerbated by the co-prescription of other drugs such as calcium channel blockers, macrolide antibiotics, fibrates, amiodarone and grapefruit juice.

Whilst patients may tolerate a statin extremely well, a myopathy or rhabdomyolysis can quite esily be precipitated by the addition of these agents.

Next question

Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Question: 22 of 100

A 45-year-old HIV-seropositive man attended the outpatient clinic for the results of a fasting serum lipid test.

He had been diagnosed with HIV disease two years previously and was started on highly active antiretroviral therapy. One year after commencing antiretrovirals, his CD4 count had risen from 10 cells/mm^3 to 120 cells/mm^3 with an undetectable viral load.

His current medications consisted of zidovudine, lamivudine, lopinavir, aciclovir, fluconazole and co-trimoxazole.

Fasting lipid profile revealed:

Serum cholesterol	4.1 mmol/l	(<5.2)
Serum triglyceride	18.2 mmol/l	(0.45-1.69)

Which of the following medications is most likely to be responsible for these results?

(Please select 1 option)

- ○ Co-trimoxazole
- ○ Fluconazole
- ○ Lamivudine
- ○ Lopinavir
- ○ Zidovudine

◉	Lopinavir ✓ Correct
○	Zidovudine

Lipodystrophy, lipoatrophy and alterations in serum lipid values have been observed in patients with human immunodeficiency virus (HIV) disease taking highly active antiretroviral therapy.

Elevated serum lipid levels have been associated with premature coronary artery disease.

Hypertriglyceridaemia is also thought to contribute to central fat deposition, and insulin resistance that is also seen in these patients.

Abnormalities of serum lipid levels are likely to be multifactorial in patients with HIV disease, but appear much commoner in patients taking protease inhibitors.

Isolated hypertriglyceridaemia can occur in HIV disease in the absence of protease inhibitors, but extremely high serum triglycerides have been documented in some patients treated with these drugs.

If the elevation in lipid levels is modest, measures such as dietary modification and exercise may be tried first. Omega-3 fish oils may also be beneficial in reducing modestly-elevated serum triglycerides.

In refractory cases, or where there is extreme isolated hypertriglyceridaemia, a fibrate should be used.

In addition, patients with HIV disease may also have elevated serum lipid levels due to familial hyperlipidaemia.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 27 mins 15 secs

Question: 23 of 100

A 41-year-old male on routine risk factor screening is noted to have a blood pressure of 146/86 mm/Hg.

His investigations reveal:

Fasting plasma glucose	5.8 mmol/L	(3.0-6.0)
Total cholesterol	6.2 mmol/L	(<5.2)
Triglyceride	12.8 mmol/L	(0.45-1.69)
HDL-cholesterol	0.8 mmol/L	(>1.55)

Which is the most appropriate treatment for his lipid profile?

(Please select 1 option)

- Ezetimibe
- Fenofibrate
- Nicotinic acid slow release
- Rosuvastatin
- Simvastatin

Submit answer | Skip question | Remove Tag | Remove question

http://my.onexamination.com/Assessment/Que
onexamination.com

Shop

HDL-cholesterol	0.8 mmol/L	(>1.55)

Which is the most appropriate treatment for his lipid profile?

(Please select 1 option)

○	Ezetimibe
○	Fenofibrate
○	Nicotinic acid slow release ← This is the correct answer
○	Rosuvastatin
◉	Simvastatin ✕ Incorrect answer selected

This patient is likely to have type V hyperlipoproteinaemia characterised by an excess of triglyceride containing lipoproteins and an increased risk of pancreatitis.

Nicotinic acid primarily reduces plasma TG levels via inhibition of hepatic TG synthesis suppressing FFA supply to the liver. It is currently the most effective TG reducing pharmacotherapy producing reductions of up to 30% in plasma TG at a dose of 2 g a day.

Its use is limited by side effects mainly flushing and an exacerbation of insulin resistance. The flushing may be diminished by gradual dose escalation, consumption following a low fat snack and concomitant aspirin use.

Alternative therapies in the event of intolerance to nicotinic acid include fenofibrate as a good second choice or alternatively omega-3 fatty acids.

Next question | Remove Tag | Remove question

EN 9:03 AM 2/28/2011

Question: 24 of 100

A 65-year-old male presents with arthralgia and sleep disturbance following the introduction of simvastatin.

He has a history of hypertension and ischaemic heart disease for which he is receiving aspirin, atenolol and eprosartan together with simvastatin 40 mg OD which has been introduced in the last one month. Previously, he had been taking atorvastatin but this was changed to simvastatin after he complained of arthralgia.

Investigations reveal:

Creatine phosphokinase (CPK)	156 U/l	(40-170)
Total cholesterol	5.1 mmol/l	(<5.2)
LDL-cholesterol	3.1 mmol/l	(<3.36)
Triglycerides	1.7 mmol/l	(0.45-1.69)
HDL-cholesterol	1.2 mmol/l	(>1.55)

Which is the most appropriate treatment for his lipid profile?

(Please select 1 option)

- Ezetimibe
- Fenofibrate
- Nicotinic acid slow release
- Omega-3 fatty acids
- Rosuvastatin

http://my.onexamination.com/Assessment/Que onexamination.com

(Please select 1 option)

○	Ezetimibe ← This is the correct answer
○	Fenofibrate
◉	Nicotinic acid slow release ✕ Incorrect answer selected
○	Omega-3 fatty acids
○	Rosuvastatin

The primary treatment target in this case is a total cholesterol (TC) less than 4 mmol/l and low-density lipoprotein cholesterol (LDL C) less than 2 mmol/l. Plasma triglyceride and high-density lipoprotein cholesterol (HDL-C) are already at the currently accepted target levels.

This patient describes typical statin-associated side effects which are generally a class effect and dose related. The most common adverse event with statin therapy is arthralgia or myopathy, often with normal CPK levels. Myositis and rhabdomyolysis are rare statin-associated myopathy side effects and are defined on the basis of CPK levels greater than 10x normal along with features of muscle pain and myoglobinuria (for rhabdomyolysis).

Risk factors predisposing to statin myopathy include advanced age, trauma, thyroid dysfunction and concomitant medication that can raise statin bioavailability including amiodarone, verapamil and many other agents that are metabolised by the cytochrome P450 enzyme system.

Ezetimibe monotherapy produces reductions in TC and LDL-C of around 20%, and since tolerability issues are likely to occur with another statin ezetimibe is the best treatment option.

Clinical trial data have demonstrated continuing event rate reduction to LDL-C levels below 2 mmol/l, and a meta-analysis of lipid lowering trials has demonstrated a 1 mmol/l reduction in LDL-C is associated with a 23% RRR in CHD events, irrespective of baseline risk and the method of cholesterol reduction.

EN 9:07 AM 2/28/2011

Work Smart Session - MRCP Part 1

Time taken: 33 mins 11 secs

Question: 25 of 100

A 55-year-old male with ischaemic heart disease is seen for review. He reports that he has developed some muscle aches and pains and you attribute this to a myalgia associated with simvastatin.

His creatinine kinase is within the normal range. However, his dyslipidaemia is still sub-optimal and you wish to add in a further agent.

Which of the following agents would not be an appropriate additional therapy for this patient in view of his presentation?

(Please select 1 option)

○	Cholestyramine
○	Ezetimibe
○	Gemfibrozil
○	Nicotinic acid
○	Omega-3 fatty acids

Submit answer | Skip question | Tag Question | Remove question

presentation?

- Shop

(Please select 1 option)

○	Cholestyramine
○	Ezetimibe
◉	Gemfibrozil ✓ Correct
○	Nicotinic acid
○	Omega-3 fatty acids

This patient presents with a probable statin-induced myalgia which often improves with time. Sometimes stopping therapy briefly or re-introducing a different statin may resolve the myalgia.

Statin-induced myositis is relatively uncommon, occurring in approximately 0.1-0.2%, but the risk of myositis and the potentially fatal rhabdomyolysis is increased with gemfibrozil in prone subjects in combination with a statin, and as such should be avoided.

Additional agents could include omega-3 fatty acids and ezetimibe.

Nicotinic acid is less used, due to problems with flushing though it can be useful particularly in hypertriglyceridaemia.

Cholestyramine can also be used.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 34 mins 4 secs

Question: 26 of 100

A 25-year-old female who is 20 weeks pregnant with her first child is admitted with palpitations.

The ECG reveals a supraventricular tachycardia (SVT) and this self terminates 20 minutes after admission. Subsequently she has further runs of symptomatic SVT.

What would be the most appropriate treatment for this patient's paroxysmal supraventricular tachycardia?

(Please select 1 option)

- Amiodarone
- Disopyramide
- Flecainide
- Metoprolol
- Verapamil

Submit answer | Skip question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

A 25-year-old female who is 20 weeks pregnant with her first child is admitted with palpitations.

The ECG reveals a supraventricular tachycardia (SVT) and this self terminates 20 minutes after admission. Subsequently she has further runs of symptomatic SVT.

What would be the most appropriate treatment for this patient's paroxysmal supraventricular tachycardia?

(Please select 1 option)

○	Amiodarone
○	Disopyramide
○	Flecainide
◉	Metoprolol ✓ Correct
○	Verapamil

Tachyarrhythmias may increase during pregnancy although the causes are not entirely clear.

Regarding the termination of acute SVT, adenosine appears to be safe in pregnancy. In the case of the prevention of recurrent SVT then verapamil or beta-blockers have data supporting their use.

Current AHA/EHA criteria for the treatment of SVTs in pregnancy do suggest using metoprolol (level of evidence 1B) rather than verapamil (C), although they recommend avoiding the former in the first trimester.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Question: 27 of 100

A 62-year-old male is admitted with an inferior myocardial infarction (MI) and receives thrombolysis, aspirin, atenolol, simvastatin and lisinopril. His ECG shows good ST segment resolution.

The following day he develops some pain in the legs and a dusky discolouration of the lower limbs. On closer examination there is a diffuse petechial rash over the lower legs, particularly the feet, but all peripheral pulses are palpable.

Investigations reveal:

Haemoglobin	13.3 g/dl	(12-16)
Platelets	145 x 10^9/l	(150-400)
White cell count	12.1 x 10^9/l	(4-11)
Neutrophils	6.5 x 10^9/l	(1.5-7)
Lymphocytes	3.5 x 10^9/l	(1.5-4)
Eosinophils	1.2 x 10^9/l	(0.04-0.4)
IgE antibody	3 kU/l	(<2)

Which of the following is the most likely cause for his current problems?

(Please select 1 option)

- ○ Allergic reaction to thrombolysis
- ○ Aspirin allergy
- ○ Cholesterol emboli
- ○ Peripheral vascular disease
- ○ Polyarteritis nodosa

Investigations reveal:

Haemoglobin	13.3 g/dl	(12-16)
Platelets	145 x 10^9/l	(150-400)
White cell count	12.1 x 10^9/l	(4-11)
Neutrophils	6.5 x 10^9/l	(1.5-7)
Lymphocytes	3.5 x 10^9/l	(1.5-4)
Eosinophils	1.2 x 10^9/l	(0.04-0.4)
IgE antibody	3 kU/l	(<2)

Which of the following is the most likely cause for his current problems?

(Please select 1 option)

◉	Allergic reaction to thrombolysis ✕ Incorrect answer selected
○	Aspirin allergy
○	Cholesterol emboli ← This is the correct answer
○	Peripheral vascular disease
○	Polyarteritis nodosa

This patient is an arteriopath as suggested by the acute MI, and one day after thrombolysis develops this petechial rash in the lower limbs with raised white cell count - marked eosinophilia and raised IgE.

Rather than allergy, this suggests cholesterol embolisation syndrome.

Next question

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 37 mins 51 secs

Question: 28 of 100

A 67-year-old man with insulin-dependent diabetes with a broad complex pulseless tachyarrhythmia (with a protected airway) has been defibrillated three times.

He has just finished receiving two minutes of cardiopulmonary resuscitation (CPR) and has received adrenaline.

Which of the following is the next step in the management of the arrest?

(Please select 1 option)

○	Adrenaline 1 mg
○	Amiodarone 300 mg
○	DC shock
○	Lidocaine 100 mg
○	Removal of oxygen and then DC shock

Submit answer | Skip question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 40 mins 15 secs

Question: 28 of 100

A 67-year-old man with insulin-dependent diabetes with a broad complex pulseless tachyarrhythmia (with a protected airway) has been defibrillated three times.

He has just finished receiving two minutes of cardiopulmonary resuscitation (CPR) and has received adrenaline.

Which of the following is the next step in the management of the arrest?

(Please select 1 option)

○	Adrenaline 1 mg
◉	Amiodarone 300 mg ✓ Correct
○	DC shock
○	Lidocaine 100 mg
○	Removal of oxygen and then DC shock

After three DC shocks and a further cycle of two minutes of CPR the next step is amiodarone 300 mg intravenously and then a fourth shock.

If amiodarone is not available lidocaine is a suitable alternative.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 40 mins 15 secs

Question: 29 of 100

A 66-year-old man with insulin-dependent diabetes with a treated potassium of 5.4 mmol/l (3.5-5) and palpitations develops pulseless ventricular tachycardia. The anaesthetist is supporting airway and breathing.

Which of the following is the next step in his management?

(Please select 1 option)

- Adrenaline 1 mg
- Amiodarone 300 mg
- Cardiopulmonary resuscitation (CPR) 15:2 for two minutes
- Defibrillation at 150J biphasic
- Praecordial thump

Submit answer | Skip question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Time taken: 40 mins 50 secs

Work Smart Session - MRCP Part 1

Question: 29 of 100

A 66-year-old man with insulin-dependent diabetes with a treated potassium of 5.4 mmol/l (3.5-5) and palpitations develops pulseless ventricular tachycardia. The anaesthetist is supporting airway and breathing.

Which of the following is the next step in his management?

(Please select 1 option)

○	Adrenaline 1 mg
○	Amiodarone 300 mg
○	Cardiopulmonary resuscitation (CPR) 15:2 for two minutes
○	Defibrillation at 150J biphasic ← This is the correct answer
◉	Praecordial thump ✕ Incorrect answer selected

In the case of ventricular tachycardia and ventricular fibrillation immediate defibrillation is the treatment of choice.

The other options come further down the algorithm and CPR is now recommended at 30:2.

A praecordial thump can be administered immediately following a witnessed cardiac arrest.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 5 mins 37 secs

Question: 2 of 100

Which one of the following is true regarding acute pulmonary embolism?

(Please select 1 option)

○	A normal ECG excludes the diagnosis
○	Embolectomy is more effective than thrombolysis in improving survival
○	Heparin is as effective as thrombolytic therapy
○	The presence of hypoxaemia is an indication for thrombolysis
◉	Thrombolysis administered through a peripheral vein is as effective as through a pulmonary artery catheter ✓ Correct

Embolectomies are rarely done nowadays due to the excellent results with thrombolysis.

Thrombolytic therapy is reserved for those with severely compromised circulation (equally effective through peripheral vein or via catheter in pulmonary artery).

Heparin reduces risk of further embolism (anticoagulant) and reduces pulmonary vasoconstriction.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 5 mins 37 secs

Question: 3 of 100

A 24-year-old woman develops infective endocarditis involving the aortic valve.

She receives a porcine bioprosthesis because of her desire to have children and not to take anticoagulant medication.

After ten years, she must have this prosthetic valve replaced.

Which of the following pathological findings in the bioprosthesis has most likely led to the need for replacement?

(Please select 1 option)

- Calcification with stenosis
- Dehiscence
- Infective endocarditis
- Strut failure
- Thrombosis

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd. All rights reserved. Terms and conditions. Privacy policy. A A A

Questions Set : REF20464 - Mozilla Firefox
File Edit View History Bookmarks Tools Help
http://my.onexamination.com/Assessment/Questions.aspx?id=687609&ws=true
Most Visited Getting Started Latest Headlines
Convert
Questions Set : REF20464

From BMJ Learning

Dashboard
Questions
Scores
Community
Shop
Help

Time taken: 40 mins 50 secs

Work Smart Session - MRCP Part 1

Question: 30 of 100

A 62-year-old male with a history of ischaemic heart disease is admitted with chest pain of 13 hours' duration and some ST depression inferolaterally.

Which of the following would be the most appropriate treatment option for this patient?

(Please select 1 option)

- IV diamorphine 10 mg
- Oral aspirin 600 mg
- Oral isosorbide mononitrate 30 mg
- Oxygen 100%
- Subcutaneous low molecular weight heparin

Submit answer | Skip question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done

The National Collaborating Centre

for Chronic Conditions

Funded to produce guidelines for the NHS by NICE

ATRIAL FIBRILLATION

National clinical guideline for
management in primary and secondary care

Published by

Royal College
of Physicians
Setting higher medical standards

Acknowledgements

The Guideline Development Group would like to thank the following people for their valuable input during the development of this guideline:

Mr Steven Barnes, Mrs Susan Clifford, Mr Rob Grant, Dr Bernard Higgins, Ms Jane Ingham, Ms Ester Klaeijsen, Dr Ian Lockhart, Ms Louise Martin, Ms Jill Parnham.

Mission statement

The Royal College of Physicians plays a leading role in the delivery of high quality patient care by setting standards of medical practice and promoting clinical excellence. We provide physicians in the United Kingdom and overseas with education, training and support throughout their careers. As an independent body representing over 20,000 Fellows and Members worldwide, we advise and work with government, the public, patients and other professions to improve health and healthcare.

The National Collaborating Centre for Chronic Conditions

The National Collaborating Centre for Chronic Conditions (NCC-CC) is a collaborative, multi-professional centre undertaking commissions to develop clinical guidance for the NHS in England and Wales. The NCC-CC was established in 2001. It is an independent body, housed within Clinical Standards Department at the Royal College of Physicians of London. The NCC-CC is funded by the National Institute for Health and Clinical Excellence (NICE) to undertake commissions for national clinical guidelines on an annual rolling programme.

Citation for this document

National Collaborating Centre for Chronic Conditions. *Atrial fibrillation: national clinical guideline for management in primary and secondary care*. London: Royal College of Physicians, 2006.

Copyright

All rights reserved. No part of this publication may be reproduced in any form (including photocopying or storing it in any medium by electronic means and whether or not transiently or incidentally to some other use of this publication) without the written permission of the copyright owner. Applications for the copyright owner's written permission to reproduce any part of this publication should be addressed to the publisher.

Copyright © 2006 Royal College of Physicians of London

ISBN 1 86016 282 7

ROYAL COLLEGE OF PHYSICIANS
11 St Andrews Place, London NW1 4LE
www.rcplondon.ac.uk

Registered charity No 210508

Typeset by Dan-Set Graphics, Telford, Shropshire

Printed in Great Britain by The Lavenham Press Ltd, Sudbury, Suffolk

Contents

	Members of the Guideline Development Group	vi
	Preface	viii
	List of abbreviations	ix
	DEVELOPMENT OF THE GUIDELINE	
1	**Introduction**	
1.1	Definition	3
1.2	Classification	3
1.3	Epidemiology	4
1.4	Prognosis	7
1.5	Guideline structure	7
1.6	How to use this guideline	8
2	**Methodology**	
2.1	About the guideline	9
2.2	Guideline development	10
2.3	Disclaimer	15
2.4	Funding	15
3	**Key messages of the guideline**	
3.1	Priorities for implementation	17
3.2	AF care pathway	18
3.3	Treatment strategy decision tree	18
3.4	Audit criteria	19
3.5	Areas for future research	20
	THE GUIDELINE	
4	**Identification and diagnosis**	
4.1	Presenting symptoms/pulse palpitation	25
4.2	Electrocardiography	27
4.3	Ambulatory ECG recording	29
4.4	Echocardiography	31
5	**Cardioversion**	
5.1	Electrical versus pharmacological cardioversion	35
5.2	Pharmacological cardioversion	37
5.3	Electrical cardioversion with concomitant antiarrhythmic drugs	40
5.4	Transoesophageal echocardiography-guided cardioversion	44
5.5	Cardioversion treatment algorithm	47

6	**Treatment of persistent AF**	
6.1	Rate control versus rhythm control	49
6.2	Rhythm control for persistent AF	52
6.3	Antithrombotic therapy for persistent AF	55
6.4	Rhythm-control treatment algorithm for persistent AF	58
7	**Treatment for permanent AF**	
7.1	Rate control for permanent AF	59
7.2	Antithrombotic therapy for permanent AF	61
7.3	Rate-control treatment algorithm for permanent AF	66
8	**Treatment for paroxysmal AF**	
8.1	Rhythm control for paroxysmal AF	67
8.2	Treatment strategy for paroxysmal AF	71
8.3	Antithrombotic therapy for paroxysmal AF	73
8.4	Rhythm-control treatment algorithm for paroxysmal AF	75
9	**Treatment for acute-onset AF**	
9.1	Acute AF in haemodynamically unstable patients	77
9.2	Antithrombotic therapy for acute-onset AF	80
9.3	Haemodynamically unstable AF treatment algorithm	82
10	**Postoperative AF**	
10.1	Drug prophylaxis for postoperative AF	83
10.2	Treatment for postoperative AF	88
11	**Antithrombotic therapy**	
11.1	Initiating antithrombotic therapy	91
11.2	Antithrombotic therapy in acute stroke patients	92
11.3	Antithrombotic therapy following a stroke or TIA	94
11.4	Antithrombotic therapy for asymptomatic AF	96
11.5	Risks of long-term anticoagulation	96
11.6	Risk factors for stroke and thromboembolism	100
11.7	Stroke risk stratification algorithm	104
11.8	The cost effectiveness of oral anticoagulation as thromboprophylaxis	105
12	**Monitoring and referral**	
12.1	Anticoagulation self-monitoring	107
12.2	Follow-up post cardioversion	110
12.3	Referral	114

APPENDICES
Appendix A: Health economics modelling 121
Appendix B: Stroke risk stratification models 123
Appendix C: Clinical questions and search strategies 125
Appendix D: Drug classification and licensing 129
Appendix E: Glossary of terms 131
Appendix F: Stakeholders 145
Appendix G: Scope 149

REFERENCES 155

Members of the Guideline Development Group

Dr Michael Rudolf, NCC-CC (*Chair*)
Consultant Respiratory Physician, Ealing Hospital NHS Trust

Professor Gregory Lip, NCC-CC *(Clinical Advisor)*
Professor of Cardiovascular Medicine, University Department of Medicine, City Hospital, Birmingham

Mrs Lina Bakhshi, NCC-CC
Information Scientist, Royal College of Physicians of London

Professor John Camm, British Cardiac Society
Consultant Cardiologist, St. George's Hospital Medical School, London

Dr Mark Davis, Primary Care Cardiovascular Society
General Practitioner, Moorfield House Surgery, Leeds

Mr Richard Deacon, Royal College of Nursing
Senior Charge Nurse, Leeds Teaching Hospitals NHS Trust

Dr Richard Dewar, Royal College of Physicians of London
Consultant Physician in General & Elderly Care Medicine, Pontypridd and Rhondda NHS Trust

Dr Martin Fotherby, British Geriatrics Society
Senior Lecturer in Age and Stroke Medicine, University of Leicester

Dr Jane Fisher, NCC-CC
Project Manager, Royal College of Physicians of London

Mrs Bernadette Ford, NCC-CC
Information Scientist, Royal College of Physicians of London

Dr Michael Hughes, NCC-CC
Research Fellow/Project Manager, Royal College of Physicians of London

Professor Lalit Kalra, King's College London, invited as an expert in stroke medicine to attend GDG meetings 3, 4, 11 and 14
Consultant Stroke Physician, King's College Hospital NHS Trust, London

Mr Simon Kendall, Society of Cardiothoracic Surgeons, invited as an expert in cardiothoracic surgery to attend GDG meetings 4 and 7
Consultant Cardiothoracic Surgeon, James Cook University Hospital, Middlesbrough

Dr Clifford Mann, British Association for Emergency Medicine
Consultant in Accident and Emergency Medicine, Taunton and Somerset NHS Trust

Dr Duncan McRobbie, Royal Pharmaceutical Society
Principal Clinical Pharmacist, Guy's and St Thomas' NHS Foundation Trust, London

Mr Leo Nherera, NCC-CC
Health Economist, Royal College of Physicians of London

Dr Stephen Rogers, Royal College of General Practitioners
Senior Lecturer in Primary Care, University College, London

Dr Peter Rose, invited as an expert in haematology to attend GDG meetings 3 and 4
Consultant Haematologist, South Warwickshire General Hospitals NHS Trust

Mr Peter Rose, The Stroke Association
Patient/Carer Representative, Information Service Organiser for the East of England, The Stroke Association

Mrs Fiona Sayers, Royal College of Nursing
Nurse Practitioner, Frimley Park Hospital NHS Foundation Trust, Surrey

Mr David Smith, British Cardiac Patients Association
Patient/Carer Representative, Trustee, British Cardiac Patients Association

Dr Neil Sulke, British Cardiac Society
Consultant Cardiologist, East Sussex Hospitals NHS Trust, Eastbourne

Preface

The association of an irregular pulse with morbidity has been recognised since antiquity, and as long ago as 1628 William Harvey observed cardiac irregularity directly in animals. The modern emphasis on electrical demonstration of atrial fibrillation (AF) dates back a mere 100 years to the first publication by William Einthoven of an electrocardiogram showing the abnormality. Even the treatment of this disorder has a long and venerable history: William Withering published *An account of the foxglove and some of its medical uses* in 1785, and digoxin, the active extract of his remedy, remains in use today.

A patient developing AF in 2006 is faced with a wide array of potential therapies. A number of drugs can be employed to control the rapid heart rate, which is often an intrinsic part of AF; attempts can be made to restore sinus rhythm using drugs or direct current electrical shock; and an increasing number of surgical procedures are described. Despite the wide number of options available, there is an acknowledgement that AF is too frequently treated with the almost automatic prescription of monotherapy with digoxin: this is still a useful drug over 200 years on but the best option for only a minority of patients. This failure to appreciate or implement proper treatment options in such a common condition makes AF an excellent topic for a national clinical guideline.

The guideline covers aspects of diagnosis and the management of AF in a number of different circumstances. It covers paroxysmal, persistent and permanent AF, considers AF developing after surgical procedures, and offers advice on haemodynamically unstable AF. Many of the recommendations relate to control of AF and the important decision of whether to attempt to restore sinus rhythm or concentrate on control of the heart rate. In a linked set of recommendations, the importance of considering anticoagulation in all these patients is emphasised. This is sometimes neglected in clinical practice, but anticoagulation is of enormous potential benefit because of its role in stroke prevention, and one of the key recommendations in the guideline is that the risk of thromboembolism should be formally assessed. A simple clinical model that includes advice on appropriate prophylaxis is suggested for this purpose. Other key recommendations cover the use of the electrocardiogram in diagnosis, and the preference in most patients for beta-blockers or rate-limiting calcium antagonists over digoxin for rate control.

The work of producing the guideline has been in the hands of a Guideline Development Group (GDG) comprising a small team from the National Collaborating Centre for Chronic Conditions working together with patients and health professionals with particular interest and experience in the management of AF. They have used the available evidence and their own clinical and personal judgement to produce guidance that is both clinically relevant and methodologically sound.

The GDG has had to evaluate a large amount of evidence during this process, and debate on some of the recommendations has been lively. The members have been driven throughout by the desire to produce a guideline that will be of value throughout the NHS. I am grateful to them for their hard work and for their expertise, and I am confident that they have produced a guideline that deserves to meet that aim.

Dr Bernard Higgins MD FRCP
Director, National Collaborating Centre for Chronic Conditions

List of abbreviations

AF	Atrial fibrillation
ARR	Absolute risk reduction
AV	Atrioventricular
AVJ	Atrioventricular junction (also called atrioventricular node)
bid	Twice daily
BSA	Body surface area
CABG	Coronary artery bypass graft
CHF	Congestive heart failure
CI	Confidence interval
Class Ic	Vaughan-Williams Class Ic antiarrhythmic drug
Class II	Vaughan-Williams Class II antiarrhythmic drug
Class III	Vaughan-Williams Class III antiarrhythmic drug
cm	Centimetre
CTR	Cardiothoracic ratio
CV	Cardioversion
CXR	Chest X-ray
DC	Direct current
ECG	Electrocardiogram
ECV	Electrical cardioversion
GDG	Guideline Development Group
Hg	Mercury
ICD	Implantable cardioverter defibrillator
ICER	Incremental cost-effectiveness ratio
ICH	Intracranial haemorrhage
INR	International normalised ratio
IV	Intravenous
LAA	Left atrial appendage
LAA-A	Left atrial appendage area
LAA-V	Left atrial appendage flow velocity
LAD	Left atrial diameter (synonymous with left-atrial dimension)
LA	Left atrium
LBBB	Left bundle branch block
LMWH	Low molecular weight heparin
LV	Left ventricular
LVEDD	Left ventricular end diastolic diameter
LVESD	Left ventricular end systolic diameter
LVEF	Left ventricular ejection fraction

LVFS	Left ventricular fractional shortening
LVH	Left ventricular hypertrophy
M	Metre
mg	Milligram
MI	Myocardial infarction
mm	Millimetre
mmol	Joule
N	Number of study participants
NCC-CC	National Collaborating Centre for Chronic Conditions
NICE	National Institute for Health and Clinical Excellence
NNT	Numbers needed to treat
NPV	Negative predictive value
NR	Not reported
NS	Not statistically significant
NSAID	Non-steroidal anti-inflammatory drug
NSF	National service framework
NYHA	New York Heart Association (functional classification)
OR	Odds ratio
p	Probability of a result happening by chance rather than because of a genuine effect
PCV	Pharmacological cardioversion
PPV	Positive predictive value
PVI	Pulmonary vein isolation
QALY	Quality-adjusted life-years
qid	Four times daily
RA	Right atrium
RAA	Right-atrial appendage
RBBB	Right bundle branch block
RCT	Randomised controlled trial
RR	Relative risk
sec	Second
SVT	Supraventricular tachycardia
TDP	Torsades des pointes
TEE	Thromboembolic event
TIA	Transient ischaemic attack
tid	Three times daily
TOE	Transoesophageal echocardiogram
TTE	Transthoracic echocardiogram
UK	United Kingdom
WMI	Wall motion index
WPW	Wolff–Parkinson–White syndrome

DEVELOPMENT OF THE GUIDELINE

1 Introduction

1.1 Definition

Atrial fibrillation (AF) is an atrial tachyarrhythmia characterised by predominantly uncoordinated atrial activation with consequent deterioration of atrial mechanical function. Another closely related atrial arrhythmia is atrial flutter, and this will also be discussed in the guideline insofar as its treatment coincides with that of AF itself.

On the electrocardiogram, AF is described by the absence of consistent P waves; instead there are rapid oscillations or fibrillatory waves that vary in size, shape and timing and are generally associated with an irregular ventricular response when atrioventricular (AV) conduction is intact. The patient may experience AF as palpitations, chest pain, dizziness, or in extreme cases loss of consciousness. In many cases, however, it may occur asymptomatically.

The ventricular response in AF depends on many things, including AV nodal properties, the level of vagal and sympathetic tone and drugs that affect AV nodal conduction such as beta-blockers, non-dihydropyridine calcium-channel blockers (calcium antagonists) and digitalis glycosides. However, regular relative risk (RR) intervals on the electrocardiogram (ECG) may occur, for example, in the presence of heart block associated with conduction disease or drug therapy. In patients with permanent ventricular pacing, the diagnosis may require temporary pacemaker inhibition in order to visualise AF activity. A rapid, irregular, sustained, wide QRS complex tachycardia could suggest AF with conduction via an accessory pathway.

1.2 Classification

Recent guidelines suggest classification of AF based on the temporal pattern of the arrhythmia (see Table 1.1).

Table 1.1 Classification of AF subtypes

Terminology	Clinical features	Pattern
Initial event (first detected episode)	Symptomatic Asymptomatic (first detected) Onset unknown (first detected)	May or may not reoccur
Paroxysmal	Spontaneous termination <7 days and most often <48 hours	Recurrent
Persistent	Not self-terminating Lasting >7 days or prior cardioversion	Recurrent
Permanent ('Accepted')	Not terminated Terminated but relapsed No cardioversion attempt	Established

Table reprinted with permission from Levy S, Camm AJ, Saksena S et al. International consensus on nomenclature and classification of atrial fibrillation. *Europace* 2003;5:119–22.[1]

AF is considered *recurrent* when a patient experiences two or more episodes. These episodes may be paroxysmal if they terminate spontaneously, defined by consensus as 7 days, or persistent if the arrhythmia requires electrical or pharmacological cardioversion for termination. Successful termination of AF does not alter the classification of persistent AF in these patients.

Long-standing AF (defined as over a year) that is not successfully terminated by cardioversion, or when cardioversion is not pursued, is classified as permanent.

Paroxysmal AF, in which the frequency of paroxysms is low, may degenerate into either paroxysmal AF with more frequent paroxysms, or a sustained form of AF. Similarly, persistent AF may degenerate into permanent AF. Despite its name, the reversion of permanent AF to normal sinus rhythm is also possible, particularly in those cases where the AF is caused by an underlying disease process which is successfully treated (eg thyroid disease), or where a specialist procedure is performed that modifies the electrophysiological properties of the heart.

Without treatment, AF can sometimes result in a degree of haemodynamic instability which can represent a critical condition that requires immediate intervention to alleviate symptoms of breathlessness, chest pain and loss of consciousness, and restore haemodynamic stability.

1.3 Epidemiology

1.3.1 Prevalence

AF is the commonest sustained cardiac arrhythmia. Much of the epidemiology of AF is derived from data from predominantly white populations, and information on AF in non-white populations is scarce. Hospital practice data may give a biased view of the clinical epidemiology of AF, since only one-third of patients with AF may actually have been admitted to hospital.[2]

The prevalence of AF roughly doubles with each advancing decade of age, from 0.5% at age 50–59 years to almost 9% at age 80–89 years.[3] Conversely, AF is very uncommon in infants and children, unless concomitant structural or congenital heart disease is present.

In the UK, the Renfrew–Paisley study[4] found that of an original cohort of men and women aged 45–64 years (N=15,406) there were 100 (0.65%; 95% CI 0.53 to 0.79%) documented cases of AF. The prevalence of AF increased with age and more cases were detected in men (53 of 7,052) than women (47 of 8,354)[4] as shown in Figure 1.1. In the West Birmingham AF project, the prevalence of AF was 2.4% in two general practices[2] and further extension of this project showed that the prevalence of AF among Indo-Asians aged over 50 years in the general practice population was 0.6%.[5] The Newcastle survey screened 4,843 people aged 65 years or more in general practices and found a prevalence of AF of 4.7%.[6] Among UK hospital admissions, AF is present in 3–6% of acute medical admissions.[7,8]

The 4-year incidence of AF in the Renfrew–Paisley project was 0.54 cases per 1,000 person years[4] (see Figure 1.2).

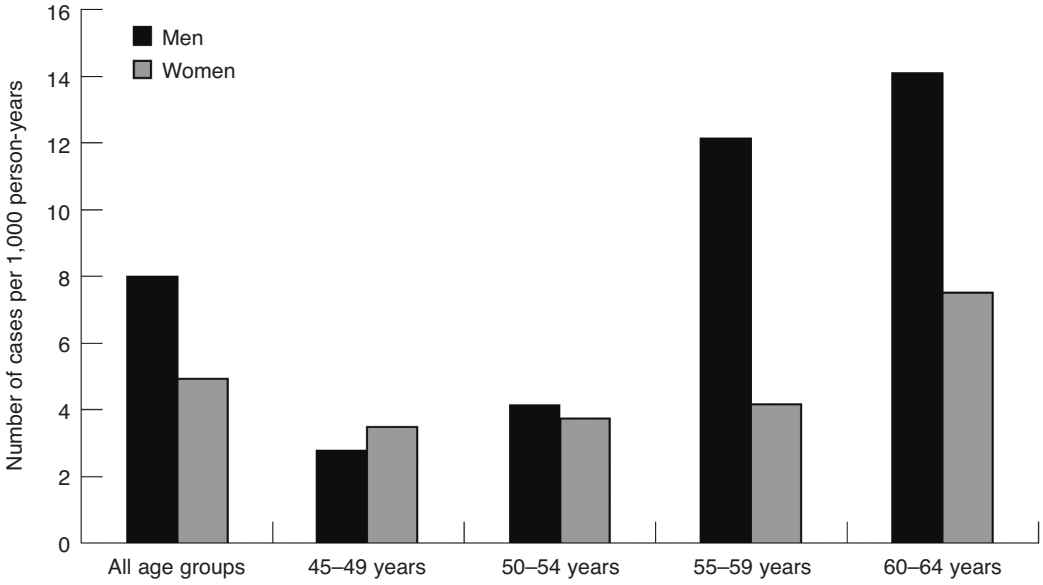


Figure 1.1 Prevalence of AF in the Renfrew–Paisley project.[4*]

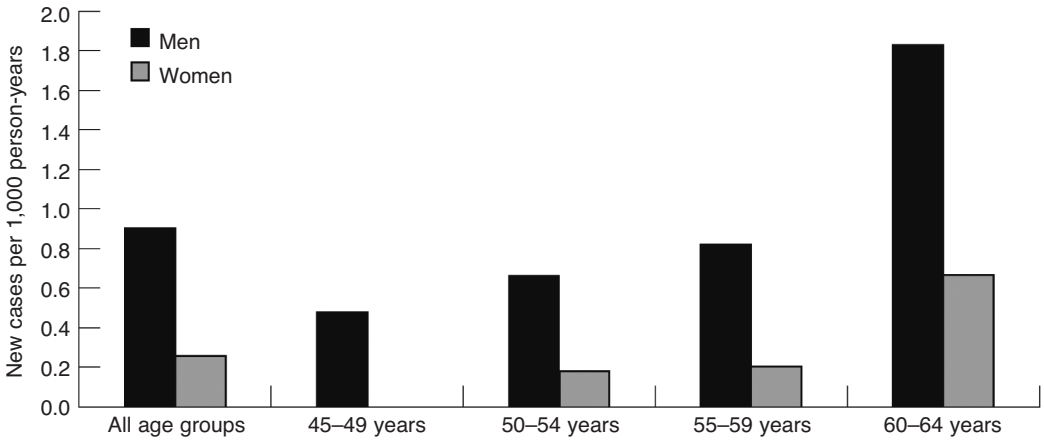


Figure 1.2 Incidence of AF in the Renfrew–Paisley project.[4] *Figures 1.1 and 1.2 were reproduced with permission of BMJ Publishing Ltd from Stewart S, Hart CL, Hole DJ et al. Population prevalence, incidence, and predictors of atrial fibrillation in the Renfrew/Paisley study. *Heart* (British Cardiac Society) 2001;86:516–21.

1.3.2 Risk factors

There are many risk factors for developing AF. As discussed above, there is an increasing prevalence and incidence of AF with increasing age. In the Framingham study[9] the development of AF was associated with increasing age (odds ratio (OR) 2.1 for men and 2.2 for women, $p < 0.0001$), diabetes (OR 1.4 for men and 1.6 for women), hypertension (OR 1.5 for men and 1.4 for women), and valve disease (OR 1.8 for men and 3.4 for women). It is also commonly associated with, and complicated by, congestive heart failure and strokes.

AF is often caused by coexisting medical conditions. These causes can be cardiac and non-cardiac (see Table 1.2).

Table 1.2 Common cardiac and non-cardiac causes of AF

Cardiac causes of AF	Non-cardiac causes of AF
Common cardiac causes: ischaemic heart disease rheumatic heart disease hypertension sick sinus syndrome pre-excitation syndromes (eg Wolff–Parkinson–White).	Acute infections, especially pneumonia
Less common cardiac causes: cardiomyopathy or heart muscle disease pericardial disease (including effusion and constrictive pericarditis) atrial septal defect atrial myxoma.	Electrolyte depletion
	Lung carcinoma
	Other intrathoracic pathology (eg pleural effusion)
	Pulmonary embolism
	Thyrotoxicosis

AF is also common after surgery, especially cardiothoracic operations such as thoracotomy and coronary artery bypass graft. Overall, the presence of the AF after surgery not only results in prolongation of hospital stay but may also increase risk of heart failure, stroke, or thromboembolism, and greater hospital costs. The incidence of postoperative AF depends on many risk factors apart from the type of procedure, such as age and the patient's preoperative physiology and electrolyte balance.

Many dietary and lifestyle factors have also been associated with AF. These include excessive alcohol or caffeine consumption and emotional or physical stress. In the case of alcohol, AF may develop as a consequence of an excessive intake of alcohol over a relatively short period – a so-called 'holiday heart'. In one series of younger patients (aged <65 years) with new onset AF, alcohol caused or contributed to the arrhythmia in 63% of cases.[10]

Lone AF is defined as AF without overt structural heart disease, and defined by a normal clinical history and examination, ECG, chest X-ray and, more recently, the echocardiogram. There are implications of labelling patients with this diagnosis, as this group is often considered to be at 'low risk', although recent data have been inconclusive.

A diagnosis of lone AF is only considered a diagnosis of exclusion if there is:

- no history of cardiovascular disease or hypertension
- no abnormal cardiac signs on physical examination
- a normal chest X-ray and, apart from the presence of AF, a normal ECG (ie no indication of prior myocardial infarction or left ventricular hypertrophy)
- normal atria, valves and left ventricular size and function by echocardiography.

1.4 Prognosis

The adverse effects of AF are the result of haemodynamic changes related to the rapid and/or irregular heart rhythm, and thromboembolic complications related to a prothrombotic state associated with the arrhythmia. AF is associated with an odds ratio for death of 1.5 for men and 1.9 in women, which does not vary by age, but most of the excess of mortality attributed to AF occurs early after diagnosis of AF.[11]

Onset of AF can result in a reduction in cardiac output of up to 10–20% regardless of ventricular rate. The presence of fast ventricular rates can push an already compromised ventricle into heart failure. An uncontrolled AF rate may even precipitate critical cardiac ischaemia.

AF is associated with a prothrombotic state – intra-atrial blood stasis, structural heart disease or blood vessel abnormalities and abnormal platelets and haemostasis – leading to a predisposition to thrombus formation (thrombogenesis).[12] This prothrombotic state predisposes to stroke and thromboembolism in AF, with an approximately five-fold greater risk than that of people without AF.[13] In stroke patients, concurrent AF is associated with greater disability, longer in-hospital patient stay and lower rate of discharge to own home. The incidence of strokes attributable to AF increases from 1.5% at age 50–59 years to 23.5% at age 80–89 years.[14]

In terms of the direct effects on patients' quality of life, AF can also result in reduced exercise tolerance, as well as impairment in cognitive function.

1.5 Guideline structure

Chapter 2 details the methodology used in the construction of this guideline. This includes the protocols used for the searching, selection and appraisal of evidence, and the grading of recommendations according to the strength of their supporting evidence.

The remaining chapters deal with specific issues in the diagnosis and treatment of AF. For ease of reference, wherever possible different forms of AF have been considered in distinct chapters, as follows:

- persistent AF (Chapter 6)
- permanent AF (Chapter 7)
- paroxysmal AF (Chapter 8)
- acute-onset AF (Chapter 9)
- postoperative AF (Chapter 10).

Most of these chapters include an easy-to-use flowchart showing the recommendations relevant to the particular form of AF.

There are also chapters dedicated to the identification and diagnosis of AF, as well as to antithrombotic therapy and cardioversion.

1.6 How to use this guideline

- The purpose of this guideline is to support clinical judgement, not to replace it. This means the treating clinician should:
  - take into consideration any contraindications in deciding whether or not to administer any treatment recommended by this guideline
  - consider the appropriateness of any recommended treatment for a particular patient in terms of the patient's relevant clinical and non-clinical characteristics.
- Wherever possible, before administering or changing any treatment the treating clinician should follow good practice in terms of:
  - discussing with the patient why the treatment is being offered and what health outcomes are anticipated
  - highlighting any possible adverse events or side effects that have been associated with the treatment
  - obtaining explicit consent for the treatment.
- For those recommendations involving pharmacological treatment, the most recent edition of the *British National Formulary* (**www.bnf.org.uk**) should be followed for the determination of:
  - indications
  - drug dosage
  - method and route of administration
  - contraindications
  - supervision and monitoring
  - product characteristics.

  Exceptions to the above are cases where guidance is provided within the recommendation itself.
- The guideline will normally only make drug recommendations that fall within licensed indications. If a drug is recommended outside of its licensed indication this will be made clear in the guideline (see Appendix D).

2 Methodology

2.1 About the guideline

2.1.1 Aim

With this document the National Collaborating Centre for Chronic Conditions (NCC-CC) has aimed to provide a user-friendly, clinical, evidence-based guideline for the National Health Service (NHS) in England and Wales that:

- offers best clinical advice for AF
- is based on best published evidence and expert consensus
- takes into account patient choice and informed decision-making
- defines the major components of NHS care provision for AF
- indicates areas suitable for clinical audit
- details areas of uncertainty or controversy requiring further research
- provides a choice of guideline versions for differing audiences.

2.1.2 Scope

The guideline was developed in accordance with a scope which detailed the remit of the guideline originating from the Department of Health and specified those aspects of AF to be included and excluded. Prior to the commencement of the guideline development, the scope was subjected to stakeholder consultation in accordance with processes established by the National Institute for Health and Clinical Excellence (NICE).[15] The full scope is shown in Appendix G.

This guideline sets out best practice for the diagnosis and treatment of AF in both primary and secondary care. It also considers which patients benefit from referral for specialist investigations or procedures and offers guidance in this respect.

Most of the recommendations made in this guideline apply to both AF and the closely related arrhythmia atrial flutter (in those cases where the two conditions are indistinguishable). Exceptions are recommendations concerning diagnosis and opportunistic case-detection, which apply only to AF.

Although the guideline covers the majority of AF cases, it does not consider those patients for whom there is a need for highly specialised clinical input. In particular, it does not consider paediatric cases of AF, or gestational AF.

With the exception of the use of prophylactic drugs to prevent postoperative AF and the use of typical symptoms in guiding opportunistic case-detection, the guideline will not consider issues of public health screening or interventions.

The guideline does not make any recommendations in terms of health service delivery for AF treatment, although it does consider the effectiveness of different service models. In particular, it considers the effectiveness of self-management of anticoagulation compared to clinic-based management, and the use of pill-in-the-pocket therapy compared with continuous drug therapy or emergency department treatment.

2.1.3 Audience

The guideline is intended for use by the following people or organisations:

- all healthcare professionals
- people with AF and their carers
- patient support groups
- commissioning organisations
- service providers.

2.1.4 Patient involvement

The NCC-CC was keen to ensure that the views and preferences of people with AF and their carers informed all stages of the guideline. This was achieved by:

- having a person with AF and a representative of a user organisation on the Guideline Development Group (GDG)
- consulting the Patient Information Unit (PIU) housed within NICE during the pre-development (scoping) and final validation stages of the guideline.

2.1.5 Guideline limitations

Limitations to the guideline are as follows:

- Clinical guidelines usually do not cover issues of service delivery, organisation or provision (unless specified in the remit from the Department of Health).
- NICE is primarily concerned with health services and so recommendations are not provided for social services and the voluntary sector. However, the guideline may address important issues in how NHS clinicians interface with these other sectors.
- Generally the guideline does not cover rare, complex, complicated or unusual conditions.

2.2 Guideline development

2.2.1 Background

The development of this evidence-based clinical guideline draws upon the methods described by the NICE *Guideline development methods* manual[16] (**www.nice.org.uk/page.aspx?o=201982**) and the methodology pack[17] specifically developed by the National Collaborating Centre for Chronic Conditions (NCC-CC) for each chronic condition guideline (**www.rcplondon.ac.uk/college/ceeu/ncccc_index.htm**). The developers' roles and remit are summarised below.

▷ National Collaborating Centre for Chronic Conditions

The NCC-CC was set up in 2001 and is housed within the Royal College of Physicians. The NCC-CC undertakes commissions received from the National Institute for Health and Clinical Excellence (NICE).

A multiprofessional partners' board inclusive of patient groups and NHS management governs the NCC-CC.

▷ NCC-CC technical team

The technical team met approximately two weeks before each GDG meeting and comprised:

- the GDG group leader
- the GDG clinical advisor
- an information scientist
- a research fellow
- a health economist
- a project manager
- administrative personnel.

▷ Guideline Development Group[16]

The GDG met 14 times between July 2004 and December 2005 and comprised a multidisciplinary team of professionals, service users (people with AF or carers), and user organisation representatives who were supported by the technical team.

The GDG membership details, including patient representation and professional groups, are listed at the front of this guideline (see pages vi–vii).

Members of the GDG declared any interests in accordance with the NICE technical manual.[16] A register is available from the NCC-CC for inspection upon request (**ncc-cc@rcplondon.ac.uk**).

▷ Sign-off workshop[17]

At the end of the guideline development process the GDG met to review and agree the guideline recommendations.

2.2.2 The guideline development process

There are ten basic steps in the process of producing a guideline.

▷ Step 1: Developing evidence-based questions

The technical team drafted a series of clinical questions that covered the guideline scope. The GDG and Project Executive refined and approved these questions, shown in Appendix C.

▷ Step 2: Systematically searching for the evidence

The information scientist developed a search strategy for each question. Key words for the search were identified by the GDG. In addition, the health economist searched for additional papers to inform detailed health economic work (eg modelling). Papers that were published or accepted for publication in peer-reviewed journals were considered as evidence by the GDG. Conference paper abstracts and non-English language papers were excluded from the searches.

Each clinical question dictated the appropriate study design that was prioritised in the search strategy but the strategy was not limited solely to these study types. The research fellow or health economist identified titles and abstracts from the search results that appeared to be

relevant to the question. Exclusion lists were generated for each question together with the rationale for the exclusion. The exclusion lists were presented to the GDG. Full papers were obtained where relevant. See Appendix C for literature search details.

▷ Step 3: Critically appraising the evidence

The research fellow or health economist, as appropriate, critically appraised the full papers. In general no formal contact was made with authors but there were *ad hoc* occasions when this was required in order to clarify specific details. Critical appraisal checklists were compiled for each full paper. One research fellow undertook the critical appraisal and data extraction. The evidence was considered carefully by the GDG for accuracy and completeness.

All procedures are fully compliant with:

- NICE methodology as detailed in the *Guideline development methods – information for National Collaborating Centres and guideline developers* manual.[16]
- NCC-CC quality assurance document and systematic review chart, available at **www.rcplondon.ac.uk/college/ceeu/ncccc_index.htm**

▷ Step 4: Incorporating health economic evidence

There were constraints in the health economic resources and so the following approach was agreed for this guideline. Health economics was incorporated alongside the clinical questions.

- Searches in relevant databases were done by the information scientist using economic filters on the related clinical questions.
- No study design criteria were imposed a priori, ie the searches were not limited to randomised control trials (RCTs) or formal economic evaluations.
- Titles and abstracts identified in the economic searches were reviewed by the health economist and full papers were obtained once they met the inclusion/exclusion criteria.
- The full papers were critically appraised by the health economist and the relevant data were presented to the GDG.

Cost-effectiveness evidence from the UK was preferred, but all relevant evidence was considered, including non-UK studies.

The GDG identified areas for additional economic work. Five key areas were identified and three were given priority. The GDG agreed on the model structures. The health economist performed supplemental literature searches using key search terms in Medline and an Internet search engine to obtain additional information for modelling. None of the identified priority areas were modelled for various reasons (see Appendix A for details).

▷ Step 5: Distilling and synthesising the evidence and developing recommendations

The evidence from each full paper was distilled into an evidence table and synthesised into evidence statements before being presented to the GDG. This evidence was then reviewed by the GDG and used as a basis upon which to formulate recommendations.[2]

▷ Step 6: Grading the evidence statements and recommendations

The criteria for grading evidence and classifying recommendations are shown in Table 2.1.

Evidence tables are available at
www.rcplondon.ac.uk/pubs/online_home.htm

Table 2.1 Criteria for grading evidence and recommendations. Note that diagnostic study levels of evidence and classification of recommendations were also included.[16]

Levels of evidence		Classification of recommendations	
Level	**Type of evidence**	**Class**	**Evidence**
1++	High-quality meta-analysis (MA), systematic reviews (SR) of randomised controlled trials (RCTs), or RCTs with a very low risk of bias.	A	Level 1++ and directly applicable to the target population *or* level 1+ and directly applicable to the target population **AND** consistency of results. Evidence from NICE technology appraisal.
1+	Well-conducted MA, SR or RCTs, or RCTs with a low risk of bias.		
1–	MA, SR of RCTs, or RCTs with a high risk of bias.	Not used as a basis for making a recommendation.	
2++	High-quality SR of case-control or cohort studies. High-quality case-control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal.	B	Level 2++, directly applicable to the target population and demonstrating overall consistency of results. *or* extrapolated evidence from 1++ or 1+.
2+	Well-conducted case-control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal.		
2–	Case-control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal	Not used as a basis for making a recommendation.	
3	Non-analytic studies (for example case reports, case series).	C	Level 2+, directly applicable to the target population and demonstrating overall consistency of results *or* extrapolated evidence from 2++.
4	Expert opinion, formal consensus.	D	Level 3 or 4 *or* extrapolated from 2+ *or* formal consensus.
		D (GPP)	A good practice point (GPP) is a recommendation based on the experience of the GDG.

Diagnostic study level of evidence and classification of recommendation was also included.[2]

▷ Step 7: Agreeing the recommendations

The sign-off workshop employed formal consensus techniques to:

- ensure that the recommendations reflected the evidence base
- approve recommendations based on lesser evidence or extrapolations from other situations
- reach consensus recommendations where the evidence was inadequate
- debate areas of disagreement and finalise recommendations.

The sign-off workshop also reached agreement on the following:

- five priorities for implementation
- five key research recommendations
- algorithms.

In prioritising key recommendations for implementation, the sign-off workshop also took into account the following criteria:

- high clinical impact
- high impact on reducing variation
- more efficient use of NHS resources
- allowing the patient to reach critical points in the care pathway more quickly.

The audit criteria provide suggestions of areas for audit in line with the key recommendations for implementation.[16]

▷ Step 8: Structure of the guideline

The guideline is divided into sections for ease of reading. For most sections the layout is similar and is described below:

- The *clinical introduction* sets a succinct background and describes the current clinical context.
- The *methodological introduction* describes any issues or limitations that were apparent when reading the evidence base.
- *Evidence statements* provide a synthesis of the evidence base and usually describe what the evidence showed in relation to the outcomes of interest.
- *Health economics* presents, where appropriate, an overview of the cost effectiveness of the evidence base.
- *From evidence to recommendations* highlights the debate of the GDG. This section sets out the GDG decision-making rationale providing a clear and explicit audit trail from the evidence to the evolution of the recommendations.
- The *recommendations* section provides stand-alone, action-orientated recommendations.
- *Evidence tables* are not published as part of the full guideline but are available online at **www.rcplondon.ac.uk/pubs/books/af/** These describe comprehensive details of the primary evidence that was considered during the writing of each section.

▷ Step 9: Writing the guideline

The first draft version of the guideline was drawn up by the technical team in accordance with the decision of the GDG. The guideline was then submitted for two formal rounds of public and stakeholder consultation prior to publication.[16] The registered stakeholders for this guideline are detailed in Appendix F. Editorial responsibility for the full guideline rests with the GDG.

Table 2.2 describes the versions of the guideline that are available.

Table 2.2 Versions of this guideline

Full version	Details the recommendations. The supporting evidence base and the expert considerations of the GDG. Available at **www.rcplondon.ac.uk/pubs/online_home.htm**
NICE version	Documents the recommendations without any supporting evidence. Available at **www.nice.org.uk/page.aspx?o=guidelines.completed**
Quick reference guide	An abridged version. Available at **www.nice.org.uk/page.aspx?o=guidelines.completed**
Information for the public	A lay version of the guideline recommendations. Available at **www.nice.org.uk/page.aspx?o=guidelines.completed**

▷ Step 10: Updating the guideline

Literature searches were repeated for all of the evidence-based questions at the end of the GDG development process allowing any relevant papers published up until 30 June 2006 to be considered. Future guideline updates will consider evidence published after this cut-off date.

Two years after publication of the guideline, NICE will commission a National Collaborating Centre to determine whether the evidence base has progressed significantly to alter the guideline recommendations and warrant an early update. If not, the guideline will be updated approximately 4 years after publication.[16]

2.3 Disclaimer

Healthcare providers need to use clinical judgement, knowledge and expertise when deciding whether it is appropriate to apply guidelines. The recommendations cited here are a guide and may not be appropriate for use in all situations. The decision to adopt any of the recommendations cited here must be made by the practitioner in light of individual patient circumstances, the wishes of the patient, clinical expertise and resources.

The NCC-CC disclaims any responsibility for damages arising out of the use or non-use of these guidelines and the literature used in support of these guidelines.

2.4 Funding

The National Collaborating Centre for Chronic Conditions was commissioned by the National Institute for Health and Clinical Excellence to undertake the work on this guideline.

3 Key messages of the guideline

3.1 Priorities for implementation

The following five recommendations have been identified by the GDG as priorities for implementation:

1. An electrocardiogram (ECG) should be performed in all patients, whether symptomatic or not, in whom AF is suspected because an irregular pulse has been detected.
2. As some patients with persistent AF will satisfy criteria for either an initial rate-control or rhythm-control strategy (for example, aged over 65 but also symptomatic):
   - the indications for each option should not be regarded as mutually exclusive and the potential advantages and disadvantages of each strategy should be explained to patients before agreeing which to adopt
   - any comorbidities that might indicate one approach rather than the other should be taken into account
   - irrespective of whether a rate-control or a rhythm-control strategy is adopted in patients with persistent AF, appropriate antithrombotic therapy should be used.
3. In patients with permanent AF, who need treatment for rate control:
   - beta-blockers or rate-limiting calcium antagonists should be the preferred initial monotherapy in all patients
   - digoxin should only be considered as monotherapy in predominately sedentary patients.
4. In patients with newly diagnosed AF for whom antithrombotic therapy is indicated (see section 11.6), such treatment should be initiated with minimal delay after the appropriate management of comorbidities.
5. The stroke risk stratification algorithm (Figure 11.1) should be used in patients with AF to assess their risk of stroke and thromboembolism, and appropriate thromboprophylaxis given.

Each of these recommendations highlights areas of current clinical practice that the GDG believe would particularly benefit from guidance. Compliance with each of these key priority areas may be audited according to the corresponding audit criteria below.

Although items 4 and 5 may be audited using the same criteria, they address two different issues relating to antithrombotic therapy in AF. The first addresses the need for appropriate antithrombotic therapy in patients with AF upon initial diagnosis; the second addresses the need for a formal assessment of stroke risk and the administration of appropriate antithrombotic therapy based on that assessment.

3.2 AF care pathway

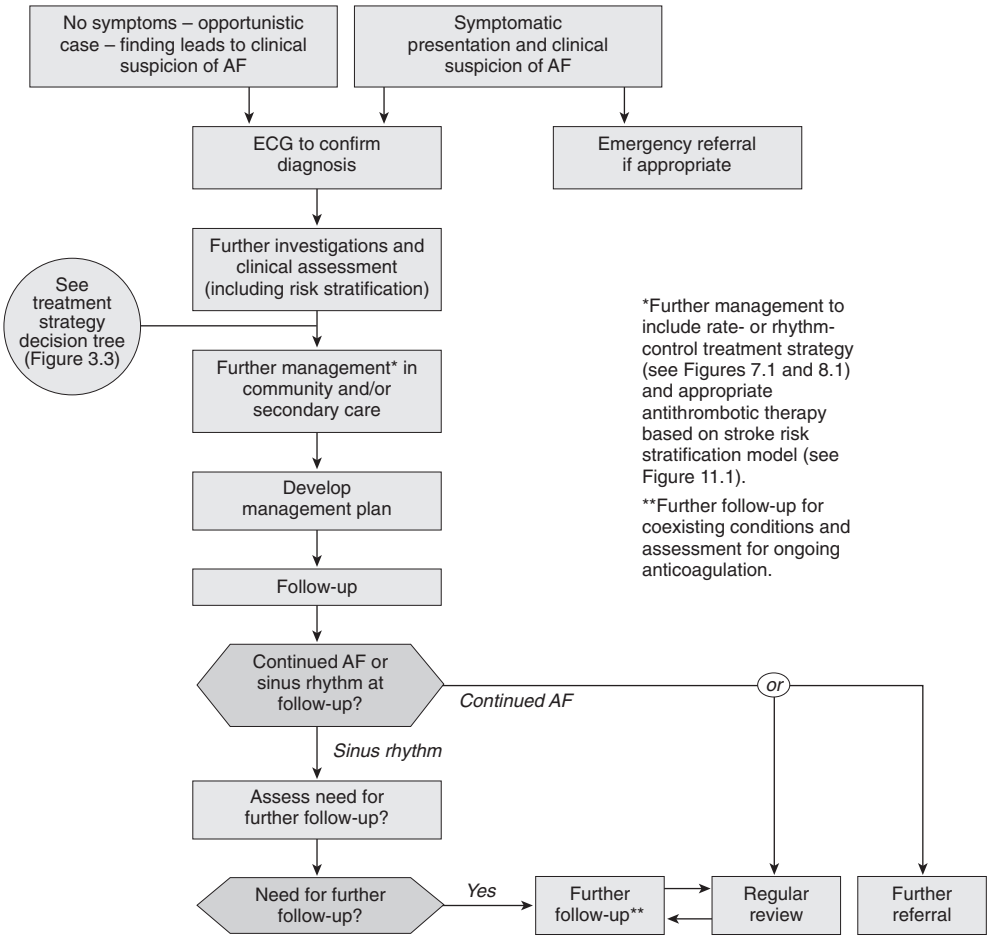


Figure 3.1 AF care pathway

3.3 Treatment strategy decision tree

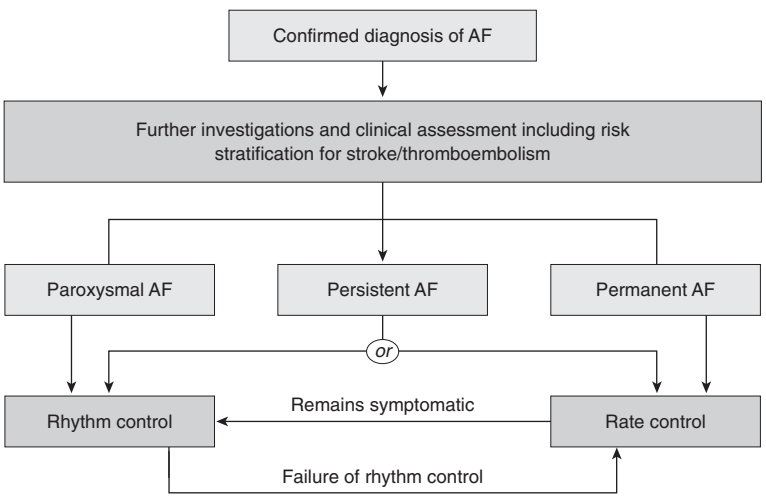


Figure 3.2 Treatment strategy decision tree

3.4 Audit criteria

Table 3.1 lists the audit criteria identified to evaluate the impact of the implementation of the five key priority areas detailed above on clinical practice and health outcomes.

Table 3.1 Audit criteria for the key priorities for implementation

Criterion	Exception	Definition of terms
1. All people presenting to primary or secondary care with a history of hypertension, heart failure, diabetes or stroke and noted to have an irregular pulse to be offered an ECG and any new diagnosis of AF recorded.	None.	Percentage of patient records with a new diagnosis of AF made following an ECG made on the basis of detection of an irregular pulse.
2. All AF patients in whom a rate-control or rhythm-control strategy is initiated to have their involvement in choosing a treatment strategy recorded.	Postoperative or haemodynamically unstable patients, or those otherwise not able to engage in a decision-making process.	Percentage of patient records with a record of involvement of the patient in the decision-making process.
3. All patients who are prescribed digoxin as initial monotherapy for rate control to have the reason for this prescription recorded where it is not obvious (eg sedentary patient, presence of contraindication to alternative agents).	None.	Percentage of patient records with a prescription of digoxin for initial rate-control monotherapy where the reason for digoxin prescription is: • sedentary patient • presence of contra-indications to beta-blockers or rate-limiting calcium antagonists • other reasons.
4 and 5. All patients should be assessed for risk of stroke/ thromboembolism and given thromboprophylaxis according to the stroke risk stratification algorithm (see Figure 11.1) and have this assessment and any antithrombotic therapy recorded.	Haemodynamically unstable patients or those in whom assessment is impossible or inappropriate.	Percentage of patient records with a record of risk assessment and thromboprophylaxis consistent with the stroke risk stratification algorithm.

Note: numbers correspond to the numbered list of key priorities for implementation.

3.5 Areas for future research

The GDG has identified the following five questions as key areas for further research:

▷ Cardioversion

Although cardioversion is a core treatment for many patients with AF, there is little evidence that compares the different modes (electrical and pharmacological), particularly in terms of cost effectiveness. Further, the studies that have considered the efficacy of preloading with antiarrhythmic drugs prior to electrical cardioversion have not reported long-term efficacy in maintaining sinus rhythm, or the cost effectiveness of this strategy.

- In patients scheduled for elective cardioversion what is the optimal form of cardioversion, in terms of the pre-cardioversion use of antiarrhythmic drugs, the mode of cardioversion (electrical or pharmacological), the cost effectiveness of each procedure and the impact on quality of life?

▷ Echocardiography

Echocardiography allows cardiac abnormalities such as left ventricular impairment to be diagnosed earlier than would be possible from signs and symptoms alone. However, no study has addressed the issue of whether performing routine echocardiography on all newly diagnosed AF patients would be more cost effective in diagnosing and treating heart disease earlier, than performing echocardiography only on those patients in whom there is a clinical suspicion of undiagnosed heart disease.

- What is the cost effectiveness of performing a routine echocardiographic examination in all newly diagnosed AF patients, compared to only selective examination based on clinical criteria?

▷ Anticoagulation with antiplatelet therapy

In the general AF population, the evidence suggests that combined therapeutic anticoagulation with antiplatelet therapy does not reduce the incidence of stroke or thromboembolism compared with therapeutic anticoagulation alone, and it may increase the incidence of bleeding. However, it is unclear whether there are certain subgroups of patients with AF for whom the therapeutic effects of combination therapy may be greater than either monotherapy. In particular, it is unclear whether combination therapy is justified in those AF patients who have stent implantation or a history of myocardial infarction (MI).

- Is there any additional benefit, in terms of overall vascular events, from combined anticoagulation with antiplatelet therapy for any subgroups of patients with AF such as those with prior MI or stent implantation?

▷ Pill-in-the-pocket treatment

Some patients with paroxysmal AF may have paroxysms infrequently. In these patients, the continuous use of antiarrhythmic drugs to suppress paroxysms may not be justified relative to their toxicity. No study has been undertaken in such patients in a UK population to determine whether a pill-in-the-pocket treatment strategy would be clinically or cost effective

compared with either the emergency department administration of treatment or continuous antiarrhythmic drug therapy.

- What is the clinical and cost effectiveness of pill-in-the-pocket treatment for those with paroxysmal AF compared with hospital-based administration or continuous antiarrhythmic therapy?

▷ Anticoagulation in paroxysmal AF

The frequency of paroxysms in patients with paroxysmal AF varies widely between patients. It remains unclear, however, whether the risk of stroke or thromboembolism varies between those with only infrequent paroxysms and those with more frequent paroxysms. It is also unclear whether, if the risk of stroke or thromboembolism is reduced in those with infrequent paroxysms, the use of anticoagulation is justified in such a low-risk group.

- What is the optimal anticoagulation strategy for those patients with paroxysmal AF who have infrequent paroxysms, and those who have more frequent paroxysms?

THE GUIDELINE

4 Identification and diagnosis

4.1 Presenting symptoms/pulse palpitation

AF can present in the setting of a wide variety of cardiac and non-cardiac conditions, it is often asymptomatic and can present with vague non-specific symptoms. Too often, AF is only detected after the patient presents with serious complications of AF, such as a stroke, thromboembolism or heart failure. The initial diagnosis of AF depends on associating symptoms such as breathlessness, dyspnoea, palpitations, syncope/dizziness or chest discomfort with AF.

Most of the data on presentation of AF patients have been based on white Caucasian populations, and limited data are available in relation to ethnicity and AF.[18] Furthermore, there may be important differences between hospital-based cohorts compared with community or population-based studies, as many do not present to hospital care, and if they do, it is often in the context of associated comorbidity such as ischaemic heart disease or heart failure. Indeed, many patients with AF in general practice remain asymptomatic. However, as AF commonly occurs in association with risk factors, such as hypertension, diabetes and ischaemic heart disease, opportunistic assessment of such patients for the presence of AF may be prudent, especially since such patients are frequently seen for check-ups in primary care.

While general population screening is beyond the scope of this guideline, targeted/opportunistic screening of symptomatic patients or those with risk factors may allow identification of AF patients. One recent study[19,20] aims to determine the baseline prevalence and the incidence of AF based on a variety of screening strategies and in doing so to evaluate the incremental cost effectiveness of different screening strategies, including targeted or whole population screening, compared with routine clinical practice, for detection of AF in people aged 65 and over. This study[20] – whose publication date fell outside of the date limits of the systematic literature search – reported that the baseline prevalence of AF in subjects older than 65 was 7.2%, with a higher prevalence in men (7.8%) and among patients aged 75 or older (10.3%), and indicated that the only strategy that improved on routine practice was opportunistic screening.

4.1.1 Methodological introduction

The results of nine studies are included in this report. Seven studies were critically appraised.[7,8,21–25] Of these, none reported the frequency of presenting symptoms in primary care in a UK (or other) population. Patients presenting to secondary care generally present with more severe symptoms. The studies:

- did not use a consistent terminology to classify AF symptoms. 'Dizziness' was also referred to as 'near syncope'[21] and 'chest pain' was also referred to as 'chest discomfort'[22]
- were single-centre studies
- had a variable proportion of patients presenting with *de novo* AF versus those with a previous history of AF.

Three of the appraised studies were not based on UK populations.[21–23] One study[8] reported the frequency of presenting symptoms between ethnic groups (white, Asian and black groups) but the numbers were too small to perform statistical comparisons.

4.1.2 Evidence statements

Dyspnoea, chest pain and palpitations were found to be the most common presenting symptoms in emergency admissions with newly diagnosed or previously diagnosed AF in the UK[7,8] or USA.[26–28]

Table 4.1 Presenting symptoms associated with emergency AF admissions

Study	N	Dyspnoea %	Chest pain %	Palpitations %	Dizziness /syncope %
Zarifis et al[8]	245	47.1	19.9	16.2	16.2
Lip et al[7]	170	51.8	34.1	25.9	18.8
Michael et al[26]	289	7	10	78	3
Burton et al[27]	266	12	24	40	9

Similar results were found in patients with chronic[23] (more than 7 days since onset of symptoms) and lone AF.[21]

In one study[24] (N=756) dyspnoea was the most commonly reported symptom in chronic and recent-onset AF (46.8%); palpitations were the most commonly reported symptom in paroxysmal AF (79.0%).[28]

Table 4.2 Presenting symptoms between paroxysmal, chronic and recent-onset AF patients

Symptom	Total	Paroxysmal	Chronic	Recent-onset
Palpitations (%)	54.1	79	44.7	51.5
Chest pain (%)	10.1	13.2	8.2	11
Dyspnoea (%)	44.4	22.8	46.8	58
Syncope/dizziness (%)	10.4	17.4	8	9.5
Fatigue (%)	14.3	12.6	13.1	18
Other (%)	0.9	0	1.8	0
None (%)	11.4	5.4	16.2	7

In two studies, stroke was reported as a presenting symptom of AF at rates of 5.1% and 3.2% respectively[22,25] and occurred at a rate of 12.7% in a study population combining both new-onset and previously diagnosed AF.[8,28]

4.1.3 From evidence to recommendations

Those with undiagnosed AF can receive treatment sooner if an opportunistic case finding is undertaken using manual pulse palpation in those presenting with symptoms commonly associated with AF. It was therefore considered good practice to check the blood pressure and pulse (manually) in all patients who present with breathlessness, dyspnoea, palpitations, syncope/dizziness or chest discomfort.

Many patients presenting with stroke are also found to be in AF, indicating a missed opportunity to diagnose the pre-existing AF and administer appropriate antithrombotic therapy.

RECOMMENDATION

R1 In patients presenting with any of the following:

- breathlessness/dyspnoea
- palpitations
- syncope/dizziness
- chest discomfort
- stroke/TIA

manual pulse palpation should be performed to assess for the presence of an irregular pulse that may indicate underlying AF. **C**

4.2 Electrocardiography

As with many chronic disorders, AF may be symptomatic or asymptomatic, and episodes of either can occur in the same patient.

Most symptomatic patients with AF present with symptoms related to the arrhythmia. However, such patients can have a wide variety of other cardio-respiratory presenting symptoms and clinical features[7,24] (see section 4.1).

Many patients with AF are asymptomatic and are picked up in general practice. One study[2] found that a third of AF patients had not had hospital contact for symptoms related to AF. Asymptomatic AF can be discovered incidentally during clinical examination by cardiac auscultation, 12-lead ECG recording, or 24-hour Holter recording that may have been performed for unrelated reasons.

The patient may also have presented with associated medical problems, such as heart failure, stroke or thromboembolism, and coincidental AF is detected. The duration of AF may be unknown in such patients, and whether AF was the cause or effect of the acute problem (eg stroke or heart failure) may be uncertain.

Many patients with risk factors for developing AF, such as hypertension and diabetes, do attend regular checkups with their GPs. In these cases then, there is the possibility of opportunistic case finding.

4.2.1 Methodological introduction

The two studies performed in UK primary care[29,30] evaluated the finding of an irregular pulse as a screening test for AF. Both studies included populations of over 65-year-olds and confirmed the diagnosis of AF by ECG.

4.2.2 Evidence statements

In one study,[29] the diagnostic accuracy of pulse palpation was compared between different age and gender groups in a primary care population aged 65 or over, and is summarised in Table 4.3. (II)

Table 4.3 Diagnostic accuracy of pulse palpitation between different age and gender groups

	Women 75+	Women 65–74	Men 75+	Men 65–74
Sensitivity	93 (66 to 100)	100 (16 to 100)	95 (75 to 100)	100 (54 to 100)
Specificity	71 (66 to 77)	86 (81 to 91)	71 (65 to 77)	79 (74 to 84)
PPV	14 (7 to 22)	8 (1 to 25)	23 (14 to 34)	12 (4 to 23)
NPV	99 (97 to 100)	100 (98 to 100)	99 (96 to 100)	100 (98 to 100)

All values are percentages with 95% confidence intervals.

One study[30] measured the diagnostic accuracy of three different methods of nurse-based screening for AF based on the presence of either continuous or intermittent pulse irregularities over a minimum of 20 seconds in a population aged over 65. The results are as shown in Table 4.4. (II)

Table 4.4 Comparison of the diagnostic accuracy of three different methods of pulse palpation to screen for the presence of AF

	Method 1	Method 2	Method 3
Sensitivity	91 (82 to 97)	72 (59 to 82)	54 (41 to 66)
Specificity	74 (72 to 77)	94 (93 to 96)	98 (97 to 99)
PPV	19 (15 to 23)	44 (35 to 54)	61 (47 to 73)
NPV	99 (98 to 100)	98 (97 to 99)	97 (96 to 98)

All values are percentages with 95% confidence intervals. Method 1: diagnostic accuracy based on the detection of any pulse irregularity; method 2: diagnostic accuracy based on the detection of frequent or continuous irregularities; method 3: diagnostic accuracy based on the detection of only continuous irregularities.

4.2.3 From evidence to recommendations

An irregular pulse was found to be sensitive to the presence of AF.[29] The positive predictive value was greater in those over 75 years old, as the prevalence of AF is known to be higher in this population. The negative predictive value of a regular pulse (>96%) was also emphasised. The results of a second study[30] suggested it would be prudent to consider any pulse irregularity as requiring further investigation to determine whether AF is present.

One study[19,20] whose publication date fell outside of the date limits of the systematic literature search confirmed the above results in an elderly UK population (over 65 years old). The study also showed that opportunistic case-detection for AF is a more cost-effective strategy than systematic screening and is associated with fewer ischaemic strokes and a greater proportion of diagnosed AF cases.

The evidence did not consider clinical indicators other than an irregular pulse and it was agreed that where there were other clinical indicators suggestive of AF, an ECG should still be performed. Nonetheless, the majority of patients presenting with AF will have an irregular pulse that may occur in the absence of any symptoms, and it is unlikely that AF will be present if the pulse is normal.

The diagnosis of AF does not require a 12-lead ECG recording. In the case of atrial flutter, however, a 12-lead ECG may be necessary, and may also occur in the presence of a regular pulse. The recommendation made below therefore applies only to AF case detection.

RECOMMENDATION

R2 An electrocardiogram (ECG) should be performed in all patients, whether symptomatic or not, in whom AF is suspected because an irregular pulse has been detected. **B(DS)**

4.3 Ambulatory ECG recording

Many patients with intermittent AF have asymptomatic paroxysms. In one study[31] it was estimated that only 1 in 12 paroxysms are symptomatic. Nonetheless, these patients remain at risk of complications associated with AF.

In patients with daily paroxysms, clinical practice is to perform a 24-hour Holter monitor, but this is less useful in patients who get paroxysms at intervals of more than 24 hours. In the latter category of patients, event ECGs (including transtelephonic monitors ('cardiomemos') and some implanted systems) are commonly used to detect/diagnose AF.

4.3.1 Methodological introduction

Ambulatory-ECG was defined as any electrocardiographic recording device that continuously recorded cardiac electrical activity while the patient was able to move around relatively freely without hindrance. Ambulatory-ECG included both Holter-monitoring and implanted recorders such as programmed pacemakers that generated a continuous ECG recording.

Event-ECG was defined as any electrocardiographic recording device which recorded only particular events, identified either automatically by a software program to detect arrhythmic episodes or by the onset of symptoms (when the patient manually switches on the device for the duration of the symptomatic episode), or a combination of the two. As with ambulatory-ECGs, event-ECGs record cardiac electrical activity while the patient is able to move around relatively freely without hindrance.

Studies were included if the sample population was reported to be patients with either suspected AF or suspected atrial arrhythmia. No studies compared the diagnostic accuracy of event-ECG devices with ambulatory-ECG devices over the same duration.

4.3.2 Evidence statements

One cross-over study[32] of patients suspected of atrial arrhythmia based on palpitations compared a patient-triggered event recorder over a mean period of 70 hours with a 48-hour Holter monitor. The event recorder detected proportionately more symptomatic episodes than the Holter monitor (67% of recorded episodes associated with symptoms versus 35% respectively; $p<0.001$) **(1b)**. Similarly, the event recorder yielded more arrhythmia diagnoses (19% versus 0% respectively; $p<0.005$). **(1b)**

In one study[33] which compared 24-hour Holter monitoring with automatic and patient triggered event recording (each over 30 days), the automatically-triggered event recorder had a higher diagnostic yield than the patient-triggered event recorder, which in turn had a higher diagnostic yield for diagnoses of AF than the Holter monitor (24%, 13% and 5% respectively). The automatically triggered event recorder was also more effective than the patient-triggered event recorder in detecting asymptomatic episodes of AF (52 events versus 1 event respectively).[34]

In one study[35] of 139 patients admitted with symptoms of acute stroke or transient ischaemic attack (TIA) who were ECG-negative for AF/flutter, seven (5%) were picked up in a second round of monitoring using a 24-hour Holter monitor. A further five (6%) patients were diagnosed with AF/flutter in a third round of monitoring using a 7-day event recorder (with both patient and automated triggering).[34]

4.3.3 From evidence to recommendations

No studies were found to compare the positive diagnostic yield per unit time between an ambulatory-ECG diagnostic tool and an event-ECG tool where the recordings were interpreted in a comparable manner.

One study[35] found that the use of event-ECG detected cases of AF remained undetected by both non-ambulatory and ambulatory-ECG. In addition, the study found that the use of ambulatory-ECG detected cases of AF remained undetected by non-ambulatory-ECG.

Also, a strategy of event-ECG diagnosis detected more symptomatic episodes and more positive diagnoses of atrial arrhythmias, including AF, than the strategy of ambulatory-ECG diagnosis.

RECOMMENDATION

R3 In patients with suspected paroxysmal AF undetected by standard ECG recording:

- a 24-hour ambulatory ECG monitor should be used in those with suspected asymptomatic episodes or symptomatic episodes less than 24 hours apart
- an event recorder ECG should be used in those with symptomatic episodes more than 24 hours apart. **B(DS)**

4.4 Echocardiography

Although most cardiologists will perform a transthoracic echocardiogram (TTE) on patients with AF referred to cardiology clinics,[36] echocardiography is not undertaken on all patients seen in primary or non-specialist secondary care.[2,7,8,37]

Regarding the use of echocardiography to identify stroke risk factors, although most stroke risk stratification criteria (see Appendix A) lay emphasis on clinical risk factors, there is a perception that TTE is mandatory to decide on antithrombotic therapy. In one study[38] echocardiography revealed cardiac abnormalities in many AF patients, although most had other clinical risk factors for thromboembolism and often echocardiography did not alter the management decision.

In clinical practice echocardiography has also been used to assess the risk of recurrent AF post cardioversion, as well as to assess the risk of developing postoperative AF. Finally, transoesophageal echocardiography (TOE) has been used to guide cardioversion (TOE-guided cardioversion (see section 5.4)), but this is a specialist investigation. TOE can also be used by specialists to assess the risk of stroke and thromboembolism.[39]

4.4.1 Methodological introduction

The results of 29 studies were included in this report. Studies were considered for inclusion if echocardiographic (TTE or TOE) variables were stratified into normal and abnormal ranges and tested, alongside clinical variables, as independent risk factors for clinically defined outcomes.

The clinical outcomes considered were:

- AF pathophysiology
- the recurrence of AF following successful cardioversion
- stroke or thromboembolism
- vascular death.

The presence of intracardiac thrombus was not considered as an echocardiographic measure of structural or functional heart disease. Rather, it was considered as a consequence of the disease.

4.4.2 Evidence statements

▷ AF pathophysiology

One study[40] found a left atrial diameter greater than 50 mm to be the only significant independent echocardiographic predictor for the development of a greater AF burden, in terms of the amount of time spent in AF or the frequency of AF episodes ($p<0.05$). (2++)

One study[41] found that in patients developing AF, it is more likely to lead to haemodynamic instability in patients with an atrial filling fraction less than 40% (RR 2.7; p<0.0001), or left-ventricular dysfunction (p<0.03) during sinus rhythm. (2+)

▷ Post-cardioversion recurrence

Left atrial haemodynamic dysfunction, as measured by a left atrial appendage velocity (LAA-V) greater than 40 cm/sec, has been found to be a significant independent predictor of maintained sinus rhythm following cardioversion in one study[42] (OR 5.2, 95% CI 2.7 to 10; p<0.0001). In another study,[43] a ratio of left atrial appendage area (LAA-V) over the left atrial area (LA area) greater than 0.009 was found to be an independent predictor of maintained sinus rhythm (OR 6.4; 95% CI 1.9 to 2.4; p=0.004). (2+)

Left atrial haemodynamic dysfunction, as measured by the presence of spontaneous echo contrast (SEC) in the left atrium, has not been found to be an independent predictor of sinus rhythm maintenance following cardioversion.[42,44] (2++)

Based on the results of four studies,[42,45–47] left atrial diameter is not an independent predictor of sinus rhythm maintenance following cardioversion (2+). However, two studies[44,48] did find a left atrial diameter of less than 45 mm (p=0.02) or less than 41 mm (p=0.008) to be an independent predictor. (2++)

One study,[45] while not finding left atrial diameter to be an independent predictor of sinus rhythm maintenance following cardioversion, did find a right atrial diameter of less than 37 mm to be an independent predictor (OR 5.9; 95% CI 1.4 to 25; p<0.02). (2+)

The presence of moderate or severe heart failure (NYHA>1) has been found to be an independent predictor of AF recurrence following cardioversion in one study[49] (p<0.0005) (2++). Another study,[46] found no such relationship between left ventricular dysfunction, when measured as either left ventricular end diastolic diameter (LVEDD) or left ventricular end systolic diameter (LVESD), and sinus rhythm maintenance. (2+)

One study[42] did not find the presence of mitral regurgitation to be an independent predictor AF recurrence following cardioversion (2+). Another study[50] found the presence of mitral annular abnormalities to be able to effectively predict the recurrence of AF at 12 months following cardioversion (positive predictive value (PPV) 79%, negative predictive value (NPV) 85%). (2+)

▷ Stroke or thromboembolism

Two studies[51,52] did not find aortic stenosis to be an independent predictor of stroke or thromboembolism. (2+)

One study[53] found the presence of complex aortic plaque to be an independent predictor of stroke in those over 70 years (OR 4.0, 95% CI 1.1 to 14; p=0.03). The same study did not find the same result in those under 70. (2++)

Based on the results of four studies,[51,53–55] it is unclear whether left atrial haemodynamic dysfunction, as measured by the presence of SEC, is an independent predictor of stroke or thromboembolism. (2++)

Based on the results of two studies,[55,56] left atrial haemodynamic dysfunction, as measured by LAA-V less than 20 cm/sec, is an independent predictor of stroke or thromboembolism (2+). Another study[53] found a similar result in those under 70 years, but not in those over 70 years. (2++)

Based on the results of six studies,[52,54,57–60] it is unclear whether an enlarged left atrium, measured either in terms of area or diameter, is an independent predictor of stroke or thromboembolism. (2+)

Based on the results of three studies,[57,61,62] (echocardiographically detected) left ventricular dysfunction is an independent predictor of stroke or thromboembolism: (2++)

- RR = 2.5 (1.5 to 4.4), p<0.001[61]
- RR = 2.6 (1.4 to 4.9), p=0.003[57]
- OR = 1.8 (1.2 to 2.7), p=0.003.[62]

Two other studies[51,54] did not find left ventricular dysfunction to be an independent predictor. (2+)

Based on the results of two studies,[52,62] left ventricular hypertrophy is an independent predictor of stroke or thromboembolism: (2+)

- OR = 2.8 (1.8 to 4.4), p=0.0001[62]
- OR = 6.56, p<0.01.[52]

Another study[51] did not find left ventricular hypertrophy to be an independent predictor. (2+)

Two studies[51,52] did not find mitral annular calcification to be an independent predictor of stroke or thromboembolism. (2+)

A meta-analysis of three clinical trials[61] (N=1,066) failed to find either mitral valve prolapse or regurgitation (of any degree) to be independent predictors of stroke or thromboembolism (2++). However, the results of a smaller study (N=290)[59] suggested that moderate-to-severe mitral regurgitation may be an independent negative predictor of stroke (OR 0.45, 95% CI 0.20 to 0.97) in a population at a low risk of stroke. (2++)

▷ Vascular death

One study[63] found that left-atrial haemodynamic dysfunction, as indicated by spontaneous echo contrast, was an independent predictor of vascular death in patients with AF, defined as either fatal non-haemorrhagic stroke, MI, congestive heart failure (CHF), systemic embolism or sudden cardiac death syndrome (RR 7.96, 95% CI 1.6 to 41; p=0.013) (2++). The study did not find the presence of structural, valvular or aortic cardiovascular disease to be independent predictors. (2++)

4.4.3 From evidence to recommendations

Echocardiography is able to identify factors that are independently predictive of successfully maintaining sinus rhythm following cardioversion. In particular, LAA-V measured by TOE is able to independently predict the successful maintenance of sinus rhythm following cardioversion.[42,43] TOE may therefore be used, in addition to other clinical variables, in determining the appropriateness of pursuing a rhythm-control strategy involving cardioversion.

In most cases risk stratification for stroke or thromboembolism and the decision to administer appropriate thromboprophylaxis can be made on purely clinical (non-echocardiographic) characteristics. However, the stroke risk may be unclear in some patients, in which case echocardiography may be useful in refining the risk. In particular, TOE may be used to identify the presence of complex aortic plaque[53] and impaired left atrial haemodynamics.[53,55,56] TTE may be used to identify left ventricular dysfunction or hypertrophy,[57,61,62] that may not be associated with overt heart failure.[52,62]

In many patients with AF, there may be indications other than the AF itself that make it necessary to perform an echocardiographic examination. For example, it may be used to identify suspected co-present heart disease. TOE may further be used to detect cardiac abnormalities not identified through TTE (eg patent foramen ovale).

The recommendations made here are specifically for those instances where echocardiography is used in relation to AF and how the results may influence the choice of treatment strategy or antiarrhythmic drug.

RECOMMENDATIONS

R4 Transthoracic echocardiography (TTE) should be performed in patients with AF:

- for whom a baseline echocardiogram is important for long-term management, such as younger patients **D(GPP)**
- for whom a rhythm-control strategy that includes cardioversion (electrical or pharmacological) is being considered **C**
- in whom there is a high risk or a suspicion of underlying structural/functional heart disease (such as heart failure or heart murmur) that influences their subsequent management (for example, choice of antiarrhythmic drug) **D(GPP)**
- in whom refinement of clinical risk stratification for antithrombotic therapy is needed (see section 11.6). **C**

R5 TTE should not be routinely performed solely for the purpose of further stroke risk stratification in patients with AF for whom the need to initiate anticoagulation therapy has already been agreed on appropriate clinical criteria (see section 11.6). **D(GPP)**

R6 Transoesophageal echocardiography (TOE) should be performed in patients with AF:

- when TTE demonstrates an abnormality (such as valvular heart disease) that warrants further specific assessment **D(GPP)**
- in whom TTE is technically difficult and/or of questionable quality and where there is a need to exclude cardiac abnormalities **D(GPP)**
- for whom TOE-guided cardioversion is being considered. **D(GPP)**

5 Cardioversion

5.1 Electrical versus pharmacological cardioversion

Cardioversion is performed as part of a rhythm-control treatment strategy, and if successful restores sinus rhythm.[64] However, not all attempts at cardioversion are successful, and at one year post cardioversion approximately 50% of patients are back in AF.[65]

There are two types of cardioversion: electrical (ECV) and pharmacological (PCV). The optimal techniques and recommended protocols for performing cardioversion have been widely discussed in the literature.[64,66–68] PCV involves the use of various antiarrhythmic drugs, some of which may also be used to maintain sinus rhythm after electrical cardioversion (see section 6.1) or concomitantly with ECV (see section 5.3). Current clinical practice regards PCV as the preferred strategy in patients presenting with AF of recent onset (within 48 hours); ECV is regarded as the preferred strategy where the AF is more prolonged. Cardioversion is not normally attempted until possible underlying precipitants (eg thyrotoxicosis, infections) have been successfully treated and any electrolyte abnormalities corrected.

In clinical practice, young patients who develop AF but have no underlying structural heart disease often have an acute identifiable precipitant for their AF (eg alcohol). These cases often revert spontaneously to sinus rhythm without the need to attempt cardioversion (ECV or PCV).

5.1.1 Methodological introduction

Two studies were used to measure the success and failure rates of cardioversion but neither used double blinding and they may have been subject to expectation bias or confounding. Both studies had short follow-up periods, and therefore the incidence of thromboembolism or longer-term adverse events were not reliably measured. Neither study considered outcome measures such as exercise capacity or overall quality of life. There were conflicting results for the outcome measure 'duration of hospital stay', so no reliable conclusions could be drawn regarding health economic outcome measures.

5.1.2 Evidence statements

No difference has been found in rates of successful cardioversion between ECV and PCV as the initial treatment strategy (73% versus 74% respectively,[69] and 77% versus 81% respectively[70]). (1+)

Patients who had PCV as the initial treatment option, followed by ECV if sinus rhythm was not restored, were more likely to be cardioverted than those patients in whom the treatment preference was reversed (96% versus 84% respectively; $p<0.05$)[69] (1+). Similar results were observed for a subgroup of patients with lone AF (100% versus 77% $p<0.01$) although no significant differences have been found for those with either chronic or recent-onset AF or those with structural heart disease.[69] (1+)

Initiating treatment with PCV cost less per successful cardioversion than initiating treatment with ECV in all patients (US$1,240 versus US$1,917 p=0.002).[69] Initial PCV also cost less per successful cardioversion in patients with lone AF (US$965 versus US$2,021), and in patients with structural heart disease (US$1,223 versus US$1,814). Mean cost per patient was US$1,188 in the initial PCV and US$1,603 in the initial ECV group. The increased cost of ECV was attributed to heart monitoring, medications and oxygen.

5.1.3 From evidence to recommendations

Few studies set out to compare which patients would benefit most from ECV versus PCV. Two studies[69,70] failed to find any difference between these strategies when used as the initial treatment option. Concern was expressed regarding the overall applicability of the results of one study[70] to UK clinical practice. The health economics data supported the clinical outcomes that using PCV as first-line treatment followed by ECV if PCV failed was the most cost effective. The health economic study costings were based on US dollars.

The evidence failed to address many issues (eg incidence of thromboembolism and stroke, and improvements to quality of life). The choice of strategy was considered to be dependent on local facilities and available expertise. It was recognised that some clinicians perform elective cardioversion under general anaesthesia, while others performed the procedure under sedation. Also, there has been a move towards nurse-led cardioversion services.[71–73]

As the treatments were considered equally effective, highlighting patient choice was important. Informing patients that neither treatment has been shown to be more effective than the other is important and can help to prevent patients becoming disillusioned when cardioversion fails.

It was concluded that the available evidence suggested pharmacological and electrical cardioversion to be of comparable efficacy in recent onset AF. However, it was felt that in more prolonged cases of AF electrical cardioversion is the preferred option based on clinical experience and current clinical practice. It was also felt preferable to attempt cardioversion as soon as possible following AF onset to maximise the likelihood of a successful outcome.

RECOMMENDATION

R7 In patients with AF without haemodynamic instability for whom cardioversion is indicated:

- the advantages and disadvantages of both pharmacological and electrical cardioversion should be discussed with patients before initiating treatment **D(GPP)**
- where AF onset was within 48 hours previously, either pharmacological or electrical cardioversion should be performed **B**
- for those with more prolonged AF (onset more than 48 hours previously) electrical cardioversion should be the preferred initial treatment option. **D(GPP)**

5.2 Pharmacological cardioversion

Clinical practice commonly uses Vaughan-Williams Class Ia, Ic and III antiarrhythmic drugs for PCV.[68] However, these agents are associated with a risk of proarrhythmia in the presence of electrolyte abnormalities and ischaemic or structural heart disease.[74–76] This risk should be considered when choosing drugs for individual patients. The fast-acting intravenous beta-blocker esmolol has also been used and shown to be effective.[77,78] Digoxin has been shown to be ineffective for use in PCV.[79–81]

Patients undergoing PCV are usually admitted to hospital and have the antiarrhythmic drug administered intravenously, under ECG monitoring. These drugs may also be administered orally, and have been shown to have comparable efficacy to intravenous administration at 24 hours.[82–85] On occasion, an oral antiarrhythmic agent may be prescribed for those patients with paroxysmal AF where the drug has previously been known to work effectively and safely, and there are no contraindications (see section 8.2).

In the UK, the most commonly used drugs for PCV in patients with persistent AF are amiodarone, flecainide, propafenone and sotalol. This section addresses the efficacy of amiodarone versus the other three drugs.

5.2.1 Methodological introduction

The results of 15 studies are reported; one was a meta-analysis,[86] and the remainder were RCTs.

The meta-analysis[86] compared the efficacy of amiodarone to the Class Ic agents flecainide or propafenone, but did not report the individual drug comparisons separately. The results of two studies[85,87] included in the meta-analysis were not reported separately, one[85] because a statistical comparison was not made between the study drugs, and the other[87] because the study was only available in Italian.

All of the studies considered the comparison between two intravenously or orally administered antiarrhythmic drugs. Studies comparing the oral administration of one drug with the intravenous administration of another were excluded on the basis that the route of administration could confound the results of drug efficacy.

Regarding the comparison between the two Class III agents, amiodarone and sotalol, only one study[88] compared intravenous amiodarone with intravenous sotalol, but with additional oral administration of each drug as required. Although not licensed in the UK, results involving the intravenous preparation of propafenone have been included in this report as conclusions may be extrapolated to flecainide (as an intravenous flecainide preparation is licensed in the UK), or to oral preparations of propafenone.

With one exception,[89] all of the studies were in patients with acute- or recent-onset AF (in all cases less than 2 weeks). However, in three studies[88,90,91] only patients with acute-onset of less than 24 or 48 hours were considered. All studies excluded patients with moderate-to-severe heart failure (New York Heart Association (NYHA) grade greater than II) or left ventricular dysfunction. All studies reported the restoration of sinus rhythm as primary outcome, rather than the frequency of side effects associated with each drug.

5.2.2 Evidence statements

▷ Amiodarone versus sotalol

One study[88] reported no significant difference in efficacy between an intravenous/oral combination of amiodarone and sotalol for the restoration of sinus rhythm in patients with AF or atrial flutter of less than a 24-hour duration (**1+**). A similar result was reported in another study[89] using only oral administration, where both drugs were administered prior to electrical cardioversion. (**1++**)

One study[88] reported no significant difference in the frequency of adverse side effects between amiodarone and sotalol for the cardioversion of acute-onset AF or atrial flutter (two instances of heart failure in the amiodarone-treated group – both of which occurred in patients with impaired left ventricular function (LVEF) <40% – versus two instances of hypotension in the sotalol-treated group). (**1+**)

▷ Amiodarone versus flecainide/propafenone

A meta-analysis[86] of seven primary studies comparing parenteral or oral formulations of amiodarone with either flecainide or propafenone, found flecainide/propafenone to be more effective than amiodarone in restoring sinus rhythm within the first 8 hours after administration, but not at 24 hours (see Table 5.1). (**1+**)

Table 5.1 Relative risk of remaining in AF with flecainide or propafenone compared with amiodarone over different time periods

Time (hours)	RR (95% CI)
2	0.35 (0.24 to 0.50)
5	0.44 (0.31 to 0.61)
8	0.57 (0.57 (sic.) to 0.80)
24	0.95 (0.83 to 1.09)

▷ Amiodarone versus flecainide

One study[90] (N=100) found intravenous flecainide to be more effective in terms of restoring sinus rhythm than intravenous amiodarone throughout the follow-up period of 12 hours, as well as in terms of the median time taken to restore sinus rhythm (**1+**). The results of another smaller study[92] did not find any significant difference throughout a follow-up period of 8 hours. (**1+**)

▷ Amiodarone versus propafenone

Three studies[90,91,93] found intravenous propafenone to be more effective and faster in restoring sinus rhythm than intravenous amiodarone for up to 8 hours following drug administration (**1+**). At 24 hours, the two drugs were comparable.[91,93] (**1+**)

One study[94] found no significant difference between propafenone and amiodarone in terms of restoring sinus rhythm when effectively administered as a single oral dose (with additional oral doses if sinus rhythm was not restored within 24 hours. (1+)

▷ Flecainide versus propafenone

Based on the results of four studies,[90,95–97] it is inconclusive whether intravenous flecainide is more effective than intravenous propafenone (see Table 5.2). (1+)

Table 5.2 Percentage of study participants reverting to sinus rhythm following administration of flecainide or propafenone

Study	N	Time (hours)	Flecainide	Propafenone	p
Martinez-Marcos et al[90]	100	1	58	60	NS
Kingma et al[97]	70	1	86	55	<0.002
Kondili et al[96]	40	1	50	25	NS
Martinez-Marcos et al[90]	100	8	82	68	NS
Martinez-Marcos et al[90]	100	12	90	72	0.022

Three studies[90,95,96] found no significant difference in the mean time taken to restore sinus rhythm between intravenous flecainide and intravenous propafenone. (1+)

Based on the results of two studies, propafenone and flecainide are comparable in their efficacy[85,98] and speed[85] in restoring sinus rhythm when administered orally. (1+)

5.2.3 From evidence to recommendations

The evidence relied heavily on one study[90] with a relatively small number of patients (N=100). The evidence suggested that Class Ic drugs (flecainide and propafenone) are more effective than amiodarone at cardioverting patients with recent-onset AF at 2, 5, and 8 hours after administration. However, at 24 hours the difference in efficacy disappears, indicating that amiodarone has a longer period of onset than the Class Ic drugs. This result is also consistent with all of the primary studies, with no study finding any significant difference in efficacy at 24 hours or longer periods of observation.

The results of one study[90] suggested that flecainide and propafenone are comparable in terms of the time taken to revert to sinus rhythm (ie cardioversion), although at 12 hours flecainide was associated with a greater likelihood of reversion to sinus rhythm than propafenone was. A separate, unblinded study[88] suggested that for use in pharmacological cardioversion amiodarone and sotalol were comparable to each other in terms of both efficacy and safety.

It was noted that the trials excluded patients with structural or functional heart disease (left ventricular dysfunction). There were concerns about the use of Class I and Class III anti-arrhythmic drugs in these patients, although amiodarone was considered to be safe. The evidence assessing the use of digoxin for PCV was excluded from the literature search as this was considered to be an inappropriate use of this drug.

RECOMMENDATION

R8 In patients with persistent AF, where the decision to perform pharmacological cardioversion using an intravenous antiarrhythmic agent has been made:

- in the absence of structural heart disease,* a Class 1c drug (such as flecainide or propafenone) should be the drug of choice **B**
- in the presence of structural heart disease,* amiodarone should be the drug of choice. **D(GPP)**

*Coronary artery disease or left ventricular dysfunction.

5.3 Electrical cardioversion with concomitant antiarrhythmic drugs

Electrical cardioversion (ECV) alone is not always successful in inducing or maintaining sinus rhythm. In some cases, there is complete failure of ECV ('complete shock failure' or 'no conversion'). In other cases, AF recurs within a few minutes after a short period of sinus rhythm (immediate recurrence), sometimes recurrence is delayed from 1 day to 2 weeks (subacute or early recurrence), and sometimes AF recurrence occurs beyond 2 weeks (late recurrence).[99]

It is estimated that complete shock failure and immediate recurrence occur in approximately 25% of patients undergoing ECV, and subacute/early recurrences occur within 2 weeks in another 25%.[99]

In clinical practice, patients who have had a failed ECV or PCV or a relapse to AF while maintained on antiarrhythmic drugs, often have a further attempt at cardioversion, normally using ECV.

It is perceived that the concomitant administration of antiarrhythmic drugs increases the likelihood of successful cardioversion and the maintenance of sinus rhythm post cardioversion; this section addresses the evidence for this.

5.3.1 Methodological introduction

All 11 studies were RCTs, comparing either an antiarrhythmic drug with placebo[100–104] or comparing two or more antiarrhythmic drugs.[105,105–110] The results focus on the efficacy of concomitant antiarrhythmic drugs in ECV as none of the studies had sufficient power to detect differences in side effects.

Many of the studies considered the administration of antiarrhythmic drugs in both the pre-cardioversion and post-cardioversion periods. It is also unclear in many studies whether adjunctive rate-control therapy, such as digoxin or beta-blockers, was being prescribed in addition to the antiarrhythmic drugs.

The studies were similar in terms of patient population, drug dosages and outcome measures. There was some variance in the classification of successful cardioversion, as well as the policy on the inclusion or exclusion of patients with spontaneous cardioversion occurring prior to elective cardioversion.

5.3.2 Evidence statements

▷ Restoration of sinus rhythm

Four studies[101,105–107] compared pre-cardioversion amiodarone to rate-control drugs or placebo in relation to the incidence of successful cardioversion (see Table 5.3).

Table 5.3 Comparison of amidarone with various controls in terms of the incidence of successful cardioversion

	Study	N	Control	Amiodarone (%)	Control (%)	p
(1+)	Villani et al[105]	74	Digoxin	91	67	<0.05
(1+)	Villani et al[105]	90	Diltiazem	91	76	<0.05
(1+)	Capucci et al[107]	61	Diltiazem	87	65	<0.05
(1++)	Channer et al[101]	161	Placebo	72	79	NS
(1+)	Jong et al[106]	77	Various*	87	58	<0.05

*Study used either verapamil or propranolol to control ventricular rate.

One study[89] found that, in terms of the proportion of patients in whom sinus rhythm was restored either spontaneously or through the administration of electrical cardioversion, amiodarone and sotalol had equal efficacy (p=0.98) when administered from 28 days prior to scheduled cardioversion (**1++**). The study also found that those receiving either amiodarone or sotalol in the 28-day period prior to scheduled cardioversion had a higher prevalence of sinus rhythm at the end of the period, either through spontaneous restoration of sinus rhythm or through the administration of electrical cardioversion (p=0.01). (**1++**)

Six studies[100,102–105,108] compared various other antiarrhythmic drugs pre-cardioversion to rate-control drugs or placebo in relation to successful cardioversion (see Table 5.4).

Table 5.4 Comparison of various antiarrhythmic drugs with various controls in terms of the incidence of successful cardioversion

	Test/control	N	Test (%)	Control (%)	p
(1+)	Diltiazem/digoxin[105]	76	67	76	NS
(1++)	Flecainide/placebo[100]	54	73	82	NS
(1+)	Procainamide/placebo[104]	100	83	78	NS
(1+)	Propafenone/placebo[102]	35	73	74	NS
(1+)	Propafenone/placebo[103]	100	84.4	82.4	NS
(1+)	Verapamil/digoxin[108]	100	67	89	<0.05

One study[100] found pre-cardioversion flecainide use resulted in more successful first shocks in comparison with placebo (65% versus 30%, respectively; p=0.04). (**1++**)

▷ Recurrence of AF

The administration of amiodarone throughout the pre- and post-cardioversion period is associated with a reduced rate of relapse to AF compared with placebo or other drugs with a primary chronotropic effect (see Table 5.5).

Table 5.5 Comparison of amiodarone with other drugs or placebo in terms of the incidence of late AF recurrence post cardioversion

	Study	N	Control	Period (months)	Amiodarone (%)	Control (%)	p
(1+)	Villani et al[105]	74	Digoxin	1	28	78	<0.01
(1+)	Villani et al[105]	90	Diltiazem	1	28	56	<0.01
(1+)	Capucci et al[107]	61	Diltiazem	2	31	52	<0.01
(1++)	Channer et al[101]	161	Placebo	2	34	80	<0.001
(1+)	Jong et al[106]	77	Various*	2	37	77	<0.05

*Verapamil or propranolol.

It is unclear whether the administration of antiarrhythmic drugs pre-cardioversion decreases the likelihood of AF recurrence either in the first 48 hours following successful cardioversion or at up to 12 weeks (see Table 5.6).

Table 5.6 Comparison of antiarrhythmic drugs with control drugs in terms of the incidence of early or late AF recurrence post cardioversion

	Test/Control	N	Period	Test (%)	Control (%)	p
(1+)	Amiodarone/diltiazem[107]	61	24 hours	5	10	NS
(1+)	Amiodarone/digoxin[105]	74	24 hours	3	12	<0.01
(1+)	Diltiazem/digoxin[105]	76	24 hours	12	2	<0.01
(1+)	Amiodarone/diltiazem[105]	90	24 hours	3	2	NS
(1+)	Propafenone/placebo[103]	100	48 hours	12.2	35.8	<0.05
(1++)	Flecainide/placebo[100]	54	4 weeks	55	52	NS
(1+)	Verapamil/digoxin[108]	100	8 weeks	84	63	0.03
(1+)	Verapamil/digoxin[108]	100	12 weeks	91	72	0.03

One study[109] found the addition of verapamil to propafenone to be more effective than propafenone alone in terms of the incidence of post-cardioversion AF recurrence at 1 week and 3 months (1+). Another study[110] found no significant difference in the incidence of post-cardioversion AF recurrence at 1 week or 1 month between verapamil in addition to amiodarone and amiodarone alone. (1+)

▷ Defibrillation energy

It is inconclusive whether the administration of antiarrhythmic drugs is associated with either a reduced mean amount of energy per successful shock[102,104,105] or the total amount of energy per successful cardioversion attempt.[100,101,103,106] (**1++**)

5.3.3 From evidence to recommendations

Amiodarone and sotalol generally increased the likelihood of a successful cardioversion in comparison with controls in trials.[89,105–107] The historical literature regarding the amount of energy delivered during ECV was not considered to reflect current practice. These studies administered a low energy level shock and then escalated to a higher energy level shock. Therefore it was unclear whether the administration of antiarrhythmic drugs decreased the energy requirement for successful cardioversion. Furthermore, biphasic defibrillators (which deliver lower energy shocks) are increasingly used.

The evidence was also confounded by:

- the same antiarrhythmic drugs either being administered following a successful cardioversion for the long-term maintenance of sinus rhythm,[111,112] or
- the use of pre-cardioversion loading of antiarrhythmics not being reported in trial protocols, or considered as a comparison in long-term follow-up studies of sinus rhythm maintenance.

Measuring the immediate recurrence of AF was of limited value compared with recurrences in the longer term. From the limited data available based on small patient numbers, there was support for the use of amiodarone, sotalol and, possibly, propafenone in reducing the incidence of AF recurrences post cardioversion.

None of the evidence reflected concerns regarding potential adverse effects of antiarrhythmic drugs such as amiodarone. It was therefore not considered appropriate to recommend its use for routine ECV, although it may be beneficial in cases with a perceived increased risk of unsuccessful electrical cardioversion (eg long duration of AF).

There was no evidence found to support the use of other antiarrthymic drugs. Further, the concomitant use of digoxin did not improve cardioversion success.

RECOMMENDATION

R9 When patients with AF are to undergo elective electrical cardioversion and there is cause for heightened concern about successfully restoring sinus rhythm (such as previous failure to cardiovert or early recurrence of AF), concomitant amiodarone or sotalol* should be given for at least 4 weeks before the cardioversion. **B**

*Sotalol to be progressively titrated from 80 mg twice daily up to 240 mg twice daily.

5.4 Transoesophageal echocardiography-guided cardioversion

Cardioversion of AF is associated with an increased risk of stroke and thromboembolism. In order to minimise this risk, anticoagulation is conventionally recommended for a minimum of 3 weeks before and during cardioversion, and for a minimum of 4 weeks after cardioversion. Even when pre-cardioversion transoesphageal echocardiography (TOE) fails to demonstrate left atrial thrombus, some patients have a thromboembolism post cardioversion (especially if no anticoagulation has been administered).[68,113]

As it may take some time to achieve therapeutic international normalised ratio for 3 consecutive weeks, some patients may wait months before cardioversion is attempted. As it is perceived that patients are more likely to successfully cardiovert the shorter the time they have been in AF, strategies to facilitate early cardioversion have been explored.

One strategy is TOE-guided cardioversion, where a patient with AF of more than 48 hours duration has a TOE to assess for intracardiac thrombus. In the absence of thrombus, heparin is usually given and cardioversion is performed. Anticoagulation with warfarin is subsequently continued for a minimum of 4 weeks. Patients in whom a thrombus is identified by TOE are considered at high risk of post-cardioversion thromboembolism and are usually treated with conventional therapeutic anticoagulation for at least 3 to 4 weeks before the TOE is repeated (see Figure 5.1). This strategy requires an experienced TOE operator, especially since visualisation of thrombus may be operator-dependent.

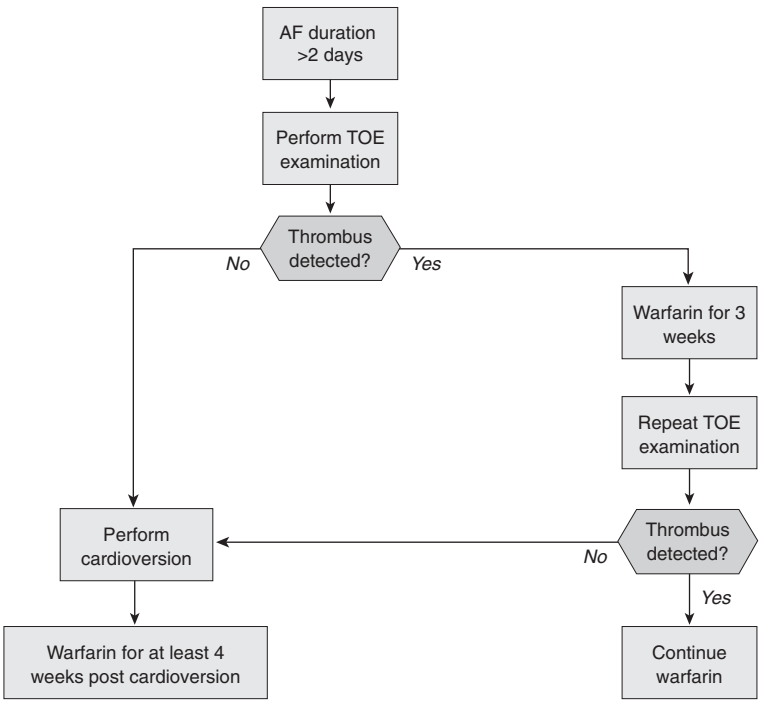


Figure 5.1 Cardioversion with TOE-guided strategy

5.4.1 Methodological introduction

Only studies where a comparison was made between a strategy of TOE-guided cardioversion and cardioversion without a prior TOE were included.

The primary clinical outcome of these studies was that the incidence of post-cardioversion thromboembolic events and other outcomes reported included the restoration and maintenance of sinus rhythm.

Of the two studies considering clinical outcomes included, one was a RCT,[114] and the other a cohort study.[115] In the former, in addition to the use of TOE examination, both the duration of anticoagulation and treatment were different between the two groups; in the later study, only the use of TOE examination was different between the two groups. Neither of the studies were adequately powered.

Of the two studies considering health economic outcomes,[116,117] one[117] estimated the cost per quality-adjusted life-year (QALY) of three strategies:

(1) conventional therapy transthoracic echocardiography (TTE) and warfarin therapy for one month before cardioversion)
(2) initial transthoracic echocardiography followed by transoesophageal echocardiographic-guided cardioversion and early cardioversion if no thrombus is detected (TTE/TOE)
(3) initial TOE-guided cardioversion with early cardioversion if no thrombus is detected.

The other study[116] estimated the costs and incremental cost per QALY of TOE-guided anticoagulation versus conventional anticoagulation based on the Assessment of Cardioversion Using Transoesophageal Echocardiography (ACUTE) trial.[114]

5.4.2 Evidence statements

One study[114] did not find any significant difference between TOE-guided cardioversion and a conventional strategy in terms of the incidence of thromboembolic events, stroke, successful initial cardioversion or maintenance of sinus rhythm at 8 weeks (**1+**). The difference in terms of mortality was of borderline significance (p=0.06) in favour of the conventional strategy. (**1+**)

A second study also failed to find any significant effect on the incidence of all embolic events between the two strategies.[115] (**2+**)

One study[114] found a lower incidence of bleeding events with a TOE-guided strategy compared with a conventional strategy (2.9% versus 5.5%, respectively; p=0.03). (**1+**)

TOE-guided cardioversion (US$ 2,774) costs less than TTE/TOE-guided cardioversion (US$3,070) and conventional strategy (US$3,106). Including the gains in QALYs, TOE-guided cardioversion is the least costly strategy with similar effectiveness (TOE accumulated 8.49 QALYs, TTE/TOE and conventional therapy both accumulated 8.48). The sensitivity analysis indicated that the results depend on a lower risk of cardioversion-related thromboembolism after negative TOE compared with conventional therapy.[117]

Overall, there was no significant difference in the mean costs per patient between TOE-guided and conventional care in the simulation model (US$3,503.09 versus US$3,423.52) and the hospital charge data from the ACUTE trial data (US$6,508 versus US$6,239, p=0.50). The analytic model indicated the initial treatment costs per patient were higher in the TOE group

(US$2,639.67 versus US$2,429.01), but outcome-associated costs were lower (US$863.42 versus US$994.51). The decision model indicated that the TOE-guided strategy costs US$185 more than conventional therapy when all treatment and outcome data are included (US$7,090 versus US$6,905). An incremental cost per QALY of TOE-guided cardioversion was calculated at US$15,455.[116]

5.4.3 From evidence to recommendations

Overall, the clinical studies suggest that TOE-guided cardioversion is of comparable efficacy to conventional strategy.[114,115] Although bleeding was reduced in the TOE-guided strategy, this was perceived to be a result of the shorter time spent on anticoagulation, and therefore TOE-guided cardioversion could be deemed preferable in patients with an increased bleeding risk. The health economic studies suggested that TOE-guided cardioversion may be a cost-effective treatment strategy.

The theoretical advantage of early cardioversion being more likely to be successful was not supported by the current clinical trial data. However, the studies were underpowered to detect significant differences in this, and in mortality and embolic event rates. TOE-guided cardioversion was considered a specialised procedure requiring appropriately experienced staff and appropriate facilities. However, it was considered that TOE-guided cardioversion should be an available treatment, as some patients would prefer the option of not being on prolonged anticoagulation.

RECOMMENDATION

R10 In patients with AF of greater than 48 hours duration, in whom elective cardioversion is indicated:

- both TOE-guided cardioversion and conventional cardioversion should be considered equally effective **B**
- a TOE-guided cardioversion strategy should be considered:
  - where experienced staff and appropriate facilities are available, and **D(GPP)**
  - where a minimal period of pre-cardioversion anticoagulation is indicated due to patient choice or bleeding risks. **C**

5.5 Cardioversion treatment algorithm

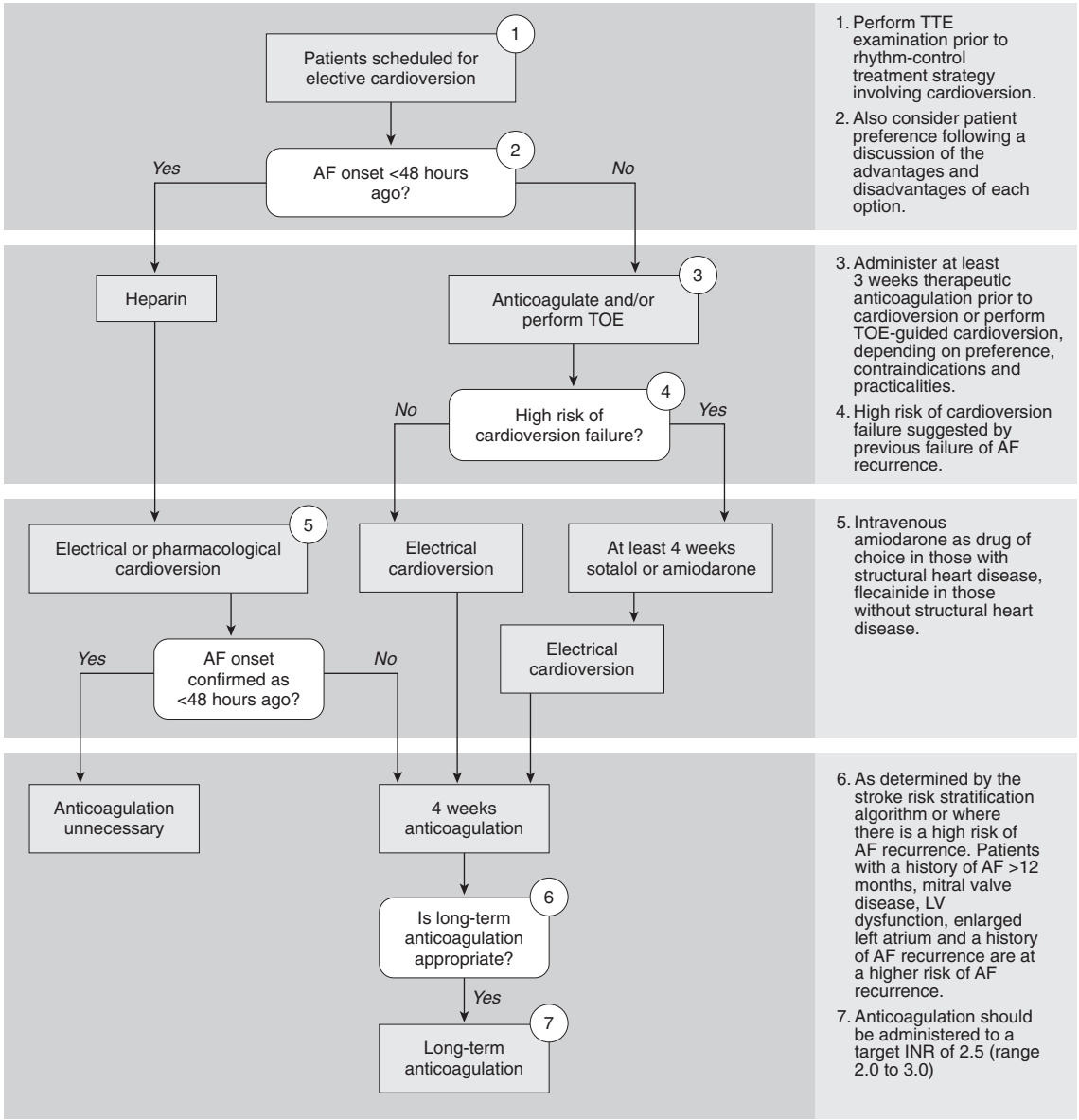


Figure 5.2 Cardioversion treatment algorithm

6 Treatment for persistent AF

6.1 Rate control versus rhythm control

AF is associated with increased mortality and morbidity. Currently, there are two main treatment strategies, rate control and rhythm control.

Rate control involves the use of chronotropic drugs or electrophysiological/surgical interventions to reduce the rapid heart rate (ventricular rate) often found in patients with AF. Although the atria continue to fibrillate with this strategy, it is nonetheless thought to be an effective treatment as it improves symptoms and reduces the risk of associated morbidity. However, the persistence of the arrhythmia continues the risk of stroke and thromboembolic events occurring. This risk is reduced by administering antithrombotic drugs (see section 7.2).

Rhythm control involves the use of electrical or pharmacological cardioversion or electrophysiological/surgical interventions to convert the arrhythmia associated with AF to normal sinus rhythm. Patients who have been successfully cardioverted are generally administered antiarrhythmic drugs for the long term to help prevent the recurrence of AF. The rhythm-control strategies also require the appropriate administration of antithrombotic therapy to reduce the risk of stroke and thromboembolic events occurring (see section 6.2).

There remain uncertainties about the most appropriate initial treatment strategy for individual patients. This section addresses which strategy is most suitable for which patient groups.

6.1.1 Methodological introduction

Five randomised controlled trials[118–122] were included in this evidence report, along with one pre-defined substudy[123] of one of the original trials. Each study compared rate-control strategies to rhythm-control strategies and involved the use of various drug therapies within each strategy.

In all rate-control treatment groups, concomitant antithrombotic therapy was administered, whereas in rhythm-control treatment groups it was administered to patients only when it was considered appropriate by the treating physician.

The follow-up periods and number of participants varied widely between the studies and only two studies[118,119] included participants who had undergone at least one previous attempt at electrical cardioversion.

None of the studies were double-blind, and in some the participants were able to swap between the different treatment groups. For example, upon multiple failed attempts at cardioversion, participants were treated according to rate-control protocols. An intention-to-treat analysis was employed in those studies where swapping was allowed.

One meta-analysis was also included.[124] Because the meta-analysis only considered the outcomes of mortality and ischaemic stroke, the results of the four primary studies will be reported for other outcomes.

Two studies[125,126] compared the cost effectiveness of the two strategies. One study[125] estimated the incremental cost per life-year gained in rhythm control versus rate control. The other study[126] estimated the cost per avoided endpoint (cardiovascular morbidity or mortality).

6.1.2 Evidence statements

For those older than 65 or those with coronary artery disease, a significant difference has been found in favour of rate control in terms of all-cause mortality.[121] (**1+**)

For those with heart failure (congested heart failure (CHF) or left ventricular ejection fraction (LVEF) <50%), the adoption of a rhythm-control strategy is associated with a lower incidence of all-cause mortality[121] (**1+**). Another study[123] reported that the overall incidence of adverse cardiovascular events in those with predominantly mild heart failure (NYHA II) was comparable between rate control and rhythm control. (**1+**)

Overall, a non-significant difference has been found in terms of all-cause mortality between rate and rhythm control[124] (13.0% versus 14.6%, p=0.09). (**1+**)

In patients with recurrent AF, a strategy of rhythm control was associated with a higher incidence of proarrhythmic events (torsades de pointes (0.8% with rhythm control versus 0.2% with rate control; p=0.007), QT prolongation (1.9% versus 0.3%; p<0.001) and bradycardic events than a strategy of rate control.[121] (**1+**)

In patients with recurrent AF, a strategy of rhythm control is associated with a higher rate of adverse pulmonary events (7.3% in rhythm control, 1.7% in rate control; p<0.001), gastrointestinal events (2.7% in rhythm control, 2.1% in rate control; p<0.001) or other non-cardiac adverse events (25.4% in rhythm control, 14.0% in rate control; p<0.001) than a strategy of rate control.[121] (**1+**)

In patients with recurrent AF, a strategy of rhythm control is associated with a higher rate of hospital admissions than is a strategy of rate control (54% versus 26%; p<0.001,[119] 74% versus 12%; p<0.001,[122] 80% versus 73%; p<0.001).[121] (**1+**)

In patients with recurrent AF, no significant difference has been found in quality of life,[120] myocardial infarction[121] or development of congestive heart failure[121] between strategies of rate control and rhythm control (**1+**); however, two studies did record a significant improvement in the level of physical functioning in both treatment groups.[119,120] (**1+**)

In patients with recurrent AF, no significant difference has been found in 5-year cumulative rates of thromboembolic or haemorrhagic events between strategies of rate control and rhythm control.[121] (**1+**)

The rate-control strategy cost US$5,077 less per person than the rhythm-control strategy (US$20,546 versus US$25,623).[125] Using low and high cost estimates in the sensitivity analysis, rate control saved from US$2,189 to US$5,481 per person. Including the mean survival gain of 0.08 of a year in rate control using original trial data, the rate-control strategy was both less costly and more effective and therefore is preferable to rhythm control.

In a study conducted in the Netherlands the rate-control strategy cost €898 less per person than the rhythm-control strategy (€7,386 versus €8,284).[126] Based on the difference in primary endpoints (cardiovascular morbidity or mortality) in rate versus rhythm control (17.5% versus

21.2%) from original trial data, rate control saves €24,944 per endpoint avoided. The higher costs with rhythm control were attributed to ECV, hospital admissions and antiarrhythmic medication.[126]

6.1.3 From evidence to recommendations

No study found rate control to be inferior to rhythm control or vice-versa for the outcome measures of mortality[118–122] or quality of life.[120] However, one study[121] found mortality to be higher for rhythm control in those with coronary heart disease, those without heart failure and those over 65 years old. The same study did not find rhythm control to be associated with lower mortality in those with heart failure.

Rates of hospitalisation, as well as rates of adverse events, were higher among participants treated with rhythm-control treatment plans.[119,121,122] The results were generally consistent across studies and considered older participants with elevated risk of stroke,[118,121] as well as younger participants.[120,122]

It was felt that many of the stroke and thromboembolic events in the rhythm-control arm were related to the lack of appropriate use of antithrombotic therapy. Rates of anticoagulation were often not controlled between the two treatment arms in many of the studies. For example, in one study[121] anticoagulation was mandatory in the rate-control treatment arm, but in the rhythm-control arm continuous anticoagulation was encouraged but could be stopped at the physician's discretion if sinus rhythm had apparently been maintained for at least 4 (and preferably 12) consecutive weeks. Anticoagulation therapy use may have had some effect on the outcome of the study, and in a subsequent post hoc analysis,[127] the use of anticoagulation therapy was an independent predictor of survival.

Although one study[121] reported a higher incidence of adverse pulmonary events associated with rhythm control, it was not reported whether this was due to the particular choice of rhythm-control drug used rather than the strategy itself.

The health economic evidence concluded that a rate-control strategy was more cost-effective than a rhythm-control strategy. However, it was unclear whether the UK setting and outcome costs of inadequate anticoagulation would affect the results.

RECOMMENDATIONS

R11 As some patients with persistent AF will satisfy criteria for either an initial rate-control or rhythm-control strategy (for example, aged over 65 but also symptomatic):

- the indications for each option should not be regarded as mutually exclusive and the potential advantages and disadvantages of each strategy should be explained to patients before agreeing which to adopt
- any comorbidities that might indicate one approach rather than the other should be taken into account
- irrespective of whether a rate-control or a rhythm-control strategy is adopted in patients with persistent AF, appropriate antithrobotic therapy should be used. **D(GPP)**

R12 A rate-control strategy should be the preferred initial option in the following patients with persistent AF:

- over 65 years old **B**
- with coronary artery disease **B**
- with contraindications to antiarrhythmic drugs **D(GPP)**
- unsuitable for cardioversion* **D(GPP)**
- without congestive heart failure. **B**

R13 A rhythm-control strategy should be the preferred initial option in the following patients with persistent AF:

- those who are symptomatic **D(GPP)**
- younger patients **C**
- those presenting for the first time with lone AF **D(GPP)**
- those with AF secondary to a treated/corrected precipitant **D(GPP)**
- those with congestive heart failure. **C**

*Patients unsuitable for cardioversion include those with:

- contraindications to anticoagulation
- structural heart disease (eg large left atrium >5.5 cm, mitral stenosis) that precludes long-term maintenance of sinus rhythm
- a long duration of AF (usually >12 months)
- a history of multiple failed attempts at cardioversion and/or relapses, even with concomitant use of antiarrhythmic drugs or non-pharmacological approaches
- an ongoing but reversible cause of atrial fibrillation (eg thyrotoxicosis).

6.2 Rhythm control for persistent AF

In persistent AF, antiarrhythmic drugs are prescribed to increase the likelihood of maintaining sinus rhythm following successful electrical or pharmacological cardioversion.

The use of antiarrhythmic drugs to maintain sinus rhythm post cardioversion is addressed in this section. In UK clinical practice, prophylactic drug treatment is not usually used in cases of a first-detected episode of AF, especially if AF is secondary to a precipitant that has since been corrected. Without antiarrhythmic drugs, the recurrence rate is high. Reversible cardiovascular and non-cardiovascular precipitants of AF are usually actively managed first. Predictors of recurrences of AF are considered elsewhere (see section 12.2).

Clinical studies have shown the efficacy of various antiarrhythmic drugs (amiodarone, propafenone, disopyramide, sotalol, flecainide, quinidine and azimilide) against no treatment, placebo or digoxin.[64,68,128] It is clear from these trials that the use of antiarrhythmic drugs does improve maintenance of sinus rhythm post cardioversion. But despite treatment, relapse to AF occurs in approximately 50% of patients by 12 months (see section 12.2). Moreover, the need for antiarrhythmic drugs has to be balanced against adverse effects and a higher mortality in some patients.[129]

UK clinical practice commonly uses Class Ic, beta-blockers or Class III antiarrhythmic drugs to maintain sinus rhythm, and this section compares their relative efficacy.

6.2.1 Methodological introduction

The literature search and evidence appraisal processes for this question resulted in 12 studies being included in this evidence report.

Studies were considered for inclusion if the efficacy of antiarrhythmic drugs was measured in a study population or subpopulation with a history of AF requiring electrical or chemical cardioversion, and an indication for long-term antiarrhythmic therapy for the maintenance of sinus rhythm.

Studies that consider the use of antiarrhythmic therapy specifically for reducing the frequency of recurrent episodes of AF in those patients with a history of paroxysmal AF are considered elsewhere (see section 8.1).

All but two[111,130] of the studies included in this report were RCTs.

No studies compared the efficacy of amiodarone, flecainide or propafenone with a beta-blocker such as metoprolol. However, five studies[89,111,131–133] compared amiodarone with the Class III beta-blocker sotalol, and three studies[134–136] compared propafenone with sotalol. Two studies[130,137] compared a Class Ic agent (flecainide or propafenone) with amiodarone. One study[112] compared amiodarone with either sotalol or propafenone, and one study[138] compared sotalol with the beta-blocker bisoprolol.

All studies except one[138] explicitly excluded patients with severe heart failure. Most also excluded those with moderate heart failure (typically defined as an NYHA grade greater than II).

Most of the studies were not powered to detect clinically significant differences in drug side effects, and many reported the composite endpoint of either recurrence of AF or occurrence of a drug-related side effect or drug withdrawal.

6.2.2 Evidence statements

▷ Sotalol versus propafenone

Two studies[134,135] found no difference in the proportion of patients with AF maintaining sinus rhythm at 12 months between sotalol and propafenone (**1+**). One study[135] also found a similar result when only those subgroups with a history of paroxysmal or persistent AF were considered. (**1+**)

One study[136] found propafenone resulted in a lower incidence of side effects or AF recurrence than sotalol (52% versus 81%; $p<0.001$). (**1+**)

▷ Sotalol versus amiodarone

Three studies[89,131,132] found amiodarone to be significantly associated with an increased likelihood of remaining in sinus rhythm compared with sotalol at 12[89,131,132] and 24[132] months following cardioversion (**1++**). Similar results were found for the likelihood of remaining in sinus rhythm without side effects[111,132] and the monthly incidence of AF recurrence or side effects.[133] (**1+**)

One study[89] also found amiodarone to be associated with an increased likelihood of remaining in sinus rhythm compared with sotalol regardless of the duration of AF and whether or not the AF was associated with symptoms (**1++**). However, the study found no significant difference between the two drugs in those patients with ischaemic heart disease. (**1++**)

▷ Sotalol versus beta-blockers

One study[138] found no difference in the percentage of patients with recurrent AF during a mean follow-up period of approximately 8 months between 5 mg/day bisoprolol and 160 mg/day sotalol (42% versus 41%) (**1+**). There were two cases of proarrhythmia and two cases of bradycardia in the sotalol group and two cases of bradycardia in the bisoprolol group.

▷ Flecainide versus amiodarone

One study[130] of patients with recurrent AF found no significant difference in the efficacy of flecainide and amiodarone over a period of 3 months in terms of the rate of recurrent AF (38% versus 32%). (**2++**)

▷ Propafenone versus amiodarone

One study[112] comparing either propafenone or sotalol with amiodarone found amiodarone to be associated with a higher proportion of patients remaining in sinus rhythm after an average follow-up period of 468 days (39% versus 69%; $p<0.001$) (**1+**). Sotalol and propafenone were similar in terms of efficacy. Amiodarone was also associated with a lower incidence of drug-related side effects requiring discontinuation compared with sotalol/propafenone (46% versus 34%; $p=0.01$), although the incidence of drug discontinuation between the propafenone and sotalol patients was not reported separately. (**1+**)

One study[137] found no significant difference between propafenone and amiodarone in terms of the percentage of patients maintaining sinus rhythm over 24 months (52% versus 59%; $p=0.058$) (**1+**). When the composite outcome of remaining in sinus rhythm without side effects was considered, the two drugs were similar (51% versus 42%; $p=0.44$). (**1+**)

6.2.3 From evidence to recommendations

An escalating approach to drug therapy could be recommended based on associated comorbidity and the need for increasingly effective antiarrhythmic drugs. For example, a beta-blocker or sotalol could be prescribed in the first instance, and where this was not tolerated, or was ineffective, other drugs could be administered.

This escalation of drug use is not totally in keeping with the evidence on efficacy, which is in favour of amiodarone, but also incorporates concerns regarding the adverse effects. In the case of amiodarone, such adverse effects may become apparent only after long-term use and include pulmonary, hepatic, ophthalmic and thyroid toxicity.

RECOMMENDATIONS

R14 An antiarrhythmic drug is not required to maintain sinus rhythm in patients with persistent AF in whom a precipitant (such as chest infection or fever) has been corrected and cardioversion has been performed successfully, providing there are no risk factors for recurrence. **D(GPP)**

R15 In patients with persistent AF who require antiarrhythmic drugs to maintain sinus rhythm and who have structural heart disease*:

- a standard beta-blocker should be the initial treatment option **D(GPP)**
- where a standard beta-blocker is ineffective, contraindicated or not tolerated amiodarone should be used. **A**

R16 In patients with persistent AF who require antiarrhythmic drugs to maintain sinus rhythm and who do not have structural heart disease*:

- a standard beta-blocker should be the initial treatment option **D(GPP)**
- where a standard beta-blocker is ineffective, contraindicated or not tolerated
  - a Class Ic agent or **C**
  - sotalol** **D(GPP)**

should be given

- where other drug classes are ineffective, contraindicated or not tolerated amiodarone should be administered. **B**

*Coronary artery disease or left ventricular dysfunction.
**Progressively titrated from 80 mg twice daily up to 240 mg twice daily.

6.3 Antithrombotic therapy for persistent AF

Patients with persistent AF may be treated with either a rate-control or rhythm-control treatment strategy. Where a rhythm-control treatment strategy is chosen, there is the need for appropriate use of antithrombotic therapy to prevent acute stroke or other thromboembolic events occurring during or shortly after cardioversion. Where a rate-control strategy is chosen, patients should be treated as outlined for permanent AF (see Chapter 7).

It is known that the presence of AF increases the risk of thromboembolic stroke,[13] but it is less clear whether this risk can be reduced by cardioversion (ECV or PCV) to normal sinus rhythm, assuming sinus rhythm is maintained and antithrombotic therapy is continued. The rate- versus rhythm-control trials have not resolved this issue as many of the patients relapsed into AF and had been administered inadequate thromboprophylaxis (see section 6.1).

Appropriate thromboprophylactic measures are essential in patients considered for cardioversion since it has been shown that cardioversion of AF of more than 48 hours duration increases the short-term (peri-cardioversion) risk of stroke and thromboembolism.[139,140] Data from the rate-control versus rhythm-control trials suggest that consideration should be given to long-term anticoagulation in patients at high risk of stroke and/or AF recurrence in view of the frequent asymptomatic recurrences of the arrhythmia leading to thromboembolism in the presence of risk factors.[65]

In the past, there have been no prospective randomised placebo-controlled trials testing the efficacy of anticoagulation (versus placebo) in the prevention of peri-cardioversion thromboembolism, but several retrospective studies and/or case series have suggested benefit from the use of therapeutic warfarin in this setting. Cardioversion of atrial flutter presents similar risks and requires similar anticoagulation.

The administration of antithrombotic therapy peri-cardioversion applies to both electrical and pharmacological cardioversion strategies.

Apart from the periods leading up to and following cardioversion, there is no evidence to suggest that the choice of antithrombotic therapy should be any different from that recommended for patients with permanent AF (see section 7.2).

6.3.1 Methodological introduction

The results of a meta-analysis of 25 primary studies[141] and three primary studies[142–144] are included in this report. Only one[144] of the primary studies was a RCT.

The meta-analysis included in this report[141] pooled the results of multiple primary studies comparing the effectiveness of anticoagulation or the effectiveness of TOE screening for the prevention of acute embolic events (ischaemic stroke or transient ischaemic attack or systemic embolism) post cardioversion.

None of the studies examined rates of thromboembolism in emergency versus elective cardioversion, and in particular whether acute anticoagulation with heparinoids is an effective means of stroke prevention in comparison to oral anticoagulation.

No studies compared the effectiveness of any form of anticoagulation post cardioversion against placebo or the effectiveness of antiplatelet agents against either anticoagulation or placebo.

6.3.2 Evidence statements

Based on the results of two primary studies[142,143] and one meta-analysis,[141] anticoagulation prior to cardioversion has been found to be associated with a reduced rate of thromboembolic complications post cardioversion when compared with no anticoagulation. (**2++**)

Anticoagulation reaching an international normalised ratio (INR) greater than 2.0 at the time of cardioversion has been found to be associated with a significantly lower rate of thromboembolic complications 4 weeks post cardioversion when compared with lower values (including those receiving no anticoagulation).[142,143] (**2+**)

Anticoagulation prior to cardioversion has been found to be associated with a reduced rate of acute thromboembolic complications post cardioversion when compared with TOE screening for the presence of thrombi prior to cardioversion and the exclusion of screen-positive patients.[141] (**2++**)

Anticoagulation with enoxaparin throughout the peri-cardioversion period is as effective as unfractionated heparin peri-cardioversion followed by oral anticoagulation with a coumarin derivative post cardioversion.[144] (**1+**)

6.3.3 From evidence to recommendations

Anticoagulation administered to a target INR of 2.5 (with a range of 2.0 to 3.0) prior to cardioversion is effective in reducing the frequency of acute thromboembolic complications post cardioversion. In studies involving anticoagulation to resolve any intracardiac thombi, a duration of 3 to 4 weeks prior to cardioversion has often been specified.[114,145] It was therefore considered necessary for anticoagulation to be therapeutic (within the INR range 2.0 to 3.0) for a minimum of 3 weeks prior to cardioversion for resolution or endothelisation of any pre-existing thrombus. In practice this may be verified as three consecutive weekly INR measurements within the therapeutic range.

Anticoagulation is more effective than screening patients for thrombi using TOE alone as a means of reducing the frequency of thromboembolic complications of cardioversion.[141]

Based on a period of 4 weeks for the return of atrial contractile function post cardioversion, it was considered that anticoagulation should remain at therapeutic levels throughout this time. Even in patients with a successful cardioversion, evidence from the AFFIRM study[121,127] suggests that longer-term anticoagulation may be necessary in the presence of stroke and thromboembolism risk factors (see section 11.6) or risk factors for AF recurrence (see section 12.2). The evidence from AFFIRM showed that, although sinus rhythm is associated with reduced mortality, patients enrolled in the rhythm-control treatment strategy had a similar incidence of stroke to those in the rate-control treatment strategy.

It is noteworthy that many of the risk factors for thromboembolism in AF are similar to those for AF recurrence.

RECOMMENDATIONS

R17 Before cardioversion, patients should be maintained on therapeutic anticoagulation with warfarin (INR 2.5, range 2.0 to 3.0) for a minimum of 3 weeks. **C**

R18 Following successful cardioversion, patients should remain on therapeutic anticoagulation with warfarin (INR 2.5, range 2.0 to 3.0) for a minimum of 4 weeks. **D(GPP)**

R19 In patients with persistent AF where cardioversion cannot be postponed for 3 weeks:

- heparin should be given and the cardioversion performed, and **D**
- warfarin should then be given for a minimum of 4 weeks post cardioversion. **D(GPP)**

R20 Anticoagulation should be continued for the long term in patients with AF who have undergone cardioversion where there is a high risk or AF recurrence* or where it is recommended by the stroke risk stratification algorithm (Figure 11.1). **D(GPP)**

R21 In patients with AF of confirmed duration of less than 48 hours undergoing cardioversion, anticoagulation following successful restoration of sinus rhythm is not required. **D(GPP)**

R22 Patients with atrial flutter should be given antithrombotic therapy in the same manner as those with AF. **D(GPP)**

*Factors indicating a high risk of AF recurrence include:

- a history of failed attempts at cardioversion
- structural heart disease (mitral valve disease, left ventricular dysfunction or an enlarged left atrium)
- a prolonged history of AF (greater than 12 months)
- previous recurrences of AF.

6.4 Rhythm-control treatment algorithm for persistent AF

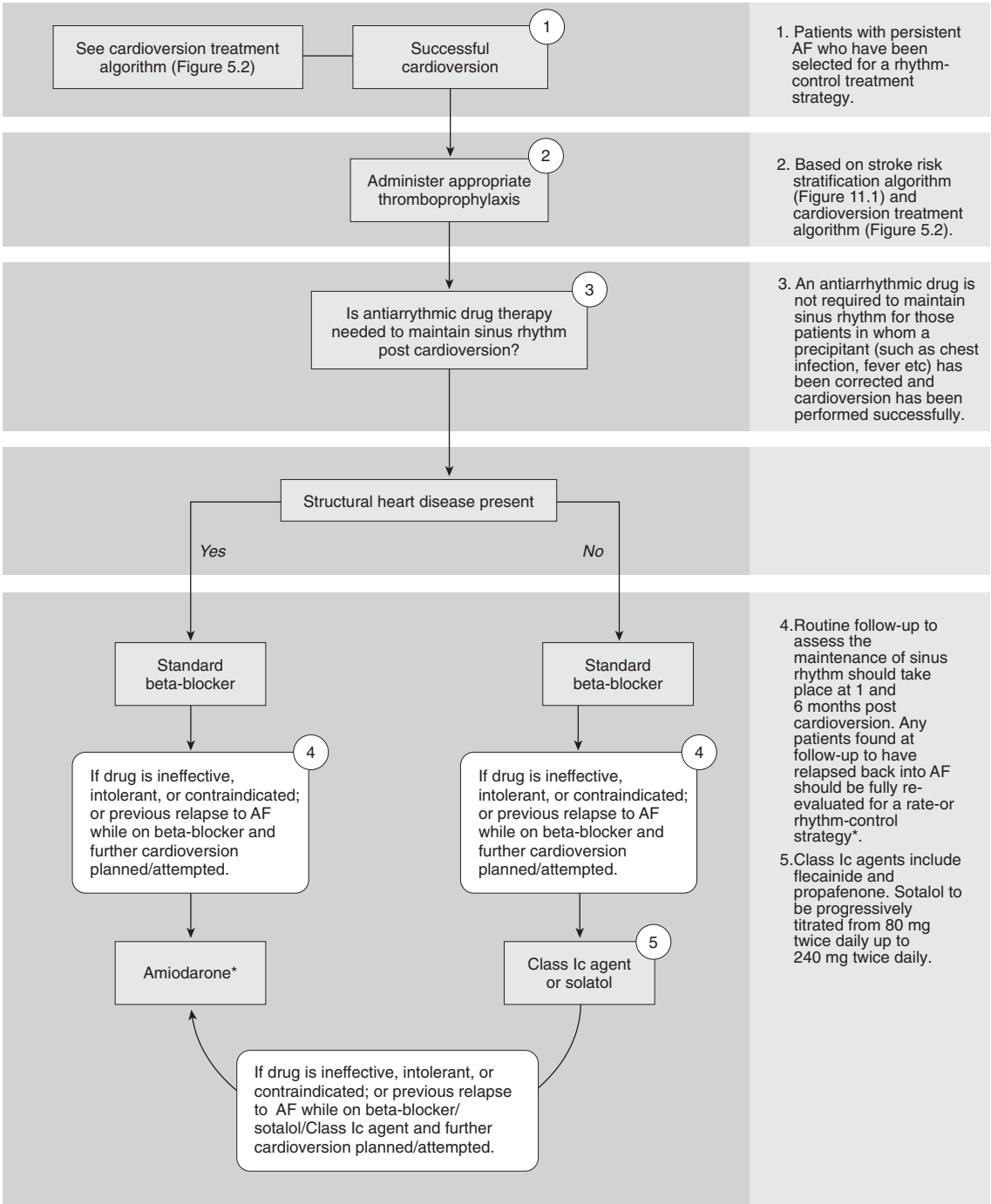


Figure 6.1 Rhythm-control treatment algorithm for persistent AF. *If rhythm control fails, consider the patient for rate-control strategy or specialist referral in those with lone AF or ECG evidence of underlying electrophysiological disorder (eg Wolff–Parkinson–White syndrome).

7 Treatment for permanent AF

7.1 Rate control for permanent AF

The aims of heart rate control are to minimise symptoms associated with excessive heart rates and prevent tachycardia-associated cardiomyopathy.[146] A recent consensus[147] statement has suggested a target resting heart rate of less than 90 bpm and less than 180 bpm during exercise in patients with AF.

Historically, cardiac glycosides such as digoxin have been used but have limited efficacy in a hyperadrenergic state such as thyrotoxicosis, fever, acute volume loss, postoperative state and during exertion.[148] In clinical practice, digoxin monotherapy may only be adequate for the older, sedentary patient.[149] Other agents for rate control include beta-blockers and the rate-limiting non-dihydropyridine calcium-channel blockers ('calcium antagonists') such as diltiazem and verapamil. These are used for rate control, both at rest and during exercise, and are perceived to be more effective than digoxin in the critically ill.[65,150] Diltiazem is regarded as preferable to verapamil, in view of the latter's negative inotropic effect and potential drug interaction with digoxin. Beta-blockers and calcium antagonists may also worsen acute heart failure.

One short acting intravenous beta-blocker, esmolol, is useful when oral drugs cannot be given or if there is uncertainty over tolerance of the beta-blocker.

Rate control may not always be achieved with a single drug. Combination therapy, for example digoxin plus a beta-blocker or rate-limiting calcium-channel blocker is often considered for AF uncontrolled with a single agent. If these two classes of drugs are ineffective or not tolerated, amiodarone or diltiazem-beta-blocker combination therapy are third-line pharmacological options used by specialists. Alternatively, a non-pharmacological approach (mainly atrio-ventricular node ablation coupled with pacing) can be considered, but is beyond the scope of this review.

7.1.1 Methodological introduction

This section considered the efficacy of:

- beta-blockers,
- digoxin and
- calcium antagonists.

Of the 12 studies that were included, all but one[151] were either randomised or serial crossover trials. Consequently, the total number of participants was relatively low.

For the comparison of calcium antagonists and beta-blockers, three studies were found, one of which[152] used the beta-blocker betaxolol, which is not available orally in the UK. In this and a second study,[153] the patients were also receiving digoxin, which may have confounded the results.

There is consistency in the results between different drugs within the same class for both the comparison of calcium antagonists versus digoxin and beta-blockers versus digoxin.

7.1.2 Evidence statements

▷ Calcium antagonists versus digoxin

Seven studies[154–160] found no difference in average heart rate between calcium antagonists verapamil or diltiazem and digoxin either at rest or during periods of normal daily activity (**1++**). However, seven studies[153,155–160] found calcium antagonists resulted in a lower heart rate during exercise, compared with digoxin. (**1++**)

▷ Beta-blockers versus digoxin

Three studies[151,154,161] found no difference in average heart rate between digoxin and beta-blockers while at rest or during periods of normal daily activity (**1++**). However, the beta-blockers atenolol[154] and labetalol[161] controlled heart rate during exercise more effectively than digoxin did (**1++**). One additional study[153] found that atenolol significantly reduced average heart rate in comparison to digoxin both at rest and after exercise. (**1+**)

▷ Beta-blockers versus calcium antagonists

One crossover study[154] found no difference between the calcium antagonist diltiazem and the beta-blocker atenolol in terms of either the mean heart rate over 24 hours or during exercise (**1+**). A second crossover study[153] found no difference in the mean heart rate at rest or post-exercise between the calcium antagonist verapamil and atenolol (**1+**). However, a third study[152] found the beta-blocker betaxolol to be more effective than diltiazem both over 24 hours and during exercise. (**1+**)

▷ Beta-blockers with digoxin versus beta-blockers

One crossover study[154] found the beta-blocker atenolol used in combination with digoxin to be associated with a lower heart rate over 24 hours than atenolol alone (**1+**). In another study[161] using the beta-blocker labetalol the reported differences were not statistically significant (**1++**). Neither study found any statistically significant differences in heart rate during periods of exercise. (**1++**)

▷ Calcium antagonists with digoxin versus calcium antagonists

Four crossover studies[154,156,159,162] found the calcium antagonists diltiazem or verapamil used in combination with digoxin to be more effective in controlling heart rate over 24 hours, as well as during periods of exercise, than either diltiazem or verapamil alone. (**1++**)

7.1.3 From evidence to recommendations

When used as monotherapies, both calcium antagonists and beta-blockers were more effective than digoxin in controlling heart rate at high levels of physical exertion, but there was no difference during normal daily activities. Based on the results of two studies there was no significant difference in terms of the effectiveness of heart rate control between calcium antagonists and beta-blockers.[152,154]

During rest the combination of beta-blockers with digoxin was more effective than beta-blockers alone for the control of heart rate.[154,161] The combination of calcium antagonists with digoxin was more effective than calcium antagonists alone for the control of heart rate both during normal activities and rest, as well as during exercise.[154,156,159]

None of the studies were sufficiently large to make comparisons in terms of side effects. In particular, no study reported any intolerance to beta-blockers.

RECOMMENDATIONS

R23 In patients with permanent AF, who need treatment for rate control:

- beta-blockers or rate-limiting calcium antagonists should be the preferred initial monotherapy in all patients **A**
- digoxin should only be considered as monotherapy in predominately sedentary patients. **D(GPP)**

R24 In patients with permanent AF where monotherapy is inadequate:

- to control the heart rate only during normal activities, beta-blockers or rate-limiting calcium antagonists should be given with digoxin **B**
- to control the heart rate during both normal activities and exercise, rate-limiting calcium antagonists should be given with digoxin. **B**

7.2 Antithrombotic therapy for permanent AF

The aim of antithrombotic therapy in patients with permanent AF is to prevent ischaemic stroke and other thromboembolic events. This section examines which type of antithrombotic therapy (anticoagulation, antiplatelet drugs or no treatment) has been shown to be effective in treating patients with permanent AF.

The high risk of ischaemic stroke and other thromboembolic events in AF has long been recognised. In particular, AF patients with valvular heart disease have an elevated risk of stroke and other thromboembolic events. Specifically, the presence of mitral valve stenosis has been shown to be a substantial risk for stroke and thromboembolism, with these events occurring in 9 to 20% of patients, of whom up to 75% have cerebral emboli.[163,164] A person with mitral stenosis in sinus rhythm who develops AF increases their risk of thromboembolism by three to seven times.[164,165] The risk of systemic emboli in rheumatic mitral disease is much greater in both the elderly and those with poor cardiac function, but correlates poorly with mitral valve calcification, mitral valve area, or left atrial size.

Percutaneous balloon mitral commissurotomy decreases the risk of systemic embolism, but mitral valvuloplasty does not appear to. Successful mitral valvuloplasty does not therefore eliminate the need for continued anticoagulation.[164] Because of the risk of stroke and thromboembolism, it has been considered unethical to conduct placebo-controlled trials of antithrombotic therapy in patients with mitral valve disease.

Similarly, the presence of AF without any valve disease (non-valvular AF) increases the risk of stroke and thromboembolism five-fold.[13] Silent cerebral infarction is also a common problem[166] and there is a distinct clustering of stroke events at the time of onset of AF as well.[167] In contrast

to valvular AF, however, in the past two decades many large randomised trials have examined the value of antithrombotic therapy in non-valvular AF.[168]

Because of the increasingly elderly population, AF is likely to become more common, and the issues associated with thromboprophylaxis will become an even greater public health problem. Despite the higher risk associated with stroke in the elderly, as well as the greatest benefit of anticoagulation, the elderly are the group of patients where there is suboptimal use of thromboprophylaxis for AF. This is thought to be because of the perceived increased risk associated with comorbidity, interactions with concomitant drug therapies and bleeding in these patients.[169] Suboptimal use of thromboprophylaxis may also be due to patient factors, where some patients choose the option of 'informed dissent' and decline an effective treatment option.[170]

The purpose of this section is to review the evidence on antithrombotic therapies (oral anti-coagulation and/or antiplatelet therapy) as a means of preventing stroke and thromboembolism in patients with permanent AF.

7.2.1 Methodological introduction

The results of eight meta-analyses, four RCTs and two unrandomised controlled trials of oral anticoagulation using vitamin K antagonists such as warfarin, and antiplatelet therapy in patients with AF were included. Results relating to the antiplatelet agent triflusal were included but no recommendations were made on this drug as it is not currently licensed for use in the UK.

Most of the trials were large randomised trials, consisting almost entirely of patients with permanent non-valvular AF.

7.2.2 Evidence statements

▷ Adjusted-dose warfarin versus placebo

Two studies,[171,172] found that compared with placebo, adjusted-dose warfarin was associated with a reduction in ischaemic stroke: (**1+**)

- ARR = 3.1% (62% RRR)[171]
- OR = 0.34 (95% CI 0.25 to 0.46).[172]

However, in one study adjusted-dose warfarin was found to be associated with an increased risk of major haemorrhage (OR 2.35, 95% CI 1.30 to 4.24)[172] (**1+**). The same study[172] also found no significant difference in terms of overall mortality (OR 0.74, 95% CI 0.53 to 1.04). (**1+**)

▷ Adjusted-dose warfarin versus control treatment (aspirin or placebo)

One study[173] found adjusted-dose warfarin (compared with aspirin or placebo controls) to be associated with a significant reduction in the incidence of ischaemic stroke as well as the composite outcomes of haemorrhagic or ischaemic stroke, and vascular events (myocardial infarction, stroke, haemorrhage, vascular death) (**1+**). The same study[173] also found no significant effect for the incidence of myocardial infarction, systemic embolism or intracranial haemorrhage (ICH). (**1+**)

▷ Adjusted-dose warfarin versus antiplatelet therapy (aspirin or indobufen)

Two meta-analyses[171,174] found adjusted-dose warfarin (compared with antiplatelet therapy with aspirin or indobufen) to be significantly associated with an absolute risk reduction of ischaemic stroke: (**1+**)

- ARR = 0.8% (36% RRR), p<0.05[171]
- ARR = 2.3% (2.0% versus 4.3%; p<0.001).[174]

One meta-analysis[174] found that when the composite outcome of either ischaemic stroke or ICH was considered, it resulted in an absolute risk reduction of 2.1% (2.4% versus 4.5%; p<0.001). (**1+**)

In one meta-analyses[174] adjusted-dose warfarin was found to be associated with an increase in incidence of major haemorrhage (increased absolute risk of 0.9% (2.2% versus 1.3%; p<0.05)), however, in a second meta-analysis no significant difference was found.[175] (**1+**)

One study[175] found adjusted-dose warfarin (compared with antiplatelet therapy with aspirin or indobufen) to be associated with a reduced incidence of non-fatal stroke, although no significant difference has been found for fatal stroke, nor overall mortality (**1+**). In another study,[176] adjusted-dose warfarin was found to be associated with a reduced incidence of severe ischaemic stroke in those where an ischaemic stroke occurs. (**2+**)

▷ Adjusted-dose warfarin versus fixed, low-dose warfarin

One meta-analysis[172] found adjusted-dose warfarin to be associated with a reduced risk of stroke (OR 0.38, 95% CI 0.24 to 0.60) compared with fixed, low-dose warfarin. In a second study[177] only the composite outcome of all thrombotic events was found to be significant (RR 0.50, 95% CI 0.25 to 0.97). (**1+**)

No significant difference has been found in the incidence of overall mortality,[172] vascular or haemorrhagic death[177] or major haemorrhage[172] between fixed, low-dose warfarin and adjusted-dose warfarin. (**1+**)

▷ Adjusted-dose warfarin versus fixed, low-dose warfarin with aspirin

One meta-analysis[172] found adjusted-dose warfarin (compared with fixed, low-dose warfarin) significantly reduced the incidence of stroke (OR 0.38, 95% CI 0.24 to 0.60). However a larger meta-analysis[177] found no significant difference (**1+**). No significant difference has been found in terms of overall mortality,[172] vascular or haemorrhagic death[177] or major haemorrhage[172] between fixed, low-dose warfarin with aspirin and adjusted-dose warfarin. (**1+**)

One study[176] found that at an INR greater than or equal to 2.0, adjusted-dose warfarin was associated with a reduced incidence of severe ischaemic stroke in those where an ischaemic stroke occurs compared with when the INR is less than 2.0. (**2+**)

▷ Antiplatelet therapy with aspirin or dipyridamole and placebo

Based on the results of two studies,[172,178] no significant difference has been found between antiplatelet therapy with aspirin or dipyridamole and placebo in terms of:

- overall mortality[172] (1+)
- vascular death[178] (1+)
- myocardial infarction[178] (1+)
- systemic embolism[178] (1+)
- vascular event[178] (1+)
- major haemorrhage.[172,178] (1+)

One meta-analysis[171] found antiplatelet therapy to be associated with an absolute risk reduction for stroke of 1.9% (24% relative risk reduction), however, in two smaller meta-analyses[172,178] no significant differences were found. (1+)

▷ Triflusal with acenocoumarol versus acenocoumarol monotherapy

One study[179] which compared triflusal (600 mg per day) in combination with acenocoumarol (INR of 1.25 to 2.00) with acenocoumarol monotherapy (INR of 2.0 to 3.0) found that the composite outcome of overall (haemorrhagic and ischaemic) stroke incidence, vascular death or systemic embolism was lower in the combination therapy group than in the acenocoumarol monotherapy group (0.92% per year versus 2.70% per year; $p<0.05$) (1+). A similar association was found when the number of severe bleeding events was added to the overall incidence of stroke or systemic embolism (1.48% per year versus 3.78% per year; $p<0.05$) (1+). No statistically significant difference was reported in the incidence of severe bleeding events. (1+)

7.2.3 From evidence to recommendations

The studies included wide variations in the dose of aspirin (75 mg to 325 mg per day). Similarly, the studies differed in the degree of anticoagulation, with earlier studies using a higher level of anticoagulation (INR range of 2.0 to 4.5) than more recent studies.

Oral anticoagulation with vitamin K antagonists (such as warfarin) was the most effective thromboprophylactic treatment in the prevention of cardioembolic stroke. A target INR of 2.5 (range 2 to 3) should be maintained for the majority of patients.[176] However, anticoagulation is associated with an increased rate of haemorrhagic stroke and other bleeding events.[172] Nonetheless, it remains effective for the prevention of stroke overall.[174,175] No association between anticoagulation and mortality has been found for either vascular-related deaths[173] or all forms of death.[172]

The true efficacy of warfarin prophylaxis may have been underestimated as most strokes in patients randomised to warfarin occurred when the patients were not taking warfarin or when they were significantly under-anticoagulated. Further underestimates may have risen from the inconvenience of dosing adjustments and the need for regular blood tests to monitor INR levels, dietary restrictions, the risk of minor and major bleeding, and under-appreciation or lack of knowledge of the risk of stroke, or they may not adhere strictly to the treatment regimen, thereby placing themselves at greater risk for stroke or a major bleed.[169,180]

The dose of aspirin for AF thromboprophylaxis is subject to controversy. The relative stroke risk reduction of aspirin in AF patients is approximately 22%.[171] This is similar to that seen in a general population and the reduction of vascular events (22%) for antiplatelet therapy versus

control in 'high risk' patients with vascular disease.[181] Moreover, in the latter cases no differences have been reported in aspirin doses between 75 to 325 mg.[181] However, higher aspirin doses may be associated with more adverse effects.

AF commonly co-exists with vascular disease, and the benefits of aspirin in AF may simply relate to the effect on vascular disease, rather than on thrombogenesis in AF *per se*. This is supported by the thrombi associated with AF being fibrin rich ('red clot') and more related to coagulation abnormalities.

In trials specifically of AF populations comparing aspirin with placebo, the one trial[182] that tested aspirin 75 mg/day did not show a significant benefit for the prevention of stroke in patients with permanent AF. Similarly, in another trial[183] aspirin (most at 325 mg per day) was given in a non-randomised manner, and no significant benefit was seen. However, in another trial[184] using aspirin 325 mg/day, aspirin was reported to result in a significant 42% reduction in stroke, but was best for those aged under 75 years and did not prevent severe strokes or recurrent strokes.

Because aspirin 325 mg tablets are unavailable in the UK, and in view of the controversy over trial evidence in relation to the pathophysiological data, it was considered reasonable to recommend the use of aspirin at a dose of 75 to 300 mg/day as thromboprophylaxis.

It was noted that the addition of aspirin to oral anticoagulation (warfarin or fluindione) produced no extra benefit for stroke prevention but may increase bleeding risk. It was therefore felt that to prevent strokes in patients with AF, aspirin should not be given as adjunctive therapy to warfarin although there may be other reasons for co-prescribing aspirin. For example, aspirin 75 mg a day is commonly prescribed for vascular disease (eg carotid, coronary or peripheral artery disease), and if AF is also present, warfarin – if indicated for stroke prevention – is also commonly given. It is a matter for clinical judgement on the appropriateness, duration and safety (eg risk of bleeding) of the concomitant administration of warfarin with aspirin. It was noted that another antiplatelet agent (trifusal, not available in the UK) was of benefit when administered together with the oral anticoagulant acenocoumarol.

It was stressed that the risk of stroke and thromboembolism in AF patients is not homogeneous, and risk stratification is essential (see section 11.6).

RECOMMENDATIONS

R25 In patients with permanent AF a risk–benefit assessment should be performed and discussed with the patient to inform the decision whether or not to give antithrombotic therapy. **D(GPP)**

R26 In patients with permanent AF where antithrombotic therapy is given to prevent strokes and/or thromboembolism (see section 11.6):

- adjusted-dose warfarin should be given as the most effective treatment **A**
- adjusted-dose warfarin should reach a target INR of 2.5 (range 2.0 to 3.0) **A**
- where warfarin is not appropriate, aspirin should be given at 75 to 300 mg/day **B**
- where warfarin is appropriate, aspirin should not be co-administered with warfarin purely as thromboprophylaxis, as it provides no additional benefit. **B**

7.3 Rate-control treatment algorithm for permanent AF

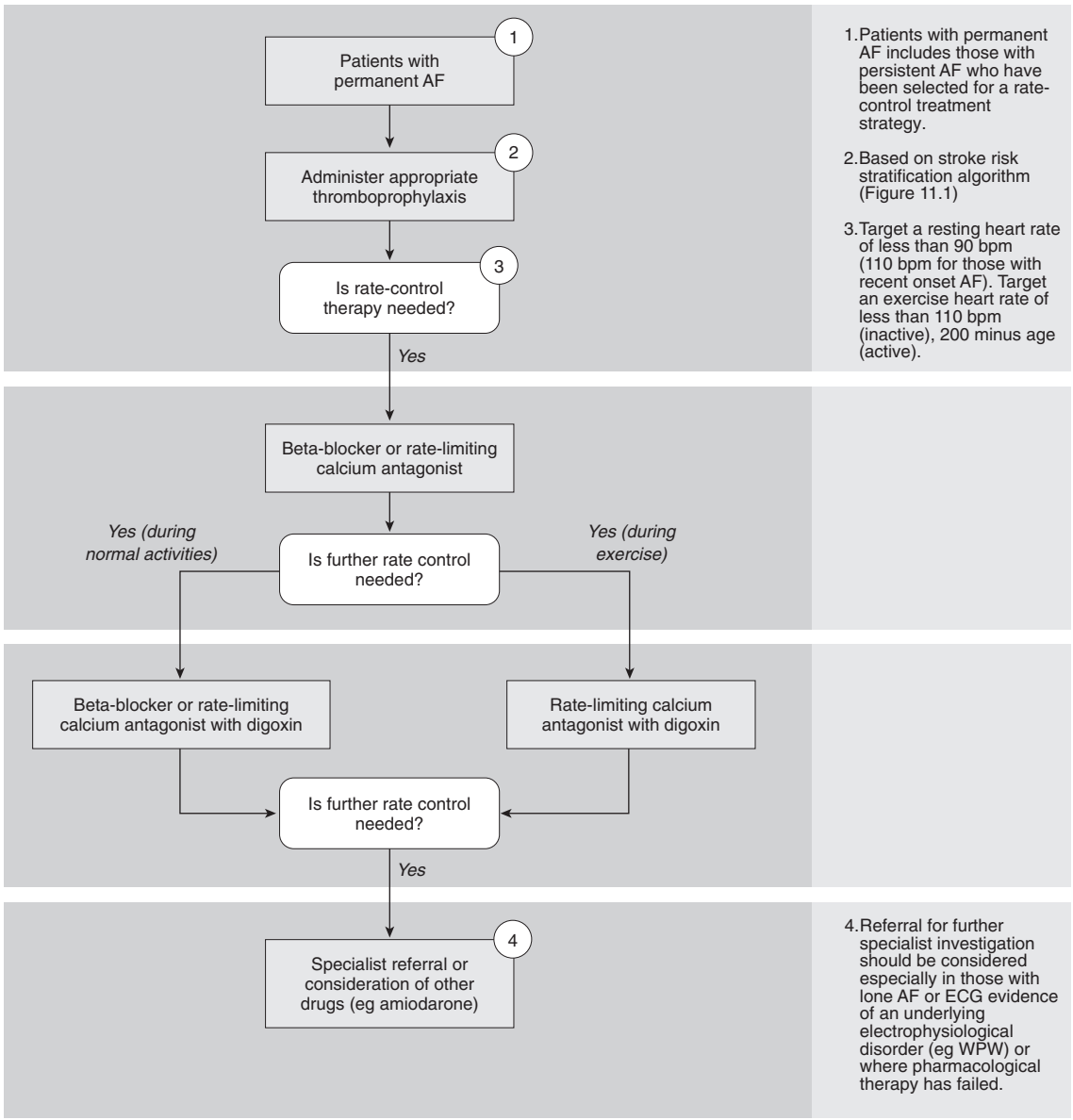


Figure 7.1 Rate-control treatment algorithm for permanent (and some cases of persistent) AF

8 Treatment for paroxysmal AF

8.1 Rhythm control for paroxysmal AF

The three main aims of treatment for paroxysmal AF are:

(i) to suppress paroxysms of AF and maintain long-term sinus rhythm

(ii) to control heart rate during paroxysms of AF if they occur

(iii) to prevent the complications associated with paroxysmal AF, ie stroke- and tachycardia-induced cardiomyopathy.[185]

This section of the guideline essentially deals with the first aim.

Many patients with paroxysmal AF can be highly symptomatic.[31] Paroxysms of AF that are persistent (that is, lasting more than 7 days) can be considered for cardioversion to sinus rhythm (see Chapter 5).

However, the abolition of symptoms of paroxysmal AF does not necessarily mean abolition of the AF *per se*, as heart rate slowing may abolish symptoms but allow asymptomatic episodes to continue.[186] In patients with symptomatic recurrences, it may be appropriate to document the frequency of arrhythmia by Holter monitoring or event recording (see section 4.4 above). If symptoms are abolished by therapy, repeat monitoring to ascertain whether asymptomatic episodes of AF are present is occasionally performed.

If attacks of paroxysmal AF are frequent, in current clinical practice chronic prophylaxis is usually used with drugs to reduce the frequency of paroxysms after removal of precipitating factors such as caffeine, alcohol, stress, and adequate treatment of underlying diseases such as myocardial ischaemia, thyrotoxicosis and heart failure.[185] If episodes of paroxysmal AF are infrequent, a pill-in-the-pocket approach can be considered (see section 8.2).

In the long term, few patients achieve complete suppression of paroxysms of AF. In clinical practice, clinicians commonly use beta-blockers or low-dose sotalol as first-line drugs, and if the patient is still getting symptomatic paroxysms, Class Ic and III drugs are used, depending on associated comorbidity and structural heart disease.

In UK clinical practice, the drugs commonly used for paroxysmal AF are beta-blockers, Class Ic agents (flecainide, propafenone) and Class III agents (sotalol, amiodarone). This section addresses the comparative efficacy of these agents.

8.1.1 Methodological introduction

Studies were considered for inclusion in this report if results were reported for a population or subpopulation with paroxysmal AF. Studies were excluded if the treatment drugs were not prescribed as regular medication for paroxysmal AF.

Nine studies were appraised, two[187,188] were entirely comprised of paroxysmal AF patients, although the follow-up times were relatively short (12 months or less) compared with other

studies in a general AF population. The remaining studies were undertaken in general AF populations and either reported the results for those with paroxysmal AF separately, or reported no significant interaction between AF type and drug efficacy, hence allowing extrapolation of the results to those with paroxysmal AF only.

All of the studies were either single-blinded or double-blinded RCTs with two active treatment arms. Studies that made comparisons with placebo or digoxin were not considered. All of the studies excluded patients with moderate-to-severe heart failure (typically defined as an NYHA grade greater than II).

One study based in Canada compared the costs of amiodarone treatment with propafenone/sotalol treatment.[189] The cost analysis was based on 1-year follow-up data of 392 patients randomised to low-dose amiodarone (200 mg/day) or alternative first-line therapy (sotalol or propafenone) in a multicentre open label trial.[112]

8.1.2 Evidence statements

▷ Propafenone versus sotalol

One study[187] found no significant difference in the proportion of patients experiencing a reduction in recurrent AF episodes between propafenone and sotalol (80 to 160 mg bid) over a minimum of 3 months. (**1++**)

One study[136] showed a significant difference in terms of the proportion of patients maintaining sinus rhythm between propafenone and sotalol (up to 480 mg/day) in favour of propafenone after 25 months of administration (**1+**). However, over shorter periods two other studies[134,135] found no significant difference. (**1++**)

One study[187] involving both persistent and paroxysmal AF participants found no significant difference in the rates of either intolerable or tolerable side effects between sotalol (80 to 160 mg bid) and propafenone. (**1++**)

▷ Amiodarone versus sotalol

Two studies involving subgroups of patients with paroxysmal AF[132,133] found amiodarone to be significantly associated with a lower rate of AF recurrence[133] and a higher prevalence of sinus rhythm[132] at 12 months and at 24 months compared to sotalol (160 to 480 mg/day[132] or 160 to 320 mg/day[133]). (**1+**)

▷ Beta-blockers versus sotalol

One small, open-label crossover study[188] found no significant difference between atenolol and sotalol (80 mg bid) in the frequency of recurrent episodes of AF or the average duration of recurrent episodes. (**1+**)

▷ Propafenone versus amiodarone

One study,[112] in a population of both persistent and paroxysmal AF patients, found amiodarone to be significantly associated with a higher prevalence of sinus rhythm at a mean

follow-up of approximately 15.6 months compared with propafenone or sotalol (69% versus 39%, respectively; p<0.001) (1+). The same study also reported comparable efficacy between propafenone and sotalol, as well as comparable outcomes in each arm of the study for paroxysmal and persistent AF patients (1+). In another study[137] involving a subgroup of 92 patients with paroxysmal AF, 40% of those treated with amiodarone had a recurrence of AF at 24 months, compared with 83% of those treated with propafenone (p=0.19) (1+). When the composite endpoint of either AF recurrence or occurrence of side effects was considered, the figures were 58% versus 53%, respectively (p=0.51). (1+)

One study[189] found that the average cost per patient for AF-related procedures and hospitalisations was significantly lower in the amiodarone group than the sotalol/propafenone group (US$532 versus US$898, p=0.03). This cost advantage increased when the costs of hospitalisations associated with strokes were included (US$541 versus US$947, p=0.02). However, the total mean hospital costs (US$1,854 versus US$1,834, p=0.96) and the total mean hospital costs plus physician costs (US$2,586 versus US$2,482, p=0.83) were similar in both groups.

8.1.3 From evidence to recommendations

Much of clinical practice in the management of paroxysmal AF has been based on relatively small trials of short duration in (mainly) symptomatic subjects. Most pharmacological studies of paroxysmal AF have concentrated on the reduction of symptomatic recurrences of paroxysmal AF, despite many having asymptomatic episodes. Many studies have also involved mixed populations with paroxysmal AF, paroxysmal atrial flutter or persistent AF.

Those patients who are asymptomatic or have rare paroxysms (eg only a few paroxysms a year) may decide not to take routine medication or to use a pill-in-the-pocket strategy, and the patient's views need to be considered. Similarly, where paroxysms are induced by precipitants (eg caffeine or alcohol), these need to be avoided by the patient, in which case treatment may not be necessary or a pill-in-the-pocket strategy could be adopted.

An escalating approach to drug therapy in paroxysmal AF could be recommended depending on the frequency of a patient's paroxysms and the need for increasingly effective antiarrhythmic drugs. For example, a beta-blocker could be prescribed in the first instance and in patients where this did not adequately control the paroxysms a Class Ic drug could be administered followed by amiodarone as a third-line option. This escalation of drug use is in the opposite direction of the evidence on efficacy alone as this did not fully cover the issue of the side effects (especially long-term) of the more efficacious agents.

Propafenone appeared to be at least as effective as sotalol in preventing the recurrence of AF for up to 12 months following administration,[134,187] although for longer periods propafenone was more effective.[136] The two drugs were comparable in terms of side effects.[187] It was noted that Class Ic agents (propafenone and flecainide) should be used with caution in patients with structural heart disease or coronary artery disease.

Amiodarone was more effective than sotalol[132,133] and propafenone[112] in the prevention of recurrent AF. Due to concerns regarding contraindications of Class Ic agents in patients with left ventricular dysfunction, amiodarone was regarded as the drug of choice in these patients with symptomatic paroxysms despite initial beta-blocker therapy.

The concerns over the long-term toxicity of amiodarone were not addressed in the evidence. Although the clinical evidence demonstrated that amiodarone was the most effective drug, its long-term use in patients with infrequent paroxysms needed to be fully weighed against the risk of side effects, especially since some (eg lung fibrosis) could be serious.

The advice given in the *British National Formulary* suggested that Class I and III agents should be administered under a hospital physician, but it was stressed that this did not necessarily mean that the patient had to be hospitalised and it was the decision to administer the drug that required the necessary expertise.

The evidence only addressed the suppression of paroxysms and did not cover the control of heart rate or the prevention of complications from paroxysmal AF (eg stroke). It was considered important that patients have their symptoms and medication reviewed regularly to determine whether a patient:

- had any side effects
- had a continued need for treatment
- could have their medication dose reduced.

It was also considered important that patients should not be left on medication long-term without review.

In terms of the cost of AF, amiodarone was cheaper than sotalol or propafenone, although this was based on a one-year follow-up study and costs of side effects may not have been adequately included in the analysis.

RECOMMENDATIONS

R27 Where patients have infrequent paroxysms and few symptoms, or where symptoms are induced by known precipitants (such as alcohol, caffeine), a 'no drug treatment' strategy or a pill-in-the-pocket strategy should be considered and discussed with the patient. **D(GPP)**

R28 In patients with symptomatic paroxysms (with or without structural heart disease,* including coronary artery disease) a standard beta-blocker should be the initial treatment option. **D(GPP)**

R29 In patients with paroxysmal AF and no structural heart disease:*

- where symptomatic suppression is not achieved with standard beta-blockers, either
  - a Class Ic agent (such as flecainide or propafenone), or **D(GPP)**
  - sotalol** **D(GPP)**

  should be given.
- where symptomatic suppression is not achieved with standard beta-blockers, Class Ic agents or sotalol, either
  - amiodarone, or **B**
  - referral for non-pharmacological intervention (see section 12.3)

  should be considered. **A**

R30 In patients with paroxysmal AF and coronary artery disease:

- where standard beta-blockers do not achieve symptomatic suppression, sotalol should be given* **D(GPP)**
- where neither standard beta-blockers nor sotalol achieve symptomatic suppression, either
  - amiodarone, or **B**
  - referral for non-pharmacological intervention (see section 12.3) **A**

  should be considered.

R31 In patients with paroxysmal AF with poor left ventricular function:

- where standard beta-blockers are given as part of the routine management strategy and adequately suppress paroxysms, no further treatment for paroxysms is needed **D(GPP)**
- where standard beta-blockers do not adequately suppress paroxysms, either
  - amiodarone or **B**
  - referral for non-pharmacological intervention (see section 12.3) **A**

  should be considered.

R32 Patients on long-term medication for paroxysmal AF should be kept under review to assess the need for continued treatment and the development of any adverse effects. **D(GPP)**

*Coronary artery disease or left ventricular dysfunction.
**Progressively titrated from 80 mg twice daily up to 240 mg twice daily.

8.2 Treatment strategy for paroxysmal AF

In selected patients with recurrent paroxysmal AF, out-of-hospital initiation of antiarrhythmic drugs may be possible, allowing for earlier treatment, a shorter duration of AF and a presumed likelihood of restoring and maintaining sinus rhythm. A pill-in-the-pocket approach is used in those not taking drugs regularly due to infrequent symptoms/paroxysms, or can be taken as an 'extra' drug dose in those already on a low maintenance of that particular drug. This approach is different to the out-of-hospital use of antiarrhythmic drugs in patients with recurrent persistent AF, where the aim may be to achieve pharmacological cardioversion *per se* or to improve the likelihood of subsequent elective electrical cardioversion (see Chapter 5), or to maintain sinus rhythm (see section 6.1).

The main concern with a pill-in-the-pocket approach is the risk of proarrhythmia often associated with antiarrhythmic drugs. Thus, the pill-in-the-pocket approach has generally been advocated only in those patients with a low risk of proarrhythmia and other adverse side effects. Such patients are typically those with no structural heart disease, absence of heart failure or left ventricular dysfunction, and where there is evidence that the antiarrhythmic drug used has previously worked successfully with no adverse effects (eg after at least one inpatient trial of the drug administered as a single oral dose, under ECG monitoring).

The antiarrhythmic drugs amiodarone and propafenone have both been considered in a number of trials comparing the safety and efficacy of a single oral dose of the drug with the intravenous administration of the same drug.[82–85] In all of these trials, patients were selected

on the basis of relatively young age and the absence of any severe underlying structural heart disease. There was no incidence of ventricular proarrhythmia reported in either the intravenous or oral administration arms of these trials, and the incidence of successful cardioversion within 8 or 24 hours was comparable in most cases.

The objective of this section is to determine in which patients a single oral-dose antiarrhythmic drug may be safely used as a pill-in-the-pocket approach.

8.2.1 Methodological introduction

Studies were included if a comparison was made in terms of the safety, efficacy and impact on healthcare resources between the out-of-hospital self-administration of pharmacological cardioversion and the supervised, in-hospital administration in a well-defined patient cohort with either AF or supraventricular tachycardia (SVT). Studies were not included if the pharmacological agents were administered prophylactically.

Both of the included studies were based in Italy and compared the rates of hospital admission and emergency room treatment in a single cohort of patients in the period before and the period after the self-administration of antiarrhythmic drugs for the termination of either paroxysmal AF[190] or paroxysmal SVT.[191]

Neither study specified the treatment protocol during the period before the self-administration of antiarrhythmic drugs, or made a comparison between the two periods in terms of safety and efficacy.

8.2.2 Evidence statements

One study[190] found that the average number of admissions per month for emergency treatment was significantly lower during treatment of paroxysmal AF using a pill-in-the-pocket approach with Class Ic drugs than during conventional treatment (4.9 versus 45.6, $p<0.001$) in a population of patients with the following criteria: (2+)

- age 18 to 75
- left ventricular ejection fraction (LVEF) greater than 50%
- no history of severe heart disease
- systolic blood pressure (BP) greater than 100 mmHg
- heart rate greater than 70 bpm.

Another study found a similar result using similar selection criteria among patients with paroxysmal SVT.[191] (2+)

8.2.3 From evidence to recommendations

The limited evidence suggested that pill-in-the-pocket treatment was associated with a lower incidence of inpatient and emergency hospital admissions than conventional treatment.[190,191] It was uncertain whether the pill-in-the-pocket strategy was associated with more adverse events, or reduced episode duration when compared to in-hospital treatment.

Within the UK, the number of patients managed in this way is currently thought to be small, and patients need to be made more aware of this treatment option, although strict selection

criteria are deemed necessary. In particular, it was considered that patient education in its use is vital.

Therapy for paroxysmal AF should be tailored to the patient. For example, episodes of AF for 1 to 2 minutes once a year or for 10 hours twice a day are both paroxysmal AF, but their impact on the patient's quality of life, if symptomatic, would be quite different. In patients with infrequent and brief paroxysms, the regular use of antiarrhythmic therapy may not be necessary (and is commonly not prescribed in current clinical practice). Such patients may be suitable for the pill-in-the-pocket approach. However, for infrequent but protracted and symptomatic paroxysmal AF, rapid cardioversion of each event and/or antiarrhythmic drug prophylaxis may be considered.

RECOMMENDATION

R33 In patients with paroxysmal AF, a pill-in-the-pocket strategy should be considered in those who:

- have no history of left ventricular dysfunction, or valvular or ischaemic heart disease; and
- have a history of infrequent symptomatic episodes of paroxysmal AF; and
- have a systolic blood pressure greater than 100 mm Hg and a resting heart rate above 70 bpm; and
- are able to understand how to, and when to, take the medication. **C**

8.3 Antithrombotic therapy for paroxysmal AF

Patients with paroxysmal AF appear to carry the same risk of stroke and thromboembolism as those with persistent AF.[192] Whether the risk is dependent upon the frequency of the paroxysms or their duration is unclear.[193] In addition, patients frequently get asymptomatic paroxysms[31] and may still be at risk of thromboembolism. There is evidence of some clustering of thromboembolic events around the time of onset of AF[167,194] and following successful cardioversion.[139] Compared with permanent AF, patients with paroxysmal AF tend to be younger[18] and have a lower prevalence of associated clinical risk factors.

8.3.1 Methodological introduction

No studies were found that considered the efficacy of antithrombotic therapy compared with placebo in a population comprising only paroxysmal AF patients.

However, subgroups of patients with paroxysmal AF were reported in two meta-analyses. One meta-analysis[192] pooled data from the aspirin treatment arms of three serial trials and compared ischaemic stroke rates in the paroxysmal AF subgroup with those of non-paroxysmal AF patients. The second study[174] compared the effects of anticoagulation and antiplatelet therapy on rates of ischaemic stroke and major bleeding in a subgroup of participants with paroxysmal AF.

8.3.2 Evidence statements

One meta-analysis[174] found that in patients treated with aspirin, the incidence of stroke was similar in those with paroxysmal AF and those with non-paroxysmal AF. (**2++**)

One meta-analysis[192] found adjusted-dose warfarin to be associated with a reduced incidence of ischaemic stroke compared with aspirin (1.5% versus 4.7%, respectively, $p<0.05$), although no significant difference was found in terms of the incidence of bleeding events. The study also found the efficacy of warfarin in reducing the incidence of stroke to be comparable between those with paroxysmal and those with non-paroxysmal AF. (**1+**)

8.3.3 From evidence to recommendations

The data from clinical trials were limited by the relatively small number of patients with paroxysmal AF (approximately 12% of subjects in five randomised trials).[192] There was some evidence that patients with paroxysmal AF receiving aspirin experience a similar rate of ischaemic stroke as patients with non-paroxysmal AF who receive aspirin.[192]

The effectiveness of anticoagulation compared with antiplatelet therapy in reducing the rate of ischaemic stroke is similar for patients with either paroxysmal AF or non-paroxysmal AF.[174] The rate of adverse bleeding events associated with anticoagulation is also similar between the two groups.[174]

In current clinical practice, the indicators for antithrombotic therapy are highly variable (often depending on the clinical presentation of symptoms). For example, the more frequent a patient's paroxysms the more likely they will be prescribed anticoagulants, despite the risk of stroke being determined by the presence of associated risk factors. It was concluded that patients with paroxysmal AF required a similar degree of anticoagulation as patients with permanent AF, but that further studies would be required to confirm this.

RECOMMENDATION

R34 Decisions on the need for antithrombotic therapy in patients with paroxysmal AF should not be based on the frequency or duration of paroxysms (symptomatic or asymptomatic) but on appropriate risk stratification, as for permanent AF (see section 11.6). **B**

8.4 Rhythm-control treatment algorithm for paroxysmal AF

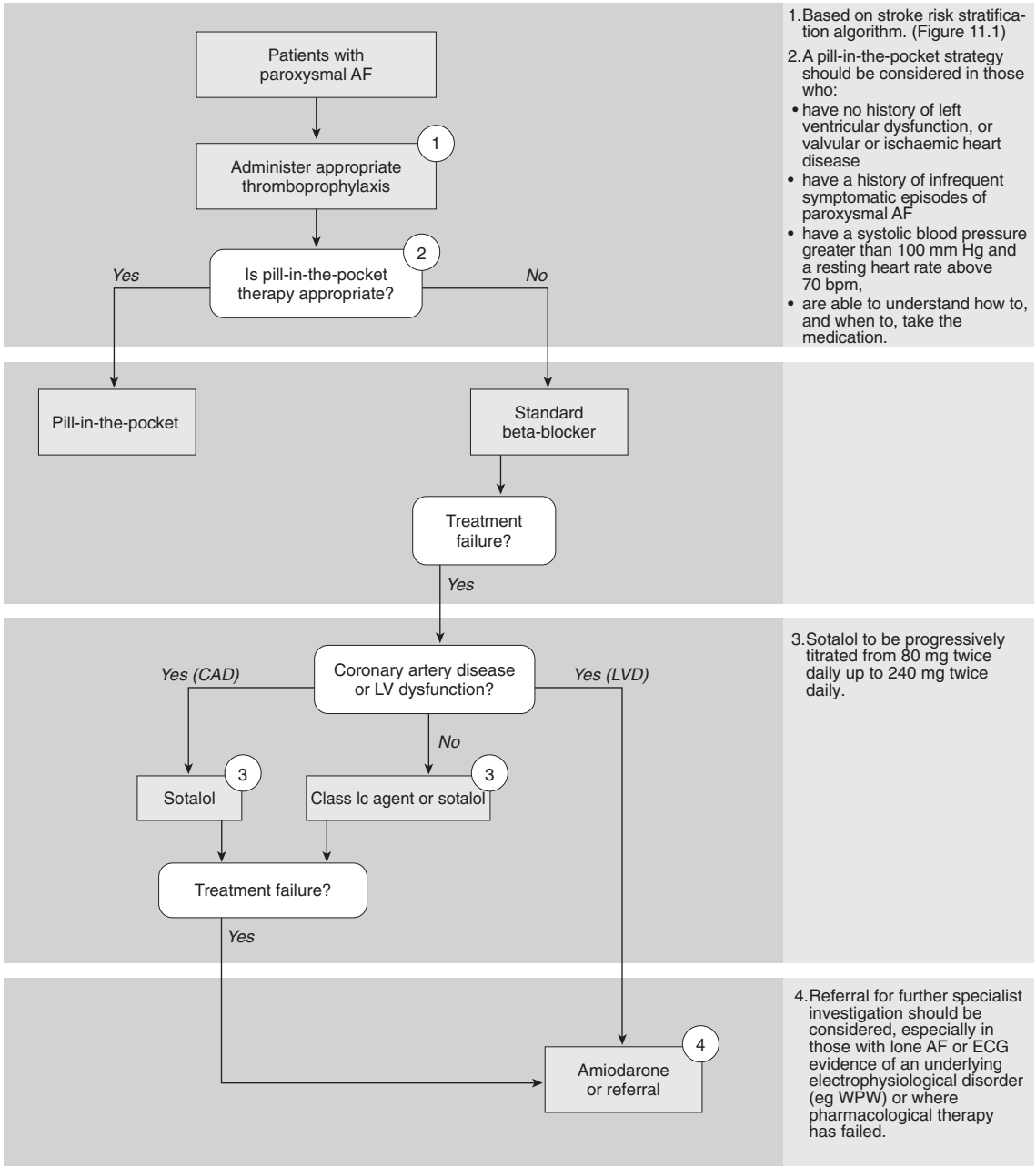


Figure 8.1 Rhythm-control treatment algorithm for paroxysmal AF

9 Treatment for acute-onset AF

9.1 Acute AF in haemodynamically unstable patients

Although most patients in AF present without haemodynamic compromise, there is a small group of patients who are significantly compromised by the onset of AF. These patients require immediate hospitalisation and urgent intervention to prevent further deterioration.

Those considered at highest risk from haemodynamic instability caused by AF have been defined as:[195]

- those with a ventricular rate greater than 150 bpm
- ongoing chest pain, or
- critical perfusion.

In these circumstances, the concerns regarding intervention in the absence of anticoagulation and echocardiography are counterbalanced by the need for urgent treatment. This may include the need to treat important problems such as hypoxia, left ventricular failure, acute ischaemia, pyrexia and electrolyte disorders.

A number of specific issues are recognised in current UK practice for the management of patients with AF in the presence of haemodynamic instability:[65]

- The slow onset of digoxin makes it inappropriate for use in this situation.
- Patients whose AF is associated with thyrotoxicosis will not respond to any strategy that does not first treat the underlying thyroid disease.
- Patients with an accessory pathway such as Wolff–Parkinson–White (WPW) syndrome are particularly at risk following the onset of AF because they can present with high ventricular rates (greater than 200 bpm) and may need specific management.

Treatment with AV node blockers (eg adenosine, digoxin, verapamil, diltiazem) will unmask or exacerbate a rapid AF due to a WPW syndrome and are therefore contraindicated in such patients.[196]

In patients with AF associated with an unacceptably high ventricular rate the primary aim is one of rate control. In other patients with acceptable ventricular rates whose cardiac function has been compromised by AF onset in the context of other cardiac abnormalities (eg hypertensive heart disease, valvular heart disease), rate control is unlikely to bring about clinical improvement and there is a need for the restoration of sinus rhythm.

In clinical practice, amiodarone is the most common agent used in the management of patients presenting in AF with haemodynamic compromise, as it appears to have a hybrid effect of rapid reduction in ventricular rate in most patients with a proportion of these reverting to sinus rhythm over a longer period. An alternative choice suitable for use in patients with invasive monitoring is esmolol, which is an intravenous beta-blocker with a short half-life, which allows for accurate and frequent titration.

9.1.1 Methodological introduction

No studies were found that made a direct comparison between different treatment strategies in haemodynamically unstable patients. However, one observational study[26] was found reporting outcomes between different emergency interventions for AF. This study was in a mixed population including haemodynamically stable patients, and excluded those in whom immediate electrical cardioversion (ECV) or intubation was indicated on the basis of severe haemodynamic instability or respiratory failure. Nonetheless, the mean ventricular rate reported in this study did suggest the presence of rapid AF in a substantial proportion of the included patients.

In addition, three other studies were found reporting the effectiveness of either diltiazem in the acute control of ventricular rate[197] or amiodarone for acute pharmacological cardioversion[112,198] in patients with rapid AF.

Only one study[198] was found in the context of severe haemodynamic instability, occurring in an intensive-care setting in ventilated patients with severely impaired left ventricular dysfunction.

No studies were found reporting the effectiveness of ECV in the successful treatment of AF in the context of haemodynamic instability, although one study[26] did report the effectiveness of ECV in a population consisting primarily of acute-onset AF patients with a fast ventricular rate and a previous attempt at pharmacological cardioversion (PCV).

Studies that considered head-to-head drug comparisons for either ventricular rate-control or PCV are not considered here. For a comparison of drugs for use in PCV, see section 5.2 above; for use in ventricular rate control see section 7.1 above.

9.1.2 Evidence statements

One observational study[26] found that ECV successfully restored sinus rhythm in 89% of patients presenting with acute-onset AF and a mean ventricular rate of 122 bpm. Eighty-three per cent were refractory to an earlier attempt at pharmacological cardioversion using procainamide (which was successful in 50% of cases at doses between 500 and 1000 mg and had an incidence of adverse events of 9%).[28] The study reported no complications associated with ECV.[28]

Three studies[198–200] found the intravenous administration of amiodarone (eg 5 mg/kg over 5 minutes) to be an effective treatment for the restoration of sinus rhythm in patients with varying degrees of haemodynamic instability, including a group of intubated patients with severely impaired cardiac function.[28,198] However, one study[199] found an increased risk of bradycardia following amiodarone in those presenting with a slower initial heart rate. (2+)

One study[26] found the administration of rate-controlling drugs (beta-blockers, rate-limiting calcium antagonists or digoxin) to be an effective strategy to reduce ventricular rate in 75% of AF patients with a fast ventricular rate.[28] A similar result was reported in another study[197] with the rate-limiting calcium antagonist diltiazem.[28]

Two studies[198,200] found the intravenous administration of amiodarone (5 mg/kg over 3 to 5 minutes[200] or 300 mg bolus via central line[198]) to be an effective strategy to control ventricular rate in haemodynamically impaired patients.[28]

9.1.3 From evidence to recommendations

Based on limited available evidence, pharmacological rate-control and both pharmacological and electrical cardioversion are effective treatment options for the acute management of patients presenting with various degrees of haemodynamic instability.

In UK clinical practice, very sick patients with fast AF and haemodynamic compromise were often inappropriately administered iv flecainide. Flecainide should not be used in such patients unless they are known to have rapid AF consequent upon a WPW syndrome.

It was noted that the use of AV node blockers would unmask or exacerbate a rapid AF due to a WPW syndrome and their use is contraindicated in these patients. Digoxin was less effective in haemodynamically compromised patients due to its slow onset of action and possible adrenergic activity.

Intravenous amiodarone is widely used as it both rapidly reduces ventricular heart rate and cardioverts AF. In an emergency setting, amiodarone is likely to be administered intravenously via a peripheral line.

RECOMMENDATIONS

R35 In patients with a life-threatening deterioration in haemodynamic stability following the onset of AF, emergency electrical cardioversion should be performed, irrespective of the duration of the AF. **D**

R36 In patients with non life-threatening haemodynamic instability following the onset of AF:

- electrical cardioversion should be performed **D**
- where there is a delay in organising electrical cardioversion, intravenous amiodarone should be used **D**
- in those with known Wolff–Parkinson–White syndrome:
  - flecainide may be used as an alternative for attempting pharmacological cardioversion
  - atrioventricular node-blocking agents (such as diltiazem, verapamil or digoxin) should not be used. **D(GPP)**

R37 In patients with known permanent AF where haemodynamic instability is caused mainly by a poorly controlled ventricular rate, a pharmacological rate-control strategy should be used. **D**

R38 Where urgent pharmacological rate-control is indicated, intravenous treatment should be with one of the following:

- beta-blockers or rate-limiting calcium antagonists **D**
- amiodarone, where beta-blockers or calcium antagonists are contraindicated or ineffective. **D**

9.2 Antithrombotic therapy for acute-onset AF

The aim of this section is to examine which antithrombotic therapy, if any, is most effective in treating patients with acute-onset AF, including the postoperative setting.

The onset of AF is associated with a cluster of thromboembolic events,[167] but the development of intra-atrial thrombi, and the immediate risk of thromboembolism, is perceived to be minimal within the first 48 hours.

In one study of 357 patients with symptomatic acute-onset AF of less than 48 hour duration (of whom 250 converted spontaneously to sinus rhythm and 107 underwent cardioversion without any anticoagulation), thromboembolism only occurred in three patients.[140] In another series of 258 patients undergoing cardioversion for AF of less than 2 days duration, only one embolic event occurred out of 198 patients who did not receive pre- or post-cardioversion warfarin.[143] However, in a further study, patients with acute AF of an apparent duration of less than 3 days were found to have an intra-atrial thrombus detected by TOE in approximately 15% of cases.[201] This raises the possibilities that either the development of intra-atrial thrombus may be more rapid than previously suspected and/or that some cases of presumed recent-onset AF may have had the arrhythmia (possibly asymptomatically) for longer.

Thus, in patients presenting *de novo* with AF, a clear history of arrhythmia onset is necessary in order to guide appropriate antithrombotic therapy and, if performed, the safety of cardioversion.

9.2.1 Methodological introduction

No studies were found that addressed this clinical area.

9.2.2 From evidence to recommendations

Although no randomised trials have specifically addressed the issue of acute-onset AF, common clinical practice indicates that cardioversion may be safely performed without the need for oral anticoagulation if AF has been present for less than 48 hours.[202] However, in cases of uncertainty about arrhythmia onset, anticoagulation therapy is warranted.

The GDG discussed the use of intravenous unfractionated heparin and subcutaneous low molecular weight heparin (LMWH). Both drugs are routinely used in clinical practice in the acute and peri-cardioversion periods. It was agreed that anticoagulation with heparin could be started at the presentation of acute AF while the INR remains subtherapeutic during the initiating phase of oral anticoagulation.

Acute AF may present with a fast ventricular response, leading to haemodynamic instability, which may require urgent direct current (DC) cardioversion. Where the degree of haemodynamic instability is life threatening (for example, cardiogenic shock), DC cardioversion may need to be performed rapidly and in such cases would take priority over the need for anticoagulation.

RECOMMENDATIONS

R39 In patients with acute AF who are receiving no, or subtherapeutic, anticoagulation therapy: **D(GPP)**

- in the absence of contraindications, heparin should be started at initial presentation
- heparin should be continued until a full assessment has been made and appropriate antithrombotic therapy has been started, based on risk stratification (see section 11.6).

R40 In patients with a confirmed diagnosis of acute AF of recent onset (less than 48 hours since onset), oral anticoagulation should be used if:

- stable sinus rhythm is not successfully restored within the same 48-hour period following onset of acute AF, or
- there are factors indicating a high risk of AF recurrence,* or
- it is recommended by the stroke risk stratification algorithm (see Figure 11.1). **D(GPP)**

R41 In patients with acute AF where there is uncertainty over the precise time since onset, oral anticoagulation should be used, as for persistent AF (see section 6.2). **D(GPP)**

R42 In cases of acute AF where the patient is haemodynamically unstable, any emergency intervention should be performed as soon as possible and the initiation of anticoagulation should not delay any emergency intervention. **D(GPP)**

*Factors indicating a high risk of AF recurrence include:

- a history of failed attempts at cardioversion
- structural heart disease (mitral valve disease, left ventricular dysfunction or an enlarged left atrium)
- a prolonged history of AF (greater than 12 months)
- previous recurrences of AF.

9.3 Haemodynamically unstable AF treatment algorithm

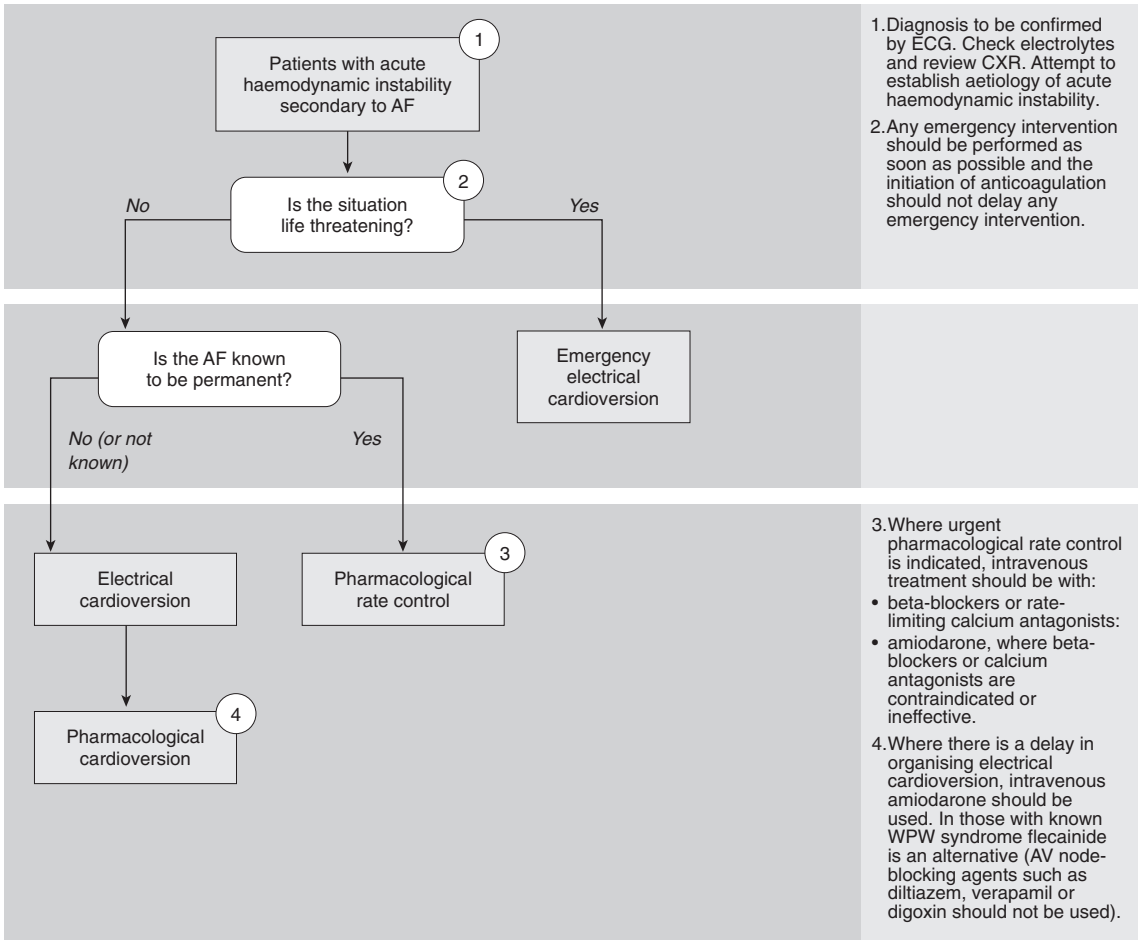


Figure 9.1 Haemodynamically unstable AF treatment algorithm

10 Postoperative AF

Postoperative AF (post-op AF) following cardiothoracic surgery is a significant problem, occurring in approximately 33% of patients after coronary heart surgery.[203] The occurrence following valvular heart surgery is even higher.[204]

Post-op AF is associated with a greater risk of mortality and morbidity.[205] Evidence is also emerging[206] that post-op AF predisposes people to a significantly increased risk of stroke and thromboembolism, suggesting that patients should be anticoagulated where post-op AF persists for more than 48 hours.[207]

Although post-op AF can be transient and generally self-limiting, treatment is indicated for those patients who remain symptomatic, become haemodynamically unstable, and develop cardiac ischaemia or heart failure. Conventional treatment strategies have included ECV, atrial overdrive pacing using temporary epicardial pacing leads (if atrial flutter is the dominant rhythm), pharmacological rate control and antithrombotic therapy. Cardioversion may also be attempted prior to hospital discharge.

Management of medical comorbidities (eg hypoxia) and the correction of underlying electrolyte imbalance (especially potassium and magnesium) is well recognised[208,209] in the prevention of post-op AF. Most units have strategies to maintain the serum potassium above 4 mmol per litre and some will often endeavour to maintain the serum potassium higher than 4.5 mmol per litre.[210] One recent meta-analysis[211] found that magnesium administration is an effective prophylactic measure for the prevention of post-op AF, but did not significantly alter length of stay or in-hospital mortality.

Currently, there is significant variation in the management of post-op AF. The aim of this chapter is to assess whether the perioperative administration of antiarrhythmic drugs is effective prophylaxis to prevent post-op AF (section 10.1), and in those cases where post-op AF develops, to determine which is the most effective treatment strategy (section 10.2).

10.1 Drug prophylaxis for postoperative AF

10.1.1 Methodological introduction

Of the studies considering prophylaxis, the majority concerned the prevention of post-op AF following cardiac surgery, and most of these results are summarised in a meta-analysis.[212] The other studies[213–218] considered non-cardiac thoracic procedures (eg pneumonectomy).

The reporting of side effects associated with antiarrhythmic drugs was not consistent, with many studies having too few participants to make any meaningful comparisons.

Studies were included if comparison was made between an antiarrhythmic drug or cardiac glycoside available in the UK, and a placebo or no-treatment control. The management of electrolyte imbalance (eg magnesium or potassium) was not assessed.

Five US studies[218,219–222] considering the cost-effectiveness of drug prophylaxis were appraised and met quality criteria.

- Two studies[219,220] estimated the mean cost per case of post-op AF avoided, of oral amiodarone prophylaxis versus no prophylaxis in patients undergoing coronary bypass grafting (CABG).
- One study[221] estimated the cost per AF averted of intravenous amiodarone therapy in CABG, valve and CABG plus valve patients, according to their predicted risk of postoperative AF.
- One study[218] estimated the median total hospital costs in patients with and without oral amiodarone prophylaxis based on the medical records of patients after pulmonary resection.
- One study[222] estimated the total hospitalisation costs in a RCT of oral amiodarone prophylaxis versus placebo in patients undergoing cardiopulmonary bypass.
- One study[219] estimated the total hospital costs in oral amiodarone prophylaxis versus placebo groups based on the Atrial Fibrillation Suppression Trial.

10.1.2 Evidence statements

▷ Drug prophylaxis in cardiac surgery

Amiodarone

In a meta-analysis of 14 studies[212] which compared amiodarone with placebo or no treatment, amiodarone administered pre-, intra- or postoperatively was found to be associated with a reduced incidence of post-op AF or other supraventricular arrhythmia (OR 0.54, 95% CI 0.44 to 0.67; p<0.00001) (**1+**). Similar results were found in other primary studies.[223–230] (**1++**)

In one study[231] amiodarone was significantly associated with a reduced incidence of post-op AF lasting longer than 24 hours, and episodes that required treatment, compared with placebo. (**1++**)

One study[224] found that amiodarone resulted in a reduced duration of post-op AF compared with no treatment (11.0 versus 16.2 days; p<0.001) (**2+**). Two smaller studies[222,232] found no significant difference in the duration of post-op AF. (**1++**)

One study[231] found rapid preoperative amiodarone loading resulted in more nausea than placebo (31.3% versus 16.0%; p=0.018), this was not observed with slow loading (21.4% versus 16.0%) (**1++**). There was no difference reported in the incidence of hypotension for either strategy. (**1++**)

Beta-blockers (excluding sotalol)

One meta-analysis of 28 studies[212] found beta-blockers (excluding sotalol) resulted in less post-op AF and other supraventricular arrhythmias (OR 0.35, 95% CI 0.26 to 0.49; p<0.00001) (**1+**). This result is consistent with the results of other primary studies,[226,230,233–235] in one of which[226] there was a significant increase in postoperative symptomatic bradycardia (less than 40 bpm) compared with placebo (16.1% versus 3.1%; p<0.05). (**1+**)

Sotalol

A meta-analysis of eight studies[212] found sotalol reduced post-op AF and other supraventricular arrhythmias compared with control (OR 0.36, 95% CI 0.23 to 0.56) (**1+**). Two other primary

studies[226,236] showed similar results, one of which[226] found a significant association between the use of sotalol (240 mg three times a day) and the incidence of postoperative symptomatic bradycardia (<40 bpm) compared with placebo (12.7% versus 3.1%; p<0.05) (**1+**). The study did not report any incidence of pro-arrhythmic side effects associated with sotalol.

Rate-limiting calcium antagonists

Four studies[237–240] found the rate-limiting calcium antagonist diltiazem to be significantly associated with a lower incidence of post-op AF compared with placebo or no treatment (**1++**). A similar result has also been found for the rate-limiting calcium antagonist verapamil.[241] (**1+**)

Propafenone

One study[242] found propafenone administered at 675 mg/day (although not at 450 mg/day) decreased post-op AF compared with placebo. (**1++**)

Procainamide

One study[243] found no difference in the incidence of post-op AF between procainamide and placebo but did reduce the number of patient days spent in post-op AF (16 versus 19 days; p<0.05) (**1++**). It was found to be significantly associated with an increased incidence of nausea compared with placebo (64% versus 32%; p<0.01) (**1++**). Another smaller study[244] (N=46) found procainamide to be significantly associated with a reduced incidence of post-op AF compared with placebo (3.9% versus 10.6%; p<0.04). (**1++**)

Digoxin

A meta-analysis of two studies,[235] as well as another primary study[245] not included in the meta-analysis found digoxin did not reduce post-op AF when compared with no treatment. (**1+**)

▷ Drug prophylaxis in thoracic (non-cardiac) surgery

Beta-blockers

One study[246] found beta-blockers to be effective in reducing post-op AF compared with placebo in favour of beta-blockers (6.7% versus 40.0%; p<0.05) (**1+**). Another[217] found a non-significant reduction in any arrhythmia requiring treatment but increased incidences of post-operative bradycardia and hypotension respectively (25% versus 4% compared with placebo; p=0.018; 49% versus 26% compared with placebo; p=0.003). (**1++**)

Rate-limiting calcium antagonists

One study[213] found diltiazem did not significantly reduce the overall incidence of post-op AF; but when considering those over 60 years old only (15% versus 25%; p=0.05), or when other cardiac arrhythmias were included (14% versus 26%; p=0.03), diltiazem was effective (**1++**). Another study[214] did not find diltiazem effective compared with placebo (8% versus 15%). (**1+**)

Flecainide

One study[215] found flecainide effectively reduced all postoperative cardiac arrhythmia requiring treatment (including AF) compared with placebo (0% versus 6%; p<0.05). (**1++**)

Digoxin

One study[216] found no other treatments compared with digoxin in reducing the incidence of post-op AF following pneumonectomy (31% versus 28%). (**2+**)

Amiodarone

One study[218] found amiodarone reduced post-op AF compared with no treatment (9.7% versus 33%; p=0.025) following pneumonectomy. (**2+**)

Health economics

There was no significant difference in total hospital costs in oral amiodarone prophylaxis versus placebo (US$15,565 + US$9,832 versus US$16,126 + US$8,043, p=0.12) and a higher percent of episodes of AF prevented (77% versus 62%).[219]

There was no significant difference between median total hospital costs (US$30,800 (20,400–96,900) in 50 patients without prophylaxis versus US$26,700 (11,000–55,900) in 31 patients with low dose oral amiodarone prophylaxis). Significantly less patients developed postoperative AF with low dose oral amiodarone (9.7% versus 33%, p=0.0253).[218]

One study[222] found a significantly lower mean total cost of hospitalisation in the oral amiodarone group compared with placebo in patients undergoing cardiopulmonary bypass surgery (US$18, 375 + US$13,863 versus US$26,491 + US$23,837, p=0.03).

One study[219,220] estimated the mean cost per AF event avoided was lower in the oral amiodarone group versus no prophylaxis (US$15,750, 95% CI US$15,591 to US$15,999 versus US$17,426, 95% CI US$17,252 to US$17,600). Multivariate sensitivity analysis indicated these findings were most sensitive to the cost of hospitalisation and frequency of AF.

One study[221] indicated the cost effectiveness of prophylactic intravenous amiodarone therapy varied according to the type of cardiac surgery and predicted risk of postoperative AF. As the risk of AF in the targeted patients increases, the cost-effectiveness ratio improves.

- For CABG patients, the ICERs ranged from US$10,938 for the highest risk patients to US$55,854 per AF averted in the lowest risk patients.
- For valve replacement patients the ICERs ranged from US$4,219 in the highest risk patients to US$43,011 per AF averted in the lowest risk patients.
- For CABG and valve replacement patients the ICERs ranged from US$69 for the highest risk patients to US$39,698 per AF averted in the lowest risk patients.

10.1.3 From evidence to recommendations

Although no specific evidence was evaluated regarding the association between electrolyte balance and the incidence of post-op AF, it was agreed that scrupulous attention to electrolyte balance was important.

Drug prophylaxis to reduce the risk of post-op AF relates to the need to:

- continue existing medication (eg beta-blockers)
- administer a drug preoperatively (eg beta-blockers or amiodarone), or
- administer a drug in the immediate postoperative period (eg sotalol or amiodarone).

In many of the studies, the majority of patients were already taking beta-blockers pre-operatively, and these were either discontinued in the postoperative period or continued, despite the use of beta-blockers being recognised as an independent (negative) predictor of post-op AF.[247,248] In those studies where beta-blockers were continued postoperatively, the results may be confounded by this additional cardioprotective effect, which may be insensitive to additional antiarrhythmic medication, particularly beta-blockers, thus underestimating the effectiveness of the prophylaxis.

Alternatively, in those studies where beta-blockers were discontinued, the incidence of post-op AF may be exaggerated by the withdrawal of the cardioprotective effects of beta-blockers, which in some patients may have been preventing the development of arrhythmias aetiologically independent from post-op AF.

For non-cardiac thoracic surgery, there was evidence for efficacy of the same drugs as used in cardiac surgery in the prevention of post-op AF.

It was agreed that beta-blockers, including sotalol, were effective prophylactic drugs, and that those patients who were receiving pre-existing therapy with these drugs would benefit from a reduced risk of post-op AF if those drugs were continued, unless there were compelling reasons to withdraw them (eg postoperative hypotension or bradycardia).

It was agreed that digoxin is not effective in preventing postoperative AF.[235,245]

Administering amiodarone slowly over 5 to 7 days preoperatively and continuing during the perioperative period is more effective and associated with fewer side effects than more rapid loading.[231]

There is an increased risk of bradycardia associated with the use of beta-blockers and nausea associated with procainamide, as well as with amiodarone when loaded rapidly in the pre-operative period.

Data from the USA suggest the prophylactic administration of amiodarone for the prevention of post-op AF is cost effective, particularly in high-risk patients, compared with no prophylaxis for certain cardiac procedures. It was noted that there may be cost differentials between the UK and the USA for antiarrhythmic drugs.

RECOMMENDATIONS

R43 In the prophylaxis and management of postoperative AF, the appropriate use of antithrombotic therapy and correction of identifiable precipitants (such as electrolyte imbalance or hypoxia) is recommended. **D(GPP)**

R44 In patients undergoing cardiothoracic surgery:

- the risk of postoperative AF should be reduced by the administration of one of the following:
  - amiodarone **A**
  - a beta-blocker **A**
  - sotalol **A**
  - a rate-limiting calcium antagonist **B**
- digoxin should not be used. **B**

R45 In patients undergoing cardiac surgery on pre-existing beta-blocker therapy, this treatment should be continued unless contraindications develop (such as postoperative bradycardia or hypotension). **A**

10.2 Treatment for postoperative AF

10.2.1 Methodological introduction

The results of nine studies considering the treatment of postoperative AF were included, all except one[249] were prospective RCTs. The other was placebo-controlled[250] with a 2 × 2 crossover study design with no reported wash-out period between crossover. Of the reported RCTs, none had the statistical power to identify effect sizes that may be considered clinically significant.

A rate-control strategy was defined as one which involved the administration of drugs to control heart rate; a rhythm-control strategy was defined as one which involved treatment with electrical or pharmacological cardioversion or the administration of drugs known to be effective in pharmacological cardioversion. In many studies the objectives of each treatment group were not explicitly reported, in which case a comparison of a rate-control treatment strategy with a rhythm-control treatment strategy was presumed based on the established differential actions of the interventions considered. The duration of follow-up times varied between the studies (less than 1 hour to 30 days).

One study[250] compared rhythm control to no-treatment. All of the other studies compared rate control with pharmacological rhythm control. There were no studies comparing either rate control with rhythm control using electrical cardioversion or rate control versus no treatment.

None of the studies reported results for patients with post-op AF and haemodynamic instability requiring urgent medical intervention.

10.2.2 Evidence statements

In patients with post-op AF, where various rhythm- and rate-control strategies have been compared (see Tables 10.1 and 10.2), rhythm control results in:

- greater cardioversion within 1 hour but not after 24 hours[250–255]
- shorter time for restoration of sinus rhythm[256]
- no difference in ventricular rate control[250,255]
- higher rates of therapeutic effectiveness[255]
- no difference in relapse rates.[256]

Table 10.1 Comparison of rhythm-control treatments for post-op AF with rate-controlling treatments or no treatment in terms of percentage of patients reverting to sinus rhythm

	Comparison	N	Period (hours)	Rhythm (%)	Control (%)	p
(1+)	Flecainide/digoxin[255]	29	1	60	0	<0.001
(1+)	Propafenone/placebo[250]	14	1	43	0	<0.001
(1+)	Procainamide/digoxin[252]	30	12	93	60	<0.05
(1+)	Sotalol/digoxin*[253]	40	12	85	85	NS
(1+)	Propafenone/various**[251]	32	24	35	50	NS
(1+)	Amiodarone/digoxin[254]	30	24	93	87	NS

*Digoxin with additional disopyramide if sinus rhythm was not restored within 2 hours.
**Various = uncontrolled use of beta-blockers, calcium antagonists or digoxin in both treatment arms.

Table 10.2 Comparison of rhythm-control treatments for post-op AF with rate-controlling treatments or no treatment

	Outcome	N	Test/control	Test	Control	p
(1+)	Conversion time, hours	50	Rhythm-control drugs/ rate-control drugs*[256]	11.2	11.8	NS
(1+)	Therapeutic rate control	24	Propafenone/no treatment[250]	26%	2%	<000.1
(1+)	Therapeutic rate control**	29	Flecainide/digoxin[255]	7%	14%	NS
(1+)	Therapeutic effectiveness	29	Flecainide/digoxin[255]	67%	14%	<0.001
(1+)	AF recurrence at 1 week	50	Rhythm-control drugs/ rate-control drugs*[256]	24%	28%	NS
(1+)	AF recurrence at 4 weeks	50	Rhythm-control drugs/ rate-control drugs*[256]	6%	12%	NS
(1+)	AF recurrence at 8 weeks	50	Rhythm-control drugs/ rate-control drugs*[256]	4%	9%	NS
(1+)	AF recurrence	40	Sotalol/digoxin†[253]	5%	35%	<0.05

*Rhythm-control drugs: sotalol, procainamide, propafenone or amiodarone.
Rate-control drugs: diltiazem, verapamil, beta-blockers or digoxin.
**HR <100 bpm within 45 minutes of administration.
†Digoxin with additional disopyramide if sinus rhythm was not restored within 2 hours.

Two studies[249,256] of various rhythm-control versus rate-control strategies have shown shorter overall length of hospital stay with rhythm-control strategies but results for postoperative length of stay have been inconsistent (see Table 10.3).

Table 10.3 Comparison of rhythm-control and rate-control treatments in terms of length of stay (days)

	Study	N	LOS measure	Rhythm	Rate	p
(1+)	Lee *et al*[256]	50	Hospital	9.0	13.2	<0.05
(1+)	Lee *et al*[256]	50	Post-op only	7.4	9.7	<0.01
(2+)	Shah *et al*[249]	101	Post-op only	8.3	6.3	<0.01

LOS measure = length of hospital stay measure.

10.2.3 From evidence to recommendations

The GDG agreed that the evidence suggested a trend towards a strategy of rhythm control over rate control. The evidence suggested that rhythm control produced a decreased time to cardioversion, prolonged maintenance of cardioversion, and decreased length of overall hospital stay.[256]

However, the data supported the use of a rhythm-control strategy in achieving sinus rhythm only in the short term. In the longer term, there is little difference in the maintenance of sinus rhythm between either strategy.[250–255] It was noted that the number of study participants was relatively small and the follow-up periods were relatively short. Overall, it was concluded that a rhythm-control strategy provided short-term benefits.

RECOMMENDATIONS

R46 Unless contraindicated, a rhythm-control strategy should be the initial management option for the treatment of postoperative AF following cardiothoracic surgery. **C**

R47 Unless contraindicated, postoperative AF following non-cardiothoracic surgery should be managed as for acute-onset AF with any other precipitant. **D(GPP)**

11 Antithrombotic therapy

11.1 Initiating antithrombotic therapy

AF is an independent predictor of stroke, with an annual risk that is 5 to 6 times higher than patients in sinus rhythm. However, this risk is not homogeneous, ranging from an annual risk of 1% in patients aged over 65 years old with no risk factors, to over 12% per year in patients who have a history of prior stroke, transient ischaemic attack or thromboembolism. Not only is AF a major risk factor for stroke, but when strokes occur in association with AF, the patients suffer substantial mortality, morbidity, disability and longer hospital stays compared with stroke patients without AF.

The benefits of thromboprophylaxis in patients with AF are well established in randomised trials, and most guidelines recommend the use of anticoagulation with warfarin for high-risk patients. However, there continues to be wide variation in management. In particular, the elderly are at the highest risk of stroke, and would benefit most from thromboprophylaxis. However, the elderly have more comorbidities and concomitant therapies that may preclude anticoagulant therapy. Also, most of the evidence on thromboprophylaxis has been based on hospital-managed populations and the application to primary care management and anticoagulation monitoring is still uncertain.

Common practice upon detection or initial presentation of a patient with AF in the community or when an AF patient presents to a non-specialist is to refer to a specialist clinic to decide on appropriate antithrombotic therapy. For example, in a survey of accident and emergency consultants in the UK, many were reluctant to make a decision regarding anticoagulation, and preferred referral to a medical or cardiology team.[257]

This may lead to delays in the institution of appropriate thromboprophylaxis, and may increase a patient's risk of stroke or thromboembolism. However, risk stratification for thromboprophylaxis can be easily performed on clinical criteria (see section 11.6).

Evidence-based guidance is required to determine whether it is beneficial to start antithrombotic therapy immediately following the initial diagnosis of AF, rather then delay initiation, pending assessment at a specialist clinic.

11.1.1 Methodological introduction

The literature search and evidence appraisal processes for this question resulted in no studies suitable for appraisal.

11.1.2 From evidence to recommendations

Although there was no appraisable evidence base, the issue of early versus delayed administration of anticoagulation in acute patients newly diagnosed with AF was considered of great importance. It was agreed that the administration of anticoagulation after treating comorbidities (eg hypertension) was good clinical practice.

RECOMMENDATION

R48 In patients with newly diagnosed AF for whom antithrombotic therapy is indicated (see section 11.6), such treatment should be initiated with minimal delay after the appropriate management of comorbidities. **D(GPP)**

11.2 Antithrombotic therapy in acute stroke patients*

Approximately a third of patients presenting with an acute stroke are found to have AF. These patients have high mortality and morbidity. Prior to the administration of antithrombotic therapy, intracranial haemorrhage needs to be excluded, and an assessment of the risk from haemorrhagic transformation in patients with large cerebral infarcts needs to be made. While warfarin is superior to aspirin for the secondary prevention of stroke in AF,[258] there is uncertainty about the optimal timing of administration of anticoagulants following acute stroke. The presumption is that most of these patients have cardiogenic embolism, from intracardiac thrombi, but many patients with AF can also develop lacunar strokes secondary to hypertension and other comorbidities and in such cases warfarin is less effective.[259]

The mortality benefits of aspirin therapy following acute stroke[260] are less marked among patients with AF. This may be due to the embolisation of pre-formed intra-atrial thrombus rather than newly formed platelet-thrombus adhering to carotid and cerebral artery atheroma, or may be a reflection of a lesser role of platelets in AF-related stroke.

The purpose of this section is to determine the most appropriate antithrombotic therapy – if any – during the acute post-stroke phase, considering the efficacy of antithrombotic therapies to reduce recurrent stroke, as well as the increased risk of intracranial haemorrhage (ICH) and other major bleeding events.

11.2.1 Methodological introduction

One systematic review[260] considered the results of three primary trials. The trials included peri-stroke patients of varying aetiology. The included studies reported a mean time to treatment of between 19 and 25 hours. Data regarding the subgroup with AF had been published or made available to the authors of the review. All the evidence statements are derived solely from the subgroup comparisons of AF patients.

No trials involving warfarin or any other oral antithrombotic treatment for the prevention of acute recurrent stroke were found.

One of the primary studies included in the systematic review was of a Chinese population.

11.2.2 Evidence statements

In patients with AF the incidence of acute recurrent ischaemic stroke was comparable between treatment with LMWH and aspirin.[260] Another trial found a significant association when

*NICE is developing a clinical guideline on the diagnosis and management of stroke (publication is expected for 2008).

heparin was compared with a no-heparin control group (2% versus 5%; p=0.001) (**1+**). However, the trial also found that the incidence of haemorrhagic stroke was higher in the heparin group (2.8% versus 0.4%), thus offsetting the reduction in ischaemic stroke. (**1+**)

No significant association has been found between the use of aspirin in comparison with either placebo or control and the incidence of acute recurrent stroke (ischaemic or haemorrhagic) or acute mortality (2 to 4 weeks post-stroke).[260] (**1+**)

11.2.3 From evidence to recommendations

It was agreed that there were little data on which to formulate an evidence-based recommendation on when to initiate oral anticoagulation in a patient with AF following a stroke or TIA. In the absence of evidence, it was therefore agreed to base recommendations on pre-existing guidelines in the area.[202]

It was agreed that cerebral imaging may be performed (by MRI or CT scan) to exclude haemorrhage, and antithrombotic therapy should commence at approximatey 2 weeks after the stroke or TIA where there is no evidence of haemorrhage. It should be noted, however, that the discrimination between haemorrhage and ischaemic stroke with CT scanning can only be made reliably within a few days of the event. At later times gradient echo MRI may be the only reliable method.

In patients with AF who have had a large infarction or uncontrolled hypertension, antithrombotic therapy may be delayed. Although AF is widely recognised as a significant risk factor for ischaemic stroke, patients with AF may have other risk factors. AF may not be responsible for all strokes occurring in AF patients. Nonetheless, secondary stroke prevention is warranted and AF patients who have experienced an ischaemic stroke will benefit from appropriate antithrombotic therapy according to the recommendations below and the stroke risk stratification algorithm (Figure 11.1) regardless of aetiology.

RECOMMENDATIONS

R49 In all patients with AF who have had an acute stroke, any uncontrolled hypertension should be appropriately managed before antithrombotic therapy is started. **D(GPP)**

R50 In patients with AF and an acute stroke:

- imaging (CT scan or MRI) should be performed to exclude cerebral haemorrhage
- in the absence of haemorrhage, anticoagulation therapy should begin after 2 weeks
- in the presence of haemorrhage, anticoagulation therapy should not be given
- in the presence of a large cerebral infarction, the initiation of anticoagulation therapy should be delayed. **D(GPP)**

R51 In patients with AF and an acute TIA:

- imaging (CT scan or MRI) should be performed to exclude recent cerebral infarction or haemorrhage
- in the absence of cerebral infarction or haemorrhage, anticoagulation therapy should begin as soon as possible. **D(GPP)**

11.3 Antithrombotic therapy following a stroke or TIA

AF is an independent predictor of stroke[13] with the risk approximately five times that of people without AF. The absolute risk for an individual patient, however, increases with age and depends upon the presence of other risk factors such as valvular heart disease, other cardiovascular disease or cardiac risk factors. Conversely, anticoagulation therapy substantially reduces the risk of stroke in 'at risk' patients with AF.[174,260]

In stroke patients, concurrent AF is associated with greater disability, longer in-hospital patient stay and lower rate of discharge to their own home, and in most studies AF is associated with decreased survival.[261,262]

Patients who have suffered and survived an acute stroke or transient ischaemic attack are at the highest risk of recurrent stroke and thromboembolism, approximately 12% per year.[258] Assessment and treatment of comorbidities (especially hypertension) is essential, as is an accurate risk–benefit assessment. The highest risk patients are the elderly, and this is probably the group where anticoagulation treatment is most difficult.

The objective of this section is to provide evidence-based guidelines on which is the best thromboprophylactic agent for post-stroke AF patients.

11.3.1 Methodological introduction

Five primary studies[258,259,263–265] and two meta-analyses[266,267] were identified. One study[258] was included in both meta-analyses. One study compared warfarin, aspirin and placebo.[258] All studies recruited AF patients with a prior stroke or TIA except one[179] that included 44% of AF patients without a prior stroke or TIA.

11.3.2 Evidence statements

One meta-analysis[266] found warfarin to be associated with a reduced incidence of recurrent stroke (ischaemic or haemorrhagic) and vascular events (including stroke, myocardial infarction, systemic embolism and vascular death) but an increased incidence of bleeding events, compared with placebo. (**1+**)

There was no significant difference in the mortality rate between adjusted-dose warfarin and placebo.[258] (**1++**)

Low molecular weight heparin is associated with a significant reduction in embolic events and overall mortality when compared with no treatment.[265] (**1+**)

Acenocoumarol administered to a target INR of 1.25 to 2.00, in conjunction with 600mg/day triflusal, reduces the incidence of stroke (ischaemic or haemorrhagic), vascular death or systemic embolism compared with acenocoumarol alone administered to a target INR of 2.0 to 3.0179 (**1+**). No association has been found in rates of severe bleeding or overall incidence of adverse events.[179] (**1+**)

Adjusted dose warfarin is associated with a reduced incidence of recurrent stroke (ischaemic or haemorrhagic),[258,264] and vascular events[258] compared with aspirin (**1++**). Warfarin has also been found to be associated with an increased incidence of bleeding events compared with aspirin.[258] (**1++**)

No significant difference has been found in the mortality rate between adjusted-dose warfarin and aspirin.[258] (1++)

Warfarin has been found to be associated with a greater reduction in the incidence of overall stroke recurrence following a presumed primary cardioembolic stroke in comparison with aspirin, but not following a presumed primary lacunar stroke.[258] (1++)

No significant difference between aspirin and placebo has been found in the overall incidence of vascular events, mortality or bleeding events.[258] (1++)

No association has been found between the use of dipyridamole and placebo in the incidence of recurrent ischaemic stroke. A similar result was found when dipyridamole was combined with aspirin and compared with placebo.[264] (1++)

11.3.3 From evidence to recommendations

Anticoagulation with warfarin has a strong beneficial effect in the prevention of recurrent strokes for post-stroke and post-TIA patients with AF when compared with both placebo[258,266] and aspirin.[267] This effect is significant for any category of secondary stroke. However, anticoagulation also increases rates of haemorrhagic events in comparison with both placebo and aspirin.

The GDG agreed that antiplatelet agents such as aspirin and dipyridamole are ineffective thromboprophylactic agents and should be administered to post-stroke AF patients only to treat other comorbidities or vascular disease.

The GDG noted that the use of low adjusted-dose anticoagulation with acenocoumarol in combination with the antiplatelet triflusal was more effective than conventional adjusted-dose anticoagulation with acenocoumarol alone for the prevention of stroke.[179] It is unclear whether similar results apply to anticoagulation with warfarin instead of acenocoumarol or other antiplatelet agents. The GDG noted that trifusal is not used in the UK, and that previous studies of warfarin and aspirin combination therapy have been less effective or have had more adverse effects than with warfarin alone. Therefore the GDG did not make any recommendations in this area.

RECOMMENDATIONS

R52 In patients with AF who are either post-stroke, or have had a TIA:

- warfarin should be administered as the most effective thromboprophylactic agent **A**
- aspirin or dipyridamole should not be administered as thromboprophylactic agents unless indicated for the treatment of comorbidities or vascular disease. **D(GPP)**

R53 Treatment of post-stroke or post-TIA patients with warfarin should only begin after treatment of relevant comorbidities (such as hypertension) and assessment of the risk–benefit ratio. **D(GPP)**

11.4 Antithrombotic therapy for asymptomatic AF

Many patients develop AF asymptomatically, and only present to medical care when complications such as stroke or heart failure occur. One study reported that in patients with paroxysmal AF, only 1 in 12 paroxysms appeared to be symptomatic.[31] Consequently, cases of AF are often detected, particularly in the elderly, during a general practice visit for an unrelated problem. The elderly, as a group, have a high morbidity from stroke, thromboembolism and impaired cognitive function.

It is not known whether asymptomatic AF *per se* is a potential risk factor for stroke. It is currently not clear how best to manage patients with asymptomatic AF, either in relation to treatment using a rate-control or a rhythm-control strategy, or in terms of the need for antithrombotic therapy.

11.4.1 Methodological introduction

No studies were found that addressed this clinical area.

11.4.2 From evidence to recommendations

The GDG noted that there was no evidence upon which to base recommendations on the use of antithrombotic therapy in patients with asymptomatic AF. The group noted that many patients had AF diagnosed but that the opportunity for antithrombotic therapy was not always considered. The group agreed that asymptomatic AF should be treated no differently to symptomatic AF.

RECOMMENDATION

R54 Patients with asymptomatic AF should receive thromboprophylaxis as for symptomatic AF (refer to section 6.3 for persistent AF, section 7.2 for permanent AF and section 8.2 for paroxysmal AF). **D(GPP)**

11.5 Risks of long-term anticoagulation

In order to provide adequate thromboprophylaxis with minimal risk of bleeding, current clinical practice aims for a target INR of between 2.0 and 3.0; INRs of more than 3.0 are associated with increases in bleeding and INRs of less than 2.0 are associated with increases in stroke risk.[176,182]

In one pooled analysis, the annual rate of major haemorrhage (defined as an intracranial haemorrhage, a haemorrhage requiring at least two units of blood, or an event requiring hospital admission) was 1% in control patients and 1.3% in warfarin-treated patients.[168] The annual risks of intracranial haemorrhage increased from 0.1% in control to 0.3% in warfarin groups, which represents an excess of two intracranial bleeds per annum per 1,000 patients treated. Even low-dose aspirin increases the risk of major haemorrhage by two-fold, especially in the settling of uncontrolled hypertension. Indeed, the correct treatment and monitoring of

hypertension and other associated comorbidities is regarded as extremely important in minimising the risk of bleeding in patients on prophylactic warfarin.

The most devastating complication associated with warfarin prophylaxis is the risk of intracranial haemorrhage, which is a particular problem in the elderly, in whom frailty, poor mobility, forgetfulness or poor compliance with medication, concomitant medications (resulting in drug interactions), and frequent falls may jeopardise the benefits from warfarin. These factors are often cited as reasons for non-prescription of warfarin in the elderly, where the absolute benefit is likely to be greatest in view of their high risk.[169]

There is also some evidence[268] that the combined use of warfarin with antiplatelet agents such as aspirin and clopidogrel significantly increases the risk of bleeding beyond that associated with the single use of any one of these agents. This raises a particular dilemma in those patients with both atrial fibrillation and coronary or peripheral artery disease, who are often co-prescribed warfarin and antiplatelet therapy. With the increasing use of drug-eluting stents, for which 6 to 12 months aspirin-clopidogrel use has recently been recommended, advice on how best to manage patients who have both AF and a drug-eluting stent who also require anticoagulation is currently lacking.[269]

This section aims to identify those risk factors for bleeding in patients with AF receiving oral anticoagulation.

11.5.1 Methodological introduction

'Long-term' anticoagulation was assumed to mean periods of anticoagulation administration of longer than 4 weeks. Studies that considered outcomes in populations with a mean period of anticoagulation of less than 4 weeks were excluded.

Studies were included in this report if they documented the incidence of complications associated with long-term oral anticoagulation, such as drug toxicity or adverse side effects, and measured and compared the risk of these complications between different groups of patients.

The reporting of risk will be made for both multivariate risk analyses, as well as univariate associations, wherever a multivariate calculation has not been reported.

11.5.2 Evidence statements

▷ Overall bleeding risk

One large study[270] (N=10,093) in an elderly population (mean age 77 years), reported a yearly incidence of 1.5% major bleeding events, of which 0.3% were intracranial haemorrhage.[28]

In another study[271] (N=677), in a population receiving both anticoagulation and antiplatelet therapy, the yearly incidence of major bleeding events was 1.1%, of which 0.6% were intracranial haemorrhage.[28] The study reported a yearly incidence of 11.8% minor bleeding events.[28]

▷ Bleeding risk factors

One study[272] found that patients older than 75 years were more likely to suffer bleeding complications than younger patients (2+). A similar result was found in another study.[273] (2+)

One small study[274] (N=101) did not find any significant difference in the incidence of bleeding complications between those aged 75 years or over and those aged 60 to 69 years. (2+)

Four studies[270,272,275,276] found no association between gender and bleeding complications, although female gender was found to be of borderline significance as an independent risk factor in two other studies.[270] (2+)

One study[271] failed to find diabetes to be a significant independent risk factor of bleeding complications (2+). A further three studies[272,275,276] failed to find any significant association between diabetes and bleeding. (2+)

One study[271] did not find hypertension to be a significant predictor of bleeding complications, although another larger study[168] found both systolic and diastolic blood pressure to be significantly higher in those patients with bleeding complications than in those without bleeding complications. (2+)

One study[270] found anaemia to be significantly associated with bleeding complications in an elderly cohort of patients. (2+)

Two studies[271,276] found a history of MI to be a significant independent predictor of bleeding complications (2+). A similar result was found for the presence of ischaemic heart disease.[276] (2+)

Two studies[271,272] failed to find a history of stroke or thromboembolism to be independent predictors of bleeding complications. (2+)

One study[276] did not find any significant association between cerebrovascular disease and incidence of bleeding complications although another larger study[277] found cerebrovascular disease to be a significant independent predictor of intracranial haemorrhage. (2++)

One study[270] found the concomitant use of antiplatelet drugs in anticoagulated patients to be a significant independent predictor of bleeding complications (2+). However, the same study did not find an increased number of additional medications – including non-steroidal anti-inflammatory drugs (NSAIDs) – to be a significant independent predictor of bleeding complications when risk was correlated with an increase of one additional drug. (2+)

One study[278] found a significant difference in bleeding complications between those patients prescribed at least three additional medications and those prescribed less than three. (2++)

One study[270] found a history of bleeding to be a significant independent predictor of future bleeding events. (2+)

11.5.3 From evidence to recommendations

The following risk factors were identified as being associated with bleeding in AF cohorts:

- over 75 years of age
- antiplatelet drug use
- uncontrolled hypertension
- history of bleeding or ICH
- anaemia
- polypharmacy.

It was considered unclear whether controlled hypertension or previous MI were independent predictors of stroke. For example, patients with previous MI were likely to be taking antiplatelet therapy, and may have other comorbidities, such as uncontrolled hypertension. Anaemia was a risk factor in the studies presented, probably because of an underlying bleeding source (eg peptic ulcer).

Poor anticoagulation control could also be considered as another risk factor for bleeding, particularly since the risk increased with INRs of greater than 3.0.[277] The use of concomitant antiplatelet therapy (aspirin or clopidogrel) was identified as a risk factor to bleeding; NSAIDs were thought to have a similar risk. Obvious bleeding factors, such as recent bleeding peptic ulcer or intracranial bleeding, are contraindications to anticoagulation, in view of the high risk associated with these conditions.

One criticism of the randomised trials is that they do not reflect real world practice, only randomising a minority of those screened, who tended to be at lower risk and monitored closely by intense trial protocols. One prospective UK cohort study, designed to determine if trial efficacy of warfarin for stroke prevention in AF translated into clinical effectiveness, reported that the rate of stroke (2% per year, 95% CI 0.7 to 4.4) compared with patients in the pooled studies (1.4% per year). Major bleeding rates (1.7% versus 1.6%) were also comparable.[176,279,280]

It was noted that many of the risk factors for bleeding (eg aged over 75 years, hypertension) were also risk factors for stroke (see section 11.6). Thus, it may be appropriate to undertake an assessment of bleeding risk as part of the clinical assessment of patients prior to starting antithrombotic therapy.

RECOMMENDATIONS

R55 Both the antithrombotic benefits and the potential bleeding risks of long-term anticoagulation should be explained to and discussed with the patient. **D(GPP)**

R56 The assessment of bleeding risk should be part of the clinical assessment of patients before starting anticoagulation therapy. Particular attention should be paid to patients who:

- are over 75 years of age **D**
- are taking antiplatelet drugs (such as aspirin or clopidogrel) or non-steroidal anti-inflammatory drugs **C**
- are on multiple other drug treatments (polypharmacy) **C**
- have uncontrolled hypertension **C**
- have a history of bleeding (for example, peptic ulcer or cerebral haemorrhage) **C**
- have a history of poorly controlled anticoagulation therapy. **D(GPP)**

11.6 Risk factors for stroke and thromboembolism

AF itself is an independent risk factor for stroke[14] and results in an independent increase in mortality *per se*.[11]

Stroke risk is also perceived to vary according to age and the presence of hypertension, diabetes mellitus, previous stroke or transient ischemic attack and poor cardiac function.

Transthoracic and transoesophageal echocardiography features have also been associated with a high risk of stroke (see section 4.3). Echocardiography therefore complements risk stratification on clinical grounds.

The objective of this section is to identify those risk factors for stroke or thromboembolism in patients with AF that should be incorporated into a comprehensive risk stratification algorithm.

11.6.1 Methodological introduction

All of the included studies were based in populations where the vast majority of people were receiving no anticoagulant drug during the course of the study period, and which identified independent risk factors of stroke or thromboembolism.

The use of aspirin or any other drug with presumed antithrombotic efficacy will not be reported here as a (negative) risk factor for stroke or thromboembolism. Echocardiographic risk factors are considered elsewhere (see section 4.3).

Although many studies considered the composite outcome of (ischaemic) stroke, TIA or thromboembolism, for the purposes of brevity this report will refer to the entire range of outcomes simply as 'stroke'.

11.6.2 Evidence statements

▷ Demographic risk factors

Of 10 studies that considered increasing age as a risk factor for stroke, either as a continuous variable or as incremental decades, six[168,192,281–284] found increasing age to be a significant risk factor, while the remaining studies[59,285–287] did not find increasing age to be significant. (2++)

Of three studies[60,288,289] that considered being elderly as a risk factor for stroke (by dichotomising age into younger and older age groups), one relatively small (N=272) study[60] did not find being aged over 70 years to be a significant risk factor (2+). In another study[288] (N=740) in a population with intermittent AF (at enrolment), being aged over 65 years was a significant risk factor for stroke (RR 3.3, 95% CI 1.92 to 5.81) (2+). In another study[289] (N=265) of a population without a previous stroke, being aged over 75 years was a significant risk factor for stroke (OR 1.72, 95% CI 1.04 to 2.84). (2+)

Based on the results of 11 studies[52,59,60,62,192,281–283,285,286,288] in various populations of AF patients, it is unclear whether gender is a significant independent risk factor. (2++)

One study[290] (N=854) found being female and over 75 years old to be a significant independent predictor of stroke (OR 3.7, 95% CI 2.2 to 6.2; $p<0.001$). (2++)

One study[168] (N=1593) did not find smoking to be a significant independent predictor of stroke (2+). However, the study did find a higher incidence of stroke in smokers than non-smokers ($p<0.05$). (2+)

▷ Clinical risk factors

Seven studies[62,168,192,281,283,284,287] found a history of stroke or TIA to be a significant independent predictor of secondary stroke (2++). Another study[285] based in a population with a prior stroke or TIA found a previous non-cerebrovascular thromboembolism to be a significant independent predictor of secondary stroke. (2++)

Based on the results of seven studies,[52,168,192,281,282,289,291] hypertension (controlled or uncontrolled) has been found to be a significant independent risk factor in both AF and atrial flutter (2++). However, another four studies[60,62,284,286] failed to find any significant relationship between hypertension and stroke. (2++)

Three studies[192,281,285] found systolic blood pressure greater than 160 mm Hg to be a significant independent predictor of stroke in general AF populations (2++). However, one study[192] failed to find it to be a significant independent risk factor specifically in patients with intermittent AF. (1+)

Based on the results of eight studies[52,60,62,168,282,284,287,290] that considered various measures of structural heart disease as risk factors for stroke, it is unclear whether congestive heart failure (CHF) is a risk factor for stroke[168,282,284,287] (2++), although the presence of structural heart disease generally has been found to be a significant independent predictor.[60] (2+)

One study[282] did not find the presence of ischaemic heart disease to be a significant independent predictor of stroke (2++). A similar result was found in the case of angina in another study.[168] (2+)

Two studies[168] found the presence of diabetes to be a significant independent predictor of stroke in a general AF population (2+). Another study[62] based in an elderly population did not find it to be an independent risk factor. (2+)

Two studies[282,286] based in AF populations without a previous stroke[286] or without any risk factors, including previous stroke and presence of CHF or left ventricular dysfunction,[282] did not find diabetes to be a significant independent predictor of stroke (2++). One study[291] based in a population with atrial flutter did not find diabetes to be a significant independent predictor of stroke. (2+)

Four studies considered a history of MI as a risk factor for stroke. Three studies[52,168,286] found MI to a significant independent risk factor (2+). The remaining study[62] based in an elderly population did not find MI to be a significant independent risk factor. (2+)

Two studies[60,284] did not find AF subtype (paroxysmal or non-paroxysmal) to be a significant independent predictor of stroke. (2++)

One study[285] based in a population with a previous stroke or TIA found an AF duration of greater than 1 year to be a significant independent predictor of secondary stroke. (2++)

One study[62] did not find obesity to be a significant independent predictor of stroke. (2+)

11.6.3 From evidence to recommendations

Many of the studies used highly selected populations that would affect the relative risk of the factors considered. The main data appraised came from cohort studies, epidemiological studies and clinical trials. Many of the clinical trials randomised only a small proportion of those initially screened, and excluded patients with valvular heart disease, thyroid disease or intercurrent illnesses such as chest infections.

Based on the evidence, the following were identified as independent risk factors for stroke in AF:

- previous stroke or TIA
- being elderly (aged over 75)
- structural heart disease
- hypertension
- previous MI.

The evidence for diabetes as an independent predictor of stroke in AF was not considered convincing, but overall was regarded as an important indicator for increased risk in the general AF population.

While MI was identified as an independent stroke risk factor, underlying left ventricular dysfunction may confound this result. Echocardiographically demonstrated left ventricular dysfunction is a known risk factor for stroke, but heart failure cannot always be diagnosed on clinical grounds alone. It was therefore agreed that heart failure should be on the list of risk factors even though the evidence was inconclusive.

Other risk factors such as peripheral artery disease were debated, but limited evidence was available. However, coronary and peripheral artery diseases were regarded as part of the clinical spectrum of atherothrombotic vascular disease that contributed to stroke risk. For example, complex aortic plaque on TOE was an independent stroke risk factor[292] (see section 4.3) and ischaemic stroke in AF could be associated with carotid artery disease.[293] For this reason vascular disease should be incorporated into a risk stratification model.

The evidence was unclear as to whether being female is a stroke risk factor. It was agreed that there was no known plausible biological reason for females with AF to have a higher stroke risk than men, and it was thus agreed that being female should not be included in any risk stratification algorithm.

Although none of the appraised studies considered AF patients with thyroid disease, it was agreed that this should not be considered as a risk factor for stroke.

All of the above factors, which are not mutually exclusive and may be cumulative, have been used in the development of various risk stratification algorithms (see Appendix B). These algorithms have been designed to assist the clinician in assessing individual patients for thromboprophylaxis. They can help in the identification of patients with AF who are at an increased risk of stroke and who would benefit most from anticoagulation therapy, while low-risk patients could be managed with antiplatelet therapy.

There is a need for an algorithm that stratifies stroke risk into three tiers to allow:

- high-risk patients to be identified for thromboprophylaxic anticoagulation therapy
- low-risk patients to be identified for antiplatelet use for thromboprophylaxis
- moderate-risk patients to be identified where further specialist referral may be necessary.

In addition to risk stratification it was accepted that patients preferences should be considered as some patients will still decline anticoagulation treatment for a variety of reasons. These include:

- the inconvenience of dosing adjustments and regular blood tests to monitor INR levels
- dietary restrictions
- the risk of minor and major bleeding, and
- under-appreciation or lack of knowledge regarding the risk of stroke, or poor adherence to the treatment regimen.

Many patients with AF possess limited knowledge of AF and its consequences and therapy. Only a minority reported feeling that their doctor had given them enough information about their warfarin therapy.

The following criteria were identified that should be addressed by any risk stratification algorithm for use in a UK population:

- incorporation of the risk factors identified above
- inclusion of a three-strata model (high, moderate and low risk)
- easy to use (no complex scoring system)
- patients with previous stroke or TIA automatically classified as high risk
- can be used for both primary and secondary prevention
- practical and applicable for use in both primary and secondary care.

A summary of the published risk stratification algorithms is shown in Appendix B. The benefits and drawbacks of each were discussed, with emphasis on a balance between evidence, clinical applicability and practicality, as well as refinement for a UK population. It was agreed that few had addressed the cumulative nature of risk factors where a combination (eg hypertension plus diabetes) would confer a greater risk than either alone.

It was noted that none of the published algorithms had been derived or validated in a UK population but one had subsequently been modified for this purpose.[294] Various other problems were highlighted regarding the applicability of the published algorithms:

- With the exception of one model,[283] non-warfarin trial participants had often been used as validation populations.
- One was based on a complex mathematical model.[283]
- Some only used a two-tier model (low and moderate–high risk) to stratify patients.[28,168,290,295]
- One was based on a point scoring system.[296]
- One did not necessarily identify a patient with a previous stroke or TIA as 'high risk'.[296]
- One model was only applicable for secondary prevention.[285]

It was agreed to suggest a revised algorithm based on the only model that had been optimised for use in a UK setting.[294] This was based on a modification of the AF investigators' algorithm,[168] but had been expanded into a three-tier model following consultation with primary and secondary care clinicians and was implemented (31/08/1997) and subsequently validated as a regional audit project in primary care by a large UK health authority.

RECOMMENDATIONS

R57 The stroke risk stratification algorithm (section 11.7) should be used in patients with AF to assess their risk of stroke and thromboembolism, and appropriate thromboprophylaxis given. **C**

R58 Risk stratification should be reconsidered whenever individual risk factors are reviewed. **D(GPP)**

11.7 Stroke risk stratification algorithm

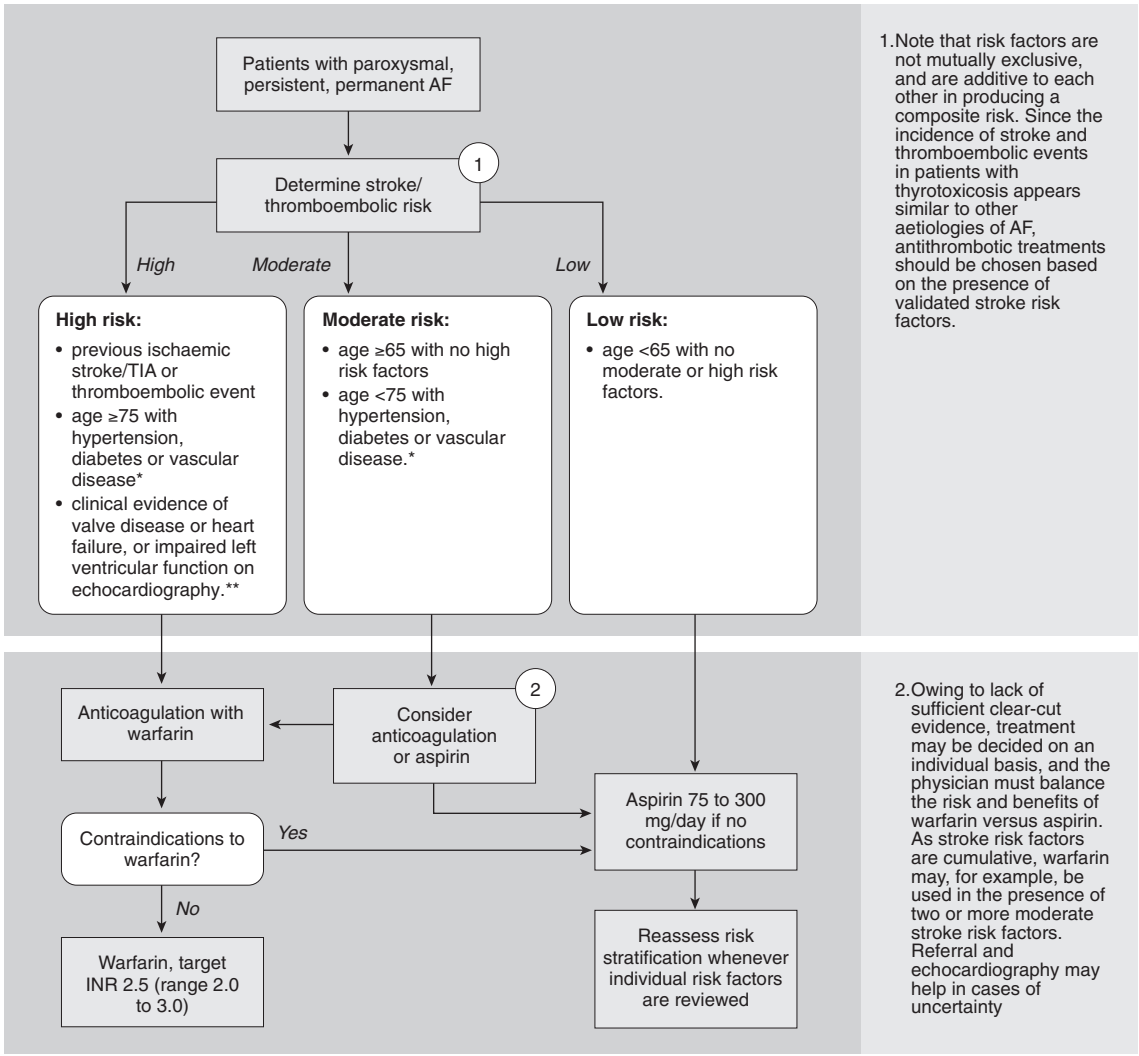


Figure 11.1 Stroke risk stratification algorithm. *Coronary artery disease or peripheral artery disease. **An echocardiogram is not needed for routine assessment, but refines clinical risk stratification in the case of moderate or severe LV dysfunction and valve disease.

11.8 The cost effectiveness of oral anticoagulation as thromboprophylaxis

The purpose of this section is to consider the health economic aspects of oral anticoagulation in patients with AF. In particular, since the risk of stroke is not homogenous throughout the AF population (see section 11.6), the administration of oral anticoagulation as thromboprophylaxis may be cost effective in high-risk patients, but not cost effective in lower risk patients. In those patients in whom oral anticoagulation is not cost effective, antiplatelet therapy may be more appropriate, or no treatment.

11.8.1 Methodological introduction

Eight published cost-effectiveness studies compared warfarin with no anticoagulation and/or warfarin with aspirin. Five of the cost-effectiveness studies were US-based,[297–301] two were conducted in the UK[302,303] and one in Sweden.[304]

Discounted survival or quality-adjusted survival was estimated using the prevalence over time of stroke, haemorrhagic events and mortality associated with AF. The ranges of outcomes incorporated in the models were very similar. All the studies drew from a relatively robust, up-to-date evidence of effectiveness of warfarin in preventing strokes. This is also presented in the review of effectiveness and consists of a meta-analysis of the effectiveness of warfarin in non-valvular AF patients.[305]

Most studies considered a healthcare system perspective (NHS for the two UK studies) and included discounted, direct costs of anticoagulation therapy (physicians or outpatient visits, drugs and prescription costs) and costs of hospitalisation for stroke and major haemorrhagic events.

11.8.2 Evidence statements

▷ Anticoagulation versus no anticoagulation

In general patients with AF, anticoagulation treatment is relatively cost effective compared with no anticoagulation. Three studies[297,300,302] reported on cost effectiveness of warfarin compared with no warfarin in a general AF population. The only UK study[302] reported an ICER ranging between £1,751 and £13,221 per life-year gained free from stroke. Studies from other countries reported cost-effectiveness ratios of US$1,907.[297] Another study[304] estimated that the cost per stroke prevented stratified according to risk of bleeding to be Swedish krona (SKR)171,000 per stroke prevented if the risk of bleeding is 0.3%, to SKR417,000 if the risk of bleeding is 2%. The other study[300] estimated a reduction in healthcare costs of US$1,514 per year.

Four studies[297–299,303] compared anticoagulation with no anticoagulation in patients with a low risk of stroke. In this subgroup of patients anticoagulation was found not to be cost effective, with higher costs and loss in quality of life compared with no anticoagulation.

In patients with medium to high risk for stroke, anticoagulation with warfarin was found to be cost effective, with estimated ICERs ranging between dominance[297,298] and ICERs of between US$1,434/QALY[299] and £6,000/QALY.[303] One study[303] also found that the ICER decreased as blood pressure increased.

In patients at high risk of stroke (more than two risk factors of stroke) all studies[297–299,303] found that anticoagulation was dominant, ie had lower costs and improved quality adjusted survival.

In elderly patients, the cost effectiveness of anticoagulation was found to depend on the level of risk of stroke. For high-risk patients, the ICERs ranged between dominance (lower costs and better outcomes) for individuals with high-risk factors.[297,299,302] For low-risk patients, anticoagulation was dominated by no anticoagulation.

▷ Anticoagulation versus antiplatelet therapy

Three studies[297,300,302] compared anticoagulation treatment with aspirin in general patients with AF. The ICERs ranged from US$2,000 in patients with low implantable cardiac defibrillator (ICH) risk (0.2%) to approximately US$7,000 in patients with high ICH risk (1.2%).[380] One study[297] had an ICER of US$4484/quality-adjusted life-years (QALY) while another study[300] found that warfarin treatment resulted in cost savings. Thus, in general patients with AF, warfarin was found to be cost effective compared with aspirin.

In low-risk patients, one study[298] estimated small improvements in QALYs which were realised at substantial costs compared with aspirin (US$370,000/QALY for 65 year olds and US$110,000/QALY for 75-year-olds).

In patients with AF who have a medium to high risk of stroke, one study[298] calculated an ICER of US$8,000/QALY for anticoagulation with warfarin. The cost-effectiveness advantage was found to decrease as the risk of bleeding increased.

In elderly patients with a moderate risk of stroke, one study[298] found that warfarin was cost effective compared with aspirin with an estimated ICER of US$500/QALY.

11.8.3 Evidence to recommendations

The health economic analysis suggested that the studies comparing warfarin with no anticoagulation and warfarin with aspirin were of good quality and summarised the evidence as follows:

- In patients with AF, anticoagulation treatment is cost effective compared with no anticoagulation.
- In patients at high risk of stroke, anticoagulation is cost effective, but not for those with a low risk of stroke.
- Aspirin is cost effective in low-risk patients compared with warfarin, but not in higher risk patients.

It was agreed that the health economics evidence was consistent with the stroke risk stratification algorithm (Figure 11.1).

12 Monitoring and referral

12.1 Anticoagulation self-monitoring

The increasing use of oral anticoagulation therapy as thromboprophylaxis in AF has increased the need for anticoagulation monitoring and encouraged a move towards 'point of care' or 'near patient' testing and patient self-monitoring. This may take several forms, whereby the patient has an anticoagulation-monitoring test performed at:

- the GP clinic using an INR testing machine based in the clinic itself, or
- the GP clinic but using an INR testing machine based in a central laboratory (normally at a hospital) where the blood sample is sent, or
- home using a personal INR testing machine allowing the patient to alter the dose of anticoagulation (self-monitoring).

Point of care for INR testing within primary care eliminates time lost in waiting for test results to be processed, by informing the patient of any changes to their INR and of any resulting change in dosing advice.[306]

Patient self-monitoring of oral anticoagulation gives a greater degree of autonomy. However, evidence is also required regarding the clinical utility and cost effectiveness of self-monitoring in order to recommend its routine use in clinical practice.

This section provides an opportunity to assess the evidence on whether self-monitoring is as effective as management using hospital laboratory testing and other conventional management strategies.

12.1.1 Methodological introduction

Studies were included if self-monitoring strategies were compared with traditional supervised-management strategies for the monitoring and dose-adjustment of long-term oral anti-coagulation. In the former case, self-monitoring could involve either the patient testing their own INR values and recording those values for appraisal by a supervising clinician responsible for dose-adjustment, or the patient performing both their own INR testing and dose-adjustment. In the latter case, testing was performed centrally or by clinicians using near-patient testing devices and clinicians made the dose-adjustment decisions.

The manufacturer or local distributor of the testing device funded all of the studies, either directly or indirectly.

Two studies had populations solely comprising AF patients.[307,308] The other studies included a proportion of AF patients within a general anticoagulated population[309–316] and others either included only patients with prosthetic heart valves[317,318] or did not report the number of patients with AF.[319–321] However, the results of the studies were consistent across all patient populations. A recently published meta-analysis[322] of 10 of the RCTs included in the guideline review was subsequently identified. The pooled results for relevant outcomes are included in the evidence statements below.

Two studies[323,324] were found that reported health economic outcomes of self-monitoring in comparison with supervised management. One study[323] was a cost-effectiveness analysis and the other[324] developed a comparative cost analysis where cost functions were developed and analysed to determine the break-even point in total cost between the two systems.

12.1.2 Evidence statements

Based on the results of 10 studies,[307,308,311,314–7,319–21] it is inconclusive whether self-monitoring is associated with improved control of INR compared with supervised management, when measured as the percentage of INR measurements within the target range. (**1++**)

No difference was found in the number of dose adjustments per INR measurement between self-monitoring (0.42) and supervised management (0.37)[312] (**2++**). However, the number of dose adjustments per patient was higher in the self-monitoring group (22.4 versus 3.4; $p<0.005$).[312] (**2++**)

Self-monitoring is associated with a lower rate of hospital admissions than supervised management in patients with prosthetic heart valves (15.3% versus 9.5%; $p<0.05$).[311] (**1+**)

When comparing self-management and supervised-management strategies, no significant association was found within individual studies in the rates of major thromboembolic or haemorrhagic complications.[307,310,312–315,318–20] A meta-analysis[322] of eight RCTs found self-management to be associated with significantly fewer major thromboembolic events (OR 0.41, 95% CI 0.25 to 0.70; p=0.001), but failed to detect a significant association for haemorrhagic complications (OR 0.66, 95% CI 0.37 to 1.16; p=0.15). (**1++**)

No significant difference in mortality rates between self-management and supervised-management strategies was detected within individual studies.[307,312,313,315,317–319] A meta-analysis[322] of five RCTs found self-management to be associated with significantly fewer deaths from all causes (OR 0.58, 95% CI 0.36 to 0.95; p=0.03). (**1++**)

One study[321] reported a higher incidence of major complications in those patients with conventional management than those with self-monitoring (7.3% versus 2.2%). (**1+**)

Self-monitoring was associated with a higher level of patient satisfaction and quality of life than supervised management when assessed by questionnaires.[313,318] (**1++**)

One cohort study reported patient preferences after study termination and 15 of the 17 patients from the self-monitoring group bought a near-patient testing device[307] (**2++**). The remaining two participants expressed a wish to purchase one but were financially unable to do so.

No significant association has been found between self-monitoring strategies that allow dose adjustment by patients and those where dose adjustment was determined by a clinician in terms of either the percentage of time spent within the target INR range (67% self-testing only versus 69% self-testing and self-dosing) or the percentage of measurements within the target INR range (64% self-testing only versus 66% self-testing and self-dosing).[314] (**1++**)

The cost-effectiveness results differed depending on whether or not costs incurred by patients and their carers are included with medical care costs.[323] Anticoagulation clinic testing versus usual care was cost saving when including medical costs only (US$405,560 versus US$419,514). Patient self-testing versus anticoagulation clinic testing had an incremental cost of US$24,818

per adverse event avoided or US$153,504 per QALY when including medical costs only. However, when including all costs, patient self-testing versus anticoagulation clinic testing was cost saving (US$622,727 versus US$645,671). Patient self-testing had higher medical care costs than usual care (US$526,014 versus US$419,514) but had a lower number of adverse events per 100 patients over 5 years (22.10 versus 30.65).

Results were sensitive to time spent below or above the therapeutic INR range and frequency of testing. Including medical costs only, there is approximately 80% certainty that anticoagulation clinic testing versus usual care is cost saving, and 48% certainty that patient self-testing versus anticoagulation clinic testing is cost saving.[323]

The use of near-patient testing costs less per year than conventional anticoagulation follow-up in self-care patients (€350.37N versus €378.36N, where N=number of patients). The yearly cost of near-patient testing is €133.77 plus €953.02N and equals the cost of conventional follow-up (€963.00N) when there are more than 14 patients on home-care follow-up. Sensitivity analysis indicates that small changes in the cost of near-patient management could affect the number of patients needed to make the near-patient model cost effective. The results were also sensitive to the travel costs.[324]

12.1.3 From evidence to recommendations

The evidence suggests that patient self-monitoring of oral anticoagulation is more effective in terms of patient satisfaction than supervised management.[313] However, the results of such trials should be interpreted carefully.

Many studies were conducted using a motivated patient population who were selected using strict inclusion criteria, which often included passing a cognitive test. In one study[307] the authors report that although at the end of the study period many patients wished to continue self-monitoring, this required sufficient personal financial resource to fund the purchase of the necessary equipment.

There was a difference in the cost effectiveness depending on whether patient and carer costs were included with medical costs. Further data based on the UK health setting would be required in order to determine the cost effectiveness of self-monitoring.

A recent non-commercially funded trial[325] which was published too late to be included in the above review, showed self-monitoring to be safe and effective in a UK population. This conclusion is consistent with the results from smaller trials above, most of which received commercial backing.

Increasing the adoption of self-monitoring might lead to additional pressure on GP services. It was considered that the use of self-monitoring needs to be balanced between patient preference and the ability of local services to provide support (eg patient education programmes).

It was noted that guidelines have been published in the area of patient self-monitoring of oral anticoagulation.[326] These recommend that patients undertaking anticoagulation self-monitoring should be trained by a competent healthcare professional and remain in contact with a named clinician. They also highlight the need for self-monitoring devices that have been adequately quality-assured.

RECOMMENDATION

R59 In patients with AF who require long-term anticoagulation, self-monitoring should be considered if preferred by the patient and the following criteria are met:

- the patient is both physically and cognitively able to perform the self-monitoring test, or in those cases where the patient is not physically or cognitively able to perform self-monitoring, a designated carer is able to do so
- an adequate supportive educational programme is in place to train patients and/or carers
- the patient's ability to self-manage is regularly reviewed
- the equipment for self-monitoring is regularly checked via a quality control programme. **C**

12.2 Follow-up post cardioversion

In current clinical practice review of patients after successful cardioversion is primarily to assess the maintenance of sinus rhythm. In addition the following factors are also considered:

- comorbid factors (eg heart failure, hypertension), by review
- adverse effects related to cardioversion (eg skin burns, thromboembolism)
- drug therapies (eg proarrhythmia from antiarrhythmic drugs, or bleeding from anticoagulation), and
- likelihood of arrhythmia recurrence, by assessment.

Those patients considered most likely to successfully cardiovert and maintain sinus rhythm are those who have recent onset AF (less than 12 months), those with no underlying structural heart disease, and those who have AF secondary to a precipitant (eg treated thyroid disease, fever) that has been successfully treated or corrected.

The consideration of symptoms alone as indicators of AF recurrence is not usually reliable, since many instances of recurrence occur asymptomatically.[64]

For patients with AF recurrence the decision needs to be made of whether another attempt at cardioversion should be undertaken, or a strategy of rate control should be adopted (see section 6.3), and whether the patient requires long-term antithrombotic therapy (see section 11.6).

12.2.1 Methodological introduction

Fifteen studies were included that compared different electrophysiological, radiological, clinical or demographic variables in those patients who maintained sinus rhythm post cardioversion and those who experienced AF recurrence. This information was assessed in order to recommend an optimal follow-up strategy.

The results of studies were reported only where a particular electrophysiological, radiological, clinical or demographic variable had been stratified into meaningful value ranges and the measurement of recurrence made over a specific follow-up period.

Studies that had follow-up periods of less than 1 week or that considered only specialist investigations, such as signal-averaged ECG recording, were excluded. Echocardiographic risk factors for AF recurrence are reported elsewhere (see section 4.3).

12.2.2 Evidence statements

Twelve studies reporting the proportion of patients with recurrent AF at different intervals following successful cardioversion are as shown in Table 12.1.

Table 12.1 Percentage of patients with AF recurrence following cardioversion

	Study	N	Patients	Prior CV	Period	Recurrence (%)
(2++)	Bollmann et al, 2003[327]	42	Recurrent	Yes	0.5	31
(2+)	Roijer et al, 2001[43]	62	Lone	No	1	32
(2+)	Dittrich et al, 1989[328]	65	Recurrent	No	1	31
(2+)	Duytschaever et al, 1998[46]	85	Recurrent	Yes	3.25	31
(2++)	Dmochowska-Perz et al, 2002[49]	112	Recurrent	Yes	6	55
(2++)	Aytemir et al, 1999[329]	74	Persistent	NR	6	42
(2+)	Okcun et al, 2002[330]	110	Recurrent	Yes	6	48
(2+)	Dittrich et al, 1989[328]	65	Recurrent	No	6	42
(2++)	Dogan et al, 2004[44]	64	Recurrent	No	6	44
(2++)	Guo et al, 2003[331]	60	Persistent	Yes	6	77
(2++)	Antonielli et al, 2002[42]	186	Recurrent	Yes	12	51
(2+)	Berry et al, 2001[332]	88	Recurrent	Yes	12	63
(2+)	Arnar and Danielsen, 1996[47]	44	Recurrent	Yes	12	43
(2+)	Paraskevaidis et al, 2005[50]	61	Lone	Yes	12	61
(2++)	Perez et al, 1997[333]	75	Recurrent	Yes	12	53

Prior CV = whether or not the patients enrolled in the study included those in whom a previous attempt at cardioversion had been performed.
Period = elapsed time since successful cardioversion (months).
Recurrence = percentage of patients with recurrent AF.

Up to 1 month following cardioversion, no significant differences have been found in any of the following pre-cardioversion factors in terms of the incidence of AF recurrence:

- presence of underlying heart disease[327] (2++) or cardiomegaly[208] (2+)
- gender[43] (2+)
- age greater than 70 years[43] (2+)
- AF duration of less than 2 weeks[43] (2+)
- use of antiarrhythmic drugs[43] (2+).

At approximately 3 months following cardioversion, no significant differences have been found in any of the following pre-cardioversion factors for the incidence of AF recurrence:[46] (2+)

- presence of underlying heart disease
- gender
- age greater than 70 years.

However, duration of AF of less than 12 months was found to be associated with an increased likelihood of maintaining sinus rhythm.[46] (2+)

At 6 months following cardioversion, the following pre-cardioversion factors have been found to be associated with an increased incidence of AF recurrence:

- a history of recurrent AF[49] (2++)
- chronic-obstructive pulmonary disease[330] (2+)
- heart failure.[49,330] (2++)

One study[44] found an AF duration of less than 5 days to be predictive of sinus rhythm maintenance at 6 months with sensitivity of 79% and specificity of 96% (2++). Another study[331] found AF duration to be significantly associated with incidence of AF recurrence when measured as a continuous variable, but not when dichotomised at 1 year. (2++)

Out of five studies[44,328–331] considering the association between gender and AF recurrence, only one[328] found a significantly higher proportion of men with AF recurrence at 6 months. (2++)

At 6 months following cardioversion, no significant differences have been found in any of the following pre-cardioversion factors in terms of the incidence of AF recurrence:

- age greater than 60 years[330] (2+)
- presence of any comorbid heart disease[44,331] (2+)
- presence of ischaemic heart disease[44,329–331] (2++), valvular heart disease[44] (2+) or cardiomegaly[334] (2+)
- presence of hypertension[44,329–331] (2++)
- presence of diabetes.[330] (2+)

At 12 months following cardioversion the following pre-cardioversion factors have been found to be associated with an increased incidence of AF recurrence:

- cardiomegaly[335] (2+)
- AF duration of more than 1 week.[42] (2+)

One study[335] reported a reduced risk of AF recurrence at 12 months among those patients in whom cardioversion was successful using only amiodarone prior to scheduled electrical cardioversion, compared with those in whom electrical cardioversion was required in addition to amiodarone (multivariate RR 0.075; 95% CI 0.01 to 0.54). (2++)

At 12 months following cardioversion the following pre-cardioversion factors have not been found to be associated with an increased incidence of AF recurrence:

- AF duration of more than 12 months[335] (2+) or 1 month[333] (2++)
- presence of ischaemic heart disease[42,333] or prior MI[42] (2++)
- presence of diabetes[42] (2++)
- presence of hypertension[42,333] (2++)
- gender.[50,333] (2++)

12.2.3 From evidence to recommendations

In terms of the incidence of recurrent AF, approximately one third of patients will relapse back to AF within the first month following successful cardioversion,[43,44,327,328] increasing to approximately half at 1 year.[42,47,50,332,333] There was not a large difference in the proportion of those reverting back to AF between 6 months and 1 year.

This suggests the need for routine follow-up for assessment at 1 month and 6 months following cardioversion. Those found still to be in sinus rhythm at 6 months could be discharged from secondary care and advised to attend primary care if symptoms re-occur.

A management strategy formulated prior to discharge from secondary care and shared with the patient's GP would be helpful in maintaining continuity of care.

The evidence was not considered strong enough to allow for the identification of specific patients in whom an alternative follow-up strategy would be beneficial.

It was agreed that the 1-month follow-up needs to be performed by a suitably trained healthcare professional.

In addition to assessing for relapse to AF, during each follow-up the clinician can take the opportunity to review:

- any comorbid factors (eg heart failure, hypertension)
- any adverse effects related to cardioversion (eg skin burns, thromboembolism)
- drug therapies (eg proarrhythmia from antiarrhythmic drugs, or bleeding from anticoagulation).

Furthermore, where a patient has relapsed to AF a decision needs to be made on whether an early attempt at a second cardioversion is appropriate or a rate-control strategy is more appropriate.

RECOMMENDATIONS

R60 Following successful cardioversion of AF routine follow-up to assess the maintenance of sinus rhythm should take place at 1 month and 6 months. **D**

R61 At the 1-month follow-up the frequency of subsequent reviews should be tailored to the individual patient taking into account comorbidities and concomitant drug therapies. **D**

R62 At each review the clinician should take the opportunity to re-assess the need for, and the risks and benefits of, continued anticoagulation. **D(GPP)**

R63 At 6 months, if patients remain in sinus rhythm and have no other need for hospital follow-up, they should be discharged from secondary care with an appropriate management plan agreed with their GP. **D**

R64 Patients should be advised to seek medical attention if symptoms recur. **D(GPP)**

R65 Any patient found at follow-up to have relapsed into AF should be fully re-evaluated for a rate-control or rhythm-control strategy (see section 6.3). **D(GPP)**

12.3 Referral

The purpose of this section is to identify which patients with AF might benefit from specialist investigations or interventions, but not to compare or contrast them with one another.

The most common reason for referral for specialist investigation or intervention is failed medical therapy due to antiarrhythmic drug intolerance or ineffectiveness. Secondly, those who may have an underlying electrophysiological problem, such as a pre-excitation syndrome due to an accessory pathway (eg Wolff–Parkinson–White syndrome) or those with focal AF, are commonly referred for pulmonary vein isolation. However, this procedure carries a small risk of pulmonary vein stenosis. Also, those with a family history of AF (familial AF)[336] may require specialist assessment. In addition, elderly patients may have sinus node disease that is associated with paroxysmal AF. Some[337] but not all[338] studies suggest a reduction in AF by atrial or physiological pacing. Pacemaker therapy in AF is also indicated for symptomatic low heart rates. Arrhythmia surgery, such as themaze operation, or less frequently, the corridor procedure, may be undertaken as a primary procedure – although uncommonly in the UK – or during associated cardiac surgery (eg mitral valve surgery).[339–341]

In drug-resistant, poorly tolerated AF, atrioventricular junction (AVJ) catheter ablation is an option.[342] A recent meta-analysis[343] of before-after studies in AVJ ablation and pacing showed a beneficial effect in terms of symptom severity, exercise tolerance, cardiac physiology and function, as well as hospital admissions. However, 'ablate and pace' carries a small risk of sudden death.[344,345]

Using technology similar to implantable cardioverter-defibrillators for ventricular arrhythmias, an atrial defibrillator (atrioverter) re-establishes sinus rhythm and reduces recurrences of persistent AF.[346] There is conflicting evidence on the tolerability of atrial defibrillators and of the risk of ventricular proarrhythmia.

12.3.1 Methodological introduction

Studies were included if either:

- a comparison was made between a medical treatment strategy that involved the use of either pharmacological intervention and/or electrical cardioversion (internal or external) and other device or procedure-based treatments, or
- the study compared the safety or efficacy of other device or procedure-based treatments or investigations between different patient subgroups (defined by either demographic, clinical or physiological characteristics).

Studies that compared two device- or procedure-based treatments (for example, two variants of the maze procedure) were not considered.

The following categories of device or procedure-based treatments were included:

- pulmonary vein isolation
- pacemaker therapy
- arrhythmia surgery
- AVJ catheter ablation
- atrial defibrillators.

The majority of studies not involving concomitant cardiac surgery included only medically-refractory patients. Such patients are defined in this report by: an explicit report of refractoriness in the study inclusion criteria; reported resistance to a mean of at least two antiarrhythmic drugs; or the report of patients experiencing intolerable symptoms associated with AF, either in terms of severity or (in the case of paroxysmal AF) frequency of episodes.

12.3.2 Evidence statements

▷ Pulmonary vein isolation

One study[347] comparing pulmonary vein isolation (PVI) with amiodarone therapy in a population of amiodarone-naïve patients with medically-refractory non-valvular recurrent AF found PVI to be associated with a higher prevalence of sinus rhythm at 12 months (p=0.03) and improved quality of life (p=0.048). (**1+**)

One study[348] in a population of relatively young (mean age 54 years) patients with recurrent AF (mostly PAF) with no previous use of antiarrhythmic drugs found that PVI was associated with higher rates of sinus rhythm maintenance at 12 months than pharmacological therapy with antiarrhythmic drugs (87% versus 37%; p<0.001) (**1+**). Those patients undergoing PVI also had fewer hospital admissions than those treated with drugs (9% versus 54%; p<0.001) (**1+**). In terms of quality of life, PVI was associated with a greater improvement in the following Short-Form 36 health survey subscales than drug therapy: (**1+**)

- general health
- physical functioning
- role physical
- bodily pain.

The study reported comparable efficacy between PVI and drug therapy in all other aspects of quality of life.

Two studies[349,350] found increasing age to be significantly associated with an increased incidence of AF recurrence following PVI (**2+**). However, another study[351] in a population with paroxysmal lone AF did not find age to be a significant independent predictor. (**2+**)

The results of one study[352] in patients with medically-refractory AF and a history of isthmus-mediated atrial flutter found men less likely to maintain sinus rhythm following PVI (**2+**). Another study[351] found no effect of gender and a successful outcome at 3 months. (**2+**)

Three studies[349,352,353] found that those with medically-refractory paroxysmal AF are more likely to maintain sinus rhythm following PVI than those with medically-refractory non-paroxysmal AF (**2+**). Those with medically-refractory paroxysmal AF were also found to be more likely to benefit from PVI than those with persistent AF in terms of overall treatment success (restoration and maintenance of sinus rhythm or significant improvement in symptoms at 5 months).[353] (**2+**)

One study[350] found that those with medically-refractory lone paroxysmal AF are more likely to benefit from PVI than those with comorbid paroxysmal AF in terms of prevalence of sinus rhythm at 1 month (**2+**). The results for other populations with medically-refractory lone AF is unclear.[349,352] (**2+**)

Those without a history of paroxysmal AF[353] or hypertension,[354] a left atrial diameter less than 40 mm[350] and normal left ventricular function[355] are more likely to benefit from PVI in terms of the maintenance of sinus rhythm. (2+)

▷ Pacemaker therapy

One crossover study[356] found that bi-atrial pacing was associated with a significant reduction in the amount of time spent in AF over 3 months compared with no pacing (1+). A similar result was found for right-atrial pacing alone (1+). However, no significant difference was found in terms of the frequency of AF episodes. (1+)

One small study[357] found no difference in the prevalence of structural heart disease among those maintaining sinus rhythm and those with AF recurrence following successful internal cardioversion and pacing of patients with permanent AF (63% versus 100%). (2+)

▷ Arrhythmia surgery

One study[358] of patients with AF undergoing a combined cardiac procedure with a modified maze procedure using cryoablation had a higher prevalence of sinus rhythm in the acute postoperative period compared with those undergoing cardiac procedures without any concomitant antiarrhythmic surgery (84% versus 6%; $p<0.0001$) (2+). The modified maze procedure was also associated with longer intubation and recovery times, as well as higher pulmonary artery and central venous blood pressure (2+). In the long term, the antiarrhythmia surgery was also associated with an improved NYHA grade. (2+)

Six studies[359–364] found that combining mitral valve procedures with antiarrhythmia surgery (the maze procedure or variants thereof), was more effective in restoring and maintaining sinus rhythm than mitral valve surgery alone for at least 3 years postoperatively. (1+)

One study[362] found the combination of mitral valve surgery and the maze procedure to be ineffective in improving any echocardiographically detected measure of cardiac physiology (including LVEF and left atrial diameter) compared with mitral valve surgery alone over 3 months and 12 months postoperatively (1+). Another study[363] found a similar result in NYHA grade over the same period. (1+)

One study[358] in a population with a mean duration of AF of approximately 8 years found the combination of mitral valve surgery and a modified maze procedure using cryoablation to be effective in reducing the cardiothoracic and the left atrial diameter compared with mitral valve surgery alone. (2+)

One study[362] found no differences in exercise tolerance between those patients undergoing combined mitral valve and maze surgery and those undergoing mitral valve surgery alone (1+). Another study[363] found a similar result, with the exception of maximum workload which was higher in those undergoing the maze procedure. (1+)

No significant beneficial effect of combining the maze procedure with cardiac surgery has been reported in terms of either quality of life[362] or mortality[364] at 12 months (1+). However, there is limited evidence[360] to suggest a reduction in adverse vascular events (stroke or anticoagulated-related bleeding events). (2+)

One study[365] found that combining mitral valve procedures with the corridor procedure resulted in more effective ventricular rate control than mitral valve surgery alone. (2+)

LAA filling velocity less than 20 cm/sec,[366] a duration of AF more than 10 years,[366] an enlarged left atrium[366–368] and an F wave less than 1 mm[368] are all associated with a reduced likelihood of sinus rhythm restoration and maintenance during the early postoperative period following combined cardiac surgery with PVI. (2+)

An enlarged left atrium has also been found to be associated with a longer time taken to revert to sinus rhythm following combined mitral valve surgery with the maze procedure,[369] as well as a longer time taken for the restoration of atrial contractile function in those in whom sinus rhythm was restored.[370] (2+)

It is unclear whether an enlarged left atrium is associated with a reduced likelihood of AF recurrence in the longer term after combined cardiac and antiarrhythmic surgery[369–371] (2+). However, one study[372] found a left atrial diameter of less than 57.8 mm and a left-atrial area of less than 56.25 cm^2 to have some degree of power in predicting the maintenance of sinus rhythm at 38 months following combined mitral valve surgery with the maze procedure. (2+)

One study[367] reported that the sensitivity and specificity of the regression equation 1.39-(0.387GLA)-(0.01AFD)-(0.007Age), where values over 0.843 predict postoperative sinus rhythm, was 73.2% and 88.9%, respectively (2+) (Note that GLA = 1 for the presence of a giant left atrium, 0 otherwise, and AFD is the duration of AF). However, the expression has not been validated prospectively in a separate cohort of patients.

▷ Atrioventricular junction ablation

Compared with continued pharmacological therapy, AVJ ablation is associated with a significant reduction in the number of hospital admissions[373,374] (1+), as well as the incidence of CHF.[374] (2+)

Three studies[342,373,374] found that AVJ ablation was more effective in reducing the overall severity of symptoms of AF compared with continued pharmacological treatment. (1+)

Four studies[342,373–375] are consistent in demonstrating a reduction in all symptoms commonly associated with AF, with the exception of syncope and resting dyspnoea, following AVJ ablation compared with continued pharmacological treatment (1+). However, two studies[342,375] failed to find any significant improvement in terms of overall quality of life. (1+)

The results of one study[374] in a population with lone AF found a difference in mean NYHA grade between AVJ ablation and pharmacological treatment in favour of AVJ ablation (2+). A consistent result was also found in a population with paroxysmal AF,[373] although the difference was not significant (1+). Another study[342] found no significant difference in terms of left-ventricular fractional shortening (LVFS). (1+)

One study[373] found that 24% of patients who underwent AVJ ablation developed permanent AF within 6 months, compared with no patients who continued pharmacological treatment (p=0.04) (1+). Another study[376] reported that those older than 75 years or those with comorbid cardiovascular disease are at an increased risk of developing permanent AF following AVJ ablation. (2+)

▷ Atrial defibrillator

The use of an atrial defibrillator with the defibrillator function activated is associated with a reduced burden of AF and a reduction in the number of hospital admissions compared with when the defibrillator function is de-activated[377] (2+). No significant association has been reported between the degree of patient acceptance of the implantation and use of an atrial defibrillator and patient age, gender, or the number of cardioversions performed pre-implantation.[378,28]

12.3.3 From evidence to recommendations

▷ Pulmonary vein isolation

From the evidence, it was noted that patients with the following characteristics may benefit from referral for PVI:

- patients who were resistant to pharmacological treatment
- younger rather than older patients or
- those with lone AF.

It was recognised that many of these patients may have focal AF secondary to a pulmonary vein foci and for those patients PVI may be a useful procedure.

▷ Pacemaker therapy

Other than recognised indications for pacemaker implantations such as sinus node disease, symptomatic bradycardia and chronotropic incompetence, no evidence was found to specifically identify other patients with AF who should be referred for pacemaker implantation.

▷ Arrhythmia surgery

Other than patients undergoing concomitant cardiac surgery (eg mitral valve surgery), there was no evidence to specifically identify patients for referral for arrhythmia surgery other than those who had failed other treatment options.

▷ AVJ catheter ablation

It was concluded that this technique was effective for patients with medically refractive paroxysmal AF, especially in the absence of any cardiac comorbidity.

▷ Atrial defibrillators

This technique was considered to be useful in patients with recurrent persistent AF but it should not be used in those with paroxysmal AF.

RECOMMENDATIONS

R66 Referral for further specialist intervention (for example, pulmonary vein isolation, pacemaker therapy, arrhythmia surgery, AVJ catheter ablation or use of atrial defibrillators) should be considered in the following patients:

- those in whom pharmacological therapy has failed **B**
- those with lone AF **B**
- those with ECG evidence of an underlying electrophysiological disorder (eg Wolff–Parkinson–White syndrome). **C**

R67 The reasons for referral for specialist intervention should be explained and discussed with the patient. **D(GPP)**

Appendix A: Health economics modelling

The GDG selected a number of questions for which they felt more detailed health economic input would be useful. The following three areas were given priority:

- Economic analysis of the routine use of echocardiography versus selective use in clinical practice (routine ECHO model).
- Cost-effectiveness analysis of using TOE-guided CV in patients presenting with AF lasting for more than 48 hours for the presence of thrombi before cardioversion compared with conventional 3 to 4 weeks of anticoagulation (TOE model).
- The cost effectiveness of warfarin administration in AF patients, particularly the elderly (warfarin model).

No additional modelling was performed in the guideline on these topics for the reasons outlined below.

Routine ECHO model

When the model was presented to the GDG for discussion, the group were uncomfortable with the number of assumptions required for the model and the data sources used to obtain these. The GDG felt that the need to obtain health economics evidence for routine ECHO had been superseded, since routine ECHO is not going to be recommended. The recommendation for ECHO would be based on risk stratification and clinical criteria. The group voted to move on to the next topic for modelling.

TOE model

The health economist advised that a complex model was required to overcome limitations of the ACUTE trial. The technical team felt it would be difficult to populate this model with reliable data and were wary that the GDG would not be comfortable with a large number of assumptions. The project executive, aware of time constraints, advised that a rapid costing of the ACUTE trial was the only feasible option. Guidance was sought from health economist Jo Lord who advised that the costing of the ACUTE trial would be a misleading enterprise. The main concern was that the trial fails to establish the clinical superiority of the TOE strategy compared with the conventional anticoagulation strategy. A model designed on those data would have to incorporate an increase in mortality with TOE-guided CV. For this reason it was difficult to justify the rationale for conducting this cost-effectiveness analysis. Because of this, the TOE-guided CV model was not pursued.

Warfarin model

A review of the published cost-effectiveness literature was undertaken for this area prior to undertaking the modelling exercise. A large number of studies were identified (N=8) and thus it was agreed that there was sufficient literature to answer the question and no further analysis was required.

Appendix B: Stroke risk stratification models

Stroke risk stratification models

Ref no.	Criteria (year)	Type	IV	EV	Low-risk criteria	Medium-risk criteria	High-risk criteria
379	ACCP 1 (1998)	1°/2°	No	Yes	No medium or high-risk factors	Diabetes coronary artery disease Thyrotoxicosis Age 65 to 75 years	Age >75 years History of hypertension Moderate–severe LV systolic dysfunction (by echocardiography)
202	ACCP 2 (2004)	1°/2°	No	No	No medium or high-risk factors	Age 65 to 75 years	Prior stroke/TIA or systemic embolism Age >75 years Moderate–severe LV systolic dysfunction (by echocardiography) Diabetes Hypertension
168	AFI 1 (1994)	1°/2°	Yes	Yes	No risk factors	Previous stroke or TIA History of hypertension History of diabetes Age >65 years	
294	AFI 2 (1999)+	1°/2°	No	No	Age <65 with no history of embolism, hypertension, diabetes, or other clinical risk factors	Age <65 with clinical risk factors: diabetes, hypertension, peripheral arterial disease, ischaemic heart disease. Age >65 not in high-risk group	Previous stroke or TIA Age ≥75 years AND hypertension and/or diabetes Clinical evidence of valve disease, heart failure, thyroid disease, and/or impaired left ventricular function on echocardiography
28	AFI 3 (2003)	1°/2°	Yes	Yes	No risk factors	Previous stroke or TIA Treated hypertension OR systolic blood pressure ≥160 mm Hg Previous MI OR angina Diabetes	
295	AHA/ ACC/ESC (2001)	1°/2°	No	No	No risk factors	Age ≥75 years Age >60 years with diabetes Age >60 years with coronary artery disease Heart failure (clinically determined) OR LVEF <35% Thyrotoxicosis Hypertension	
296	CHADS2 (2001)*	1°/2°	No	Yes	Score = 0	Score = 1 to 2	Score >2

continued

Stroke risk stratification models – *continued*

Ref no.	Criteria (year)	Type	IV	EV	Low-risk criteria	Medium-risk criteria	High-risk criteria
285	EAFT (1995)	2°	Yes	No	No risk factors	*Less than 3 risk factors:* • Previous (non-cerebrovascular) thromboembolism • Systolic blood pressure >160 mm Hg • Ischaemic heart disease • Cardiomegaly (CTR >50% by X-ray) • AF duration >1 year • At least one visible ischaemic cerebral lesion by CT scan	*3 or more risk factors:* • Previous (non-cerebrovascular) thromboembolism • Systolic blood pressure >160 mm Hg • Ischaemic heart disease • Cardiomegaly (CTR >50% by X-ray) • AF duration >1 year • At least one visible ischaemic cerebral lesion by CT scan
283	Framing-ham (2003)**	1°/2°	Yes	Yes	0–7	8–13	14–31
287	SPAF 1 (1992)	1°/2°	Yes	No	No risk factors	*Exactly 1 risk factor:* Previous thromboembolism History of hypertension Recent congestive heart failure	*More than 1 risk factor:* Previous thromboembolism History of hypertension Recent congestive heart failure
290	SPAF 2 (1995)	1°/2°	Yes	No	No risk factors	Previous thromboembolism Systolic blood pressure >160 mm Hg Recent episode of congestive heart failure OR LVFS ≤25% Female AND age >75 years	
282	SPAF 3 (1998)	1°	No	Yes	No risk factors	History of hypertension	Previous stroke or TIA or systemic embolism Systolic blood pressure >160 mm Hg Recent episode of congestive heart failure OR LVFS ≤25% Female AND age >75 years
192	SPAF 4 (1999)	1°/2°	Yes	No	No risk factors	Hypertension AND age ≤75 years Diabetes	Previous stroke or TIA Systolic blood pressure >160 mm Hg Hypertension AND age >75 years Female AND age >75 years
281	SPAF 5 (1999)	1°	Yes	No	No risk factors	Hypertension AND age ≤75 years Diabetes	Systolic blood pressure >160 mm Hg Hypertension AND age >75 years Female AND age >75 years

+AFI2 [294] was based on the initial AFI1 [168] risk stratification, but refined for a Birmingham primary care population by the AF Clinical Effectiveness Topic Group on behalf of the Birmingham Effectiveness Group, commissioned by Birmingham Health Authority. This was then implemented (31/8/97) as *Clinical Management in General Practice Guidelines* of the Birmingham Medical Audit Advisory Group and as a pan-Birmingham audit project in primary care by the Birmingham Health Authority.
*The CHADS2 system is based on the AFI1 and SPAF1 risk criteria, and assigns one point to CHF, hypertension, age >75, diabetes mellitus and two points to a previous stroke or TIA;
**Framingham 2003 assigned points to incremental increases in age (0 to 10 points) and blood pressure (0 to 3 points), and 6 points for being female, 5 points for diabetes and 6 points for a previous stroke or TIA. Risk stratification was made for CHADS2 and Framingham 2003 based on expected incidence of <2%, 2 to 6%, and >6% for low, medium and high-risk patients, respectively (using original cohort data).

Appendix C: Clinical questions and search strategies

The table below lists all of the systematic reviews of the relevant literature that were performed as part of the development process of this guideline. In each case the section number of this guideline is given where the results of the systematic review are presented, along with the clinical question asked, and the corresponding search strategy used.

Clinical questions and search strategies

Section number	Question wording	Study type filters used	Databases and years
4.1	In patients with diagnosed AF (including those presenting with stroke), what are the frequencies of the presenting symptoms?	All study types including hospital- and population-based	Medline 1966–2005 Embase 1980–2005 Cochrane 1800–2005 Cinahl 1982–2005
4.2	In patients with suspected AF based on an irregular pulse, how accurate is an ECG in diagnosing AF?	Diagnosis	Medline 1966–2005 Embase 1980–2005 Cochrane 1800–2005 Cinahl 1982–2005
4.3	In which patients should echocardiography be performed to identify underlying structural/functional heart disease?	Diagnosis	Medline 1966–2005 Embase 1980–2005 Cochrane 1800–2005 Cinahl 1982–2005
4.4	In patients with suspected intermittent AF, how effective is ambulatory ECG rather than event ECG in diagnosing AF?	Diagnosis	Medline 1966–2005 Embase 1980–2005 Cochrane 1800–2005 Cinahl 1982–2005
5.1	Does electrical conversion versus pharmacological conversion affect rates of thromboembolism, quality of life, exercise capacity, failure rates?	All study types	Medline 1966–2005 Embase 1980–2005 Cochrane 1800–2005 Cinahl 1982–2005
5.2	In patients with persistent AF, is amiodarone better than a) flecainide or b) propafenone for use in cardioversion?	Systematic reviews, RCTs and comparative studies	Medline 1966–2005 Embase 1980–2005 Cochrane 1800–2005 Cinahl 1982–2005
5.2	In patients with AF is amiodarone better than sotalol for use in cardioversion?	Systematic reviews, RCTs and comparative studies	Medline 1966–2005 Embase 1980–2005 Cochrane 1800–2005 Cinahl 1982–2005
5.3	What is the safety and efficacy of the adjunctive administration of antiarrhythmic drugs for use in electrical cardioversion in comparison to electrical cardioversion without adjunctive antiarrhythmic drugs?	Systematic reviews, RCTs and comparative studies	Medline 1966–2005 Embase 1980–2005 Cochrane 1800–2005 Cinahl 1982–2005

continued

Clinical questions and search strategies – *continued*

Section number	Question wording	Study type filters used	Databases and years
5.4	Is a conventional anticoagulation strategy for elective cardioversion as effective as a transoesophageal echocardiogram plus anticoagulation?	Systematic reviews, RCTs, comparative studies and observational studies	Medline 1966–2005 Embase 1980–2005 Cochrane 1800–2005 Cinahl 1982–2005
6.1	In patients with AF, is flecainide or propafenone better than beta-blockers in maintaining sinus rhythm post cardioversion?	Systematic reviews, RCTs and comparative studies	Medline 1966–2005 Embase 1980–2005 Cochrane 1800–2005 Cinahl 1982–2005
6.1	In patients with AF, is amiodarone or sotalol better than beta-blockers in maintaining sinus rhythm post cardioversion?	Systematic reviews, RCTs and comparative studies	Medline 1966–2005 Embase 1980–2005 Cochrane 1800–2005 Cinahl 1982–2005
6.1	In patients with AF, is flecainide/propafenone better than amiodarone or sotalol in maintaining sinus rhythm post cardioversion?	Systematic reviews, RCTs and comparative studies	Medline 1966–2005 Embase 1980–2005 Cochrane 1800–2005 Cinahl 1982–2005
6.2	What is the efficacy of anticoagulation therapy versus placebo for stroke prevention in: a) paroxysmal AF b) permanent AF c) peri/post cardioversion to sinus rhythm d) acute/post-op AF e) peri/post stroke f) asymptomatic AF?	Systematic reviews, RCTs and comparative studies	Medline 1966–2005 Embase 1980–2005 Cochrane 1800–2005 Cinahl 1982–2005
6.2	What is the efficacy of anticoagulation therapy versus antiplatelet therapy for stroke prevention in: a) paroxysmal AF b) permanent AF c) peri/post cardioversion to sinus rhythm d) acute/post-op AF e) peri/post stroke?	Systematic reviews, RCTs and comparative studies	Medline 1966–2005 Embase 1980–2005 Cochrane 1800–2005 Cinahl 1982–2005
6.2	What is the efficacy of antiplatelet therapy versus placebo for stroke prevention in: a) paroxysmal AF b) permanent AF c) peri/post cardioversion to sinus rhythm d) acute/post-op AF e) peri/post stroke f) asymptomatic AF?	Systematic reviews, RCTs and comparative studies	Medline 1966–2005 Embase 1980–2005 Cochrane 1800–2005 Cinahl 1982–2005
6.3	In which patients with persistent AF does rate control result in improved mortality/morbidity/quality of life over rhythm control?	All study types	Medline 1966–2005 Embase 1980–2005 Cochrane 1800–2005 Cinahl 1982–2005
6.3	In which patients with persistent AF does rhythm control result in improved mortality/morbidity/quality of life over rate control?	All study types	Medline 1966–2005 Embase 1980–2005 Cochrane 1800–2005 Cinahl 1982–2005
7.1	In patients with permanent AF, what is the efficacy of rate-limiting calcium antagonists compared with digoxin in rate control?	Systematic reviews, RCTs and comparative studies	Medline 1966–2005 Embase 1980–2005 Cochrane 1800–2005 Cinahl 1982–2005

continued

Clinical questions and search strategies – *continued*

Section number	Question wording	Study type filters used	Databases and years
7.1	In patients with permanent AF, what is the efficacy of beta-blockers compared with digoxin in rate control?	Systematic reviews, RCTs and comparative studies	Medline 1966–2005 Embase 1980–2005 Cochrane 1800–2005 Cinahl 1982–2005
7.1	In patients with permanent AF, what is the efficacy of beta-blockers compared with rate-limiting calcium antagonists in rate control?	Systematic reviews, RCTs and comparative studies	Medline 1966–2005 Embase 1980–2005 Cochrane 1800–2005 Cinahl 1982–2005
7.1	In patients with permanent AF, what is the efficacy of rate-limiting calcium antagonists in combination with digoxin compared with rate-limiting calcium antagonists monotherapy in rate control?	Systematic reviews, RCTs and comparative studies	Medline 1966–2005 Embase 1980–2005 Cochrane 1800–2005 Cinahl 1982–2005
7.1	In patients with permanent AF, what is the efficacy of beta-blockers in combination with digoxin compared with beta-blocker monotherapy in rate control?	Systematic reviews, RCTs and comparative studies	Medline 1966–2005 Embase 1980–2005 Cochrane 1800–2005 Cinahl 1982–2005
7.2	What is the efficacy of anticoagulation therapy versus placebo for stroke prevention in: a) paroxysmal AF b) permanent AF c) peri/post cardioversion to sinus rhythm d) acute/post-op AF e) peri/post stroke f) asymptomatic AF?	Systematic reviews, RCTs and comparative studies	Medline 1966–2005 Embase 1980–2005 Cochrane 1800–2005 Cinahl 1982–2005
7.2	What is the efficacy of anticoagulation therapy versus antiplatelet therapy for stroke prevention in: a) paroxysmal AF b) permanent AF c) peri/post cardioversion to sinus rhythm d) acute/post-op AF e) peri/post stroke?	Systematic reviews, RCTs and comparative studies	Medline 1966–2005 Embase 1980–2005 Cochrane 1800–2005 Cinahl 1982–2005
7.2	What is the efficacy of antiplatelet therapy versus placebo for stroke prevention in: a) paroxysmal AF b) permanent AF c) peri/post cardioversion to sinus rhythm d) acute/post-op AF e) peri/post stroke f) asymptomatic AF?	Systematic reviews, RCTs and comparative studies	Medline 1966–2005 Embase 1980–2005 Cochrane 1800–2005 Cinahl 1982–2005
8.1	In patients with paroxysmal AF, is flecainide/propafenone better than beta-blockers in reducing the frequency of paroxysms?	Systematic reviews, RCTs and comparative studies	Medline 1966–2005 Embase 1980–2005 Cochrane 1800–2005 Cinahl 1982–2005
8.1	In patients with paroxysmal AF, is amiodarone or sotalol better than beta-blockers in reducing the frequency of paroxysms?	Systematic reviews, RCTs and comparative studies	Medline 1966–2005 Embase 1980–2005 Cochrane 1800–2005 Cinahl 1982–2005
8.1	In patients with paroxysmal AF, is flecainide/propefanone better than amiodarone or sotalol in reducing the frequency of paroxysms?	Systematic reviews, RCTs and comparative studies	Medline 1966–2005 Embase 1980–2005 Cochrane 1800–2005 Cinahl 1982–2005

continued

Clinical questions and search strategies – *continued*

Section number	Question wording	Study type filters used	Databases and years
8.2	In which patients should pill-in-the-pocket therapy be recommended?	All study types	Medline 1966–2005 Embase 1980–2005 Cochrane 1800–2005 Cinahl 1982–2005
9.1	In haemodynamically unstable patients presenting with acute AF, what is the best treatment strategy (ECV, PCV or acute (iv) rate control)?	Systematic reviews, RCTs, comparative studies, case control and observational studies	Medline 1966–2005 Embase 1980–2005 Cochrane 1800–2005 Cinahl 1982–2005
10.1, 10.2	What is the best treatment strategy (rate or rhythm control or no treatment) for patients with postoperative AF?	Systematic reviews, RCTs and comparative studies	Medline 1966–2005 Embase 1980–2005 Cochrane 1800–2005 Cinahl 1982–2005
10.1	Is the perioperative administration of antiarrhythmic drugs effective prophylaxis for post-operative AF?	Systematic reviews, RCTs and comparative studies	Medline 1966–2005 Embase 1980–2005 Cochrane 1800–2005 Cinahl 1982–2005
11.1	At the diagnosis of AF does immediate anticoagulation (comparison is absence of immediate Tx or later, delayed Tx) result in reduced rates of morbidity and mortality, without increasing pt anxiety, while still being cost effective?	Systematic reviews, RCTs, comparative studies, case control and cohort studies	Medline 1966–2005 Embase 1980–2005 Cochrane 1800–2005 Cinahl 1982–2005
11.5	In people with AF what are the risks of long-term oral anticoagulation administration as thromboprophylaxis?	Treatment outcomes, systematic reviews, RCTs, and comparative studies	Medline 1966–2005 Embase 1980–2005 Cochrane 1800–2005 Cinahl 1982–2005
11.6	In patients with AF, what are the risk factors associated with stroke/TIA and thromboembolism?	Risk, systematic reviews, RCTs, comparative studies and observational studies	Medline 1966–2005 Embase 1980–2005 Cochrane 1800–2005 Cinahl 1982–2005
12.1	In patients receiving anticoagulation therapy, is self-management using near-patient testing devices in primary care as effective as management using hospital lab testing?	Systematic reviews, RCTs, comparative studies, case control and observational studies	Medline 1966–2005 Embase 1980–2005 Cochrane 1800–2005 Cinahl 1982–2005 BNI 1985–2005
12.2	When should a cardioverted patient be followed up after cardioversion?	Systematic reviews, RCTs, comparative studies and observational studies	Medline 1966–2005 Embase 1980–2005 Cochrane 1800–2005 Cinahl 1982–2005
12.3	Which patients with AF benefit from referral to specialist services for non-pharmacological treatment or electrophysiological studies?	Systematic reviews, RCTs, comparative studies and observational studies	Medline 1966–2005 Embase 1980–2005 Cochrane 1800–2005 Cinahl 1982–2005

Note: The final cut-off date for all searches was 6th June 2005.

Appendix D: Drug classification and licensing

Wherever appropriate, throughout this guideline recommendations have been formulated in terms of drug classes rather than individual drugs. The Vaughan-Williams system for classifying antiarrhythmic drugs such as flecainide (Class Ic) and amiodarone (Class III) has been used where appropriate.

In the case of rate-limiting calcium antagonists, certain drugs within this class may not be indicated for the treatment of AF. In particular, the rate-limiting calcium antagonist diltiazem hydrochloride is not indicated for AF, but nonetheless has a substantial evidence-base supporting its use.

Beta-blockers represent a wide range of agents, with different degrees of cardioselectivity. Certain beta-blockers may not be licensed specifically for AF. Sotalol is a beta-blocker that has additional Class III antiarrhythmic activity at high doses (240 to 480 mg/day). In UK practice, sotalol is often used at low doses (80 to 160 mg/day), which essentially acts in a similar manner to a standard beta-blocker (Class II) in terms of antiarrhythmic activity. In some patient groups (for example, those with a low body mass index or renal impairment), some Class III activity may even manifest at these low doses. In general, when used as a Class III antiarrhythmic agent, sotalol is often started at a dose of 80 mg twice daily for the first week and subsequently titrated to 160 mg twice daily or even higher doses after checking for adverse effects and QT prolongation on ECG.

Appendix E: Glossary of terms

Absolute risk reduction (**ARR**) The difference between the percentage incidence of adverse outcomes in the test group compared with the control group in a controlled trial, eg if the stroke rate in warfarin-treated patients is 2% compared with 5% in non-warfarin treated patients, warfarin is associated with an absolute risk reduction of 3%.

Accessory pathway An abnormal conduction circuit within the heart resulting in abnormal heart rhythms.

Adjusted dose The situation where the dosage of a drug is adjusted to attain a particular physiological value, eg the dosage of warfarin may be adjusted to attain a particular INR value.

Adverse event An event that occurs, normally as part of a pathological process or as an unintended consequence of a therapeutic intervention, which is considered to be of detrimental value to the patient in terms of their health or quality of life, eg the development of pulmonary fibrosis consequent to the long-term administration of amiodarone.

AF burden A measure of the degree to which the presence of AF has a detrimental effect on the patient's quality of life. It is normally measured either as the proportion of time spent in AF, or the number of AF episodes per unit time.

AF pathophysiology The pathological progression of AF in terms of the degeneration of the arrhythmia to a more sustained and/or symptomatic form, or the development of associated co-morbidities.

AF recurrence The recurrence of an episode of AF following one or more prior episodes of the arrhythmia in either its paroxysmal or persistent form.

AF subtype A subtype of AF based on its temporal pattern. AF subtypes are recent onset, paroxysmal, persistent and permanent.

Algorithm (**in guidelines**) A flowchart of the clinical decision pathway described in the guideline, where decision points and actions are represented by different shaped boxes and linked by arrows.

Ambulatory-ECG An ECG monitoring tool in which a continuous ECG recording is made while the patient remains able to walk around freely and pursue most normal daily activities.

Antiarrhythmic A drug or interventional procedure that has a therapeutic effect against cardiac arrhythmias.

Anticoagulation A form of thromboprophylaxis involving the use of anticoagulant drugs such as warfarin that inhibit the coagulation/clotting of blood.

Antiplatelet therapy A form of thromboprophylaxis involving the use of antiplatelet drugs (such as aspirin) that inhibit the formation of blood clots.

Antithrombotic therapy See 'thromboprophylaxis'.

Aortic plaque The deposits of atherosclerotic plaque within the aorta. The extent of aortic plaque is classified as 'simple', 'moderate' or 'complex'.

Aortic stenosis An abnormal narrowing of the aortic valve.

Arrhythmia An irregularity in the coordinated rhythm of the heart.

Arrhythmia surgery Antiarrhythmic surgical interventions to treat the abnormal heart rhythm, eg the 'maze' procedure, corridor operation. See also 'antiarrhythmic'.

Atrial arrhythmias Cardiac arrhythmias that originate in the atria. AF is an atrial arrhythmia. See also 'arrhythmia'.

Atrial contractile function A measurement of the contractile function of the atria. This is normally measured using echocardiography.

Atrial defibrillator See 'cardioverter defibrillator'.

Atrial fibrillation (AF) An atrial arrhythmia characterised by an absence of regular P waves on an electrocardiogram, and normally resulting in a fast ventricular response. See also 'atrial arrhythmia'.

Atrial filling fraction A measurement of the contractile function of the atria. This is normally measured using echocardiography.

Atrioventricular node ablation Use of energy (usually radiofrequency) to destroy tissue of the atrioventricular node to alter conduction of electrical signals through this part of the heart.

Atrioventricular-blocking drug A drug that inhibits the ability of the atrioventricular node to conduct electrical signals to the ventricles.

Audit See 'clinical audit'.

Binary A clinical variable or outcome is binary when it can only take on two possible values. In some cases variables that can take on more than two possible values, such as age, are dichotomised at a particular value to create a binary variables, such as 'under 65' and '65 or over'.

Bradycardia A slow heart beat. The occurrence of bradycardia is often recorded as an adverse event to some antiarrhythmic or chronotropic drugs. Such occurrences are referred to as bradycardic events.

Cardioembolic stroke An embolic stroke whose aetiology is presumed to be the embolisation of an intracardiac thrombus.

Cardiomegaly An abnormal enlargement of the heart. It is normally measured in terms of the cardiothoracic ratio from a chest X-ray or by measurement using echocardiography.

Cardiomemo An event recorder that records cardiac rhythm when activated by the patient.

Cardiothoracic ratio (CTR) See 'cardiomegaly'.

Cardioversion In the context of AF, cardioversion is the process of restoring normal sinus rhythm. There are two commonly used forms of cardioversion: electrical cardioversion and pharmacological cardioversion. The former involves the administration of a transthoracic electrical shock; the latter involves the administration of antiarrhythmic drugs.

Cardioverter defibrillator A defibrillator device that is implanted into the patient's chest to deliver an electrical shock to cardiovert episodes of AF. The device may be automated – automatic implanted cardioverter defibrillator – or patient-triggered. See also 'defibrillator'.

Case series Report of a number of cases of a given disease, usually covering the course of the disease and the response to treatment. There is no comparison (control) group of patients.

Case-control study Comparative observational study in which the investigator selects individuals who have experienced an event (for example, developed a disease) and others who have not (controls), and then collects data to determine previous exposure to a possible cause.

Cerebral infarction Damage to the brain following a reduction of blood supply to that area, resulting in a stroke.

Cerebrovascular disease Disease of the blood vessels within the brain. Cerebrovascular disease can be caused by blocked or otherwise damaged blood vessels and is the cause of strokes. See also 'stroke'.

Chronotropic In the context of pharmacology, the ability of a therapeutic intervention to control heart rate.

Chronotropic incompetence The inability of the body to appropriately alter heart rate during periods of physical exertion. See also 'chronotropic'.

Clinical audit A quality improvement process that seeks to improve patient care and outcomes through systematic review of care against explicit criteria and the implementation of change.

Clinically significant The result of a study is clinically significant if it is felt that the demonstrated difference in outcomes between the different arms of the study have the potential to inform and change clinical practice. A result may be statistically significant but not clinically significant, and vice versa.

Cohort study A retrospective or prospective follow-up study. Groups of individuals to be followed up are defined on the basis of presence or absence of exposure to a suspected risk factor or intervention. A cohort study can be comparative, in which case two or more groups are selected on the basis of differences in their exposure to the agent of interest.

Comparable In a statistical sense, a therapeutic intervention is said to be comparable to another if there is no statistically significant difference between them.

Compliance The extent to which a patient complies with a recommended treatment regimen.

Confidence interval (CI) A range of values which contains the true value for the population with a stated 'confidence' (conventionally 95%). The interval is calculated from sample data, and generally straddles the sample estimate. The 95% confidence value means that if the study, and the method used to calculate the interval, is repeated many times, then 95% of the calculated intervals will actually contain the true value for the whole population.

Confound The results of a study are confounded when there are thought to be other variables that were not controlled for in the study design, and where the effects of those variables on the results are unquantifiable and variable.

Congestive heart failure (CHF) Heart failure characterised by the inability of the heart to adequately support the body's physiological requirements.

Conventional anticoagulation The use of oral anticoagulation as a means of thromboprophylaxis, aiming for a target INR (usually 2.5, range 2–3) with monitoring and dose adjustment in an anticoagulation clinic. In the context of cardioversion, this is contrasted with the use of transoesophageal echocardiography to screen for the presence of thrombi and the use of parenteral anticoagulation prior to cardioversion, thus excluding the pre-cardioversion initiation of anticoagulation.

Coronary artery disease A disease which affects the arteries of the heart, normally through atherosclerosis of the coronary arteries, reducing the supply of blood to the heart and causing ischaemia and angina. See also 'ischaemic heart disease'.

Cost function A function that describes the relationship between the input prices such as labour costs, drugs, hospital stay and the quantity of outputs (health outcomes). It describes the opportunity cost, that is, what needs to be sacrificed in monetary terms in order to gain certain outcomes.

Cost effectiveness A measure of effectiveness that is relative to cost. For example, the cost effectiveness of antithrombotic therapy to prevent strokes may be measured in terms of the cost per stroke prevented. See also cost-effectiveness analysis and cost-effectiveness model.

Cost-effectiveness analysis An economic study design in which consequences of different interventions are measured using a single outcome, usually in natural units (for example, life-years gained, deaths avoided, heart attacks avoided, cases detected). Alternative interventions are then compared in terms of cost per unit of effectiveness.

Cost-effectiveness model An explicit mathematical framework, which is used to represent clinical decision problems and incorporate evidence from a variety of sources in order to estimate the costs and health outcomes.

Cost–utility analysis A form of cost-effectiveness analysis in which the units of effectiveness are quality-adjusted life-years (QALYS).

Coumarin derivative An anticoagulant drug that is derived from coumarin. Examples of coumarin derivatives include the anticoagulant warfarin.

Crossover study A study design in which the participants are first administered the control intervention, followed by the test intervention, or vice versa. In between these two study phases there is normally a wash-out period in the case of drug trials, so that the levels of the control or test drug falls to negligible amounts before the next phase of the study begins.

Cryoablation Use of cold energy ('freezing') to destroy tissue within the heart in order to alter conduction of electrical signals through this part of the heart.

CT scan Computed tomography scan, an imaging technique using X-rays.

Day case In the context of cardioversion, a day case refers to the discharge of patients following elective cardioversion on the same day on which they were admitted.

Decision analytic model/techniques A way of reaching decisions, based on evidence from research. This evidence is translated into probabilities and then into diagrams or decision trees that direct the clinician through a succession of possible scenarios, actions and outcomes.

Decision model A systematic framework of representing a clinical problem under conditions of uncertainty. It is used to determine the costs and health outcomes of a hypothetical patient cohort with disease of interest when they are treated with different clinical strategies.

Defibrillator In the context of AF, a device used to deliver the electrical shock used in electrical cardioversion.

Diagnostic accuracy The degree to which a diagnostic (or screening) tool or procedure is able to distinguish between cases and non-cases. See also 'sensitivity', 'specificity', 'negative predictive value' and 'positive predictive value'.

Diastolic Relating to the phase of the cardiac cycle where the chambers of the heart fill with blood prior to being pumped out during the subsequent systolic phase. See also 'systolic'.

Discounted survival See 'discounting'.

Discounting The process of converting the cost or benefits to be incurred or received at different points in the future to a present value so that they can be compared in commensurate units as if they all occur at the same point in time.

Dominance An intervention is said to dominate an alternative intervention if it is both more effective clinically and less costly.

Drug-eluting stents Special metallic devices which are placed within the coronary artery to reduce the likelihood of coronary stenosis recurring following angioplasty (balloon dilatation of the coronary artery). Drug eluting stents have special drugs within their structure that greatly reduce the recurrence of stenoses.

Dyspnoea Breathlessness.

Echocardiogram An examination of the heart using ultrasound-imaging techniques. An echocardiogram may be performed by placing the ultrasound device across the chest (transthoracic echocardiography), or by inserting it down the gullet to view the heart from behind (transoesophageal echocardiography).

Electrical cardioversion (ECV) See 'cardioversion'.

Electrocardiograph (ECG) A device which traces the electrical activity of the heart by recording the electrical potentials at electrodes placed at various locations around the chest. The recording produced by the electrocardiograph is referred to as an electrocardiogram.

Electrolyte abnormalities Abnormalities or an imbalance in one or more of the body's salts or other chemicals in the blood circulation.

Embolic The passage within the blood stream of a body (eg blood clot), which has formed somewhere and ends up elsewhere within the body (eg brain).

Endpoint In the context of study design, an endpoint is a pre-defined event or events whose occurrence represents the end of follow-up. A composite endpoint is one where more than one event is pre-defined, and the occurrence of any one of them represents the end of follow-up. A primary endpoint is the occurrence of the event, which is the main outcome of interest.

Event-ECG recorder An ECG recording device, which only produces an ECG recording when susceptible electrical activity is detected. It may be triggered automatically or by the patient upon the occurrence of symptoms. See 'cardiomemo'.

Exercise tolerance A measure of a patient's capacity for physical exertion.

Extra cellular fluid volume A term that refers to the fluid bathing the body's cells.

Focal AF AF secondary to a focus of abnormal cells (eg near the pulmonary veins) that can initiate AF.

Functional heart disease Abnormalities of cardiac function – either in systole or diastole.

Good practice point (GPP) Recommended good practice based on the clinical experience of the guideline development group in the absence of robust, published clinical evidence.

Grade (class) of recommendation All recommendations are assigned a grade (A, B, C, D or D(GPP)) according to the level of evidence the recommendation is based on (see 'level of evidence').

Guideline development group (GDG) The guideline development group agrees the clinical questions for the guideline, considers the evidence and develops the recommendations. The GDG membership is multidisciplinary comprising clinicians, patients and/or carers and technical experts.

Haemodynamic function An assessment of cardiac function.

Haemodynamic instability Where cardiac function is compromised so that the patient becomes clinically unstable.

Haemorrhagic death Death caused by a haemorrhagic event such as an intracranial haemorrhage.

Haemorrhagic stroke Stroke secondary to cerebral haemorrhage.

Haemorrhagic transformation The situation where there is bleeding into a (usually large) cerebral infarction, especially in the early phase of a stroke.

Health technology assessment (HTA) These consider the effectiveness, appropriateness and cost of technologies and are funded by the NHS Research and Development Division.

Heart failure See 'congestive heart failure'.

Heart murmur An audible sound with or without a stethoscope, which relates to abnormal flow within the heart or an abnormal communication within the circulatory system.

Heart rate The rate at which the heart performs a complete cycle of coordinated muscular contraction. It is measured in beats per minute (bpm).

Holter monitor An ambulatory ECG recording device.

Hyperadrenergic state Situations where there is abnormal circulating adrenaline (and similar hormones) and/or activation of the sympathetic nervous system eg 'fight or flight' reaction.

Hypertension Abnormally high blood pressure.

Hypotension Abnormally low blood pressure.

Incidence The rate at which an event occurs. Incidence normally measures the rate at which people within a population develop a particular disease or experience other adverse events.

Inconclusive A series of study results are inconclusive when the evidence of different studies do not conflict with each other, but nonetheless lack the strength to be able to reach a definite conclusion.

Incremental cost per QALY The additional cost incurred for each additional QALY. See also 'incremental cost-effectiveness ratio'.

Incremental cost-effectiveness ratio (ICER) A ratio obtained by dividing the incremental costs (cost difference) by the incremental benefits (outcome differences) for two interventions. This depicts the extra cost per unit of outcome. A decision will be made as to whether the additional cost per unit of outcome is worth paying for based on the decision-maker's willingness to pay.

Independent predictor A variable whose value predicts the occurrence of an event independent of the values of other variables.

Infarction An ischaemic lesion. Cerebral infarctions can result in stroke, and myocardial infarctions can result in a heart attack. See also 'myocardial infarction'.

Informed dissent The situation whereby a patient elects to abstain from receiving the optimal therapeutic intervention in the knowledge that this could cause them harm.

Inotropic Drugs that can stimulate the contraction of the heart.

Intention-to-treat analysis (ITT analysis) An analysis of the results of a clinical study in which the data are analysed for all study participants as if they had remained in the group to which they were randomised, regardless of whether or not they remained in the study until the end, crossed over to another treatment or received an alternative intervention.

Intermittent atrial fibrillation AF that is not sustained, but interrupted by periods of sinus rhythm. Intermittent AF is normally considered to apply to more patients than paroxysmal AF, since the periods of sinus rhythm in the former may be very brief and otherwise insignificant.

International normalised ratio (INR) A measure of the clotting ability of blood, usually following use of anticoagulant drugs. It is calculated as the ratio of the length of time it takes blood to clot over the time it would take the blood of a normal subject to clot.

Intracardiac Occurring within the chambers of the heart.

Intracranial haemorrhage A bleeding event within the brain, which may result in a haemorrhagic stroke.

Intubation Being intubated with a transoesophageal breathing tube connected to a mechanical ventilator.

Ischaemic heart disease Heart disease characterised by a reduced supply of blood to the heart. See also 'coronary artery disease'.

Ischaemic stroke Stroke caused by cerebral infarction.

Lacunar infarction Stroke secondary to blockage of the small vessels especially at the border of zones supplied by different arteries.

Left atrial appendage velocity A measurement of the blood flow within the left atrial appendage, usually on TEE.

Left bundle branch block (**LBBB**) A conduction abnormality of the heart due to impaired conduction down the left bundle of His.

Left ventricular dysfunction (**LVD**) Impaired function of the left ventricle.

Left ventricular ejection fraction (**LVEF**) The percentage of blood within the left ventricle that is ejected at each contraction.

Left ventricular end diastolic diameter (**LVEDD**) A measurement of the size of the heart on echo, referring to the internal dimension of the heart in diastole.

Left ventricular end systolic diameter (**LVESD**) A measurement of the size of the heart on echo, referring to the internal dimension of the heart in systole.

Left ventricular hypertrophy (**LVH**) Thickening of the heart muscle, usually secondary to hypertension, aortic valve narrowing etc.

Left ventricular shortening fraction (**LVFS**) A measure of left ventricular function on echo.

Level of evidence A code (eg 1++, 1+, 2++) linked to an individual study, indicating where it fits into the NICE hierarchy of evidence and how well it has adhered to recognised research principles.

Lone AF AF that occurs in the absence of any comorbid cardiovascular disease or other precipitants of AF.

Magnetic resonance imaging (**MRI**) A non-invasive imaging technique allowing detailed examination of the heart.

Management strategy The overarching plan on how to treat a particular patient. In the context of AF, there are two main management strategies – rate control and rhythm control.

Maximum workload A measure of exercise tolerance. See 'exercise tolerance'.

Medically refractory In the context of AF, a patient is medically refractory if successive trials of different drugs and attempts at cardioversion fail to adequately control the symptoms or pathophysiology of AF.

Meta-analysis A statistical technique for combining (pooling) the results of a number of studies that address the same question and report on the same outcomes to produce a summary result. The aim is to derive more precise and clear information from a large data pool. It is generally more reliably likely to confirm or refute a hypothesis than the individual trials.

Methodological limitations Features of the design or reporting of a clinical study which are known to be associated with risk of bias or lack of validity. Where a study is reported in this guideline as having significant methodological limitations, a recommendation has not been directly derived from it.

Mitral annular abnormalities Echo abnormalities of the mitral valve ring/annulus, such as mitral annular calcification.

Mitral regurgitation A backwards flow of blood through the mitral valve normally caused by a dysfunctional mitral valve disease. Mitral regurgitation is classified as 'mild', 'moderate' or 'severe'.

Mitral stenosis An abnormal narrowing of the mitral valve. It can be measured echocardiographically by the mitral valve area.

Mitral valve calcification Deposition of calcium on the mitral valve.

Mitral valve disease Common generic term for disease of the mitral valve.

Mitral valve prolapse Condition where one or more mitral valve leaflets do not appose correctly and there is backward movement of the valve into the atrium, leading to mitral regurgitation.

Mitral valvuloplasty Stretching of the mitral valve, at surgery or using a balloon technique.

Monotherapy In the context of drug therapy, the administration of a single drug for a particular indication.

Multivariate Involving multiple variables. See also 'univariate'.

Myocardial infarction (**MI**) Heart attack.

National Collaborating Centre for Chronic Conditions (**NCC-CC**) A partnership of the Clinical Effectiveness Forum for Allied Health Professions, the NHS Confederation, the Patient Involvement Unit at NICE, the Royal College of General Practitioners, the Royal College of Nursing, the Royal College of Physicians of London, the Royal College of Physicians' Patient and Carers Liaison Committee, the Royal College of Surgeons of England, and the Royal Pharmaceutical Society of Great Britain. Set up in 2000 to undertake commissions from NICE to develop clinical guidelines for the NHS.

National Institute for Health and Clinical Excellence (**NICE**) NICE is the independent organisation responsible for providing national guidance on the promotion of good health and the prevention and treatment of ill health.

National Service Framework (**NSF**) A series of reports recommending service levels and targets for particular disease groups in the UK.

Negative predictive value The proportion of individuals with a negative test result who do not have the disease.

Negative predictor A variable whose values are inversely related to the likelihood of an event occurring.

New York Heart Association (**NYHA**) **Score** A score graded between 1 and 4 that measures cardiac function. Those patients with a score of 4 are considered to have severe heart failure; those with a score of 1 are considered to have asymptomatic or mild heart failure.

Non-significant See 'statistical significance'.

Number needed to treat (**NNT**) The number of patients who must be treated to prevent a single occurrence of the outcome of interest, based on an average calculated from the available data.

Nurse-led cardioversion Practice where the cardioversion procedure is organised, performed and patient follow-up undertaken by specialist nurses.

Odds ratio (**OR**) A measure of treatment effectiveness. The odds of an event happening in the treatment group, expressed as a proportion of the odds of it happening in the control group. The 'odds' is the ratio of non-events to events.

Open-label In the context of study design, a study in which the physicians or investigators are not blinded to which patients are allocated to which treatment arm.

Pacing The situation where a device (a pacemaker) complements or replaces the natural conducting system of the heart.

Palpitations The experience of one's own heartbeat as an awareness of the heart beating or a thumping sensation originating in the chest.

Patent foramen ovale A 'hole in the heart' where there is a congenital connection between the left and right atria.

Percutaneous coronary intervention (**PCI**) Any procedure on the heart undertaken by insertion of a device (eg stent) through a small hole in an artery (eg radial artery, femoral artery).

Peripheral artery disease Atherosclerotic vascular disease involving the peripheral arteries.

Pharmacological cardioversion (**PCV**) See 'cardioversion'.

Pill-in-the-pocket A management strategy for paroxysmal AF involving the patient self-administering antiarrhythmic drugs only upon the onset of an episode of AF.

Platelet-thrombus Blood clot that is rich in platelets rather than fibrin.

Pneumonectomy Removal of whole or part of a lung.

Polypharmacy The administration of multiple drugs for one or more indications.

Pooled analysis The aggregation of patient data from multiple separate studies with the objective of increasing the likelihood of being able to detect significant associations that would otherwise have been missed.

Positive predictive value (**PPV**) The proportion of individuals with a positive test result who actually have the disease.

Precipitant A disease process, toxin, or physiological abnormality which is known to predispose towards development of AF. In many cases, AF precipitants may not be identifiable, in other cases there are identifiable precipitants such as heart failure or alcohol excess.

Pre-excitation syndrome A condition that can predispose to arrhythmia, due to an accessory pathway leading to early/premature excitation of part of the heart. Examples include Wolff–Parkinson–White syndrome and Lown–Ganong–Levine syndrome.

Prevalence The proportion of people within a population who have a particular disease.

Pro-arrhythmic Pre-disposing to the development of cardiac arrhythmias.

Prophylactic Having a preventative action against one or more adverse events.

Pulmonary vein isolation Procedure where ablation is used to create a scar that isolates the tissue of the pulmonary vein from the rest of the heart – thus, if a focus precipitating AF is from within the pulmonary veins, the abnormal electrical impulses cannot reach the heart.

Pulse palpation The act of feeling for, and counting, the pulse.

QT prolongation The prolongation of the QT interval on an electrocardiogram.

Quality of life A measure of a person's overall wellbeing, taking into consideration not only the physical morbidity associated with disease, but also how this detrimentally effects social and psychological functioning.

Quality-adjusted life-year (QALY) An index of survival that is adjusted to account for the patient's quality of life during this time. QALYs have the advantage of incorporating changes in both quantity (longevity/mortality) and quality (morbidity, psychological, functional, social and other factors) of life. Used to measure benefits in cost–utility analysis.

Randomised controlled trial (RCT) A comparative study in which participants are randomly allocated to intervention and control groups and followed up to examine differences in outcomes between the groups.

Rapid atrial fibrillation AF that is associated with a very fast heart beat.

Rate control The attempt to treat AF not through the restoration of sinus rhythm, but through the control of the ventricular rate and the management of stroke risk. See also 'rhythm control'.

Regression equation An equation that assigns weights (co-efficients) to different variables according to the degree to which they are able to predict the occurrence of a particular event or value.

Relative risk (RR) The number of times more likely or less likely an event is to happen in one group compared with another (calculated as the risk of the event in group A, divided by the risk of the event in group B).

Relative risk reduction (RRR) The percentage reduction in the relative risk gained by a particular therapeutic intervention in comparison to another. See also 'relative risk'.

Rhythm control The attempt to treat AF through the restoration and maintenance of sinus rhythm and the management of stroke risk. See also 'rate control'.

Right bundle branch block (RBBB) A conduction abnormality of the heart due to impaired conduction down the right bundle of His.

Risk stratification The process of allocating patients to different levels of risk of an adverse event occurring, based on their clinical or other characteristics.

Self-management In the context of anticoagulation, the process of the patient testing their own blood and making dose-adjustments where necessary.

Self-testing In the context of anticoagulation, the process of the patient testing their own blood and their treating physician recommending dose-adjustments where necessary.

Sensitivity The proportion of individuals classified as positive by the gold or reference standard, who are correctly identified by the study test.

Sensitivity analysis A technique used in economic evaluation or decision analysis to determine how and/or whether plausible changes in uncertain clinical or costing variables affect the main results of the analysis.

Side effect An adverse event that occurs because of a therapeutic intervention.

Significant association See 'statistical significance'.

Significant difference See 'statistical significance'.

Sinus rhythm The normal pattern of electrical activity (and subsequent muscular contraction) of the heart.

Specificity The proportion of individuals classified as negative by the gold (or reference) standard, who are correctly identified by the study test.

Spontaneous cardioversion The process of cardioversion that occurs in the absence of any therapeutic interventions.

Spontaneous echo contrast Smoke-like appearance within the chambers of the heart – usually on TOE – which indicates stasis of blood within the chamber.

Statistical significance A statistical association or difference between two or more variables that has less than a 5% chance of happening through the random concatenation of events is considered to be statistically significant.

Structural heart disease The presence of abnormalities of the heart valves, muscle, chambers etc.

Sudden cardiac death syndrome The condition whereby a patient dies suddenly and unexpectedly with no obvious precipitants.

Supervised management In the context of anticoagulation management, supervised management refers to the situation where a clinician determines any dose adjustments and takes blood measurements.

Supraventricular Pertaining to the atria, eg supraventricular arrhythmia is an abnormal heart rhythm originating in the atria.

Systematic review Research that summarises the evidence on a clearly formulated question according to a pre-defined protocol using systematic and explicit methods to identify, select and appraise relevant studies, and to extract, collate and report their findings. It may or may not use statistical meta-analysis.

Systemic emboli Emboli that has reached the systemic circulation, potentially causing a systemic embolism. See 'embolic'.

Systolic Relating to the phase of contraction of the chambers of the heart during which they eject blood following the diastolic phase. See also 'diastolic'.

Tachycardia-induced cardiomyopathy A form of cardiomyopathy (damage to the heart muscle cells) caused by an excessive heart rate.

Temporal pattern The pattern distinguishing between different subtypes of AF.

Thromboembolic stroke Thrombus that has travelled to the brain circulating leading to blockage of an artery and causing a stroke. See 'embolic', 'stroke'.

Thromboembolism The embolisation (disloading and transportation in the blood) of a thrombus.

Thromboprophylaxis The administration of antithrombotic therapy (anticoagulation, antiplatelet therapy) for the prevention of thrombus formation.

Thrombus Blood clot.

Thyrotoxicosis A disease caused by the hyperactivity of the thyroid glands.

TOE-guided cardioversion In the context of cardioversion, the management of peri-cardioversion thromboembolic risk through the use of transoesophageal echocardiography (TOE) to screen for intracardiac thrombi alongside parenteral anticoagulation. See also 'conventional anticoagulation'.

Torsades de pointes A type of ventricular arrhythmia, which is a polymorphic ventricular tachycardia characterised by 'twisting of points' and commonly associated with a prolonged QT interval on the ECG.

Transoesphageal echocardiography See 'echocardiogram'.

Transient ischaemic attack An ischaemic cerebral event which does not result in any disability or cognitive impairment beyond 24 hours.

Transthoracic echocardiography See 'echocardiogram'.

Treatment failure Failure of the prescribed drug regimen to work. Demonstrated by a lack of clinical improvement or reduction in arrhythmia, etc.

Univariate Pertaining to a single variable. See also 'multivariate'.

Valvular heart disease Diseases of heart valves, eg mitral valve disease.

Vascular death Death caused by a cardiovascular disease or adverse cardiovascular event such as an acute myocardial infarction.

Vascular disease Disease of the vascular system, including both coronary and peripheral blood vessels.

Vaughan-Williams A classification system of antiarrhythmic drugs, depending on whether the drugs activity is as a sodium-channel blocker (Class I), a beta-blocker (Class II), a repolarisation-prolonging agent (Class III), or a calcium-channel blocker (Class IV).

Ventricular arrhythmias Cardiac arrhythmias that originate in the ventricles. See also 'arrhythmia'.

Ventricular rate control See 'rate control'.

Volume loss A term that usually refers to the amount of blood lost.

Wall motion index (WMI) An echocardiographic measure of the contractile function of the ventricles.

Wash-out period A period between the different experimental phases of a crossover study to ensure that no significant traces of previously administered drugs are left in the body to confound the results.

Wolff–Parkinson–White syndrome (WPW) See 'pre-excitation syndrome'.

Appendix F: Stakeholders

The following are registered stakeholders in the development or validation of this guideline:

Black Country Cancer and Cardiac Network

Association of British Healthcare Industries

Association of the British Pharmaceuticals Industry

AstraZeneca UK Ltd

Bard Ltd

Bayer Healthcare Plc

Biotronik UK Ltd

Boehringer Ingelheim Ltd

Boston Scientific Limited

Bristol-Myers Squibb Pharmaceuticals Ltd

Caledonian Medical Ltd

CardioLogic Limited

Guidant Corporation

Johnson & Johnson Medical

Medtronic Limited

P.M.S (Instruments) Ltd

Roche Diagnostics Limited

Sanofi-Aventis

Sorin Group CRM

St Jude Medical UK Ltd

Takeda UK Limited

Bedfordshire and Hertfordshire NHS Strategic Health Authority

North East London Strategic Health Authority

Addenbrookes NHS Trust

Aintree Hospitals NHS Trust

Airedale General Hospital – Acute Trust

Barnsley Primary Care Trust

Blaenau Gwent Local Health Board

Bradford South & West Primary Care Trust

Burntwood, Lichfield and Tamworth Primary Care Trust

Cardiff and Vale NHS Trust

Chorley and South Ribble Primary Care Trust

City and Hackney Teaching Primary Care Trust

Conwy and Denbighshire NHS Trust

Conwy Local Health Board

Countess of Chester Hospital NHS Foundation Trust

Craven Harrogate and Rural District Primary Care Trust

Denbighshire Local Health Board

East and North Herts. NHS Trust

Greater Peterborough Primary Care Partnership-North Primary Care Trust

Guys & St Thomas' NHS Trust

Heart of England NHS Foundation Trust

Leeds North East Primary Care Trust

Leeds Teaching Hospitals NHS Trust

Liverpool PCTs Medicines Management Team

Luton and Dunstable Hospital NHS Trust

Maidstone and Tunbridge Wells NHS Trust

Mansfield District Primary Care Trust

Newcastle Primary Care Trust

Newcastle under Lyme Primary Care Trust

Newcastle upon Tyne Hospitals NHS Trust

North Bradford Primary Care Trust

North Cumbria Acute Hospitals NHS Trust

North East Lincolnshire Primary Care Trust

North Lincolnshire Primay Care Trust

North Tees Primary Care Trust

Northwest London Hospitals NHS Trust

Papworth Hospital NHS Trust

Princess Alexandra Hospital NHS Trust

Queen Elizabeth Hospital NHS Trust (Woolwich)

Queen Elizabeth NHS Trust (Norfolk)

Queen Victoria Hospital NHS Foundation Trust

Rotherham Primary Care Trust

Royal Brompton and Harefield NHS Trust

Royal United Hospital Bath NHS Trust

Salford Primary Care Trust

Sedgefield Primary Care Trust

Sheffield South West Primary Care Trust

Sheffield Teaching Hospitals NHS Trust

Sheffield West Primary Care Trust

South East Sheffield Primary Care Trust

Staffordshire Moorlans Primary Care Trust

Stockport Primary Care Trust

Tameside and Glossop Acute Services NHS Trust

The North West London Hospitals NHS Trust

Trafford Primary Care Trusts

University Hospital Birmingham NHS Trust

University Hospitals Coventry and Warwickshire NHS Trust

Vale of Aylesbury Primary Care Trust

Waveney Primary Care Trust

Wrightington Wigan and Leigh NHS Trust

Anticoagulation Europe

Arrhythmia Alliance

British Heart Foundation

Sudden Adult Death Trust

The Progressive Supranuclear Palsy (PSP Europe) Association

The Stroke Association

Association of British Neurologists

British Association for Nursing in Cardiac Care

British Cardiovascular Society

British Geriatrics Society

British Pacing and Electrophysiology Group

British Psychological Society

British Society for Haematology

British Society for Heart Failure

Central Liverpool Primary Care Trust

Cochrane Heart Group

Heartsave

Independent Healthcare Forum

NHS Direct

Primary Care Cardiovascular Society

Royal College of Anaesthetists

Royal College of General Practitioners

Royal College of General Practitioners Wales

Royal College of Nursing

Royal College of Pathologists

Royal College of Physicians of Edinburgh

Royal College of Physicians of London

Royal Pharmaceutical Society of Great Britain

Society and College of Radiographers

Society of Cardiothoracic Surgeons

The David Lewis Centre

The Royal Society of Medicine

UK Specialised Services Public Health Network

Academic Cardiology

Cardiology Research Department of St Barts Hospital

Society for Academic Primary Care

University of Birmingham, Department of Primary Care and General Practice

British National Formulary

Commission for Social Care Inspection

Connecting for Health

Department of Health

Healthcare Commission

Medicines and Healthcare Products Regulatory Agency (MHRA)

National Patient Safety Agency

National Public Health Service – Wales

NHS Health and Social Care Information Centre

NHS Quality Improvement Scotland

PERIGON (formerly The NHS Modernisation Agency)

Regional Public Health Group – London

Scottish Intercollegiate Guidelines Network

Welsh Assembly Government

Appendix G: Scope

Guideline title

Atrial fibrillation: the management of atrial fibrillation

▷ Short title

Atrial fibrillation

Background

The National Institute for Health and Clinical Excellence (NICE or 'the Institute') has commissioned the National Collaborating Centre for Chronic Conditions to develop a clinical guideline on AF for use in the NHS in England and Wales. This follows referral of the topic by the Department of Health and Welsh Assembly Government (see below). The guideline will provide recommendations for good practice that are based on the best available evidence of clinical and cost effectiveness.

The Institute's clinical guidelines will support the implementation of National Service Frameworks (NSFs) in those aspects of care where a framework has been published. The statements in each NSF reflect the evidence that was used at the time the framework was prepared. The clinical guidelines and technology appraisals published by the Institute after an NSF has been issued will have the effect of updating the framework.

Clinical need for the guideline

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia. The prevalence of AF increases with age and is the most common arrhythmia causing hospitalisation. In a UK cohort, the prevalence of AF was 8 per 1,000 in males, and 5 per 1,000 in females, with an incidence of 0.9 new cases per 1,000 patient years in males, and 0.2 new cases per 1,000 patient years in females. An increased incidence is associated with age, gender and the presence of other common diseases, including hypertension, heart failure, ischaemic heart disease, diabetes and peripheral artery disease.

AF is associated with a substantial mortality, and with morbidity and hospitalisation from stroke, heart failure, thromboembolism and impaired cognitive function. From a large follow-up study over 40 years, AF was associated with a 1.5 fold (male) to 1.9 fold (female) increased risk of mortality after adjustment for pre-existing cardiovascular disease.

As a common arrhythmia and a cause of substantial morbidity and mortality, AF has considerable implications for healthcare expenditure. Recently, the total cost of AF to the NHS in 2000 (using conservative 1995 prevalence figures) has been calculated to be £459 million or 0.97% of total expenditure. The cost of drug treatment for the year 2000 was estimated to be £69.5 million (including costs for anticoagulation clinic visits) and a further £271.6 million was spent on hospital admissions. These figures do not assume costs for hospitalisations where AF is a secondary diagnosis, or costs of nursing care.

A clinical need for the guideline is justified by the wide variation in management and disagreement amongst UK consultants regarding the best treatment strategies. Furthermore, many patients with AF possess very limited knowledge of AF, its consequences and therapy.

The guideline

The guideline development process is described in detail in two publications which are available from the NICE website (see further information section below). *The guideline development process – an overview for stakeholders, the public and the NHS*[15] describes how organisations can become involved in the development of a guideline. *Guideline development methods – information for national collaborating centres and guideline developers*[16] provides advice on the technical aspects of guideline development.

This document is the scope. It defines exactly what this guideline will (and will not) examine, and what the guideline developers will consider. The scope is based on the referral from the Department of Health and Welsh Assembly Government (see below).

The areas that will be addressed by the guideline are described in the following sections.

Population

▷ Groups that will be covered

The guideline will include people with:

- New onset or acute AF.
- Chronic AF, including paroxysmal (recurrent), persistent and permanent/sustained AF.
- Comorbidities that impact upon AF.
- Postoperative AF.
- Atrial flutter that is indistinguishable from AF in terms of aim of treatment.

▷ Groups that will not be covered

- People under age 18 years.
- Congenital heart disease precipitating AF.

Healthcare setting

Primary and secondary NHS healthcare settings, including referral to tertiary care.

Clinical management

Objectives of management are dependent upon clinical subtype of AF. AF is considered recurrent when a patient develops two or more episodes. These episodes may be paroxysmal if they terminate spontaneously (defined by consensus as 7 days), or persistent (usually more than 7 days) if the arrhythmia requires electrical or pharmacological cardioversion for termination. Successful termination of AF does not alter the classification of persistent AF in these patients. Longstanding AF (defined as more than 1 year) not successfully terminated by cardioversion, or when cardioversion is not pursued, is classified as permanent.

Treatment of acute, sudden onset of AF (with consideration of haemodynamic stability) will be distinguished from treatment of chronic (paroxysmal/recurrent, persistent and permanent) AF. Management of paroxysmal and persistent AF requires control of the rhythm, whilst in permanent AF; the management is generally rate control.

The guideline will include recommendations in the following areas.

▷ Identification of AF

The guideline will not cover general population screening but will include opportunistic case finding.

▷ Diagnosis and assessment criteria

The investigations required for accurate confirmation of a diagnosis of AF and assessment of comorbidity in AF including electrocardiogram (single and 12-lead), 24-hour ECG (or cardiomemo), echocardiogram (including transesophageal), chest X-ray and appropriate haematological and biochemical testing.

▷ Treatment

Treatment as defined for clinical subgroups of paroxysmal, persistent and permanent AF to include the following:

- Prophylactic antithrombotic treatment for the prevention of stroke and thromboembolism, to include antiplatelet and anticoagulation therapy as they specifically relate to AF, and take into account the following:
  - Risk stratification (for example low, medium and high risk) for thromboprophylaxis, including primary and secondary prevention.
  - Different populations (eg acute AF, and peri-stroke).
  - Use of anticoagulation in primary and secondary care setting as supported by the evidence. This includes the potential for management in primary care and self-management using near-patient testing devices.
- Rhythm control including pharmacological (oral and IV) and rhythm self-management ('pill-in-the-pocket') including maintenance of sinus rhythm post conversion.
- Pharmacological rate control (excluding non-pharmacological pacing and ablation, see below) pertaining to monotherapy and combination therapy.
- Efficacy of rate versus rhythm control.
- Selection of patients for referral to specialist services pertaining to non-pharmacological rhythm or rate control (pacing and catheter ablation) and electrophysiological studies.

▷ Review and monitoring

The review and monitoring of AF pertaining to the following:

- The benefits and harms of pharmacological and antithrombotic treatments (eg treatment side effects, and when to stop drug therapy).
- Maintenance of sinus rhythm.
- Patients in whom medical therapy has brought about no response.

Note that guideline recommendations will normally fall within licensed indications; exceptionally, and only where clearly supported by evidence, use outside a licensed indication may be recommended. The guideline will assume that prescribers will use the Summary of Product characteristics to inform their decisions for individual patients.

The following interventions/management will not be included in the guideline:

- Radical therapies that do not form common clinical management will not be addressed, including:
  - Implantable atrial defibrillator (IAD) as the evidence pertains to a selective group of patients and further clinical trials are required.
  - MAZE procedure and other arrhythmia surgery, as well as other novel/experimental non-pharmacological techniques (except for referral for these options).
  - Novel/experimental pharmaceutical antiarrhythmic agents.
- The impact of co-morbidities on AF will be considered but specific treatment of those comorbidities will not be included.
- Generic health problems where the care for people with AF disease does not differ from that of the general population (eg depression).

Status

This is the final scope, which has been through a 4-week period of consultation with stakeholders and has been reviewed by the Institute's independent Guidelines Review Panel.

NICE is in the process of developing the technology appraisal guidance. The AF guideline will signpost these technology appraisals and will consider their role in the treatment of AF.

Implantable cardioverter defibrillators (ICDs) for the treatment of arrhythmias – review of Guidance number 11. Expected date of publication July 2004

Stroke prevention: Ximelagatran in patients with stroke and other thromboembolic complications associated with fibrillation. Expected date of publication February 2006

The development of the guideline recommendations will begin in July 2004.

Further information

Information on the guideline development process is provided in:

The guideline development process – an overview for stakeholders, the public and the NHS[15]

Guideline development methods – information for national collaborating centres and guideline developers.[16]

These booklets are available as PDF files from the NICE website (**www.nice.org.uk**). Information on the progress of the guideline will also be available from the website.

Referral from the Department of Health and Welsh Assembly Government

The Department of Health and Welsh Assembly Government asked the Institute:

'To develop a guideline on the appropriate treatment of atril fibrillation (AF). This should include:

- Identification of patients with AF and appropriate risk assessment tools.
- Diagnosis and assessment.
- Appropriate treatment including:
  - antithrombotic treatment and appropriate use of antiplatelet and anti-coagulation therapy, including advice on potential for management in primary care and self-management using near patient testing devices
  - therapy to control rate of AF
  - medical and electrical cardioversion to control rhythm
  - selection of patients for referral to more specialist services, eg electrophysiological studies, pacing, catheter ablation and, if there is sufficient evidence, the role of ICDs.
- Review and monitoring of condition.'

References

1 Levy S, Camm AJ, Saksena S et al. International consensus on nomenclature and classification of atrial fibrillation; a collaborative project of the Working Group on Arrhythmias and the Working Group on Cardiac Pacing of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. *Europace.* 2003;5(2):119–122.

2 Lip GY, Golding DJ, Nazir M et al. A survey of atrial fibrillation in general practice: the West Birmingham Atrial Fibrillation Project. *British Journal of General Practice.* 1997;47(418):285–289.

3 Kannel WB, Wolf PA, Benjamin EJ et al. Prevalence, incidence, prognosis, and predisposing conditions for atrial fibrillation: population-based estimates. *American Journal of Cardiology.* 1998;82(8A):2N–9N.

4 Stewart S, Hart CL, Hole DJ et al. Population prevalence, incidence, and predictors of atrial fibrillation in the Renfrew/Paisley study. *Heart* (British Cardiac Society). 2001;86(5):516–521.

5 Lip GY, Bawden L, Hodson R et al. Atrial fibrillation amongst the Indo-Asian general practice population: the West Birmingham Atrial Fibrillation Project. *International Journal of Cardiology.* 1998;65(2):187–192.

6 Sudlow M, Thomson R, Thwaites B et al. Prevalence of atrial fibrillation and eligibility for anticoagulants in the community. *Lancet.* 1998;352(9135):1167–1171.

7 Lip GY, Tean KN, Dunn FG. Treatment of atrial fibrillation in a district general hospital. *British Heart Journal.* 1994;71(1):92–95.

8 Zarifis J, Beevers G, Lip GY. Acute admissions with atrial fibrillation in a British multiracial hospital population. *British Journal of Clinical Practice.* 1997;51(2):91–96.

9 Benjamin EJ, Levy D, Vaziri SM et al. Independent risk factors for atrial fibrillation in a population–based cohort. The Framingham Heart Study. *Journal of the American Medical Association.* 1994;271(11):840–844.

10 Lowenstein SR, Gabow PA, Cramer J et al. The role of alcohol in new–onset atrial fibrillation. *Archives of Internal Medicine.* 1983;143(10):1882–1885.

11 Benjamin EJ, Wolf PA, D'Agostino RB et al. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. *Circulation.* 1998;98(10):946–952.

12 Lip GY. Does atrial fibrillation confer a hypercoagulable state? *Lancet.* 1995;346(8986):1313–1314.

13 Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke.* 1991;22(8):983–988.

14 Wolf PA, Mitchell JB, Baker CS et al. Impact of atrial fibrillation on mortality, stroke, and medical costs. *Archives of Internal Medicine.* 1998;158(3):229–234.

15 National Institute for Clinical Excellence. *The guideline development process – an overview for stakeholders, the public and the NHS.* London: National Institute for Clinical Excellence, 2005.

16 National Institute for Clinical Excellence. *Guideline development methods: information for national collaborating centres and guideline developers.* London: National Institute for Clinical Excellence, 2004.

17 National Collaborating Centre for Chronic Conditions. *NCC-CC Methodology Pack.* London: NCC–CC;2005.

18 Freestone B, Lip G. Epidemiology and costs of cardiac arrhythmias. In: Lip G, Godtfredsen J (eds), *Cardiac Arrythmias: A clinical approach.*, Edinburgh: Mosby, 2003:3–24.

19 Swancutt D, Hobbs R, Fitzmaurice D et al. A randomised controlled trial and cost effectiveness study of systematic screening (targeted and total population screening) versus routine practice for the detection of atrial fibrillation in the over 65s. *BMC Cardiovascular Disorders.* 2004;4(1):12.

20 Hobbs FD, Fitzmaurice DA, Mant J et al. A randomised controlled trial and cost effectiveness study of systematic screening (targeted and total population screening) versus routine practice for the detection of atrial fibrillation in people aged 65 and over. The SAFE study. *Health Technology Assessment.* Winchester, 2005;9(40):1–90.

21 Davidson E, Rotenberg Z, Weinberger I et al. Diagnosis and characteristics of lone atrial fibrillation. *Chest.* 1989;95(5):1048–1050.

22 Lok N-S, Lau C-P. Presentation and management of patients admitted with atrial fibrillation: A review of 291 cases in a regional hospital. *International Journal of Cardiology.* 1995;48(3):271–278.

23 Shatoor AS, Ahmed ME, Said MA et al. Patterns of atrial fibrillation at a regional hospital in Saudi Arabia. *Ethnicity & Disease.* 1998;8(3):360–366.

24 Levy S, Maarek M, Coumel P et al. Characterization of different subsets of atrial fibrillation in general practice in France: the ALFA study. The College of French Cardiologists. *Circulation.* 1999;99(23):3028–3035.

25 Lin H, Wolf PA, Benjamin EJ et al. Newly diagnosed atrial fibrillation and acute stroke: the Framingham Study. *Stroke.* 1995;26(9):1527–1530.

26 Michael JA, Stiell IG, Agarwal S et al. Cardioversion of paroxysmal atrial fibrillation in the emergency department. *Annals of Emergency Medicine.* 1999;33(4):379–387.

27 Burton JH, Vinson DR, Drummond K et al. Electrical cardioversion of emergency department patients with atrial fibrillation. *Annals of Emergency Medicine.* 2004;44(1):20–30.

28 van Walraven C, Hart RG, Wells GA et al. A clinical prediction rule to identify patients with atrial fibrillation and a low risk for stroke while taking aspirin. *Archives of Internal Medicine.* 2003;163(8):936–943.

29 Sudlow M, Rodgers H, Kenny RA et al. Identification of patients with atrial fibrillation in general practice: a study of screening methods. *British Medical Journal.* 1998;317(7154):327–328.

30 Morgan S, Mant D. Randomised trial of two approaches to screening for atrial fibrillation in UK general practice. *British Journal of General Practice.* 2002;52(478):373–380.

31 Page RL, Wilkinson WE, Clair WK et al. Asymptomatic arrhythmias in patients with symptomatic paroxysmal atrial fibrillation and paroxysmal supraventricular tachycardia. *Circulation.* 1994;89(1):224–227.

32 Kinlay S, Leitch JW, Neil A et al. Cardiac event recorders yield more diagnoses and are more cost-effective than 48-hour Holter monitoring in patients with palpitations: a controlled clinical trial. *Annals of Internal Medicine.* 1996;124(1 Pt 1):16–20.

33 Reiffel JA, Schwarzberg R, Murry M. Comparison of autotriggered memory loop recorders versus standard loop recorders versus 24-hour Holter monitors for arrhythmia detection. *American Journal of Cardiology.* 2005;95(9):1055–1059.

34 Man-Son-Hing M, Laupacis A. Anticoagulant-related bleeding in older persons with atrial fibrillation: physicians' fears often unfounded. *Archives of Internal Medicine.* 2003;163(13):1580–1586.

35 Jabaudon D, Sztajzel J, Sievert K et al. Usefulness of ambulatory 7-day ECG monitoring for the detection of atrial fibrillation and flutter after acute stroke and transient ischemic attack. *Stroke.* 2004;35(7):1647–1651.

36 Lip G, Zarifis J, Watson R et al. Physician variation in the management of patients with atrial fibrillation. *Heart* (British Cardiac Society) 1996;75(2):200–205.

37 Lip GY. How would I manage a 60-year-old woman presenting with atrial fibrillation? *Proceedings of the Royal College of Physicians of Edinburgh.* 2005;1999(29):301–306.

38 Cantley P, McKinstry B, Macaulay D et al. Atrial fibrillation in general practice: how useful is echocardiography in selection of suitable patients for anticoagulation? *British Journal of General Practice.* 1999;49(440):219–220.

39 Klein AL, Murray RD, Grimm RA. Role of transesophageal echocardiography-guided cardioversion of patients with atrial fibrillation. *Journal of the American College of Cardiology.* 2001;37(3):691–704.

40 Flaker GC, Fletcher KA, Rothbart RM et al. Clinical and echocardiographic features of intermittent atrial fibrillation that predict recurrent atrial fibrillation. *American Journal of Cardiology.* 1995;76(5):355–358.

41 Tischler MD, Lee TH, McAndrew KA et al. Clinical, echocardiographic and Doppler correlates of clinical instability with onset of atrial fibrillation. *American Journal of Cardiology.* 1990;66(7):721–724.

42 Antonielli E, Pizzuti A, Palinkas A et al. Clinical value of left atrial appendage flow for prediction of long-term sinus rhythm maintenance in patients with nonvalvular atrial fibrillation. *Journal of the American College of Cardiology.* 2002;39(9):1443–1449.

43 Roijer A, Meurling CJ, Eskilsson J et al. Left atrial appendage outflow velocity index is superior to conventional criteria for prediction of maintenance of sinus rhythm after cardioversion. *Scandinavian Cardiovascular Journal.* 2001;35(2):119–124.

44 Dogan A, Avsar A, Ozturk M. P-wave dispersion for predicting maintenance of sinus rhythm after cardioversion of atrial fibrillation. *American Journal of Cardiology.* 2004;93(3):368–371.

45 Frick M, Frykman V, Jensen-Urstad M et al. Factors predicting success rate and recurrence of atrial fibrillation after first electrical cardioversion in patients with persistent atrial fibrillation. *Clinical Cardiology.* 2001;24(3):238–244.

46 Duytschaever M, Haerynck F, Tavernier R et al. Factors influencing long-term persistence of sinus rhythm after a first electrical cardioversion for atrial fibrillation. *Pacing and Clinical Electrophysiology.* 1998;21(1 II SUPPL.):284–287.

47 Arnar DO, Danielsen R. Factors predicting maintenance of sinus rhythm after direct current cardioversion of atrial fibrillation and flutter: a reanalysis with recently acquired data. *Cardiology.* 1996;87(3):181–188.

48 Olshansky B, Heller EN, Mitchell LB et al. Are transthoracic echocardiographic parameters associated with atrial fibrillation recurrence or stroke? Results from the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) study. *Journal of the American College of Cardiology.* 2005;45(12): 2026–2033.

49 Dmochowska-Perz M, Loboz-Grudzien K, Sokalski L et al. Factors predicting recurrence of atrial fibrillation after cardioversion. *Kardiologia Polska.* 2002;57(12):501–511.

50 Paraskevaidis IA, Dodouras T, Tsiapras D et al. Prediction of successful cardioversion and maintenance of sinus rhythm in patients with lone atrial fibrillation. *Chest.* 2005;127(2):488–494.

51 Leung DY, Black IW, Cranney GB et al. Prognostic implications of left atrial spontaneous echo contrast in nonvalvular atrial fibrillation. *Journal of the American College of Cardiology.* 1994;24(3):755–762.

52 Aronow WS, Gutstein H, Hsieh FY. Risk factors for thromboembolic stroke in elderly patients with chronic atrial fibrillation. *American Journal of Cardiology.* 1989;63(5):366–367.

53 Shinokawa N, Hirai T, Takashima S et al. A transesophageal echocardiographic study on risk factors for stroke in elderly patients with atrial fibrillation: a comparison with younger patients. *Chest.* 2001;120(3): 840–846.

54 Stollberger C, Chnupa P, Kronik G et al. Transesophageal echocardiography to assess embolic risk in patients with atrial fibrillation. ELAT study group: embolism in left atrial thrombi. *Annals of Internal Medicine.* 1998;128(8):630–638.

55 Miyazaki S, Ito T, Suwa M et al. Role of transesophageal echocardiography in the prediction of thromboembolism in patients with chronic nonvalvular atrial fibrillation. *Japanese Circulation Journal.* 2001; 65(10):874–878.

56 Kamp O, Verhorst PMJ, Welling RC et al. Importance of left atrial appendage flow as a predictor of thromboembolic events in patients with atrial fibrillation. *European Heart Journal.* 1999;20(13):979–985.

57 Pearce LA. Predictors of thromboembolism in atrial fibrillation (II): echocardiographic features of patients at risk. *Annals of Internal Medicine.* 1992;116(1):6–12.

58 Kosior D, Szulc M, Piatkowski R et al. Factors determining long-term maintenance of sinus rhythm after cardioversion of persistent atrial fibrillation. *Kardiologia Polska.* 2003;59:128–141.

59 Nakagami H, Yamamoto K, Ikeda U et al. Mitral regurgitation reduces the risk of stroke in patients with nonrheumatic atrial fibrillation. *American Heart Journal.* 1998;136(3):528–532.

60 Cabin HS, Clubb KS, Hall C et al. Risk for systemic embolization of atrial fibrillation without mitral stenosis. *American Journal of Cardiology.* 1990;65(16):1112–1116.

61 Ezekowitz MD, Laupacis A, Boysen G et al. Echocardiographic predictors of stroke in patients with atrial fibrillation: a prospective study of 1,066 patients from 3 clinical trials. *Archives of Internal Medicine.* 1998;158(12):1316–1320.

62 Aronow WS, Ahn C, Kronzon I et al. Risk factors for new thromboembolic stroke in patients <=62 years of age with chronic atrial fibrillation. *American Journal of Cardiology.* 1998;82(1):119–121.

63 Dawn B, Varma J, Singh P et al. Cardiovascular death in patients with atrial fibrillation is better predicted by left atrial thrombus and spontaneous echocardiographic contrast as compared with clinical parameters. *Journal of the American Society of Echocardiography*. 2005;18(3):199–205.

64 Conway D. Cardioversion of persistent atrial fibrillation. In: Lip GY, Godfredsen J (eds), *Cardiac arrhythmias: a clinical approach*, Edinburgh: Mosby, 2003: 299–318.

65 Lim H, Hamaad A, Lip G. Clinical review: clinical management of atrial fibrillation – rate control versus rhythm control. *Critical Care*. 8(4);271–279. 2004.

66 Rashba EJ, Gold MR, Crawford FA et al. Efficacy of transthoracic cardioversion of atrial fibrillation using a biphasic, truncated exponential shock waveform at variable initial shock energies. *American Journal of Cardiology*. 2004;94(12):1572–1574.

67 Adgey AA, Walsh SJ. Theory and practice of defibrillation: (1) atrial fibrillation and DC conversion. *Heart*. 2004;90(12):1493–1498.

68 Lip GY. Cardioversion of atrial fibrillation. *Postgraduate Medical Journal*. 1995;71(838):457–465.

69 de Paola AA, Figueiredo E, Sesso R et al. Effectiveness and costs of chemical versus electrical cardioversion of atrial fibrillation. *International Journal of Cardiology*. 2003;88(2–3):157–3.

70 Valencia MJ, Climent P, V, Marin O et al. The efficacy of scheduled cardioversion in atrial fibrillation: comparison of two schemes of treatment: electrical versus pharmacological cardioversion. *Revista Espanola de Cardiologia*. 2002;55(22–3):113–120.

71 Boodhoo L, Bordoli G, Mitchell AR et al. The safety and effectiveness of a nurse-led cardioversion service under sedation. *Heart*. 2004;90(12):1443–1446.

72 Currie MP, Karwatowski SP, Perera J et al. Introduction of nurse led DC cardioversion service in day surgery unit: Prospective audit. *British Medical Journal*. 2004;329(7471):892–894.

73 Quinn T. Early experience of nurse-led elective DC cardioversion. *Nursing in Critical Care*. 1998;3(2):59–62.

74 Naccarelli GV, Wolbrette DL, Luck JC. Proarrhythmia. *Medical Clinics of North America*. 2001;85(2): 503–526.

75 Chaudhry GM, Haffajee CI. Antiarrhythmic agents and proarrhythmia. *Critical Care Medicine*. 2000; 28(10 Suppl):N158–N164.

76 Podrid PJ. Proarrhythmia, a serious complication of antiarrhythmic drugs. *Current Cardiology Reports*. 1999;1(4):289–296.

77 Mooss AN, Wurdeman RL, Mohiuddin SM et al. Esmolol versus diltiazem in the treatment of postoperative atrial fibrillation/atrial flutter after open heart surgery. *American Heart Journal*. 2000;140(1): 176–180.

78 Hilleman DE, Reyes AP, Mooss AN et al. Esmolol versus diltiazem in atrial fibrillation following coronary artery bypass graft surgery. *Current Medical Research & Opinion*. 2003;19(5):376–382.

79 Anon. Intravenous digoxin in acute atrial fibrillation: results of a randomized, placebo-controlled multicentre trial in 239 patients. The Digitalis in Acute Atrial Fibrillation (DAAF) Trial Group. *European Heart Journal*. 1997;18(4):649–654.

80 Jordaens L, Trouerbach J, Calle P et al. Conversion of atrial fibrillation to sinus rhythm and rate control by digoxin in comparison to placebo. *European Heart Journal*. 1997;18(4):643–648.

81 Falk RH, Knowlton AA, Bernard SA et al. Digoxin for converting recent–onset atrial fibrillation to sinus rhythm. A randomized, double-blinded trial. *Annals of Internal Medicine*. 1987;106(4):503–506.

82 Andrivet P, Boubakri E, Dove PJ et al. A clinical study of amiodarone as a single oral dose in patients with recent-onset atrial tachyarrhythmia. *European Heart Journal*. 1994;15(10):1396–1402.

83 Boriani G, Capucci A, Lenzi T et al. Propafenone for conversion of recent–onset atrial fibrillation. A controlled comparison between oral loading dose and intravenous administration. *Chest*. 1995;108(2): 355–358.

84 Botto GL, Bonini W, Broffoni T et al. Randomized, crossover, controlled comparison of oral loading versus intravenous infusion of propafenone in recent-onset atrial fibrillation. *Pacing and Clinical Electrophysiology*. 1998;21(11 Pt 2):2480–2484.

85 Boriani G, Biffi M, Capucci A et al. Conversion of recent-onset atrial fibrillation to sinus rhythm: effects of different drug protocols. *Pacing and Clinical Electrophysiology.* 1998;21(11 Pt 2):2470–2474.

86 Chevalier P, Durand–Dubief A, Burri H et al. Amiodarone versus placebo and classic drugs for cardioversion of recent-onset atrial fibrillation: a meta-analysis. *Journal of the American College of Cardiology.* 2003;41(2):255–262.

87 Treglia A, Alfano C, Rossini E. A comparison between propafenone and amiodarone in the conversion to sinus rhythm of atrial fibrillation of recent onset. *Minerva Cardioangiologica.* 1994;42(6):293–297.

88 Joseph AP, Ward MR. A prospective, randomized controlled trial comparing the efficacy and safety of sotalol, amiodarone, and digoxin for the reversion of new-onset atrial fibrillation. *Annals of Emergency Medicine.* 2000;36(1):1–9.

89 Singh BN, Singh SN, Reda DJ et al. Amiodarone versus sotalol for atrial fibrillation. *New England Journal of Medicine.* 2005;352(18):1861–1872.

90 Martinez–Marcos FJ, Garcia-Garmendia JL, Ortega-Carpio A et al. Comparison of intravenous flecainide, propafenone, and amiodarone for conversion of acute atrial fibrillation to sinus rhythm. *American Journal of Cardiology.* 2000;86(9):950–953.

91 Kochiadakis GE, Igoumenidis NE, Simantirakis EN et al. Intravenous propafenone versus intravenous amiodarone in the management of atrial fibrillation of recent onset: a placebo-controlled study. *Pacing and Clinical Electrophysiology.* 1998;21(11 Pt 2):2475–2479.

92 Donovan KD, Power BM, Hockings BE et al. Intravenous flecainide versus amiodarone for recent-onset atrial fibrillation. *American Journal of Cardiology.* 1995;75(10):693–697.

93 Negrini M, Gibelli G, De Ponti C. A comparison of propafenone and amiodarone in reversion of recent-onset atrial fibrillation to sinus rhythm. *Current Therapeutic Research, Clinical & Experimental.* 1994; 55(11):1345–1354.

94 Blanc JJ, Voinov C, Maarek M. Comparison of oral loading dose of propafenone and amiodarone for converting recent-onset atrial fibrillation. PARSIFAL study group. *American Journal of Cardiology.* 1999;84(9):1029–1032.

95 Baldi N, Lenti V, Marasco G et al. Propafenone vs flecainide in the acute treatment of atrial fibrillation of recent onset: a randomized study. *New Trends in Arrhythmias.* 1992;8(1–2):499–505.

96 Kondili A, Kastrati A, Popa Y. Comparative evaluation of verapamil, flecainide and propafenone for the acute conversion of atrial fibrillation to sinus rhythm. *Middle European Journal of Medicine.* 1990;102(17): 510–513.

97 Kingma JH, Suttorp MJ. Acute pharmacologic conversion of atrial fibrillation and flutter: the role of flecainide, propafenone, and verapamil. *American Journal of Cardiology.* 1992;70(5):56A–60A.

98 Capucci A, Boriani G, Botto GL et al. Conversion of recent-onset atrial fibrillation by a single oral loading dose of propafenone or flecainide. *American Journal of Cardiology.* 1994;74(5):503–505.

99 Van Gelder IC, Tuinenburg AE, Schoonderwoerd BS et al. Pharmacologic versus direct-current electrical cardioversion of atrial flutter and fibrillation. *American Journal of Cardiology.* 1999;84(9A):147R–151R.

100 Climent VE, Marin F, Mainar L et al. Effects of pretreatment with intravenous flecainide on efficacy of external cardioversion of persistent atrial fibrillation. *Pacing and Clinical Electrophysiology.* 2004;27(3):368–372.

101 Channer KS, Birchall A, Steeds RP et al. A randomized placebo-controlled trial of pre-treatment and short- or long-term maintenance therapy with amiodarone supporting DC cardioversion for persistent atrial fibrillation. *European Heart Journal.* 2004;25(2):144–150.

102 Bianconi L, Mennuni M, Lukic V et al. Pretreatment with oral propafenone in electrical cardioversion of chronic atrial fibrillation. *New Trends in Arrhythmias.* 1993;9(4):1017–1020.

103 Bianconi L, Mennuni M, Lukic V et al. Effects of oral propafenone administration before electrical cardioversion of chronic atrial fibrillation: a placebo-controlled study. *Journal of the American College of Cardiology.* 1996;28(3):700–706.

104 Jacobs LO, Andrews TC, Pederson DN et al. Effect of intravenous procainamide on direct-current cardioversion of atrial fibrillation. *American Journal of Cardiology.* 1998;82(2):241–242.

105 Villani GQ, Piepoli MF, Terracciano C et al. Effects of diltiazem pretreatment on direct-current cardioversion in patients with persistent atrial fibrillation: A single-blind, randomized, controlled study. *American Heart Journal.* 2000;140:437–443.

106 Jong G-P, Hou Z-Y, Juang G-H et al. Short term amiodarone treatment facilitates electrical cardioversion in patients with chronic atrial flutter/fibrillation. *Acta Cardiologica Sinica.* 1995;11(1):39–46.

107 Capucci A, Villani GQ, Aschieri D et al. Oral amiodarone increases the efficacy of direct-current cardioversion in restoration of sinus rhythm in patients with chronic atrial fibrillation. *European Heart Journal.* 2000;21(1):66–73.

108 Lindholm C-J, Fredholm O, Moller S-J et al. Sinus rhythm maintenance following DC cardioversion of atrial fibrillation is not improved by temporary pre-cardioversion treatment with oral verapamil. *Heart* (British Cardiac Society), 2004;90(5):534–538.

109 De Simone A, Stabile G, Vitale DF et al. Pretreatment with verapamil in patients with persistent or chronic atrial fibrillation who underwent electrical cardioversion. *Journal of the American College of Cardiology.* 1999;34(3):810–814.

110 Bertaglia E, D'Este D, Zanocco A et al. Effects of pretreatment with verapamil on early recurrences after electrical cardioversion of persistent atrial fibrillation: a randomised study. *Heart.* 2001;85:578–580.

111 AFFIRM First-Antiarrhythmic-Drug-Substudy-Investigators. Maintenance of sinus rhythm in patients with atrial fibrillation: an AFFIRM substudy of the first antiarrhythmic drug. *Journal of the American College of Cardiology.* 2003;42(1):20–29.

112 Roy D, Talajic M, Dorian P et al. Amiodarone to prevent recurrence of atrial fibrillation: Canadian Trial of Atrial Fibrillation Investigators. *New England Journal of Medicine.* 2000;342(13):913–920.

113 Guo H, Shaheen W, Kerber R et al. Cardioversion of atrial tachyarrhythmias: anticoagulation to reduce thromboembolic complications. *Progress in Cardiovascular Diseases.* 2004;46(6):487–505.

114 Klein AL, Grimm RA, Murray RD et al. Use of transesophageal echocardiography to guide cardioversion in patients with atrial fibrillation. *New England Journal of Medicine.* 2001;344(19):1411–1420.

115 Seidl K, Rameken M, Drogemuller A et al. Embolic events in patients with atrial fibrillation and effective anticoagulation: value of transesophageal echocardiography to guide direct-current cardioversion. Final results of the Ludwigshafen Observational Cardioversion Study. *Journal of the American College of Cardiology.* 2002;39(9):1436–1442.

116 Klein AL, Murray RD, Becker ER et al. Economic analysis of a transesophageal echocardiography-guided approach to cardioversion of patients with atrial fibrillation: the ACUTE economic data at eight weeks. *Journal of the American College of Cardiology.* 2004;43(7):1217–1224.

117 Seto TB, Taira DA, Tsevat J et al. Cost-effectiveness of transesophageal echocardiographic-guided cardioversion: a decision analytic model for patients admitted to the hospital with atrial fibrillation. *Journal of the American College of Cardiology.* 1997;29(1):122–130.

118 Van Gelder IC, Hagens VE, Bosker HA et al. A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. *New England Journal of Medicine.* 2002;347(23):1834–1840.

119 Carlsson J, Miketic S, Windeler J et al. Randomized trial of rate-control versus rhythm-control in persistent atrial fibrillation: the Strategies of Treatment of Atrial Fibrillation (STAF) Study. *Journal of the American College of Cardiology.* 2003;41(10):1690–1696.

120 Gronefeld GC, Lilienthal J, Kuck KH et al. Impact of rate versus rhythm control on quality of life in patients with persistent atrial fibrillation. Results from a prospective randomized study. *European Heart Journal.* 2003;24:1430–1436.

121 Wyse DG, Waldo AL, DiMarco JP et al. A comparison of rate control and rhythm control in patients with atrial fibrillation. *New England Journal of Medicine.* 2002;347:1825–1833.

122 Opolski G, Torbicki A, Kosior D et al. Rhythm control versus rate control in patients with persistent atrial fibrillation. Results of the HOT CAFE Polish Study. *Kardiologia Polska.* 2003;59(7):1–16.

123 Hagens VE, Crijns HJ, Van Veldhuisen DJ et al. Rate control versus rhythm control for patients with persistent atrial fibrillation with mild to moderate heart failure: results from the RAte Control versus Electrical cardioversion (RACE) study. *American Heart Journal.* 2005;149(6):1106–1111.

124 de Denus S, Sanoski CA, Carlsson J et al. Rate vs rhythm control in patients with atrial fibrillation: a meta-analysis. *Archives of Internal Medicine.* 2005;165(3):258–262.

125 Marshall DA, Levy AR, Vidaillet H et al. Cost-effectiveness of rhythm versus rate control in atrial fibrillation. *Annals of Internal Medicine.* 2004;141(9):653–661.

126 Hagens VE, Vermeulen KM, TenVergert EM et al. Rate control is more cost-effective than rhythm control for patients with persistent atrial fibrillation – results from the RAte Control versus Electrical cardioversion (RACE) study. *European Heart Journal.* 2004;25(17):1542–1549.

127 Corley SD, Epstein AE, DiMarco JP et al. Relationships between sinus rhythm, treatment, and survival in the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) Study. *Circulation.* 2004;109(12):1509–1513.

128 McNamara RL, Tamariz LJ, Segal JB et al. Management of atrial fibrillation: review of the evidence for the role of pharmacologic therapy, electrical cardioversion, and echocardiography. *Annals of Internal Medicine.* 2003;139(12):1018–1033.

129 Coplen SE, Antman EM, Berlin JA et al. Efficacy and safety of quinidine therapy for maintenance of sinus rhythm after cardioversion. A meta-analysis of randomized control trials (erratum appears in *Circulation* 1991;83(2):714). *Circulation.* 1990;82(4):1106–1116.

130 De Simone A, De Pasquale M, De Matteis C et al. Verapamil plus antiarrhythmic drugs reduce atrial fibrillation recurrences after an electrical cardioversion (VEPARAF study). *European Heart Journal.* 2003;24(15):1425–1429.

131 Kochiadakis GE, Igoumenidis NE, Marketou ME et al. Low-dose amiodarone versus sotalol for suppression of recurrent symptomatic atrial fibrillation. *American Journal of Cardiology.* 1998;81(8): 995–998.

132 Kochiadakis GE, Igoumenidis NE, Marketou ME et al. Low dose amiodarone and sotalol in the treatment of recurrent, symptomatic atrial fibrillation: a comparative, placebo-controlled study. *Heart.* 2000;84(3): 251–257.

133 Kochiadakis GE, Marketou ME, Igoumenidis NE et al. Amiodarone, sotalol, or propafenone in atrial fibrillation: which is preferred to maintain normal sinus rhythm? *Pacing and Clinical Electrophysiology.* 2000;23(11 Pt 2):1883–1887.

134 Bellandi F, Simonetti I, Leoncini M et al. Long-term efficacy and safety of propafenone and sotalol for the maintenance of sinus rhythm after conversion of recurrent symptomatic atrial fibrillation. *American Journal of Cardiology.* 2001;88(6):640–645.

135 Reimold SC, Cantillon CO, Friedman PL et al. Propafenone vs sotalol for suppression of recurrent symptomatic atrial fibrillation. *American Journal of Cardiology.* 1993;71(7):558–563.

136 Kochiadakis GE, Igoumenidis NE, Hamilos ME et al. Sotalol vs propafenone for long-term maintenance of normal sinus rhythm in patients with recurrent symptomatic atrial fibrillation. *American Journal of Cardiology.* 2004;94(12):1563–1566.

137 Kochiadakis GE, Igoumenidis NE, Hamilos MI et al. Long-term maintenance of normal sinus rhythm in patients with current symptomatic atrial fibrillation: amiodarone vs propafenone, both in low doses. *Chest.* 2004;125(2):377–383.

138 Plewan A, Lehmann G, Ndrepepa G et al. Maintenance of sinus rhythm after electrical cardioversion of persistent atrial fibrillation; sotalol versus bisoprolol. *European Heart Journal.* 2001;22(16):1504–1510.

139 Bjerkelund CJ, Orning OM. The efficacy of anticoagulant therapy in preventing embolism related to DC electrical conversion of atrial fibrillation. *American Journal of Cardiology.* 1969;23(2):208–216.

140 Weigner MJ, Caulfield TA, Danias PG et al. Risk for clinical thromboembolism associated with conversion to sinus rhythm in patients with atrial fibrillation lasting less than 48 hours. *Annals of Internal Medicine.* 1997;126(8):615–620.

141 Moreyra E, Finkelhor RS, Cebul RD. Limitations of transesophageal echocardiography in the risk assessment of patients before nonanticoagulated cardioversion from atrial fibrillation and flutter: an analysis of pooled trials. *American Heart Journal.* 1995;129(1):71–75.

142 Gentile F, Elhendy A, Khandheria BK et al. Safety of electrical cardioversion in patients with atrial fibrillation. *Mayo Clinic Proceedings.* 2002;77(9):897–904.

143 Gallagher MM, Hennessy BJ, Edvardsson N et al. Embolic complications of direct current cardioversion of atrial arrhythmias: association with low intensity of anticoagulation at the time of cardioversion. *Journal of the American College of Cardiology.* 2002;40(5):926–933.

144 Stellbrink C, Nixdorff U, Hofmann T et al. Safety and efficacy of enoxaparin compared with unfractionated heparin and oral anticoagulants for prevention of thromboembolic complications in cardioversion of nonvalvular atrial fibrillation: the Anticoagulation in Cardioversion using Enoxaparin (ACE) trial. *Circulation.* 2004;109(8):997–1003.

145 Collins LJ, Silverman DI, Douglas PS et al. Cardioversion of nonrheumatic atrial fibrillation. Reduced thromboembolic complications with 4 weeks of precardioversion anticoagulation are related to atrial thrombus resolution. *Circulation.* 1995;92(2):160–163.

146 Umana E, Solares CA, Alpert MA. Tachycardia-induced cardiomyopathy. *American Journal of Medicine.* 2003;114(1):51–55.

147 Royal College of Physicians of Edinburgh. Consensus Conference on Atrial Fibrillation: final consensus statement. Proceedings of the Royal College of Physicians of Edinburgh. 1998;28:552–4.

148 Falk RH, Leavitt J. Digoxin for atrial fibrillation: a drug whose time has gone? *Ann Intern Med.* 1991;114:573–75.

149 Li-Saw-Hee FL, Lip GY. Digoxin Revisted. *Quarterly Journal of Medicine.* 1998;91:259–264.

150 Freestone B, Lip GY. Heart rate control. In: Lip GYH, Godtfredsen J (eds), *Cardiac Arrhythmias: a clinical approach.* Edinburgh: Mosby, 2003:275–298.

151 Khand AU, Rankin AC, Martin W et al. Carvedilol alone or in combination with digoxin for the management of atrial fibrillation in patients with heart failure? *Journal of the American College of Cardiology.* 2003;42(11):1944–1951.

152 Koh KK, Song JH, Kwon KS et al. Comparative study of efficacy and safety of low-dose diltiazem or betaxolol in combination with digoxin to control ventricular rate in chronic atrial fibrillation: randomized crossover study. *International Journal of Cardiology.* 1995;52(2):167–174.

153 Lewis RV, McMurray J, McDevitt DG. Effects of atenolol, verapamil, and xamoterol on heart rate and exercise tolerance in digitalised patients with chronic atrial fibrillation. *Journal of Cardiovascular Pharmacology.* 1989;13(1):1–6.

154 Farshi R, Kistner D, Sarma JS et al. Ventricular rate control in chronic atrial fibrillation during daily activity and programmed exercise: a crossover open-label study of five drug regimens. *Journal of the American College of Cardiology.* 1999;33(2):304–310.

155 Maragno I, Santostasi G, Gaion RM et al. Low- and medium-dose diltiazem in chronic atrial fibrillation: comparison with digoxin and correlation with drug plasma levels. *American Heart Journal.* 1988;116(2 Pt 1):385–392.

156 Lewis RV, Laing E, Moreland TA et al. A comparison of digoxin, diltiazem and their combination in the treatment of atrial fibrillation. *European Heart Journal.* 1988;9(3):279–283.

157 Pomfret SM, Beasley CR, Challenor V et al. Relative efficacy of oral verapamil and digoxin alone and in combination for the treatment of patients with chronic atrial fibrillation. *Clinical Science.* 1988;74(4):351–357.

158 Lewis R, Lakhani M, Moreland TA et al. A comparison of verapamil and digoxin in the treatment of atrial fibrillation. *European Heart Journal.* 1987;8(2):148–153.

159 Roth A, Harrison E, Mitani G et al. Efficacy and safety of medium- and high-dose diltiazem alone and in combination with digoxin for control of heart-rate at rest and during exercise in patients with chronic atrial fibrillation. *Circulation.* 1986;73(2):316–324.

160 Botto GL, Bonini W, Broffoni T. Modulation of ventricular rate in permanent atrial fibrillation: randomized, crossover study of the effects of slow-release formulations of gallopamil, diltiazem, or verapamil. *Clinical Cardiology.* 1998;21(11):837–840.

161 Wong CK, Lau CP, Leung WH et al. Usefulness of labetalol in chronic atrial fibrillation. *American Journal of Cardiology.* 1990;66(17):1212–1215.

162 Lang R, Klein HO, Weiss E et al. Superiority of oral verapamil therapy to digoxin in treatment of chronic atrial fibrillation. *Chest.* 1983;83(3):491–499.

163 Fleming HA, Bailey SM. Mitral valve disease, systemic embolism and anticoagulants. *Postgraduate Medical Journal.* 1971;47(551):599–604.

164 Salem DN, Stein PD, Al Ahmad A et al. Antithrombotic therapy in valvular heart disease – native and prosthetic: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest.* 2004;126(3 Suppl):457S–482S.

165 Szekely P. Systemic embolization and anticoagulant prophylaxis in rhuematic heart disease. *British Medical Journal.* 1964;1964(1):209–212.

166 Petersen P, Madsen EB, Brun B et al. Silent cerebral infarction in chronic atrial fibrillation. *Stroke.* 1987;18(6):1098–1100.

167 Wolf PA, Kannel WB, McGee DL et al. Duration of atrial fibrillation and imminence of stroke: the Framingham Study. *Stroke.* 1983;14(5):664–667.

168 Laupacis A, Boysen G, Connolly S et al. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation: analysis of pooled data from five randomized controlled trials. *Archives of Internal Medicine.* 1994;154(13):1449–1457.

169 Lane D, Lip GY. Anti-thrombotic therapy for atrial fibrillation and patients' preferences for treatment. *Age & Ageing.* 2005;34(1):1–3.

170 Howitt A, Armstrong D. Implementing evidence based medicine in general practice: audit and qualitative study of antithrombotic treatment for atrial fibrillation. *British Medical Journal.* 1999;318(7194): 1324–1327.

171 Hart RG, Benavente O, McBride R et al. Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: a meta-analysis. *Annals of Internal Medicine.* 1999;131(7):492–501.

172 Segal JB, McNamara RL, Miller MR et al. Anticoagulants or antiplatelet therapy for non-rheumatic atrial fibrillation and flutter. *The Cochrane Library.* 2004;(1)

173 Benavente O, Hart R, Koudstaal P et al. Oral anticoagulants for preventing stroke in patients with non-valvular atrial fibrillation and no previous history of stroke or transient ischemic attacks. *The Cochrane Library.* 2003;(4)

174 van Walraven C, Hart RG, Singer DE et al. Oral anticoagulants vs aspirin in nonvalvular atrial fibrillation: an individual patient meta-analysis. *Journal of the American Medical Association.* 2002;288(19):2441–2448.

175 Taylor FC, Cohen H, Ebrahim S. Systematic review of long-term anticoagulation or antiplatelet treatment in patients with non-rheumatic atrial fibrillation (erratum appears in BMJ 2001 Mar 10;322(7286):587). *British Medical Journal.* 2001;322(7282):321–326.

176 Hylek EM, Go AS, Chang Y et al. Effect of intensity of oral anticoagulation on stroke severity and mortality in atrial fibrillation. *New England Journal of Medicine.* 2003;349(11):1019–1026.

177 Perret-Guillaume C, Wahl DG. Low-dose warfarin in atrial fibrillation leads to more thromboembolic events without reducing major bleeding when compared to adjusted-dose. *Thrombosis & Haemostasis.* 2004;91(2):394–402.

178 Benavente O, Hart R, Koudstaal P et al. Antiplatelet therapy for preventing stroke in patients with non-valvular atrial fibrillation and no previous history of stroke or transient ischemic attacks. *The Cochrane Library.* 2003;(4)

179 Perez-Gomez F, Alegria E, Berjon J et al. Comparative effects of antiplatelet, anticoagulant, or combined therapy in patients with valvular and nonvalvular atrial fibrillation: a randomized multicenter study. *Journal of the American College of Cardiology.* 2004;44(8):1557–1566.

180 Lip GY, Kamath S, Jafri M et al. Ethnic differences in patient perceptions of atrial fibrillation and anticoagulation therapy: the West Birmingham Atrial Fibrillation Project. *Stroke.* 2002;33(1):238–242.

181 Antithrombotic TC. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients (erratum appears in *BMJ* 2002 Jan 19;324(7330):141). *British Medical Journal.* 2002;324(7329):71–86.

182 Petersen P, Boysen G, Godtfredsen J et al. Placebo-controlled, randomised trial of warfarin and aspirin for prevention of thromboembolic complications in chronic atrial fibrillation: the Copenhagen AFASK study. *Lancet.* 1989;1:175–179.

183 Singer DE, Hughes RA, Gress DR et al. The effect of aspirin on the risk of stroke in patients with nonrheumatic atrial fibrillation: the BAATAF Study. *American Heart Journal.* 1992;124(6):1567–1573.

184 McBride R. Stroke prevention in atrial fibrillation study: final results. *Circulation.* 1991;84(2):527–539.

185 Lip GYH, Li-Saw-Hee FL. Paroxysmal atrial fibrillation. *Quarterly Journal of Medicine.* 2001;94(12): 665–678.

186 Murgatroyd FD, Gibson SM, Baiyan X et al. Double-blind placebo-controlled trial of digoxin in symptomatic paroxysmal atrial fibrillation. *Circulation.* 1999;99(21):2765–2770.

187 Lee SH, Chen SA, Tai CT et al. Comparisons of oral propafenone and sotalol as an initial treatment in patients with symptomatic paroxysmal atrial fibrillation. *American Journal of Cardiology.* 1997;79(7): 905–908.

188 Steeds RP, Birchall AS, Smith M et al. An open label, randomised, crossover study comparing sotalol and atenolol in the treatment of symptomatic paroxysmal atrial fibrillation. *Heart.* 1999;82(2):170–175.

189 Lumer GB, Roy D, Talajic M et al. Amiodarone reduces procedures and costs related to atrial fibrillation in a controlled clinical trial. *European Heart Journal.* 2002;23(13):1050–1056.

190 Alboni P, Botto GL, Baldi N et al. Outpatient treatment of recent-onset atrial fibrillation with the 'pill-in-the-pocket' approach. *New England Journal of Medicine.* 2004;351(23):2384–2391.

191 Alboni P, Tomasi C, Menozzi C et al. Efficacy and safety of out-of-hospital self-administered single-dose oral drug treatment in the management of infrequent, well-tolerated paroxysmal supraventricular tachycardia. *Journal of the American College of Cardiology.* 2001;37(2):548–553.

192 Hart RG, Pearce LA, Rothbart RM et al. Stroke with intermittent atrial fibrillation: incidence and predictors during aspirin therapy. Stroke prevention in atrial fibrillation investigators. *Journal of the American College of Cardiology.* 2000;35(1):183–187.

193 Lip GY. Does paroxysmal atrial fibrillation confer a paroxysmal thromboembolic risk? *Lancet.* 1997;349(9065):1565–1566.

194 Petersen P, Godtfredsen J. Embolic complications in paroxysmal atrial fibrillation. *Stroke.* 1986;17(4): 622–626.

195 UK Resuscitation Council. *Advanced Life Support (ALS) Provider Manual* (4th edition) London: Resuscitation Council (UK) Trading Ltd;2004.

196 Strasberg B, Sagie A, Rechavia E et al. Deleterious effects of intravenous verapamil in Wolff–Parkinson–White patients and atrial fibrillation. *Cardiovascular Drugs & Therapy.* 1989;2(6):801–806.

197 Wang HE, O'Connor RE, Megargel RE et al. The use of diltiazem for treating rapid atrial fibrillation in the out-of-hospital setting. *Annals of Emergency Medicine.* 2001;37(1):38–45.

198 Kumar A. Intravenous amiodarone for therapy of atrial fibrillation and flutter in critically ill patients with severely depressed left ventricular function. *Southern Medical Journal.* 1996;89(8):779–785.

199 Faniel R, Schoenfeld P. Efficacy of i.v. amiodarone in converting rapid atrial fibrillation and flutter to sinus rhythm in intensive care patients. *European Heart Journal.* 1983;4(3):180–185.

200 Strasberg B, Arditti A, Sclarovsky S. Efficacy of intravenous amiodarone in the management of paroxysmal or new atrial fibrillation with fast ventricular response. *International Journal of Cardiology.* 1985;7(1):47–55.

201 Stoddard MF, Dawkins PR, Prince CR et al. Left atrial appendage thrombus is not uncommon in patients with acute atrial fibrillation and a recent embolic event: a transesophageal echocardiographic study. *Journal of the American College of Cardiology.* 1995;25(2):452–459.

202 Singer DE, Albers GW, Dalen JE et al. Antithrombotic therapy in atrial fibrillation: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest.* 2004;126(3 Suppl):429S–456S.

203 Vecht RJ, Nicolaides EP, Ikweuke JK et al. Incidence and prevention of supraventricular tachyarrhythmias after coronary bypass surgery. *International Journal of Cardiology.* 1986;13(2):125–134.

204 Creswell LL, Schuessler RB, Rosenbloom M et al. Hazards of postoperative atrial arrhythmias. *Annals of Thoracic Surgery.* 1993;56(3):539–549.

205 Almassi GH, Schowalter T, Nicolosi AC et al. Atrial fibrillation after cardiac surgery: a major morbid event? *Annals of Surgery.* 1997;226(4):501–511.

206 Likosky DS, Caplan LR, Weintraub RM et al. Intraoperative and postoperative variables associated with strokes following cardiac surgery. *Heart Surgery Forum.* 2004;7(4):E271–E276.

207 Maisel WH, Rawn JD, Stevenson WG. Atrial fibrillation after cardiac surgery. *Annals of Internal Medicine.* 2001;135(12):1061–1073.

208 Di Biasi P, Scrofani R, Paje A et al. Intravenous amiodarone vs propafenone for atrial fibrillation and flutter after cardiac operation. *European Journal of Cardio-Thoracic Surgery.* 1995;9(10):587–591.

209 Ryan TJ, Antman EM, Brooks NH. *ACC/AHA guidelines for the management of patients with acute myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Journal of the American College of Cardiology.* 1996;28:1328–1428.

210 Auer J, Weber T, Berent R et al. Serum potassium level and risk of postoperative atrial fibrillation in patients undergoing cardiac surgery. *Journal of the American College of Cardiology.* 2004;44(4):938–939.

211 Miller S, Crystal E, Garfinkle M et al. Effects of magnesium on atrial fibrillation after cardiac surgery: a meta-analysis. *Heart* (British Cardiac Society). 2005;91(5):618–623.

212 Crystal E, Connolly SJ, Ginger T et al. Interventions for preventing postoperative atrial fibrillation in patients undergoing heart surgery. *The Cochrane Library.* 2003;(4)

213 Amar D, Roistacher N, Rusch VW et al. Effects of diltiazem prophylaxis on the incidence and clinical outcome of atrial arrhythmias after thoracic surgery. *Journal of Thoracic & Cardiovascular Surgery.* 2000;120(4):790–798.

214 Van Mieghem W, Tits G, Demuynck K et al. Verapamil as prophylactic treatment for atrial fibrillation after lung operations. *Annals of Thoracic Surgery.* 1996;61(4):1083–1085.

215 Borgeat A, Biollaz J, Bayer-Berger M et al. Prevention of arrhythmias by flecainide after noncardiac thoracic surgery. *Annals of Thoracic Surgery.* 1989;48(2):232–234.

216 Amar D, Roistacher N, Burt ME et al. Effects of diltiazem versus digoxin on dysrhythmias and cardiac function after pneumonectomy. *Annals of Thoracic Surgery.* 1997;63(5):1374–1381.

217 Bayliff CD, Massel DR, Inculet RI et al. Propranolol for the prevention of postoperative arrhythmias in general thoracic surgery. *Annals of Thoracic Surgery.* 1999;67(1):182–186.

218 Lanza LA, Visbal AI, DeValeria PA et al. Low-dose oral amiodarone prophylaxis reduces atrial fibrillation after pulmonary resection. *Annals of Thoracic Surgery.* 2003;75(1):223–230.

219 Reddy P, Dunn AB, White CM et al. An economic analysis of amiodarone versus placebo for the prevention of atrial fibrillation after open heart surgery. *Pharmacotherapy.* 2002;22(1):75–80.

220 Reddy P, Richerson M, Freeman-Bosco L et al. Cost-effectiveness of amiodarone for prophylaxis of atrial fibrillation in coronary artery bypass surgery. *American Journal of Health-System Pharmacy.* 1999;56(21):2211–2217.

221 Mahoney EM, Thompson TD, Veledar E et al. Cost-effectiveness of targeting patients undergoing cardiac surgery for therapy with intravenous amiodarone to prevent atrial fibrillation. *Journal of the American College of Cardiology.* 2002;40(4):737–745.

222 Daoud EG, Strickberger SA, Man KC et al. Preoperative amiodarone as prophylaxis against atrial fibrillation after heart surgery. *New England Journal of Medicine.* 1997;337(25):1785–1791.

223 Stamou SC, Hill PC, Sample GA et al. Prevention of atrial fibrillation after cardiac surgery: the significance of postoperative oral amiodarone. *Chest.* 2001;120(6):1936–1941.

224 Katariya K, DeMarchena E, Bolooki H. Oral amiodarone reduces incidence of postoperative atrial fibrillation. *Annals of Thoracic Surgery*. 1999;68(5):1599–1603.

225 Kim MH, Rachwal W, McHale C et al. Effect of amiodarone +/- diltiazem +/- beta blocker on frequency of atrial fibrillation, length of hospitalization, and hospital costs after coronary artery bypass grafting. *American Journal of Cardiology*. 2002;89(9):1126–1128.

226 Auer J, Weber T, Berent R et al. A comparison between oral antiarrhythmic drugs in the prevention of atrial fibrillation after cardiac surgery: the pilot study of prevention of postoperative atrial fibrillation (SPPAF), a randomized, placebo-controlled trial. *American Heart Journal*. 2004;147(4):636–643.

227 Kalus JS, White CM, Caron MF et al. Indicators of atrial fibrillation risk in cardiac surgery patients on prophylactic amiodarone. *Annals of Thoracic Surgery*. 2004;77(4):1288–1292.

228 Kluger J, White CM. Amiodarone prevents symptomatic atrial fibrillation and reduces the risk of cerebrovascular accidents and ventricular tachycardia after open heart surgery: results of the Atrial Fibrillation Suppression Trial (AFIST). *Cardiac Electrophysiology Review*. 2003;7(2):165–167.

229 Inoue H. Cost-effectiveness of antiarrhythmic drugs for prevention of thromboembolism in patients with paroxysmal atrial fibrillation. *Japanese Circulation Journal*. 2001;65(9):765–768.

230 Tokmakoglu H, Kandemir O, Gunaydin S et al. Amiodarone versus digoxin and metoprolol combination for the prevention of postcoronary bypass atrial fibrillation. *European Journal of Cardio-Thoracic Surgery*. 2002;21(3):401–405.

231 White CM, Giri S, Tsikouris JP et al. A comparison of two individual amiodarone regimens to placebo in open heart surgery patients. *Annals of Thoracic Surgery*. 2002;74(1):69–74.

232 Redle JD, Khurana S, Marzan R et al. Prophylactic oral amiodarone compared with placebo for prevention of atrial fibrillation after coronary artery bypass surgery. *American Heart Journal*. 1999;138(1 Pt 1):144–150.

233 Yazicioglu L, Eryilmaz S, Sirlak M et al. The effect of preoperative digitalis and atenolol combination on postoperative atrial fibrillation incidence. *European Journal of Cardio-Thoracic Surgery*. 2002;22(3): 397–401.

234 Coleman CI, Perkerson KA, Gillespie EL et al. Impact of prophylactic postoperative (beta)-blockade on post-cardiothoracic surgery, length of stay and atrial fibrillation. *Annals of Pharmacotherapy*. 2004; 38(12):2012–2016.

235 Kowey PR, Taylor JE, Rials SJ et al. Meta-analysis of the effectiveness of prophylactic drug therapy in preventing supraventricular arrhythmia early after coronary artery bypass grafting. *American Journal of Cardiology*. 1992;69(9):963–965.

236 Matsuura K, Takahara Y, Sudo Y et al. Effect of sotalol in the prevention of atrial fibrillation following coronary artery bypass grafting. *Japanese Journal of Thoracic & Cardiovascular Surgery*. 2001;49(10): 614–617.

237 Malhotra R, Mishra M, Kler TS et al. Cardioprotective effects of diltiazem infusion in the perioperative period. *European Journal of Cardio-Thoracic Surgery*. 1997;12(3):420–427.

238 Seitelberger R, Hannes W, Gleichauf M et al. Effects of diltiazem on perioperative ischemia, arrhythmias, and myocardial function in patients undergoing elective coronary bypass grafting. *Journal of Thoracic & Cardiovascular Surgery*. 1994;107(3):811–821.

239 Hannes W, Fasol R, Zajonc H et al. Diltiazem provides anti-ischemic and anti-arrhythmic protection in patients undergoing coronary bypass grafting. *European Journal of Cardio Thoracic Surgery*. 1993;7(5): 239–245.

240 Keilich M, Kulinna C, Seitelberger R et al. Postoperative follow-up of coronary artery bypass patients receiving calcium antagonist diltiazem. *International Journal of Angiology*. 1997;6:8–12.

241 Ferraris VA, Ferraris SP, Gilliam H et al. Verapamil prophylaxis for postoperative atrial dysrhythmias: a prospective, randomized, double-blind study using drug level monitoring. *Annals of Thoracic Surgery*. 1987;43(5):530–533.

242 Kowey PR, Yannicelli D, Amsterdam E et al. Effectiveness of oral propafenone for the prevention of atrial fibrillation after coronary artery bypass grafting. *American Journal of Cardiology*. 2004;94(5):663–665.

243 Gold MR, O'Gara PT, Buckley MJ et al. Efficacy and safety of procainamide in preventing arrhythmias after coronary artery bypass surgery. *American Journal of Cardiology.* 1996;78(9):975–979.

244 Laub GW, Janeira L, Muralidharan S et al. Prophylactic procainamide for prevention of atrial fibrillation after coronary artery bypass grafting: a prospective, double-blind, randomized, placebo-controlled pilot study. *Critical Care Medicine.* 1993;21(10):1474–1478.

245 Weiner B, Rheinlander HF, Decker EL et al. Digoxin prophylaxis following coronary artery bypass surgery. *Clinical Pharmacy.* 1986;5(1):55–58.

246 Jakobsen C-J, Bille S, Ahlburg P et al. Perioperative metoprolol reduces the frequency of atrial fibrillation after thoracotomy for lung resection. *Journal of Cardiothoracic & Vascular Anesthesia.* 1997;11(6):746–751.

247 Guo Y, Hu S, Wu Q et al. Predictors of atrial fibrillation after coronary artery bypass graft surgery. *Chinese Medical Journal.* 2002;115(2):232–234.

248 Mathew JP, Fontes ML, Tudor IC et al. A multicenter risk index for atrial fibrillation after cardiac surgery. *Journal of the American Medical Association.* 2004;291(14):1720–1729.

249 Shah P, Shpigel A, Wasser T et al. Morbidity of post-coronary artery bypass surgery patients with atrial fibrillation treated with rate control versus sinus-restoring therapy. *Heartdrug.* 2001;1(4):192–196.

250 Connolly SJ, Mulji AS, Hoffert DL et al. Randomized placebo-controlled trial of propafenone for treatment of atrial tachyarrhythmias after cardiac surgery. *Journal of the American College of Cardiology.* 1987;10(5):1145–1148.

251 Soucier R, Silverman D, Abordo M et al. Propafenone versus ibutilide for postoperative atrial fibrillation following cardiac surgery: neither strategy improves outcomes compared to rate control alone (the PIPAF study). *Medical Science Monitor.* 2003;9(3):I19–I23.

252 Hjelms E. Procainamide conversion of acute atrial fibrillation after open-heart surgery compared with digoxin treatment. *Scandinavian Journal of Thoracic & Cardiovascular Surgery.* 1992;26(3):193–196.

253 Campbell TJ, Gavaghan TP, Morgan JJ. Intravenous sotalol for the treatment of atrial fibrillation and flutter after cardiopulmonary bypass. Comparison with disopyramide and digoxin in a randomised trial. *British Heart Journal.* 1985;54(1):86–90.

254 Cochrane AD, Siddins M, Rosenfeldt FL et al. A comparison of amiodarone and digoxin for treatment of supraventricular arrhythmias after cardiac surgery. *European Journal of Cardio-Thoracic Surgery.* 1994;8(4):194–198.

255 Wafa SS, Ward DE, Parker DJ et al. Efficacy of flecainide acetate for atrial arrhythmias following coronary artery bypass grafting. *American Journal of Cardiology.* 1989;63(15):1058–1064.

256 Lee JK, Klein GJ, Krahn AD et al. Rate control versus conversion strategy in postoperative atrial fibrillation: trial design and pilot study results. *Cardiac Electrophysiology Review.* 2003;7(2):178–184.

257 Williams E, Ansari M, Lip G. Managing atrial fibrillation in the accident and emergency department. *Quarterly Journal of Medicine.* 2001;94(11):609–614.

258 Anon. Secondary prevention in non-rheumatic atrial fibrillation after transient ischaemic attack or minor stroke. *Lancet.* 1993;342(8882):1255–1262.

259 Evans A, Perez I, Yu G et al. Should stroke subtype influence anticoagulation decisions to prevent recurrence in stroke patients with atrial fibrillation? *Stroke.* 2001;32(12):2828–2832.

260 Hart RG, Palacio S, Pearce LA. Atrial fibrillation, stroke, and acute antithrombotic therapy: analysis of randomized clinical trials. *Stroke.* 2002;33(11):2722–2727.

261 Lin H, Wolf PA, Kelly-Hayes M et al. Stroke severity in atrial fibrillation: the Framingham Study. *Stroke.* 1996;27(10):1760–1764.

262 Jorgensen HS, Nakayama H, Reith J et al. Acute stroke with atrial fibrillation: the Copenhagen Stroke Study. *Stroke.* 1996;27(10):1765–1769.

263 Morocutti C, Amabile G, Fattapposta F et al. Indobufen versus warfarin in the secondary prevention of major vascular events in nonrheumatic atrial fibrillation. SIFA (Studio Italiano Fibrillazione Atriale) Investigators 62. *Stroke.* 1997;28(5):1015–1021.

264 Diener HC. Antiplatelet therapy to prevent stroke: risk of brain hemorrhage and efficacy in atrial fibrillation. *Journal of the Neurological Sciences.* 1997;153(1):112.

265 Harenberg J, Weuster B, Pfitzer M et al. Prophylaxis of embolic events in patients with atrial fibrillation using low molecular weight heparin. *Seminars in Thrombosis & Hemostasis.* 1993;19(Suppl 1):116–121.

266 Saxena R. Anticoagulants for preventing stroke in patients with nonrheumatic atrial fibrillation and a history of stroke or transient ischemic attacks. *The Cochrane Library.* 2004;(Issue 4)

267 Hart RG, Pearce LA, Koudstaal PJ. Transient ischemic attacks in patients with atrial fibrillation: implications for secondary prevention: the European Atrial Fibrillation Trial and Stroke Prevention in Atrial Fibrillation III Trial. *Stroke.* 2004;35(4):948–951.

268 DiMarco JP, Flaker GC, Waldo A. Factors affecting bleeding risk during anticoagulant therapy in patients with atrial fibrillation: observations from the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) Study. *American Heart Journal.* 2005;149(4):650–656.

269 Silber S, Albertsson P, Aviles FF et al. Guidelines for percutaneous coronary interventions: the task force for percutaneous coronary interventions of the European Society of Cardiology. *European Heart Journal.* 2005;26(8):804–847.

270 Shireman TI, Howard PA, Kresowik TF et al. Combined anticoagulant–antiplatelet use and major bleeding events in elderly atrial fibrillation patients. *Stroke.* 2004;35(10):2362–2367.

271 Gullov AL, Koefoed BG, Petersen P. Bleeding during warfarin and aspirin therapy in patients with atrial fibrillation: the AFASAK 2 study (Atrial Fibrillation Aspirin and Anticoagulation). *Archives of Internal Medicine.* 1999;159(12):1322–1328.

272 Pengo V, Legnani C, Noventa F et al. Oral anticoagulant therapy in patients with nonrheumatic atrial fibrillation and risk of bleeding. A multicenter inception cohort study. *Thrombosis & Haemostasis.* 2001;85(3):418–422.

273 Anon. Bleeding during antithrombotic therapy in patients with atrial fibrillation. The Stroke Prevention in Atrial Fibrillation Investigators. *Archives of Internal Medicine.* 1996;156(4):409–416.

274 Copland M, Walker ID, Tait RC. Oral anticoagulation and hemorrhagic complications in an elderly population with atrial fibrillation. *Archives of Internal Medicine.* 2001;161(17):2125–2128.

275 Sam C, Massaro JM, D'Agostino RB, Sr. et al. Warfarin and aspirin use and the predictors of major bleeding complications in atrial fibrillation (the Framingham Heart Study). *American Journal of Cardiology.* 2004;94(7):947–951.

276 Abdelhafiz AH, Wheeldon NM. Results of an open-label, prospective study of anticoagulant therapy for atrial fibrillation in an outpatient anticoagulation clinic. *Clinical Therapeutics.* 2004;26(9):1470–1478.

277 Fang MC, Chang Y, Hylek EM et al. Advanced age, anticoagulation intensity, and risk for intracranial hemorrhage among patients taking warfarin for atrial fibrillation. *Annals of Internal Medicine.* 2004;141(10):745–752.

278 Wehinger C, Stollberger C, Langer T et al. Evaluation of risk factors for stroke/embolism and of complications due to anticoagulant therapy in atrial fibrillation. *Stroke.* 2001;32(10):2246–2252.

279 Kalra L, Yu G, Perez I et al. Prospective cohort study to determine if trial efficacy of anticoagulation for stroke prevention in atrial fibrillation translates into clinical effectiveness. *British Medical Journal.* 2000;320(7244):1236–1239.

280 Go AS, Hylek EM, Chang Y et al. Anticoagulation therapy for stroke prevention in atrial fibrillation: how well do randomized trials translate into clinical practice? *Journal of the American Medical Association.* 2003;290(20):2685–2692.

281 Hart RG, Pearce LA, McBride R et al. Factors associated with ischemic stroke during aspirin therapy in atrial fibrillation: analysis of 2012 participants in the SPAF I–III clinical trials. The Stroke Prevention in Atrial Fibrillation (SPAF) Investigators. *Stroke.* 1999;30(6):1223–1229.

282 The SPAF III Writing Committee for the Stroke Prevention in Atrial Fibrillation Investigators. Patients with nonvalvular atrial fibrillation at low risk of stroke during treatment with aspirin: Stroke Prevention in Atrial Fibrillation III Study. The SPAF III Writing Committee for the Stroke Prevention in Atrial Fibrillation Investigators. *Journal of the American Geriatrics Society.* 1998;279(16):1273–1277.

283 Wang TJ, Massaro JM, Levy D et al. A risk score for predicting stroke or death in individuals with new-onset atrial fibrillation in the community: the Framingham Heart Study. *Journal of the American Medical Association.* 2003;290(8):1049–1056.

284 Stollberger C, Chnupa P, Abzieher C et al. Mortality and rate of stroke or embolism in atrial fibrillation during long-term follow-up in the embolism in left atrial thrombi (ELAT) study. *Clinical Cardiology.* 2004;27(1):40–46.

285 van Latum JC, Koudstaal PJ, Venables GS et al. Predictors of major vascular events in patients with a transient ischemic attack or minor ischemic stroke and with nonrheumatic atrial fibrillation. European Atrial Fibrillation Trial (EAFT) Study Group. *Stroke.* 1995;26(5):801–806.

286 Petersen P. Risk factors for thromboembolic complications in chronic atrial fibrillation. The Copenhagen AFASAK study. *Archives of Internal Medicine.* 1990;150(4):819–821.

287 Anon. Predictors of thromboembolism in atrial fibrillation: I. Clinical features of patients at risk. The Stroke Prevention in Atrial Fibrillation Investigators. *Annals of Internal Medicine.* 1992;116(1):1–5.

288 Inoue H, Atarashi H. Risk factors for thromboembolism in patients with paroxysmal atrial fibrillation. *American Journal of Cardiology.* 2000;86(8):852–855.

289 Moulton AW, Singer DE, Haas JS. Risk factors for stroke in patients with nonrheumatic atrial fibrillation: a case-control study. *American Journal of Medicine.* 1991;91(2):156–161.

290 Anon. Risk factors for thromboembolism during aspirin therapy in patients with atrial fibrillation: the Stroke Prevention in Atrial Fibrillation Study. *Journal of Stroke and Cerebrovascular Diseases.* 1995;5(3):147–157.

291 Seidl K, Hauer B, Schwick NG et al. Risk of thromboembolic events in patients with atrial flutter. *American Journal of Cardiology.* 1998;82(5):580–583.

292 Anon. Transesophageal echocardiographic correlates of thromboembolism in high-risk patients with nonvalvular atrial fibrillation. The Stroke Prevention in Atrial Fibrillation Investigators Committee on Echocardiography. *Annals of Internal Medicine.* 1998;128(8):639–647.

293 Chang YJ, Ryu SJ, Lin SK. Carotid artery stenosis in ischemic stroke patients with nonvalvular atrial fibrillation. *Cerebrovascular Diseases.* 2002;13(1):16–20.

294 Lip GY, Lowe GD. ABC of atrial fibrillation. Antithrombotic treatment for atrial fibrillation. *British Medical Journal.* 1996;312(7022):45–49.

295 Fuster V, Ryden LE, Asinger RW et al. ACC/AHA/ESC guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the European Society of Cardiology Committee for Practice Guidelines and Policy Conferences (Committee to Develop Guidelines for the Management of Patients With Atrial Fibrillation), developed in collaboration with the North American Society of Pacing and Electrophysiology. *Journal of the American College of Cardiology.* 2001;38(4):1266i–1266lxx.

296 Gage BF, Waterman AD, Shannon W et al. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *Journal of the American Medical Association.* 2001;285(22):2864–2.

297 Eckman MH, Levine HJ, Salem DN et al. Making decisions about antithrombotic therapy in heart disease: decision analytic and cost-effectiveness issues. *Chest.* 1998;114(5 Suppl):699S–714S.

298 Gage BF, Cardinalli AB, Albers GW et al. Cost effectiveness of warfarin and aspirin for prophylaxis of stroke in patients with nonvalvular atrial fibrillation. *Journal of the American Medical Association.* 1995;274(23):1839–1845.

299 Desbiens NA. Deciding on anticoagulating the oldest old with atrial fibrillation: insights from cost-effectiveness analysis. *Journal of the American Geriatrics Society.* 2002;50(5):863–869.

300 Caro JJ, O'Brien JA, Klittich W et al. The economic impact of warfarin prophylaxis in nonvalvular atrial fibrillation. *Disease Management & Clinical Outcomes.* 1997;1(2):54–60.

301 O'Brien CL, Gage BF. Costs and effectiveness of ximelagatran for stroke prophylaxis in chronic atrial fibrillation. *Journal of the American Medical Association.* 2005;293(6):699–706.

302 Lightowlers S MA. Cost-effectiveness of anticoagulation in nonrheumatic atrial fibrillation in the primary prevention of ischemic stroke. *Stroke.* 1998;29(9):1827–1832.

303 Thomson R, Parkin D, Eccles M et al. Decision analysis and guidelines for anticoagulant therapy to prevent stroke in patients with atrial fibrillation (erratum appears in Lancet 2000 Apr 22;355(9213): 1466). *Lancet.* 2000;355(9208):956–962.

304 Gustafsson C, Asplund K, Britton M et al. Cost effectiveness of primary stroke prevention in atrial fibrillation: Swedish national perspective. *British Medical Journal.* 1992;305(6867):1457–1460.

305 Anon. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of pooled data from five randomized controlled trials (erratum appears in *Arch Intern Med* 1994 Oct 10;154(19):2254). *Archives of Internal Medicine.* 1994;154(13):1449–1457.

306 Murray ET, Fitzmaurice DA, McCahon D. Point of care testing for INR monitoring: where are we now? *British Journal of Haematology.* 2004;127(4):373–378.

307 Eldor A, Schwartz J. Self-management of oral anticoagulants with a whole blood prothrombin-time monitor in elderly patients with atrial fibrillation. *Pathophysiology of Haemostasis & Thrombosis.* 2002;32(3):99–106.

308 Voller H, Glatz J, Taborski U et al. Self-management of Oral Anticoagulation in Nonvalvular Atrial Fibrillation (SMAAF study). *Zeitschrift fur Kardiologie.* 2005;94(3):182–186.

309 Piso B, Jimenz–Boj E, Krinninger B et al. The quality of oral anticoagulation before, during and after a period of patient self–management. *Thrombosis Research.* 2002;106(2):101–104.

310 Cosmi B, Palareti G, Carpanedo M et al. Assessment of patient capability to self-adjust oral anticoagulant dose: a multicenter study on home use of portable prothrombin time monitor (COAGUCHECK). *Haematologica.* 2000;85(8):826–831.

311 Koertke H, Minami K, Bairaktaris A et al. INR self-management following mechanical heart valve replacement. *Journal of Thrombosis & Thrombolysis.* 2000;9 Suppl1:S41–5.

312 Watzke HH, Forberg E, Svolba G et al. A prospective controlled trial comparing weekly self-testing and self-dosing with the standard management of patients on stable oral anticoagulation. *Thrombosis & Haemostasis.* 2000;83(5):661–665.

313 Sawicki PT. A structured teaching and self-management program for patients receiving oral anticoagulation. A randomized controlled trial. *Journal of the American Medical Association.* 1999;281: 145–150.

314 Gadisseur APA, Breukink–Engbers WGM, Van Der Meer FJM et al. Comparison of the quality of oral anticoagulant therapy through patient self-management and management by specialized anticoagulation clinics in the Netherlands: a randomized clinical trial. *Archives of Internal Medicine.* 2003;163(21): 2639–2646.

315 Beyth RJ, Quinn L, Landefeld CS. A multicomponent intervention to prevent major bleeding complications in older patients receiving warfarin: a randomized, controlled trial. *Annals of Internal Medicine.* 2000;133(9):687–695.

316 Sunderji R, Gin K, Shalansky K et al. A randomized trial of patient self-managed versus physician-managed oral anticoagulation. *Canadian Journal of Cardiology.* 2004;20(11):1117–1123.

317 Sidhu P, O'Kane HO. Self-managed anticoagulation: results from a two-year prospective randomized trial with heart valve patients. *Annals of Thoracic Surgery.* 2001;72(5):1523–1527.

318 Cromheecke ME, Levi M, Colly LP et al. Oral anticoagulation self-management and management by a specialist anticoagulation clinic: a randomised crossover comparison. *Lancet.* 2000;356(9224):97–102.

319 Fitzmaurice DA, Murray ET, Gee KM et al. A randomised controlled trial of patient self-management of oral anticoagulation treatment compared with primary care management. *Journal of Clinical Pathology.* 2002;55(11):845–849.

320 Horstkotte D, Piper C, Wiemer M. Optimal frequency of patient monitoring and intensity of oral anticoagulation therapy in valvular heart disease. *Journal of Thrombosis & Thrombolysis.* 1998;5 (Suppl 1):S19–S24.

321 Menendez-Jandula B, Souto JC, Oliver A et al. Comparing self-management of oral anticoagulant therapy with clinic management: a randomized trial. *Annals of Internal Medicine.* 2005;142(1):1–14.

322 Heneghan C, onso-Coello P, Garcia-Alamino JM et al. Self-monitoring of oral anticoagulation: a systematic review and meta-analysis. *Lancet.* 2006;367(9508):404–411.

323 Lafata JE, Martin SA, Kaatz S et al. The cost-effectiveness of different management strategies for patients on chronic warfarin therapy. *Journal of General Internal Medicine.* 2000;15(1):31–37.

324 Niiranen S, Lamminen H, Niemi K et al. A cost study of new media supported near oral anticoagulant treatment follow-up. *International Journal of Medical Informatics.* 2003;70(1):19–29.

325 Fitzmaurice DA, Murray ET, McCahon D et al. Self-management of oral anticoagulation: randomised trial. *British Medical Journal.* 2005;331(7524):1057.

326 Fitzmaurice DA, Machin SJ. Recommendations for patients undertaking self-management of oral anticoagulation. *British Medical Journal.* 2001;323(7319):985–989.

327 Bollmann A, Husser D, Steinert R et al. Echocardiographic and electrocardiographic predictors for atrial fibrillation recurrence following cardioversion. *Journal of Cardiovascular Electrophysiology.* 2003;14(10 Suppl):S162–S165.

328 Dittrich HC, Erickson JS, Schneiderman T et al. Echocardiographic and clinical predictors for outcome of elective cardioversion of atrial fibrillation. *American Journal of Cardiology.* 1989;63(3):193–197.

329 Aytemir K, Aksoyek S, Yildirir A et al. Prediction of atrial fibrillation recurrence after cardioversion by p wave signal-averaged electrocardiography. *International Journal of Cardiology.* 1999;70(1):15–21.

330 Okcun B, Yigit Z, Kucukoglu MS et al. Predictors for maintenance of sinus rhythm after cardioversion in patients with nonvalvular atrial fibrillation. *Echocardiography.* 2002;19(5):351–357.

331 Guo XH, Gallagher MM, Poloniecki J et al. Prognostic significance of serial p wave signal-averaged electrocardiograms following external electrical cardioversion for persistent atrial fibrillation: a prospective study. *Pacing and Clinical Electrophysiology.* 2003;26(1 Part 2):299–304.

332 Berry C, Stewart S, Payne EM et al. Electrical cardioversion for atrial fibrillation: outcomes in 'real-life' clinical practice. *International Journal of Cardiology.* 2001;81(1):29–35.

333 Perez Y, Duval AM, Carville C et al. Is left atrial appendage flow a predictor for outcome of cardioversion of nonvalvular atrial fibrillation? A transthoracic and transesophageal echocardiographic study. *American Heart Journal.* 1997;134(4):745–751.

334 Gentili C, Giordano F, Alois A et al. Efficacy of intravenous propafenone in acute atrial fibrillation complicating open-heart surgery. *American Heart Journal.* 1992;123(5):1225–1228.

335 Galperin J, Elizari MV, Chiale PA et al. Pharmacologic reversion of persistent atrial fibrillation with amiodarone predicts long-term sinus rhythm maintenance. *Journal of Cardiovascular Pharmacology & Therapeutics.* 2003;8(3):179–186.

336 Brugada R, Tapscott T, Czernuszewicz GZ et al. Identification of a genetic locus for familial atrial fibrillation. *New England Journal of Medicine.* 1997;336(13):905–911.

337 Anderson JL, Gilbert EM, Alpert BL et al. Prevention of symptomatic recurrences of paroxysmal atrial fibrillation in patients initially tolerating antiarrhythmic therapy: a multicenter, double-blind, crossover study of flecainide and placebo with transtelephonic monitoring. Flecainide Supraventricular Tachycardia Study Group. *Circulation.* 1989;80(6):1557–1570.

338 Kerr CR, Connolly SJ, Abdollah H et al. Canadian trial of physiological pacing: effects of physiological pacing during long-term follow-up. *Circulation.* 2004;109(3):357–362.

339 Lemery R, Guiraudon G. Catheter and surgical ablation strategies in atrial fibrillation: what have we learned? *Current Opinion in Cardiology.* 2005;20(1):26–30.

340 Cox JL. Surgical treatment of atrial fibrillation: a review. *Europace.* 2004;5 Suppl 1:S20–S29.

341 Leitch JW, Klein G, Yee R et al. Sinus node-atrioventricular node isolation: long-term results with the 'corridor' operation for atrial fibrillation. *Journal of the American College of Cardiology.* 1991;17(4):970–975.

342 Marshall HJ, Harris ZI, Griffith MJ et al. Prospective randomized study of ablation and pacing versus medical therapy for paroxysmal atrial fibrillation: effects of pacing mode and mode-switch algorithm. *Circulation.* 1999;99(12):1587–1592.

343 Wood MA, Brown-Mahoney C, Kay GN et al. Clinical outcomes after ablation and pacing therapy for atrial fibrillation: a meta-analysis. *Circulation.* 2000;101(10):1138–1144.

344 Darpo B, Walfridsson H, Aunes M et al. Incidence of sudden death after radiofrequency ablation of the atrioventricular junction for atrial fibrillation. *American Journal of Cardiology.* 1997;80(9):1174–1177.

345 Twidale N, Manda V, Nave K et al. Predictors of outcome after radiofrequency catheter ablation of the atrioventricular node for atrial fibrillation and congestive heart failure. *American Heart Journal.* 1998;136(4 Pt 1):647–657.

346 Wellens HJ, Lau CP, Luderitz B et al. Atrioverter: an implantable device for the treatment of atrial fibrillation. *Circulation.* 1998;98(16):1651–1656.

347 Krittayaphong R, Raungrattanaamporn O, Bhuripanyo K et al. A randomized clinical trial of the efficacy of radiofrequency catheter ablation and amiodarone in the treatment of symptomatic atrial fibrillation. *Journal of the Medical Association of Thailand.* 2003;86 Suppl 1:8–16.

348 Wazni OM, Marrouche NF, Martin DO et al. Radiofrequency ablation versus antiarrhythmic drugs as first-line treatment of symptomatic atrial fibrillation: a randomized trial. *Journal of the American Medical Association.* 2005;293(21):2634–2640.

349 Verma A, Wazni OM, Marrouche NF et al. Pre-existent left atrial scarring in patients undergoing pulmonary vein antrum isolation: an independent predictor of procedural failure. *Journal of the American College of Cardiology.* 2005;45(2):285–292.

350 Lee SH, Tai CT, Hsieh MH et al. Predictors of early and late recurrence of atrial fibrillation after catheter ablation of paroxysmal atrial fibrillation. *Journal of Interventional Cardiac Electrophysiology.* 2004;10(3):221–226.

351 Purerfellner H, Martinek M, Aichinger J et al. Quality of life restored to normal in patients with atrial fibrillation after pulmonary vein ostial isolation. *American Heart Journal.* 2004;148(2):318–325.

352 Husser D, Bollmann A, Kang S et al. Effectiveness of catheter ablation for coexisting atrial fibrillation and atrial flutter. *American Journal of Cardiology.* 2004;94(5):666–668.

353 Oral H, Knight BP, Tada H et al. Pulmonary vein isolation for paroxysmal and persistent atrial fibrillation. *Circulation.* 2002;105(9):1077–1081.

354 Adragao P, Cavaco D., Reis SK et al. Percutaneous ablation of atrial fibrillation: assessment of outcomes at 1-year follow-up. *Revista Portuguesa de Cardiologia.* 2003;22(11):1301–1308.

355 Chen MS, Marrouche NF, Khaykin Y et al. Pulmonary vein isolation for the treatment of atrial fibrillation in patients with impaired systolic function. *Journal of the American College of Cardiology.* 2004;43(6):1004–1009.

356 Levy T, Walker S, Rochelle J et al. Evaluation of biatrial pacing, right atrial pacing, and no pacing in patients with drug refractory atrial fibrillation. *American Journal of Cardiology.* 1999;84(4):426–429.

357 Fragakis N, Shakespeare CF, Lloyd G et al. Reversion and maintenance of sinus rhythm in patients with permanent atrial fibrillation by internal cardioversion followed by biatrial pacing. *Pacing and Clinical Electrophysiology.* 2002;25(3):278–286.

358 Kawaguchi AT, Kosakai Y, Sasako Y et al. Risks and benefits of combined maze procedure for atrial fibrillation associated with organic heart disease. *Journal of the American College of Cardiology.* 1996;28(4):985–990.

359 Guang Y, Zhen–jie C, Yong LW et al. Evaluation of clinical treatment of atrial fibrillation associated with rheumatic mitral valve disease by radiofrequency ablation. *European Journal of Cardio-Thoracic Surgery.* 2002;21(2):249–254.

360 Handa N, Schaff HV, Morris JJ et al. Outcome of valve repair and the Cox maze procedure for mitral regurgitation and associated atrial fibrillation. *Journal of Thoracic & Cardiovascular Surgery.* 1999;118(4):628–635.

361 Akpinar B, Guden M, Sagbas E et al. Combined radiofrequency modified maze and mitral valve procedure through a port access approach: early and mid-term results. *European Journal of Cardio-Thoracic Surgery.* 2003;24(2):223–230.

362 Jessurun ER, van Hemel NM, Defauw JJ et al. A randomized study of combining maze surgery for atrial fibrillation with mitral valve surgery. *Journal of Cardiovascular Surgery.* 2003;44(1):9–18.

363 Deneke T, Khargi K, Grewe PH et al. Efficacy of an additional maze procedure using cooled-tip radiofrequency ablation in patients with chronic atrial fibrillation and mitral valve disease. A randomized, prospective trial. *European Heart Journal.* 2002;23(7):558–566.

364 Khargi K, Deneke T, Haardt H et al. Saline-irrigated, cooled-tip radiofrequency ablation is an effective technique to perform the maze procedure. *Annals of Thoracic Surgery.* 2001;72(3):1090–1095.

365 Velimirovic DB, Petrovic P, Djukic P et al. Corridor procedure – surgical option for treatment of chronic atrial fibrillation in patients undergoing mitral valve replacement. *Cardiovascular Surgery.* 1997;5(3):320–327.

366 Isobe N, Taniguchi K, Oshima S et al. Factors predicting success in cryoablation of the pulmonary veins in patients with chronic atrial fibrillation. *Circulation Journal.* 2004;68(11):999–1003.

367 Kawaguchi AT, Kosakai Y, Isobe F et al. Surgical stratification of patients with atrial fibrillation secondary to organic cardiac lesions. *European Journal of Cardio-Thoracic Surgery.* 1996;10(11):983–989.

368 Kamata J, Kawazoe K, Izumoto H et al. Predictors of sinus rhythm restoration after Cox maze procedure concomitant with other cardiac operations. *Annals of Thoracic Surgery.* 1997;64(2):394–398.

369 Choo SJ, Park NH, Lee SK et al. Excellent results for atrial fibrillation surgery in the presence of giant left atrium and mitral valve disease. *European Journal of Cardio-Thoracic Surgery.* 2004;26(2):336–341.

370 Yuda S, Nakatani S, Isobe F et al. Comparative efficacy of the maze procedure for restoration of atrial contraction in patients with and without giant left atrium associated with mitral valve disease. *Journal of the American College of Cardiology.* 1998;31(5):1097–1102.

371 Geidel S, Ostermeyer J, Lass M et al. Surgical treatment of permanent atrial fibrillation during cardiac surgery using monopolar and bipolar radiofrequency ablation. *Indian Pacing & Electrophysiology Journal.* 2003;3(3):93–100.

372 Chen MC, Chang JP, Chang HW. Preoperative atrial size predicts the success of radiofrequency maze procedure for permanent atrial fibrillation in patients undergoing concomitant valvular surgery. *Chest.* 2004;125(6):2129–2134.

373 Brignole M, Gianfranchi L, Menozzi C et al. Assessment of atrioventricular junction ablation and DDDR mode-switching pacemaker versus pharmacological treatment in patients with severely symptomatic paroxysmal atrial fibrillation: a randomized controlled study. *Circulation.* 1997;96:2617–2624.

374 Ueng KC, Tsai TP, Tsai CF et al. Acute and long-term effects of atrioventricular junction ablation and VVIR pacemaker in symptomatic patients with chronic lone atrial fibrillation and normal ventricular response. *Journal of Cardiovascular Electrophysiology.* 2001;12(3):303–309.

375 Brignole M, Menozzi C, Gianfranchi L et al. Assessment of atrioventricular junction ablation and VVIR pacemaker versus pharmacological treatment in patients with heart failure and chronic atrial fibrillation: a randomized, controlled study. *Circulation.* 1998;98(10):953–960.

376 Gianfranchi L, Brignole M, Menozzi C et al. Progression of permanent atrial fibrillation after atrioventricular junction ablation and dual-chamber pacemaker implantation in patients with paroxysmal atrial tachyarrhythmias. *American Journal of Cardiology.* 1998;81(3):351–354.

377 Ricci R, Quesada A, Pignalberi C et al. Dual defibrillator improves quality of life and decreases hospitalizations in patients with drug refractory atrial fibrillation. *Journal of Interventional Cardiac Electrophysiology.* 2004;10(1):85–92.

378 Burns JL, Sears SF, Sotile R et al. Do patients accept implantable atrial defibrillation therapy? Results from the Patient Atrial Shock Survey of Acceptance and Tolerance (PASSAT) Study. *Journal of Cardiovascular Electrophysiology.* 2004;15(3):286–291.

379 Laupacis A, Albers G, Dalen J et al. Antithrombotic therapy in atrial fibrillation. *Chest.* 1998;114 (5 Suppl):579S–589S.

380 OBrien CL, Gage BF. Costs and effectiveness of ximelagatran for stroke prophylaxis in chronic atrial fibrillation. *Journal of the American Medical Association.* 2005;293(6):699–706.

Questions Set : REF20464 - Mozilla Firefox
File Edit View History Bookmarks Tools Help
http://my.onexamination.com/Assessment/Questions.aspx?id=687609&ws=true
Most Visited Getting Started Latest Headlines
Convert
Questions Set : REF20464
Shop
Help

Which of the following would be the most appropriate treatment option for this patient?

(Please select 1 option)

○	IV diamorphine 10 mg
○	Oral aspirin 600 mg
○	Oral isosorbide mononitrate 30 mg
○	Oxygen 100%
◉	Subcutaneous low molecular weight heparin ✓ Correct

The treatment approach in this patient with acute coronary syndrome is

aspirin 300 mg
try some GTN.

If this fails then

isosorbitdinitrate (ISDN) intravenously
diamorphine (or morphine) 2.5 mg
4 L oxygen and
subcutaneous low molecular weight heparin.

Next question Remove Tag Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A
Done

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 42 mins 14 secs

Work Smart Session - MRCP Part 1

Question: 31 of 100

A 67-year-old female is admitted with blackouts.

Her electrocardiogram shows ventricular escape with complete heart block. As you are standing there she blacks out once more. Her rhythm strip shows P wave asystole.

Which of the following would be the initial immediate treatment here after airway and breathing?

(Please select 1 option)

○	Adenosine 6 mg
○	Atropine 0.6 mg
○	Percussion pacing
○	Transcutaneous pacing
○	Transvenous pacing

Submit answer | Skip question | Remove Tag | Remove question

Her electrocardiogram shows ventricular escape with complete heart block. As you are standing there she blacks out once more. Her rhythm strip shows P wave asystole.

Which of the following would be the initial immediate treatment here after airway and breathing?

(Please select 1 option)

○	Adenosine 6 mg
○	Atropine 0.6 mg
◉	Percussion pacing ✓ Correct
○	Transcutaneous pacing
○	Transvenous pacing

Adenosine and atropine are not front line agents in this scenario, particularly adenosine which blocks atrioventricular (AV) conduction; minus one mark if you elected this.

Transvenous pacing is not a fast enough intervention here.

Transcutaneous pacing is the immediate management but percussion pacing may be effective as a holding measure whilst this is instituted.

(Percussion pacing involves gentle thumping of the lower left sternal edge with the fist.)

Next question

Remove Tag Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 45 mins 7 secs

Work Smart Session - MRCP Part 1

Question: 32 of 100

A 43-year-old gentleman develops chest pain seven minutes after fibre-optic bronchoscopy.

The procedure had been performed without sedation following an intratracheal injection of 5 ml 2.5% cocaine solution and xylocaine spray to the pharynx for topical anaesthesia.

ECG showed an evolving anterior myocardial infarction.

Which of the following would you prefer for his management?

(Please select 1 option)

○	Beta-blockers
○	Nitrates
○	Percutaneous transluminal coronary angioplasty
○	Thrombolysis with rt-PA
○	Thrombolysis with streptokinase

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Which of the following would you prefer for his management?

(Please select 1 option)

○	Beta-blockers
◉	Nitrates ✓ Correct
○	Percutaneous transluminal coronary angioplasty
○	Thrombolysis with rt-PA
○	Thrombolysis with streptokinase

The underlying mechanism here is vasoconstriction, not thrombosis.

Cocaine is cardiotoxic and its use has been linked to:

- coronary artery spasm
- angina
- myocardial infarction
- arrhythmias
- sudden cardiac death
- myocardial contraction bands, which might act as a substrate for arrhythmias.

It is important to avoid beta-blockers in treating cocaine-induced chest pains or acute myocardial infarctions, as this may result in unopposed 1 adrenergic action with worsening coronary spasm.

Calcium channel antagonists or nitrates should be administered as early as possible.

EN
9:10 AM
2/28/2011

Time taken: 47 mins 7 secs

Work Smart Session - MRCP Part 1

Question: 33 of 100

A 45-year-old man is admitted with central crushing chest pain, sweating and vomiting of one hour duration.

He is conscious with a pulse rate of 100 bpm and a blood pressure of 200/125 mmHg. An ECG shows >2 mm ST elevation in leads I, II, aVL and V2-6.

CBC: normal
U & E: normal
Troponin T: 100 ng/ml

Apart from the presence of xanthelasma (+) there are no other positive findings on clinical examination.

He is given oxygen, aspirin, morphine and intravenous 5 mg atenolol.

What will you do next?

(Please select 1 option)

○	CABG
○	Nitroprusside infusion
○	PTCA
○	Thrombolysis with rt-PA
○	Thrombolysis with streptokinase

Submit answer | Skip question | Tag Question | Remove question

CBC: normal
U & E: normal
Troponin T: 100 ng/ml

Apart from the presence of xanthelasma (+) there are no other positive findings on clinical examination.

He is given oxygen, aspirin, morphine and intravenous 5 mg atenolol.

What will you do next?

(Please select 1 option)

○	CABG
○	Nitroprusside infusion
◉	PTCA ✓ Correct
○	Thrombolysis with rt-PA
○	Thrombolysis with streptokinase

This is a case of acute myocardial infarction.

Typically thrombolysis should be carried out in the absence of any contraindications. BP higher than 200/120 mmHg is one of the contraindications.

So the next appropriate management in this case is urgent angioplasty for extensive anterolateral infarction.

BP control should follow suit.

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Work Smart Session - MRCP Part 1

Question: 34 of 100

A 59-year-old male has been discharged from hospital following an uncomplicated admission with myocardial infarction (MI) and treated with stenting. His therapy at discharge included aspirin 75 mg daily, ramipril 10 mg daily, atenolol 50 mg daily and simvastatin 40 mg daily.

On subsequent review, one month after discharge, he is well and unaware of any chest pain. His blood pressure is 134/78 mmHg and he has a resting heart rate of 66 bpm. There are no abnormalities on auscultation of the heart or chest.

Investigations reveal:

Cholesterol	4.6 mmol/l	(<5.2)
Triglyceride	0.8 mmol/l	(0.45-1.69)
Glucose	5.6 mmol/l	(3.0-6.0)
U&E	Normal	

Which of the following therapies added to his current treatment regime would be expected to reduce mortality still further?

(Please select 1 option)

- ○ Amlodipine
- ○ Ezetimibe
- ○ Furosemide
- ○ Omega-3 fatty acids
- ○ Vitamin E

Which of the following therapies added to his current treatment regime would be expected to reduce mortality still further?

(Please select 1 option)

○	Amlodipine
○	Ezetimibe
○	Furosemide
○	Omega-3 fatty acids ← This is the correct answer
◉	Vitamin E ✕ Incorrect answer selected

Of the agents suggested, Omega-3 fatty acids (in essence fish oils) have been demonstrated in the GISSI-prevenzione study to reduce mortality in this particular group of patients with coronary artery disease on standard treatment by a further approximate 20% for all cause mortality and 40% reduction in sudden deaths versus controls.

Vitamin E therapy was associated with no significant differences.

It appears that Omega-3 Fish oils may have a benefit beside improving lipid profile with increases in high density lipoprotein (HDL) and reductions in triglyceride, as it has been suggested that they may confer some anti-arrhythmic effect.

Short-acting calcium antagonists early after MI possibly increase mortality, and certainly have no beneficial effect.

Similarly, furosemide has no data to indicate improved outcome. Ezetimibe, which inhibits cholesterol reabsorption has no data to indicate a survival advantage.

Next question | Remove Tag | Remove question

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 53 mins 15 secs

Work Smart Session - MRCP Part 1

Question: 35 of 100

What is troponin?

(Please select 1 option)

○	A component of thick filaments
○	A component of thin filaments
○	A myosin heavy chain
○	A myosin light chain
○	A substance produced by pulmonary vascular endothelium

Submit answer | Skip question | Tag Question | Remove question

Work Smart Session - MRCP Part 1

Time taken: 55 mins 17 secs

Question: 35 of 100

What is troponin?

(Please select 1 option)

○	A component of thick filaments
◉	A component of thin filaments ✓ Correct
○	A myosin heavy chain
○	A myosin light chain
○	A substance produced by pulmonary vascular endothelium

Troponin is a component of thin filaments (along with actin and tropomyosin), and is the protein to which calcium binds to accomplish this regulation.

Troponin has three subunits, TnC, TnI, and TnT.

When calcium is bound to specific sites on TnC, the structure of the thin filament changes in such a manner that myosin (a molecular motor organised in muscle thick filaments) attaches to thin filaments and produces force and/or movement.

In the absence of calcium, tropomyosin interferes with this action of myosin, and therefore muscles remain relaxed.

Next question

Tag Question | Remove question

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 55 mins 17 secs

Work Smart Session - MRCP Part 1

Question: 36 of 100

A 29-year-old male is admitted with a one hour history of severe central chest pain associated with vomiting.

It transpires that he used cocaine three hours ago. His blood pressure is 142/74 mmHg and he has a pulse of 110 beats per minute regular. His ECG reveals 3 mm ST segment elevation in leads V2-5.

Which of the following is the most appropriate treatment for this patient?

(Please select 1 option)

○	Abciximab
○	Angiography +/- PTCA
○	Isoket infusion
○	Low molecular weight heparin
○	Tissue plasminogen activator (rtPA)

A 29-year-old male is admitted with a one hour history of severe central chest pain associated with vomiting.

It transpires that he used cocaine three hours ago. His blood pressure is 142/74 mmHg and he has a pulse of 110 beats per minute regular. His ECG reveals 3 mm ST segment elevation in leads V2-5.

Which of the following is the most appropriate treatment for this patient?

(Please select 1 option)

○	Abciximab
◉	Angiography +/- PTCA ✗ Incorrect answer selected
○	Isoket infusion ← This is the correct answer
○	Low molecular weight heparin
○	Tissue plasminogen activator (rtPA)

Cocaine is a drug of widespread abuse and remains one of the commonest causes of acute myocardial infarction (MI) in men below 35 years of age.

The aetiology of cocaine-induced MI is speculated to be related to coronary artery spasm as many patients do not have overt coronary artery disease.

Consequently guidelines suggest the use of nitrates in the first instance coupled with calcium antagonists. If there is no improvement in the clinical condition, then angiography should be considered.

Reference:
ACC Guidelines 2007, J Am Coll Cardiol 2007;50;1-157

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 56 mins 36 secs

Work Smart Session - MRCP Part 1

Question: 37 of 100

Which of the following is first to rise following myocardial infarction (MI)?

(Please select 1 option)

- CK-MB
- Creatine phosphokinase
- Lactate dehydrogenase
- Myoglobin
- Troponin I

Submit answer | Skip question | Tag Question | Remove question

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 57 mins 2 secs

Work Smart Session - MRCP Part 1

Question: 37 of 100

Which of the following is first to rise following myocardial infarction (MI)?

(Please select 1 option)

○	CK-MB
○	Creatine phosphokinase
○	Lactate dehydrogenase
◉	Myoglobin ✓ Correct
○	Troponin I

Myoglobin, is a sensitive indicator of muscle injury and is first to rise following MI within two hours but is non-specific.

Troponin and CK-MB both begin to rise approximately three hours after MI. Both are far more specific of myocardial injury.

Lactate dehydrogenase (LDH) begins to rise approximately 12 hours after MI.

Next question | Tag Question | Remove question

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 57 mins 2 secs

Work Smart Session - MRCP Part 1

Question: 38 of 100

A 65-year-old is investigated for dyspnoea and is shown to have an ejection fraction of 45% on echocardiography.

How is left ventricular ejection fraction calculated?

(Please select 1 option)

○	Cardiac output/stroke volume
○	End diastolic volume/end systolic volume
○	End diastolic volume/stroke volume
○	End systolic volume/end diastolic volume
○	Stroke volume/end diastolic volume

Submit answer | Skip question | Tag Question | Remove question

Time taken: 57 mins 53 secs

Work Smart Session - MRCP Part 1

Question: 38 of 100

A 65-year-old is investigated for dyspnoea and is shown to have an ejection fraction of 45% on echocardiography.

How is left ventricular ejection fraction calculated?

(Please select 1 option)

◉	Cardiac output/stroke volume ✕ Incorrect answer selected
○	End diastolic volume/end systolic volume
○	End diastolic volume/stroke volume
○	End systolic volume/end diastolic volume
○	Stroke volume/end diastolic volume ← This is the correct answer

The left ventricle pumps only a fraction of the blood it contains.

The ejection fraction is the amount of blood pumped (stroke volume = end diastolic volume - end systolic volume) divided by the amount of blood the ventricle contains (end diastolic volume).

A normal ejection fraction is more than 55% of the blood volume.

Next question

Remove Tag Remove question

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 57 mins 53 secs

Work Smart Session - MRCP Part 1

Question: 39 of 100

Which of the following lipid abnormalities are most likely to be detected in a patient with type 2 diabetes?

(Please select 1 option)

○	Elevated HDL concentrations
○	Elevated LDL concentrations
○	Large buoyant LDL molecules
○	Reduced triglyceride concentrations
○	Small dense LDL molecules

Submit answer | Skip question | Tag Question | Remove question

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 58 mins 41 secs

Work Smart Session - MRCP Part 1

Question: 39 of 100

Which of the following lipid abnormalities are most likely to be detected in a patient with type 2 diabetes?

(Please select 1 option)

○	Elevated HDL concentrations
○	Elevated LDL concentrations
○	Large buoyant LDL molecules
◉	Reduced triglyceride concentrations ✕ Incorrect answer selected
○	Small dense LDL molecules ← This is the correct answer

In type 2 diabetes increased cholesteryl ester transfer protein (CETP) activity results in the transfer of triglycerides from very low-density lipoprotein (VLDL) to high-density lipoprotein (HDL) and low-density lipoprotein (LDL).

This results in small dense LDL which is more atherogenic being able to be oxidised more readily and penetrate endothelium and macrophages. LDL is not typically elevated in type 2 diabetes although there are qualitative changes as indicated above. HDL is typically low in the patient with type 2 diabetes.

Next question | Remove Tag | Remove question

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 6 mins 16 secs

Question: 3 of 100

A 24-year-old woman develops infective endocarditis involving the aortic valve.

She receives a porcine bioprosthesis because of her desire to have children and not to take anticoagulant medication.

After ten years, she must have this prosthetic valve replaced.

Which of the following pathological findings in the bioprosthesis has most likely led to the need for replacement?

(Please select 1 option)

◉	Calcification with stenosis ✓ Correct
○	Dehiscence
○	Infective endocarditis
○	Strut failure
○	Thrombosis

The bioprosthesis has the advantage of not requiring anticoagulation, but it does not wear well with time, and typically must be replaced within five to 10 years.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 6 mins 16 secs

Question: 4 of 100

A 60-year-old man presents with features of left ventricular failure.

He is comfortable at rest but ordinary physical activity results in fatigue and shortness of breath.

Which of the following New York Heart Association's classifications best match the severity of this man's disease?

(Please select 1 option)

○	Normal
○	NYHA Class I
○	NYHA Class II
○	NYHA Class III
○	NYHA Class IV

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Time taken: 58 mins 41 secs

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Work Smart Session - MRCP Part 1

Question: 40 of 100

A 35-year-old female presents with chest pain on exertion.

On examination she has yellow discolouration of her palmar creases and a diagnosis of remnant hyperlipidaemia (type III hyperlipidaemia) is made.

What is the cause of this hyperlipidaemia?

(Please select 1 option)

- Apo CIII homozygosity
- Apo E-2 homozygosity
- LCAT deficiency
- LDL receptor deficiency
- Lipoprotein lipase deficiency

Submit answer | Skip question | Tag Question | Remove question

- Help

What is the cause of this hyperlipidaemia?

(Please select 1 option)

○	Apo CIII homozygosity
◉	Apo E-2 homozygosity ✓ Correct
○	LCAT deficiency
○	LDL receptor deficiency
○	Lipoprotein lipase deficiency

Remnant hyperlipidaemia is associated with

- hypercholesterolaemia
- hypertriglyceridaemia
- palmar xanthomata
- early onset of cardiovascular disease.

The genotype of the condition is apo E-2/E-2 and occurs with a frequency of 1:100.

Low density lipoprotein (LDL) receptor deficiency is associated with familial hypercholesterolaemia.

Lipoprotein lipase deficiency is rare and associated with marked hypertriglyceridaemia.

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 1 hrs 15 secs

Work Smart Session - MRCP Part 1

Question: 41 of 100

A 35-year-old shop worker presents with pain in her calves which develops after 50 yards of walking. The pain settles with rest. On examination she has yellow discolouration of her palmar creases. Her fasting lipid profile reveals:

Cholesterol	9.6mmol/l (<5)
Triglycerides	7.3mmol/l (<2)

What is the likely diagnosis?

(Please select 1 option)

- Chylomicronaemia
- Familial hypercholesterolaemia
- Hypoalphalipoproteinaemia
- Type III hyperlipidaemia
- Type IV hyperlipidaemia

Submit answer | Skip question | Tag Question | Remove question

with rest. On examination she has yellow discolouration of her palmar creases. Her fasting lipid profile reveals:

Cholesterol	9.6mmol/l (<5)
Triglycerides	7.3mmol/l (<2)

What is the likely diagnosis?

(Please select 1 option)

- Chylomicronaemia
- Familial hypercholesterolaemia
- Hypoalphalipoproteinaemia
- Type III hyperlipidaemia ✓ Correct
- Type IV hyperlipidaemia

Remnant hyperlipidaemia (Type III hyperlipidaemia) is associated with elevated fasting cholesterol (usually >7.8mmol/l) and triglyceride levels (usually >5.0mmol/l) It presents with palmar xanthomata and early onset cardiovascular disease (CHD,PVD and CVA). Hypoalphalipoproteinaemia is a rare, familial condition and is associated with low HDL. Chylomicronaemia is associated particularly with hypertriglyceridaemia and not with large elevations in cholesterol. Familial hypercholesterolaemia is due to LDL-receptor deficiency, and is not associated with elevated triglyceride levels.

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 1 hrs 2 mins 1 secs

Work Smart Session - MRCP Part 1

Question: 42 of 100

A 65-year-old man presents with a six month history of deteriorating breathlessness.

He is found to have aortic stenosis.

Which one of the following physical signs provides the best clinical marker of the severity of the valvular disease?

(Please select 1 option)

○	Character of the apex beat
○	Character of the carotid pulse
○	Character of the second heart sound
○	Intensity of the murmur
○	Length of the murmur

Submit answer | Skip question | Tag Question | Remove question

A 65-year-old man presents with a six month history of deteriorating breathlessness.

He is found to have aortic stenosis.

Which one of the following physical signs provides the best clinical marker of the severity of the valvular disease?

(Please select 1 option)

○	Character of the apex beat
○	Character of the carotid pulse
○	Character of the second heart sound
○	Intensity of the murmur
◉	Length of the murmur ✓ Correct

The apex beat in aortic stenosis is not displaced but has a heaving character, the pulse is characteristically of small volume and slow rising, the second heart sound maybe inaudible or paradoxically split.

The murmur tends to become longer as the disease is more severe because of the longer ejection time needed.

The intensity of the murmur is not a good guide to severity as this will become less as the cardiac output is reduced with more severe disease.

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 1 hrs 2 mins 43 secs

Work Smart Session - MRCP Part 1

Question: 43 of 100

A 17-year-old female presents after taking an overdose of her grandmother's medication.

Investigations revealed a serum potassium of 6 mmol/L (3.5-4.9).

Which one of the following drugs is the most likely cause of this abnormality?

(Please select 1 option)

○	Aspirin
○	Digoxin
○	Fluoxetine
○	Omeprazole
○	Propranolol

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

A 17-year-old female presents after taking an overdose of her grandmother's medication.

Investigations revealed a serum potassium of 6 mmol/L (3.5-4.9).

Which one of the following drugs is the most likely cause of this abnormality?

(Please select 1 option)

○	Aspirin
○	Digoxin
○	Fluoxetine
○	Omeprazole
◉	Propranolol ✓ Correct

Betablockers, particularly propranolol, in overdose can cause hyperkalaemia by transmembrane shifts. It is useful to think of the opposite - beta-agonists such as salbutamol are far more widely known to cause hypokalaemia.

Overdose of digoxin therapy most commonly manifests as rhythm disturbance and may be exacerbated by hyper- or hypokalaemia.

Salicylate overdose causes metabolic acidosis and respiratory alkalosis.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 1 hrs 3 mins 34 secs

Work Smart Session - MRCP Part 1

Question: 44 of 100

A 72-year-old man presented following three episodes of transient loss of consciousness not associated with chest pain. There was a previous history of an anterior myocardial infarction.

On examination his blood pressure was 140/80 mmHg and the apex beat was diffuse in character and displaced to the left. There were no neurological signs.

The ECG showed sinus rhythm with occasional ventricular extrasystoles, deep anterior Q waves and ST segment elevation in leads V2 - V6, without reciprocal depression.

Which one of the following would be the most appropriate initial course of action?

(Please select 1 option)

○	Administer tissue plasminogen activator
○	Arrange an electroencephalogram
○	Arrange immediate computerised tomography (CT) brain scan
○	Observe in the coronary care unit
○	Proceed to coronary arteriography

There were no neurological signs.

The ECG showed sinus rhythm with occasional ventricular extrasystoles, deep anterior Q waves and ST segment elevation in leads V2 - V6, without reciprocal depression.

Which one of the following would be the most appropriate initial course of action?

(Please select 1 option)

○	Administer tissue plasminogen activator
○	Arrange an electroencephalogram
○	Arrange immediate computerised tomography (CT) brain scan
◉	Observe in the coronary care unit ✓ Correct
○	Proceed to coronary arteriography

The history suggests that this man has persistent ST elevation in the anterior leads, with a previous history of anterior myocardial infarction due to left ventricular (LV) aneurysm. The blackouts are cardiac syncope due to rhythm disturbance. An ECHO would quickly support the diagnosis but, because of the risk of sudden death, observation on CCU is required.

The loss of consciousness is likely to be due to recurrent arrhythmic episodes or vertebrobasilar transient ischaemic attacks (TIAs), as a result of embolisation of an LV thrombus.

The most important investigation for this patient whom you suspect has arrhythmic episodes would be telemetry/24 hour monitoring, and hence observation on the coronary care unit (CCU) is appropriate.

Next question

Remove Tag | Remove question

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 1 hrs 5 mins 18 secs

Work Smart Session - MRCP Part 1

Question: 45 of 100

A 74-year-old man presented with intermittent chest pain at rest.

Which one of the following would most strongly suggest that the pain was due to myocardial ischaemia?

(Please select 1 option)

- Associated dyspnoea
- Coexistent claudication
- Past history of cigarette smoking
- Radiation of pain to the jaw
- Relief of pain by sublingual nitrate

Submit answer | Skip question | Tag Question | Remove question

Question: 45 of 100

A 74-year-old man presented with intermittent chest pain at rest.

Which one of the following would most strongly suggest that the pain was due to myocardial ischaemia?

(Please select 1 option)

○	Associated dyspnoea
○	Coexistent claudication
○	Past history of cigarette smoking
○	Radiation of pain to the jaw ← This is the correct answer
◉	Relief of pain by sublingual nitrate ✕ Incorrect answer selected

Nitrates may relieve the pain of oesophageal spasm, as well as that of myocardial ischaemia.

Associated dyspnoea may be due to anxiety.

Coexistent claudication suggests the presence of peripheral vascular disease.

A past history of cigarette smoking is a risk factor for the development of cardiovascular disease.

However, the most specific feature of the given options which suggests that the pain is myocardial ischaemia, is the radiation to the jaw, which is relatively specific for pain of myocardial ischaemia.

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 1 hrs 6 mins 8 secs

Work Smart Session - MRCP Part 1

Question: 46 of 100

A 55-year-old male presents with dysphagia, retrosternal discomfort and weight loss. Studies reveal achalasia.

Which of the following is most likely to provide symptomatic relief?

(Please select 1 option)

○	Buscopan
○	Diazepam
○	Nifedipine
○	Omeprazole
○	Surgical cardiomyotomy

Submit answer | Skip question | Tag Question | Remove question

Question: 46 of 100

A 55-year-old male presents with dysphagia, retrosternal discomfort and weight loss. Studies reveal achalasia.

Which of the following is most likely to provide symptomatic relief?

(Please select 1 option)

○	Buscopan
○	Diazepam
○	Nifedipine
○	Omeprazole
◉	Surgical cardiomyotomy ✓ Correct

75% cure may be expected by cardiomyotomy in achalasia. Nitrates and hydralazine can help in the short term. None of other choices help the symptoms.

Oesophageal dilatation is usually attempted before laparoscopic surgical myotomy.

Further reading:
Guidelines on oesophageal dilatation BMJ Gut 2004;53(Supplement 1):i1-i6; doi:10.1136/gut.53.suppl_1.i1

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 1 hrs 6 mins 58 secs

Work Smart Session - MRCP Part 1

Question: 47 of 100

A 74-year-old woman with longstanding hypertension and rheumatoid arthritis presented with dyspnoea.

On examination she was in atrial fibrillation and was normotensive. The jugular venous pressure (JVP) was elevated. She had bilateral pitting lower limb oedema and ascites. Her echocardiogram showed normal left ventricular systolic function and bi-atrial enlargement.

What is the most likely diagnosis?

(Please select 1 option)

- ○ Constrictive pericarditis
- ○ Hypertensive heart disease
- ○ Hypothyroidism
- ○ Lymphatic obstruction
- ○ Pulmonary fibrosis

Submit answer | Skip question | Tag Question | Remove question

(Please select 1 option)

◉	Constrictive pericarditis ✓ Correct
○	Hypertensive heart disease
○	Hypothyroidism
○	Lymphatic obstruction
○	Pulmonary fibrosis

The combination of:

- shortness of breath
- atrial fibrillation
- lower limb oedema
- ascites
- raised JVP
- bi-atrial enlargement with normal systolic ventricular function

is typical of constrictive pericarditis.

Hypertension is another cause of diastolic dysfunction but this lady is normotensive and hypertension would not create such dramatic clinical signs.

Further ECHO examination would reveal peak systolic and diastolic values decreasing with inspiration, and impaired diastolic function.

Constrictive pericarditis is associated with rheumatoid arthritis, and can be a difficult clinical diagnosis.

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 1 hrs 8 mins 53 secs

Work Smart Session - MRCP Part 1

Question: 48 of 100

A 55-year old man presented with angina pectoris.

His pain was relieved by buccal glyceryl trinitrate (GTN) 5 mg. His discharge medication was isosorbide mononitrate (ISMN) 20 mg BD.

Which factor accounts for the dose difference between these two formulations?

(Please select 1 option)

○	Absorption
○	First pass metabolism
○	Lipid solubility
○	Phase II (conjugation) metabolism
○	Plasma clearance

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Which factor accounts for the dose difference between these two formulations?

(Please select 1 option)

○	Absorption ← This is the correct answer
◉	First pass metabolism ✕ Incorrect answer selected
○	Lipid solubility
○	Phase II (conjugation) metabolism
○	Plasma clearance

Buccal GTN is quickly converted to di- and mono-nitrates which have half-lives of two hours. Its effective duration of action is 30 minutes. It is metabolised by the liver to inorganic nitrite.

ISMN is not subject to first pass metabolism in the liver. The overall half-life of isosorbide mononitrate is about five hours, and that of GTN is two hours. Thus, this would result in a reduced dose of ISMN being required if related to plasma clearance.

The sublingual route (which avoids first pass effect and the need for gastrointestinal absorption) is the preferred route for achieving therapeutic effect quickly, as GTN is absorbed efficiently by this route. However, the total dose administered by this route must be limited to avoid excessive effects.

When a much longer duration is needed, oral preparations can be given that contain a sufficient amount of drug to result in sustained systemic blood levels.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 1 hrs 10 mins 9 secs

Work Smart Session - MRCP Part 1

Question: 49 of 100

A 29-year-old female presents with acute right-sided weakness.

She has one child aged four years and had two spontaneous abortions in the past. After the birth of her child she developed a DVT and required three months' anticoagulation with warfarin.

Examination revealed a right hemiparesis. A CT head scan showed a left middle cerebral artery territory infarct.

What is the most likely finding on echocardiography?

(Please select 1 option)

○	Atrial septal defect
○	Bicuspid aortic valve
○	Left atrial myxoma
○	Normal appearances
○	Ventricular septal defect

Submit answer | Skip question | Tag Question | Remove question

She has one child aged four years and had two spontaneous abortions in the past. After the birth of her child she developed a DVT and required three months' anticoagulation with warfarin.

Examination revealed a right hemiparesis. A CT head scan showed a left middle cerebral artery territory infarct.

What is the most likely finding on echocardiography?

(Please select 1 option)

○	Atrial septal defect
○	Bicuspid aortic valve
○	Left atrial myxoma
◉	Normal appearances ✓ Correct
○	Ventricular septal defect

This patient has a prothrombotic tendency suggestive of the lupus anticoagulant with recurrent abortions, previous deep vein thrombosis (DVT) and now she has developed a left hemiparesis.

This has occurred off warfarin and it is highly unlikely to be due to any right to left transference of clot.

It is more likely to be due to spontaneous infarct related to the thrombophilia and her heart is likely to be normal.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Community
- Help
- Shop

Which of the following New York Heart Association's classifications best match the severity of this man's disease?

(Please select 1 option)

○	Normal
○	NYHA Class I
○	NYHA Class II ← This is the correct answer
◉	NYHA Class III ✕ Incorrect answer selected
○	NYHA Class IV

In 1928 the New York Heart Association published a classification of patients with cardiac disease based on clinical severity and prognosis.

This classification has been updated in seven subsequent editions of Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels (Little, Brown & Co). The ninth edition, revised by the Criteria Committee of the American Heart Association, New York City Affiliate, was released March 4, 1994.

"Class II. Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea or anginal pain."

Further reading:
Classification of Functional Capacity and Objective Assessment American Heart Association

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 7 mins 6 secs

Question: 5 of 100

A 16-year-old profoundly deaf boy on holiday in the United Kingdom from Denmark presents with recurrent episodes of syncope and is found to have a long QT interval on his ECG.

His faxed medical records indicate that he has Jervell and Lange-Nielsen syndrome.

Which of the following genes is affected in this condition?

(Please select 1 option)

○	CACNA1c gene
○	Caveolin 3 related gene
○	Human ether-à-go-go related gene (hERG)
○	KCNQ1 gene
○	SCN5A gene

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 1 hrs 10 mins 56 secs

Work Smart Session - MRCP Part 1

Question: 50 of 100

A 57-year-old female school cleaner is undergoing investigation for breathlessness.

Which of the following is NOT in keeping with a diagnosis of constrictive pericarditis?

(Please select 1 option)

○	Ascites
○	Elevated JVP with absent y descent
○	Orthopnoea
○	Peripheral oedema
○	Previous cardiac surgery

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

(Please select 1 option)

○	Ascites
○	Elevated JVP with absent y descent ← This is the correct answer
○	Orthopnoea
○	Peripheral oedema
◉	Previous cardiac surgery ✕ Incorrect answer selected

Constrictive pericarditis typically impedes late diastolic ventricular filling, which produces an elevated jugular venous pressure (JVP), with prominent x and y descent.

Pulsus paradoxus is a variable finding, unless a pericardial effusion with an abnormally elevated pressure exists.

Other signs include:

- oedema
- ascites
- hepatomegaly
- orthopnoea
- dyspnoea.

Constrictive pericarditis may be a subtle cause of dyspnoea after cardiac surgery.

Next question

Remove Tag | Remove question

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 1 hrs 11 mins 40 secs

Work Smart Session - MRCP Part 1

Question: 51 of 100

Which of the following is NOT associated with left atrial myxoma?

(Please select 1 option)

○	Adrenal hyperplasia
○	A mid systolic click
○	Left atrial dilatation
○	Sudden death
○	Systemic emboli

Submit answer | Skip question | Tag Question | Remove question

Which of the following is NOT associated with left atrial myxoma?

(Please select 1 option)

◉	Adrenal hyperplasia ✕ Incorrect answer selected
○	A mid systolic click ← This is the correct answer
○	Left atrial dilatation
○	Sudden death
○	Systemic emboli

Atrial myxoma in the heart make up 50% of primary cardiac tumours.

They are most common in the left atrium arising from a pedicle on the fossa ovalis. One third present with emboli, a third with systemic inflammation (erythrocyte sedimentation rate [ESR] elevated in 1/3) and a third are asymptomatic when detected.

They can intermittently flop through the mitral valve, and cause a mid-diastolic click (tumour plop) when they stop moving.

Elevated left atrial pressures cause dilatation. Syncope can occur due to obstruction. They are more common in women.

Carney complex is a familial multiple neoplasia and lentiginosis syndrome, associated with

- primary adrenal hypercortisolism
- lentigines and naevi of the skin
- various tumours including myxoma.

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 1 hrs 12 mins 21 secs

Work Smart Session - MRCP Part 1

Question: 52 of 100

Which of the following statements regarding B-type natriuretic peptide (BNP), is correct?

(Please select 1 option)

○	BNP augments sodium reabsorption in the kidney
○	BNP causes arterial and venous smooth muscle vasodilatation
○	BNP is synthesised predominantly in the cerebrovascular circulation
○	BNP synthesis is decreased by thyroid hormone
○	The stimulus for BNP release is increased ventricular pressure load

Submit answer | Skip question | Tag Question | Remove question

Which of the following statements regarding B-type natriuretic peptide (BNP), is correct?

(Please select 1 option)

○	BNP augments sodium reabsorption in the kidney
◉	BNP causes arterial and venous smooth muscle vasodilatation ✓ Correct
○	BNP is synthesised predominantly in the cerebrovascular circulation
○	BNP synthesis is decreased by thyroid hormone
○	The stimulus for BNP release is increased ventricular pressure load

The ventricular myocardium is the primary site of BNP synthesis.

The stimulus for BNP release is myocyte stretch, rather than transmural pressure load.

BNP synthesis is increased by thyroid hormones as well as glucocorticoids, endothelin-1, angiotensin-II and tachycardia, independent of the haemodynamic effects of these factors.

In the kidney, BNP causes increased glomerular filtration rate (GFR) and inhibition of sodium reabsorption, leading to natriuresis and diuresis.

BNP leads to reduced blood pressure, and reduced pre-load due to relaxing effects on vascular smooth muscle.

For an informative review refer to Lancet 2003;362:316-22.

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 1 hrs 13 mins 32 secs

Work Smart Session - MRCP Part 1

Question: 53 of 100

A 69-year-old woman presented with an ulcer over the left ankle, which had developed over the previous nine months. She had a history of right deep vein thrombosis (DVT) five years previously.

On examination she had a superficial slough-based ulcer, 6 cm in diameter, over the medial malleolus with no evidence of cellulitis.

Which one of the following is the most appropriate next investigation?

(Please select 1 option)

○	Ankle-brachial pressure index
○	Bacteriological swab of the ulcer
○	Bilateral lower limb arteriogram
○	Right leg venogram
○	Venous duplex ultrasound scan

Submit answer | Skip question | Tag Question | Remove question

- Help

Which one of the following is the most appropriate next investigation?

(Please select 1 option)

◉	Ankle-brachial pressure index ✓ Correct
○	Bacteriological swab of the ulcer
○	Bilateral lower limb arteriogram
○	Right leg venogram
○	Venous duplex ultrasound scan

It has been reported that venous ulcerations are the most common type of ulcer affecting the lower extremities. The probable underlying cause of venous congestion, which may promote ulceration, is venous insufficiency.

The treatment of venous ulceration is control of oedema, treating any infection, and compression. However, compressive dressings or devices should not be applied if the arterial circulation is impaired.

It is thus important to identify any arterial disease, and ankle-brachial pressure index is a simple way of doing this. One may then progress to lower limb arteriogram if indicated.

There is no clinical sign of infection, and although a bacterial swab would help to rule out pathogens within the ulcer, arterial insufficiency is the more important issue.

If there is a clinical suspicion of DVT then duplex (or rarely a venogram) is indicated to decide on the indication for warfarin.

Next question

Tag Question | Remove question

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 1 hrs 14 mins 41 secs

Work Smart Session - MRCP Part 1

Question: 54 of 100

A 70-year-old woman is referred with hypertension.

Despite lifestyle advice, her GP notes blood pressure recordings averaging 170/100 mmHg. She was commenced on an antihypertensive but one month later complains of symptoms suggestive of postural hypotension.

Which one of the following is most likely to be responsible for this side effect?

(Please select 1 option)

○	Amlodipine
○	Atenolol
○	Bendroflumethiazide
○	Doxazosin
○	Lisinopril

Submit answer | Skip question | Tag Question | Remove question

Despite lifestyle advice, her GP notes blood pressure recordings averaging 170/100 mmHg. She was commenced on an antihypertensive but one month later complains of symptoms suggestive of postural hypotension.

Which one of the following is most likely to be responsible for this side effect?

(Please select 1 option)

○	Amlodipine
○	Atenolol ← This is the correct answer
◉	Bendroflumethiazide ✕ Incorrect answer selected
○	Doxazosin
○	Lisinopril

This is an odd question, as all the agents can cause postural hypotension, but one might think that the causative agent would be an alpha-blocker. However, the evidence suggests the contrary, as amongst all the classes a beta-blocker is most associated with postural hypotension in the elderly.

So, the correct answer is a beta-blocker, yet it is a lottery to determine if the RCP would have this down as their right answer.

Other agents particularly associated with postural hypotension include the centrally acting agents, like alpha methyldopa and reserpine.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 1 hrs 24 mins 59 secs

Work Smart Session - MRCP Part 1

Question: 55 of 100

A paper describes a new diagnostic test for myocardial infarction (MI).

You want to know what proportion of patients, who are classified as not having had a myocardial infarction by the test, will actually not have had a myocardial infarction.

Which one of the following measurements would indicate this?

(Please select 1 option)

○	Accuracy
○	Negative predictive value
○	Positive predictive value
○	Sensitivity
○	Specificity

Submit answer | Skip question | Tag Question | Remove question

You want to know what proportion of patients, who are classified as not having had a myocardial infarction by the test, will actually not have had a myocardial infarction.

Which one of the following measurements would indicate this?

(Please select 1 option)

○	Accuracy
○	Negative predictive value ← This is the correct answer
○	Positive predictive value
○	Sensitivity
◉	Specificity ✕ Incorrect answer selected

The proportion of 'true negatives' not having had a MI correctly identified by this test is called the negative predictive value and refers to the number accurately identified not to have MI by the new test over the number without MI identified by the test + those wrongly identified as not having had an MI.

Specificity is the number without MI accurately predicted.

Sensitivity refers to the number correctly identified with MI by the new test.

A positive predictive value refers to the number accurately identified with MI by the test over the number accurately identified with MI + those wrongly identified with MI.

Next question

Remove Tag | Remove question

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 1 hrs 25 mins 52 secs

Work Smart Session - MRCP Part 1

Question: 56 of 100

A 60-year-old man takes atenolol for hypertension.

Which of the following side effects is he most likely to be aware of two hours after taking atenolol?

(Please select 1 option)

○	Fatigue
○	Hesitancy of micturition
○	Nausea
○	Orthostatic hypotension
○	Somnolence

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Question: 56 of 100

A 60-year-old man takes atenolol for hypertension.

Which of the following side effects is he most likely to be aware of two hours after taking atenolol?

(Please select 1 option)

◉	Fatigue ✓ Correct
○	Hesitancy of micturition
○	Nausea
○	Orthostatic hypotension
○	Somnolence

Atenolol is a water soluble beta-blocker, taken once daily and is not associated with drowsiness/sleep disturbance like the lipid -soluble beta-blockers.

It is not associated with nausea or hesitancy of micturition and would be unlikely to produce significant postural hypotension in a hypertensive subject.

However, fatigue is a frequent side effect which typically is felt two hours and beyond after taking the drug.

Next question | Tag Question | Remove question

http://my.onexamination.com/Assessment/Questions.aspx

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 1 hrs 26 mins 41 secs

Work Smart Session - MRCP Part 1

Question: 57 of 100

A 34-year-old man presented for an insurance medical. He was symptom free, but clinical examination suggested a small ventricular septal defect (VSD).

Which one of the following findings was most likely to have been present?

(Please select 1 option)

○	An early diastolic murmur
○	A short systolic murmur at the left sternal edge
○	A systolic murmur maximal at the apex
○	A systolic murmur with thrill at the left sternal edge (LSE)
○	Fixed splitting of the second heart sound

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 1 hrs 28 mins 19 secs

Work Smart Session - MRCP Part 1

Question: 57 of 100

A 34-year-old man presented for an insurance medical. He was symptom free, but clinical examination suggested a small ventricular septal defect (VSD).

Which one of the following findings was most likely to have been present?

(Please select 1 option)

○	An early diastolic murmur
◉	A short systolic murmur at the left sternal edge ✕ Incorrect answer selected
○	A systolic murmur maximal at the apex
○	A systolic murmur with thrill at the left sternal edge (LSE) ← This is the correct answer
○	Fixed splitting of the second heart sound

Typically, a small VSD generates a pansystolic murmur at the LSE accompanied by a thrill. The murmur may be heard at the apex but is usually loudest at the LSE.

Very small defects may generate an early/late systolic murmur.

Fixed splitting of the heart sounds usually accompanies atrial septal defects.

Next question

Remove Tag Remove question

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 1 hrs 28 mins 19 secs

Work Smart Session - MRCP Part 1

Question: 58 of 100

You are asked to see a patient in the intensive care unit who is short of breath and tachycardic to rule out a cardiac cause of her symptoms.

A right heart catheter reveals that the mixed venous O_2 saturation is 70%; the pulmonary capillary wedge O_2 saturation is 97%. The haemoglobin is normal and the patient is afebrile.

Which of the following is the most appropriate statement that could be applied to her features?

(Please select 1 option)

○	Her cardiac output is decreased
○	Her cardiac output is normal
○	Her heart is normal
○	She has high-output failure
○	She is in shock due to a non-cardiac cause

Submit answer | Skip question | Remove question

You are asked to see a patient in the intensive care unit who is short of breath and tachycardic to rule out a cardiac cause of her symptoms.

A right heart catheter reveals that the mixed venous O_2 saturation is 70%; the pulmonary capillary wedge O_2 saturation is 97%. The haemoglobin is normal and the patient is afebrile.

Which of the following is the most appropriate statement that could be applied to her features?

(Please select 1 option)

○	Her cardiac output is decreased
○	Her cardiac output is normal ← This is the correct answer
◉	Her heart is normal ✕ Incorrect answer selected
○	She has high-output failure
○	She is in shock due to a non-cardiac cause

The right heart and wedge catheters show normal saturations, the latter suggesting that she has good pulmonary oxygenation and so these features would argue against any failure.

Decreased or high output failure would certainly argue against shock of any sort; therefore, one cannot go as far as to say that she has a normal heart, so the best response (by a process of elimination) is that she has a normal output.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 1 hrs 30 mins 16 secs

Work Smart Session - MRCP Part 1

Question: 59 of 100

Angina due to an imbalance between O_2 supply and demand without atherosclerosis would most likely be seen in which of the following circumstances?

(Please select 1 option)

- Aortic regurgitation
- Cardiac tamponade
- Pulmonary regurgitation
- Right heart failure
- Tricuspid regurgitation

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Question: 59 of 100

Angina due to an imbalance between O_2 supply and demand without atherosclerosis would most likely be seen in which of the following circumstances?

(Please select 1 option)

◉	Aortic regurgitation ✓ Correct
○	Cardiac tamponade
○	Pulmonary regurgitation
○	Right heart failure
○	Tricuspid regurgitation

Non-atherosclerotic angina would be associated with conditions such as:

- thyrotoxicosis
- aortic regurgitation
- aortic stenosis
- hypertrophic cardiomyopathy
- anaemia

to name but a few.

Next question

Tag Question | Remove question

- Shop

(Please select 1 option)

○	CACNA1c gene
○	Caveolin 3 related gene
◉	Human ether-à-go-go related gene (hERG) ✗ Incorrect answer selected
○	KCNQ1 gene ← This is the correct answer
○	SCN5A gene

Mutations in the KCNE1 and KCNQ1 genes cause Jervell and Lange-Nielsen syndrome.

The KCNE1 and KCNQ1 genes provide instructions for making proteins that work together to form a channel across cell membranes. These channels transport positively charged potassium atoms (ions) out of cells. The movement of potassium ions through these channels is critical for maintaining the normal functions of inner ear structures and cardiac muscle.

All the other genes mentioned are associated with long QT syndromes.

The human ether-à-go-go related gene (hERG) is the gene affected by drugs that lengthen QT interval inadvertently; erythromycin, terfenadine, and ketoconazole.

Further reading:
Jervell and Lange-Nielsen syndrome Genetics Home Reference

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 8 mins 43 secs

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Question: 6 of 100

A 55-year-old man is being treated for hyperlipidaemia with atorvastatin 40 mg nocte.

He has a history of ischaemic heart disease.

His fasting lipids show:

Total cholesterol	3.8 mmol/l	(<5.2)
Triglycerides	1.3 mmol/l	(0.5-1.7)
LDL-cholesterol	1.9 mmol/l	(<2.6)
HDL-cholesterol	0.7 mmol/l	(0.7-1.7)

Which of the following changes of treatment would be expected to raise his HDL cholesterol level by the greatest amount?

(Please select 1 option)

- Add cholestyramine
- Add ezetimibe
- Add fenofibrate
- Add nicotinic acid
- Switch atorvastatin to rosuvastatin

Submit answer | Skip question | Tag Question | Remove question

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 1 hrs 36 mins 27 secs

Work Smart Session - MRCP Part 1

Question: 61 of 100

A 60-year-old man's echocardiogram shows a dilated left ventricular (LV) cavity with the remainder of the other chamber sizes normal.

Which of the following is the most likely diagnosis?

(Please select 1 option)

- Aortic regurgitation (AR)
- Aortic stenosis (AS)
- Hypertensive heart disease
- Mitral regurgitation (MR)
- Mitral stenosis (MS)

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Question: 61 of 100

A 60-year-old man's echocardiogram shows a dilated left ventricular (LV) cavity with the remainder of the other chamber sizes normal.

Which of the following is the most likely diagnosis?

(Please select 1 option)

○	Aortic regurgitation (AR) ← This is the correct answer
○	Aortic stenosis (AS)
◉	Hypertensive heart disease ✕ Incorrect answer selected
○	Mitral regurgitation (MR)
○	Mitral stenosis (MS)

No echocardiographic data are provided regarding the valves, but a volume overload as with AR would result in dilatation of the left ventricle.

MR, AS, and hypertension would have the effect of causing hypertrophy and a smaller LV cavity.

MS would have little effect on LV dimensions.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 1 hrs 37 mins 43 secs

Work Smart Session - MRCP Part 1

Question: 62 of 100

In a normal heart, the oxygen saturation of a sample of blood taken from a catheter in the pulmonary capillary wedge position should be equal to a sample from which of the following?

(Please select 1 option)

- Coronary sinus
- Femoral artery
- Pulmonary artery
- Right atrium
- Right ventricle

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Which of the following is NOT typical of acute aortic regurgitation?

(Please select 1 option)

○	Decrescendo diastolic murmur
○	Hypotension
○	Mitral valve pre-closure
○	Normal cardiac output
◉	Peripheral vasodilatation ✓ Correct

Findings that would be typical include:

- Large pulse volume
- Increased pulse pressure
- A decrescendo murmur
- A low diastolic blood pressure.

Vasoconstriction not dilatation is typically found.

Further reading:
Aortic Regurgitation eMedicine

Next question

Remove Tag Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 1 hrs 39 mins 55 secs

Work Smart Session - MRCP Part 1

Question: 64 of 100

Which of the following is true regarding the coronary circulation?

(Please select 1 option)

○	Adenosine is an important mediator of metabolic vasodilatation
○	Coronary blood flow is independent of myocardial oxygen consumption due to autoregulation
○	Coronary blood flow within a normal range of blood pressure is primarily determined by perfusion pressure
○	Increased myocardial O_2 demand is met primarily by increasing O_2 extraction
○	The vasodilatory reserve of the epicardium and endocardium is equivalent under normal physiologic conditions

Submit answer | Skip question | Tag Question | Remove question

Time taken: 1 hrs 41 mins 23 secs

Work Smart Session - MRCP Part 1

Question: 64 of 100

Which of the following is true regarding the coronary circulation?

(Please select 1 option)

○	Adenosine is an important mediator of metabolic vasodilatation ← This is the correct answer
○	Coronary blood flow is independent of myocardial oxygen consumption due to autoregulation
○	Coronary blood flow within a normal range of blood pressure is primarily determined by perfusion pressure
◉	Increased myocardial O_2 demand is met primarily by increasing O_2 extraction ✕ Incorrect answer selected
○	The vasodilatory reserve of the epicardium and endocardium is equivalent under normal physiologic conditions

Adenosine has a particularly short half life, acts on specific adenosine cell surface receptors (A1 and A2) and is inactivated by adenosine deaminase. It results in coronary vasodilatation and depression of sinus node automaticity and AVN conduction.

Coronary blood flow is dependent on myocardial oxygen consumption and is pretty independently maintained throughout the ranges of blood pressure.

Increasing O_2 demands are met by increased blood supply facilitated by vasodilatation brought about by adenosine production.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 1 hrs 41 mins 23 secs

Work Smart Session - MRCP Part 1

Question: 65 of 100

Which of the following findings is the most specific for a diagnosis of myocardial infarction?

(Please select 1 option)

○	An akinetic area of LV wall motion on ECHO
○	Elevated cardiac enzymes
○	Evolution of Q waves on ECG
○	History of severe chest pain
○	ST elevation on ECG

Submit answer | Skip question | Tag Question | Remove question

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 1 hrs 43 mins 12 secs

Work Smart Session - MRCP Part 1

Question: 65 of 100

Which of the following findings is the most specific for a diagnosis of myocardial infarction?

(Please select 1 option)

○	An akinetic area of LV wall motion on ECHO
○	Elevated cardiac enzymes
◉	Evolution of Q waves on ECG ✓ Correct
○	History of severe chest pain
○	ST elevation on ECG

Cardiac enzymes may be elevated in pulmonary embolism (PE), renal failure and raised ST segments associated with pericarditis.

Akinetic wall motion on the echo may occur with any regional disease process like amyloid, etc.

The evolution of Q waves is the most suggestive of an infarct.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 1 hrs 43 mins 12 secs

Work Smart Session - MRCP Part 1

Question: 66 of 100

In a patient presenting with aortic stenosis (AS), which of the following findings would be most helpful in establishing a diagnosis of congenital bicuspid valve as the aetiology?

(Please select 1 option)

○	Age
○	Calcified leaflets
○	Commissural fusion on ECHO
○	Negative history for rheumatic fever
○	Systolic ejection click

Submit answer | Skip question | Tag Question | Remove question

Time taken: 1 hrs 44 mins 29 secs

Work Smart Session - MRCP Part 1

Question: 66 of 100

In a patient presenting with aortic stenosis (AS), which of the following findings would be most helpful in establishing a diagnosis of congenital bicuspid valve as the aetiology?

(Please select 1 option)

○	Age
○	Calcified leaflets
◉	Commissural fusion on ECHO ✕ Incorrect answer selected
○	Negative history for rheumatic fever
○	Systolic ejection click ← This is the correct answer

Age and calcified aortic root suggest calcific aortic valvular disease.

Rheumatic AS results from fibrosis of the leaflets and fusion of the commissures.

An ejection click or ejection sound, best heard at the apex, implies that the site of the stenosis is mostly valvular and of congenital origin, that is, bicuspid valvular disease.

Next question

Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 1 hrs 44 mins 29 secs

Work Smart Session - MRCP Part 1

Question: 67 of 100

The pulmonary vascular system is different from the systemic circulation in that the pulmonary system demonstrates which of the following?

(Please select 1 option)

○	High pressures, high flow rates, highly compliant vessels
○	High pressures, high flow rates, low compliance vessels
○	Low pressures, high flow rates, high compliance vessels
○	Low pressures, low flow rates, high compliance vessels
○	Low pressures, low flow rates, low compliance vessels

Submit answer | Skip question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 1 hrs 45 mins

Work Smart Session - MRCP Part 1

Question: 67 of 100

The pulmonary vascular system is different from the systemic circulation in that the pulmonary system demonstrates which of the following?

(Please select 1 option)

○	High pressures, high flow rates, highly compliant vessels
○	High pressures, high flow rates, low compliance vessels
○	Low pressures, high flow rates, high compliance vessels
◉	Low pressures, low flow rates, high compliance vessels ✓ Correct
○	Low pressures, low flow rates, low compliance vessels

The normal pulmonary circulation is characterised by low pressures, low flow rates, high compliance vessels.

Next question

Remove Tag Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 1 hrs 45 mins

Work Smart Session - MRCP Part 1

Question: 68 of 100

A 68-year-old man has been very ill for months following the onset of chronic liver disease with hepatitis C infection.

He experiences a sudden loss of consciousness and then exhibits hemiplegia on the right. A cerebral angiogram reveals lack of perfusion in the left middle cerebral artery distribution.

What is the most likely cardiac lesion to be associated with this finding?

(Please select 1 option)

○	Acute rheumatic fever
○	Left atrial myxoma
○	Libman-Sacks endocarditis
○	Non-bacterial thrombotic endocarditis
○	Paradoxical thromboembolus

Submit answer | Skip question | Tag Question | Remove question

Work Smart Session - MRCP Part 1

Question: 68 of 100

A 68-year-old man has been very ill for months following the onset of chronic liver disease with hepatitis C infection.

He experiences a sudden loss of consciousness and then exhibits hemiplegia on the right. A cerebral angiogram reveals lack of perfusion in the left middle cerebral artery distribution.

What is the most likely cardiac lesion to be associated with this finding?

(Please select 1 option)

○	Acute rheumatic fever
○	Left atrial myxoma
○	Libman-Sacks endocarditis
◉	Non-bacterial thrombotic endocarditis ✓ Correct
○	Paradoxical thromboembolus

Marantic endocarditis has platelet-fibrin thrombi that are prone to embolising.

This form of non-infective endocarditis can be seen in persons who are very debilitated or who have a hypercoagulable state.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 1 hrs 46 mins 36 secs

Work Smart Session - MRCP Part 1

Question: 69 of 100

A 35-year-old healthy woman has a faint systolic murmur on physical examination. An echocardiogram is performed, and she is found to have a bicuspid aortic valve.

In explaining the meaning of this finding to her, which is the most appropriate statement?

(Please select 1 option)

○	An aortic valve replacement is eventually likely to be required
○	Other family members are likely to have the same condition
○	She should be treated with a cholesterol-lowering agent
○	The problem has resulted from past injection drug usage
○	This is one manifestation of an underlying autoimmune disease process

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

A 35-year-old healthy woman has a faint systolic murmur on physical examination. An echocardiogram is performed, and she is found to have a bicuspid aortic valve.

In explaining the meaning of this finding to her, which is the most appropriate statement?

(Please select 1 option)

◉	An aortic valve replacement is eventually likely to be required ✓ Correct
○	Other family members are likely to have the same condition
○	She should be treated with a cholesterol-lowering agent
○	The problem has resulted from past injection drug usage
○	This is one manifestation of an underlying autoimmune disease process

Bicuspid aortic valve (BAV) is perhaps the most common form of congenital heart disease in adults (1-2% of population).

Bicuspid valves have a propensity to wear out and calcify with ageing. Bicuspid aortic valve tends to be sporadic although there is a reported familial incidence of approximately 9%.

From a review of several sources in the literature, the Aeromedical Consultation Service (ACS) at Brooks AFB calculated a 1.2% per year incidence of aortic valve surgery in individuals with BAV, although the vast majority occur in the fifth and sixth decades of life.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Shop

Triglycerides	1.3 mmol/l	(0.5-1.7)
LDL-cholesterol	1.9 mmol/l	(<2.6)
HDL-cholesterol	0.7 mmol/l	(0.7-1.7)

Which of the following changes of treatment would be expected to raise his HDL cholesterol level by the greatest amount?

(Please select 1 option)

- Add cholestyramine
- Add ezetimibe ✕ Incorrect answer selected
- Add fenofibrate
- Add nicotinic acid ← This is the correct answer
- Switch atorvastatin to rosuvastatin

Nicotinic acid is highly effective at raising high density lipoprotein (HDL) cholesterol but it is often poorly tolerated. Sustained release versions are less likely to induce flushing.

"Nicotinic acid is the most powerful HDL-cholesterol raising agent currently available, and a combination of this agent with a statin facilitates simultaneous control of both HDL-cholesterol and LDL-cholesterol." European Heart Journal Supplements, 2006, Volume 8, Suppl F, pages F23-F29

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 10 mins 20 secs

Question: 7 of 100

A 65-year-old man presented with chest pain and was found to have ST elevation in leads II, III and aVF.

He was thrombolysed and has been stable on coronary care. On the third day of admission he becomes confused and agitated, and on reviewing the history it becomes apparent that he was a heavy alcohol drinker before admission taking 80 units of alcohol per week.

Which of the following management options would be most helpful in this situation?

(Please select 1 option)

- ○ CT brain scan
- ○ Diazepam
- ○ Haloperidol
- ○ Psychiatric referral
- ○ Thiamine

Submit answer | Skip question | Tag Question | Remove question

Time taken: 1 hrs 48 mins 19 secs

Work Smart Session - MRCP Part 1

Question: 70 of 100

A 40-year-old man received an orthotopic cardiac transplant seven years ago to treat a dilated cardiomyopathy. Since that time he has been healthy, with no episodes of rejection or infection. Over the next year, however, he develops fatigue with exercise. He has worsening pedal oedema and orthopnoea.

On physical examination, his vital signs are temperature 36.3°C, pulse 78, respiratory rate 16, and BP 130/70 mm Hg. There are no murmurs, rubs, or gallops audible. Bibasilar crackles in the lungs are audible.

Which of the following conditions is most likely to account for these findings?

(Please select 1 option)

○	Angiosarcoma
◉	Coronary arteriopathy
○	Mitral valvular stenosis
○	Myocarditis
○	Pulmonary hypertension

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Question: 70 of 100

A 40-year-old man received an orthotopic cardiac transplant seven years ago to treat a dilated cardiomyopathy. Since that time he has been healthy, with no episodes of rejection or infection. Over the next year, however, he develops fatigue with exercise. He has worsening pedal oedema and orthopnoea.

On physical examination, his vital signs are temperature 36.3°C, pulse 78, respiratory rate 16, and BP 130/70 mm Hg. There are no murmurs, rubs, or gallops audible. Bibasilar crackles in the lungs are audible.

Which of the following conditions is most likely to account for these findings?

(Please select 1 option)

○	Angiosarcoma
◉	Coronary arteriopathy ✓ Correct
○	Mitral valvular stenosis
○	Myocarditis
○	Pulmonary hypertension

By five years following cardiac transplantation, nearly all patients have some degree of small coronary vascular narrowing.

Myocarditis is unlikely to be present in the absence of rejection or infection.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 1 hrs 50 mins 36 secs

Work Smart Session - MRCP Part 1

Question: 71 of 100

A 66-year-old man has developed chronic renal failure with a serum urea of 60 mmol/l (2.5-7.5) and creatinine of 650 mol/l (60-110).

Auscultation of the chest reveals a friction rub over the cardiac apex.

Which of the following types of pericarditis is he likely to have?

(Please select 1 option)

- Constrictive
- Fibrinous
- Haemorrhagic
- Purulent
- Serous

Submit answer | Skip question | Tag Question | Remove question

Question: 71 of 100

A 66-year-old man has developed chronic renal failure with a serum urea of 60 mmol/l (2.5-7.5) and creatinine of 650 mol/l (60-110).

Auscultation of the chest reveals a friction rub over the cardiac apex.

Which of the following types of pericarditis is he likely to have?

(Please select 1 option)

○	Constrictive
◉	Fibrinous ✓ Correct
○	Haemorrhagic
○	Purulent
○	Serous

The uraemia leads to exudation of fibrin onto the epicardial and pericardial surfaces.

Haemorrhagic pericarditis is more typical of tuberculosis or metastatic tumour.

Serous pericarditis is more typical of collagen vascular diseases.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 1 hrs 52 mins 2 secs

Work Smart Session - MRCP Part 1

Question: 72 of 100

A new antihypertensive drug needs to be investigated to establish its relative potency.

Which of the following techniques is most appropriate for this purpose?

(Please select 1 option)

○	Bioassay
○	Case-control study
○	Double-blind, randomised, placebo controlled study
○	Postmarketing surveillance
○	Sequential trial

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Question: 72 of 100

A new antihypertensive drug needs to be investigated to establish its relative potency.

Which of the following techniques is most appropriate for this purpose?

(Please select 1 option)

○	Bioassay ← This is the correct answer
○	Case-control study
◉	Double-blind, randomised, placebo controlled study ✕ Incorrect answer selected
○	Postmarketing surveillance
○	Sequential trial

Biological assays are designed to measure the relative potency of different preparations.

Blood pressure is highly variable and is subject to variability because of the patient's level of anxiety and the method used by the observer to measure it.

In a test of **efficacy** of an antihypertensive drug, a double-blind, randomised design would be favourable.

A sequential trial (a trial in which the data are analysed after each participant's results become available and the trial continues until a clear benefit is seen in one of the comparison groups) could also be used to assess efficacy, but there would have to be a large expected difference from placebo.

Next question

Remove Tag | Remove question

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 1 hrs 53 mins 8 secs

Work Smart Session - MRCP Part 1

Question: 73 of 100

Which one of the following statements is true about the Austin Flint murmur?

(Please select 1 option)

○	It can be distinguished from the murmur of mitral stenosis by absence of presystolic accentuation
○	It does not occur in aortic incompetence secondary to an aortitis
○	It is an early sign of aortic regurgitation (AR)
○	It is associated with a loud first heart sound.
○	It is a low frequency mid/late diastolic murmur

Submit answer | Skip question | Tag Question | Remove question

Work Smart Session - MRCP Part 1

Question: 73 of 100

Which one of the following statements is true about the Austin Flint murmur?

(Please select 1 option)

◉	It can be distinguished from the murmur of mitral stenosis by absence of presystolic accentuation ✕ Incorrect answer selected
○	It does not occur in aortic incompetence secondary to an aortitis
○	It is an early sign of aortic regurgitation (AR)
○	It is associated with a loud first heart sound.
○	It is a low frequency mid/late diastolic murmur ← This is the correct answer

The Austin Flint murmur is a low frequency mid/late diastolic murmur which may show pre-systolic accentuation and is virtually indistinguishable from that of mitral stenosis.

It is due to partial closure of the anterior leaflet of the mitral valve by the regurgitant jet.

There is no correlation between the presence of murmur and severity of AR, or aetiology.

The first heart sound is normal but in severe cases it may be absent.

Next question

Remove Tag Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 1 hrs 54 mins 18 secs

Work Smart Session - MRCP Part 1

Question: 74 of 100

A 51-year-old businessman complains of dyspnoea on exertion. He recently returned from a business trip to the USA.

He has distant heart sounds on auscultation of the chest. A chest radiograph reveals that there is a thin rim of calcification surrounding the cardiac outline.

Which of the following conditions is most likely responsible for these findings?

(Please select 1 option)

- ○ Group B coxsackie virus
- ○ Metastatic carcinoma
- ○ Sarcoidosis
- ○ Tuberculosis
- ○ Uraemia

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

He has distant heart sounds on auscultation of the chest. A chest radiograph reveals that there is a thin rim of calcification surrounding the cardiac outline.

Which of the following conditions is most likely responsible for these findings?

(Please select 1 option)

○	Group B coxsackie virus
○	Metastatic carcinoma
○	Sarcoidosis
◉	Tuberculosis ✓ Correct
○	Uraemia

The most likely diagnosis is a constrictive pericarditis.

The most probable cause for this is prior tuberculous (TB) infection which may have occurred many years previously. Acute TB would usually cause a constrictive pericarditis secondary to a pericardial effusion, but is not normally associated with calcification.

Uraemia can cause a constrictive pericarditis, as can a pericardial malignancy and coxsackie virus (secondary to a pericarditis), but calcification would be unusual.

Sarcoid can cause both pericardial as well as restrictive cardiomyopathy but calcification would be unusual.

○	10
○	13 ← This is the correct answer
◉	15 ✕ Incorrect answer selected
○	20
○	23
○	12

This is a question concerning number needed to treat (NNT). The calculation involves a little arithmetic.

The absolute risk of MI in the group is a pretty high 10%, that is, of 1000 patients on placebo 100 will have MI over five years.

The relative risk reduction is stated as 0.8, that is, 80%.

Therefore, if you treat 1000 patients for five years with the cholesterol lowering agent you will get only 20 MIs.

Thus, for 1000 patients treated you will get 80 fewer MIs.

Thus number needed to treat to get one fewer MI is 1000/80 = 12.5.

Or, if you are any good at remembering formulae you can remember the following:

1. Relative risk reduction (RRR) = Absolute risk reduction (ARR) / Control event rate (CER)

2. Numbers needed to treat (NNT) = 1 / Absolute risk reduction (ARR)

You can then just insert the figures into these formulae.

The control (or placebo) event rate (CER) is 10% or 0.10. The relative risk reduction is 0.80.

Inserting these figures into the above formulae.... RRR = ARR / CER 0.80 = ARR / 0.10 ARR = 0.80 * 0.10 = 0.08. Then the NNT can be calculated by NNT = 1 / ARR = 1 / 0.08 = 12.5.

The absolute risk of MI in the group is a pretty high 10%, that is, of 1000 patients on placebo 100 will have MI over five years.

The relative risk reduction is stated as 0.8, that is, 80%.

Therefore, if you treat 1000 patients for five years with the cholesterol lowering agent you will get only 20 MIs.

Thus, for 1000 patients treated you will get 80 fewer MIs.

Thus number needed to treat to get one fewer MI is 1000/80 = 12.5.

Or, if you are any good at remembering formulae you can remember the following:

1. Relative risk reduction (RRR) = Absolute risk reduction (ARR) / Control event rate (CER)

2. Numbers needed to treat (NNT) = 1 / Absolute risk reduction (ARR)

You can then just insert the figures into these formulae.

The control (or placebo) event rate (CER) is 10% or 0.10. The relative risk reduction is 0.80.

Inserting these figures into the above formulae…. RRR = ARR / CER 0.80 = ARR / 0.10 ARR = 0.80 * 0.10 = 0.08. Then the NNT can be calculated by NNT = 1 / ARR = 1 / 0.08 = 12.5.

However, if algebra is not your thing you could try working with real numbers.

Imagine a group of 100 patients (it makes the maths easier). In the control (or placebo group) 10% (or 10 patients) suffered an MI. The relative risk reduction is 0.8 or 80%.

Therefore, in the treatment group, there would be a reduction in events by 80% (of 10 patients) = 8 patients. The number of patients suffering an MI in the treatment would therefore be 10 - 8 = 2 patients.

It can therefore be said that treating 100 patients with the new drug would result in eight fewer MIs.

The number needed to treat to prevent one MI would be 100/8 = 12.5 patients.

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 2 hrs 52 secs

Work Smart Session - MRCP Part 1

Question: 76 of 100

A 55-year-old man with type 2 diabetes mellitus and ischaemic heart disease has been researching the internet!

He asks your opinion on laser transmyocardial revascularisation.

Which of the following statements about this technique is true?

(Please select 1 option)

- Avoids the need for major surgery
- Damages the endocardium
- Involves destruction of coronary stenoses
- Is of particular use in severe proximal coronary artery disease
- Stimulates collateral vessel formation

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Question: 76 of 100

A 55-year-old man with type 2 diabetes mellitus and ischaemic heart disease has been researching the internet!

He asks your opinion on laser transmyocardial revascularisation.

Which of the following statements about this technique is true?

(Please select 1 option)

○	Avoids the need for major surgery
◉	Damages the endocardium ✓ Correct
○	Involves destruction of coronary stenoses
○	Is of particular use in severe proximal coronary artery disease
○	Stimulates collateral vessel formation

Open chest surgery is undertaken, during which laser holes are punched from the epicardial surface into areas of suspected ischaemic or hibernating ventricular muscle. The process is not fully understood.

The epicardial end of the hole heals up leaving artificial channels communicating with the ventricular chamber and effectively forming new coronary vessels.

Laser transmyocardial revascularisation has potential in distal disease such as in diabetes.

Angioplasty and coronary artery bypass graft (CABG) are useful in proximal disease.

Further reading:
Laser Percutaneous Myocardial Revascularisation: A Treatment in Genesis Bombay Hospital Journal

Time taken: 2 hrs 4 mins 55 secs

Work Smart Session - MRCP Part 1

Question: 77 of 100

Which of the following statements is true of coronary artery anatomy?

(Please select 1 option)

○	Right bundle branch block in acute anterior myocardial infarction suggests obstruction prior to the first septal branch of the left anterior descending coronary artery
○	The AV node is supplied by the left anterior descending coronary artery
○	The left main stem is about 4 cm long
○	The posterior descending artery is usually a branch of the circumflex artery
○	The sinus node is supplied by a branch of the right coronary in over 90% of subjects

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 2 hrs 6 mins 39 secs

Work Smart Session - MRCP Part 1

Question: 78 of 100

Which of the following compounds has a vasodilating effect?

(Please select 1 option)

- Antidiuretic hormone (ADH)
- Calcitonin gene related peptide
- Endothelin
- Renin
- Somatostatin

Submit answer | Skip question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 2 hrs 7 mins 14 secs

Work Smart Session - MRCP Part 1

Question: 78 of 100

Which of the following compounds has a vasodilating effect?

(Please select 1 option)

○	Antidiuretic hormone (ADH)
◉	Calcitonin gene related peptide ✓ Correct
○	Endothelin
○	Renin
○	Somatostatin

ADH acts on the vasopressor receptors to cause vasoconstriction.

Endothelin is also a vasoconstrictor as is renin.

Somatostatin is also recognised to produce vasoconstriction of the splanchnic system.

Next question Remove Tag Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 2 hrs 7 mins 14 secs

Work Smart Session - MRCP Part 1

Question: 79 of 100

A 14-year-old boy presents with fever.

Which of the following might contribute to a diagnosis of rheumatic fever?

(Please select 1 option)

○	A CRP of 10
○	A prolonged PR interval on ECG
○	Finding target lesions on the hands
○	Finding tender nodules in the fingertips
○	Positive Romberg's sign

Submit answer | Skip question | Tag Question | Remove question

- Help

○	A CRP of 10
◉	A prolonged PR interval on ECG ✓ Correct
○	Finding target lesions on the hands
○	Finding tender nodules in the fingertips
○	Positive Romberg's sign

The modified Jones criteria include:

- Finding of preceding streptococcal infection (recent scarlet fever, raised ASOT or other streptococcal antibodies)
- Positive throat swab for Group A *Strep*.

Plus:

(a) Major Criteria:

- Carditis
- Polyarthritis
- Chorea
- Subcutaneous nodules
- Erythema marginatum.

(b) Minor Criteria:

- Fever
- Arthralgia
- Previous history of rheumatic fever

- Erythema marginatum.

(b) Minor Criteria:

- Fever
- Arthralgia
- Previous history of rheumatic fever
- Elevated acute phase reactions
- Prolonged PR interval.

Erythema marginatum involves red circular lesions which gradually enlarge with central clearing.

Sydenham's chorea consists of choreoathetoid movements with increased clumsiness, for example, deteriorating handwriting. This is often associated with emotional lability.

Target lesions suggest erythema multiforme.

A C-reactive protein (CRP) of 10 is not elevated much beyond the normal range.

Erythema marginatum initially manifests as non-specific pink macules seen over the trunk, with later blanching in the middle of the lesions and sometimes fusing of the borders resulting in a serpiginous (serpent-like) looking lesion. The rash is worsened with heat, but is characteristically evanescent. It does not itch, and can be mistaken for the rash of Lyme disease.

Sub-cutaneous nodules are pea-sized, firm and non-tender. There is no associated inflammation and they are characteristically seen on the extensor surfaces of joints such as knees and elbows and also over the spine.

© 2002 Dr Colin Melville

- Help
- Shop

Which of the following management options would be most helpful in this situation?

(Please select 1 option)

○	CT brain scan
◉	Diazepam ✓ Correct
○	Haloperidol
○	Psychiatric referral
○	Thiamine

This man is withdrawing from alcohol and this is associated with anxiety and tachycardia which is the last thing that someone who has just had a myocardial infarction (MI) should suffer from. Also there is a risk of seizure.

Benzodiazepines are the first line of treatment for withdrawal.

Thiamine is also indicated in chronic alcoholism but is not as immediately important as diazepam.

A psychiatric referral may be necessary if his symptoms prove difficult to control but usually the psychiatry team would not be keen to intervene in what is really a medical emergency; they often advise on other strategies for sedation however.

This is unlikely to be an intracerebral bleed from thrombolysis on the third day but a computerised tomography (CT) scan may be indicated if there are focal neurological signs.

Haloperidol is best avoided because of the risk of causing hypotension.

Work Smart Session - MRCP Part 1

Time taken: 11 mins 32 secs

Question: 8 of 100

A 60-year-old man presented with a rash over his forearms, shins and face when he visited cardiology clinic in the summer.

Which of the following medications is the most likely to be associated with this photosensitive rash?

(Please select 1 option)

○	Atenolol
○	Bendroflumethiazide
○	Clopidogrel
○	Digoxin
○	Ezetimibe

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 2 hrs 7 mins 40 secs

Work Smart Session - MRCP Part 1

Question: 80 of 100

A 14-year-old boy presents with hypertension.

Which of the following statements concerning hypertension in the young is true?

(Please select 1 option)

○	Abnormalities are frequently seen on DMSA scan
○	Aortic coarctation is the commonest secondary cause
○	Headache is the usual presenting feature
○	It is defined as systolic blood pressure above the 99th centile for age
○	Sodium nitroprusside is useful for the long-term treatment of severe cases

Submit answer | Skip question | Tag Question | Remove question

A 14-year-old boy presents with hypertension.

Which of the following statements concerning hypertension in the young is true?

(Please select 1 option)

◉	Abnormalities are frequently seen on DMSA scan ✓ Correct
○	Aortic coarctation is the commonest secondary cause
○	Headache is the usual presenting feature
○	It is defined as systolic blood pressure above the 99th centile for age
○	Sodium nitroprusside is useful for the long-term treatment of severe cases

Sodium nitroprusside is useful only in the short term, as cyanide levels accumulate with time.

Hypertension is usually diagnosed incidentally, and is defined as systolic blood pressure greater than the 95th centile for age.

Secondary causes are usually due to renal abnormalities, with reflux-associated scarring being the commonest renal disease. This will cause abnormalities on dimercaptosuccinic acid (DMSA) scan.

Coarctation of the aorta is the commonest non-renal cause, with pheochromocytoma/neuroblastoma, congenital adrenal hyperplasia, Cushing's syndrome and steroid therapy being rarer causes.

© 2002 Colin Melville

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 2 hrs 8 mins 30 secs

Work Smart Session - MRCP Part 1

Question: 81 of 100

Which one of the following is a recognised feature of abetalipoproteinaemia?

(Please select 1 option)

- Abnormal red blood cell morphology
- Advanced atherosclerotic vascular disease
- A high serum cholesterol
- Palmar xanthomas
- Severe mental retardation

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 2 hrs 9 mins 2 secs

Work Smart Session - MRCP Part 1

Question: 81 of 100

Which one of the following is a recognised feature of abetalipoproteinaemia?

(Please select 1 option)

◉	Abnormal red blood cell morphology ✓ Correct
○	Advanced atherosclerotic vascular disease
○	A high serum cholesterol
○	Palmar xanthomas
○	Severe mental retardation

Acanthocytes and retinitis pigmentosa are seen in abetalipoproteinaemia.

Neurodegenerative changes are seen, such as ataxia, but IQ is normal.

Next question

Tag Question Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 2 hrs 9 mins 2 secs

Work Smart Session - MRCP Part 1

Question: 82 of 100

Which of the following concerning the use of intravenous bicarbonate in cardiorespiratory arrest is correct?

(Please select 1 option)

○	Exacerbates intracellular acidosis
○	Has a positive inotropic effect on ischaemic myocardium
○	Improves oxygen release to the tissues
○	Increases cerebral blood flow
○	Reduces pre-existent hyperkalaemia

Submit answer | Skip question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Time taken: 2 hrs 9 mins 51 secs

Work Smart Session - MRCP Part 1

Question: 82 of 100

Which of the following concerning the use of intravenous bicarbonate in cardiorespiratory arrest is correct?

(Please select 1 option)

○	Exacerbates intracellular acidosis ← This is the correct answer
○	Has a positive inotropic effect on ischaemic myocardium
○	Improves oxygen release to the tissues
◉	Increases cerebral blood flow ✕ Incorrect answer selected
○	Reduces pre-existent hyperkalaemia

Bicarbonate therapy can increase extracellular pH only if the carbon dioxide (CO_2) produced can be removed by adequate ventilation.

Indeed, if hypercapnia occurs then as CO_2 crosses cell membranes easily, intracellular pH may decrease even further with further deterioration of cellular function.

Bicarbonate has a negative inotropic effect, reducing cerebral blood flow; it shifts the oxygen dissociation curve to the left, inhibiting oxygen release to tissues.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 2 hrs 9 mins 51 secs

Work Smart Session - MRCP Part 1

Question: 83 of 100

On auscultation of the heart of a 30-year-old female a loud first heart sound is heard.

Which of the following may be responsible for this auscultatory feature?

(Please select 1 option)

- A long preceding diastolic interval
- Atrial premature beat
- Increased pulmonary arterial pressure
- Increased systemic arterial pressure
- Rupture of a papillary muscle

Submit answer | Skip question | Tag Question | Remove question

Time taken: 2 hrs 11 mins 7 secs

Work Smart Session - MRCP Part 1

Question: 83 of 100

On auscultation of the heart of a 30-year-old female a loud first heart sound is heard.

Which of the following may be responsible for this auscultatory feature?

(Please select 1 option)

○	A long preceding diastolic interval
◉	Atrial premature beat ✓ Correct
○	Increased pulmonary arterial pressure
○	Increased systemic arterial pressure
○	Rupture of a papillary muscle

A loud first heart sound is due to abrupt closure of the mitral valve against a high left atrial pressure and may occur with shortened diastole, mitral stenosis or left-right shunts.

It can also be heard with atrial premature beats.

Mitral regurgitation (MR) occurs with papillary muscle rupture and thereby the first heart sound is soft. A2 and P2 are loud in systemic hypertension (HT) and pulmonary hypertension respectively.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 2 hrs 11 mins 7 secs

Work Smart Session - MRCP Part 1

Question: 84 of 100

A 26-year-old man is noted to have cyanosis of the lower limbs and clubbing of the toes but not the fingers.

Which of the following statements is true?

(Please select 1 option)

○	He has coarctation of the aorta
○	He has Eisenmenger's syndrome
○	He has had a Blalock shunt operation
○	He is likely to have a loud continuous 'machinery' murmur below the left clavicle
○	He is likely to need urgent surgery

Submit answer | Skip question | Remove Tag | Remove question

Which of the following statements is true?

(Please select 1 option)

○	He has coarctation of the aorta
◉	He has Eisenmenger's syndrome ✓ Correct
○	He has had a Blalock shunt operation
○	He is likely to have a loud continuous 'machinery' murmur below the left clavicle
○	He is likely to need urgent surgery

This is the differential cyanosis of a reversed patent ductus arteriosus (PDA). There is a right-left shunt from the pulmonary artery to the aorta just distal to the left subclavian artery.

Coarctation causes radiofemoral delay. It may be associated with PDA but there is no suggestion in this patient.

Continuous machinery murmur is the classic murmur of PDA but when the shunt reverses (as in patients with a large PDA and/or pulmonary disease) the murmur becomes softer and shorter.

When Eisenmenger's syndrome has developed surgery is associated with a very high mortality.

A Blalock shunt (anastomosis of subclavian artery to pulmonary artery) used to be performed for Fallot's tetralogy and leads to a weak left radial pulse.

Next question

Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 2 hrs 12 mins

Work Smart Session - MRCP Part 1

Question: 85 of 100

Which of the following statements concerning the treatment of acute myocardial infarction (MI) is correct?

(Please select 1 option)

○	A pansystolic murmur developing within the first 24 hours does not require further investigation
○	Dipyridamole therapy reduces reinfarction within the first year
○	Heparin is beneficial if given with streptokinase
○	Prophylactic lidocaine given in the first 48 hours is effective in preventing ventricular fibrillation
○	Treatment with a dihydropyridine calcium antagonist is associated with increased cardiovascular mortality

Submit answer | Skip question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 2 hrs 13 mins 10 secs

Work Smart Session - MRCP Part 1

Question: 85 of 100

Which of the following statements concerning the treatment of acute myocardial infarction (MI) is correct?

(Please select 1 option)

○	A pansystolic murmur developing within the first 24 hours does not require further investigation
○	Dipyridamole therapy reduces reinfarction within the first year
○	Heparin is beneficial if given with streptokinase
○	Prophylactic lidocaine given in the first 48 hours is effective in preventing ventricular fibrillation
◉	Treatment with a dihydropyridine calcium antagonist is associated with increased cardiovascular mortality ✓ Correct

GISSI II revealed no survival advantage of heparin plus streptokinase in acute MI compared with streptokinase alone.

ISIS II revealed that dihydropyridine calcium antagonists were associated with increased cardiovascular risk after MI.

Dipyridamole does not reduce risk.

A newly discovered pansystolic murmur may signify acquired mitral regurgitation (MR) or ventricular septal defect (VSD).

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Time taken: 2 hrs 13 mins 10 secs

Work Smart Session - MRCP Part 1

Question: 86 of 100

An 80-year-old man presents with an inferior MI and receives thrombolysis.

Four hours following initial presentation he becomes acutely breathless.

His ECG demonstrates sinus tachycardia (rate 108 bpm) with T wave inversion inferiorly. His ST segments are normal.

On examination his JVP is elevated at 5 cm. Chest was clear to auscultation.

Following the administration of 80 mg furosemide he deteriorates.

His BP is now 80/60 mmHg and his urine output over the last two hours is 5 mls.

What is the best investigative measure?

(Please select 1 option)

○	Arterial blood gases
○	Central venous pressure (CVP) monitoring
○	Chest x ray
○	Echocardiography
○	Pulmonary capillary wedge pressure monitoring

Submit answer | Skip question | Tag Question | Remove question

His BP is now 80/60 mmHg and his urine output over the last two hours is 5 mls.

What is the best investigative measure?

(Please select 1 option)

○	Arterial blood gases
○	Central venous pressure (CVP) monitoring
○	Chest x ray
◉	Echocardiography ✕ Incorrect answer selected
○	Pulmonary capillary wedge pressure monitoring ← This is the correct answer

The scenario is that of a right ventricular myocardial infarction (MI).

The treatment in this situation is to give fluid in order to increase left ventricular end-diastolic pressure (LVEDP).

Furosemide will only worsen the situation.

The best way to determine if adequate fluid is being given is using a Swan-Ganz catheter to monitor pulmonary capillary wedge pressure ([PCWP], a surrogate for left atrial pressure).

CVP is increased in LV failure due to the infarct, so monitoring it would not help to guide treatment.

Echocardiography would show a small volume LV with a dilated right ventricle (RV).

Next question

Remove Tag Remove question

http://my.onexamination.com/Assessment/Questions.aspx

© 2011 BMJ Publishing Group Ltd. All rights reserved. Terms and conditions Privacy policy A A A

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 2 hrs 16 mins 40 secs

Work Smart Session - MRCP Part 1

Question: 87 of 100

A 21-year-old man with hypertrophic cardiomyopathy presents in clinic with dizzy spells but has not had any syncopal episodes.

Which of the following, if present, would indicate an increased risk of sudden cardiac death?

(Please select 1 option)

○	Asymmetric septal hypertrophy with maximum wall thickness of 2.1 cm
○	Blood pressure drop of 20 mmHg during peak exercise tolerance testing
○	Left ventricular outflow tract gradient of 80 mmHg
○	Systolic anterior movement of the mitral valve on echocardiography
○	Worsening exertional angina

Submit answer | Skip question | Tag Question | Remove question

(Please select 1 option)

○	Asymmetric septal hypertrophy with maximum wall thickness of 2.1 cm
◉	Blood pressure drop of 20 mmHg during peak exercise tolerance testing ✓ Correct
○	Left ventricular outflow tract gradient of 80 mmHg
○	Systolic anterior movement of the mitral valve on echocardiography
○	Worsening exertional angina

Patients with hypertrophic cardiomyopathy (HCM) are at increased risk of sudden cardiac death due to ventricular fibrillation/tachycardia (VF/VT).

The five poor prognostic markers which are predictive of sudden cardiac death are:

1. Syncope
2. Family history of HCM and sudden cardiac death
3. Maximum left ventricular wall thickness greater than 3 cm
4. Blood pressure drop during peak exercise on stress testing
5. Documented runs of non-sustained VT on 24 hour tape.

Left ventricular outflow tract (LVOT) obstruction causes symptoms and can lead to deterioration of LV function but does not predict sudden cardiac death.

Asymmetric septal hypertrophy is a feature of HCM; in order to assess the risk for sudden cardiac death a detailed echocardiogram with measurements of the maximum left ventricular wall thickness is required.

Systolic anterior movement of the mitral valve is often seen on echocardiogram and is thought to be the mechanism behind the left ventricular outflow tract obstruction.

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 2 hrs 18 mins 22 secs

Work Smart Session - MRCP Part 1

Question: 88 of 100

A 75-year-old man with a history of anterior MI is taking amiodarone 400 mg/day for history of VT. He has a prolonged QT interval on his ECG.

What is the most appropriate management?

(Please select 1 option)

- Admit to hospital for monitoring
- Atenolol
- Change amiodarone to flecainide
- Continue with amiodarone
- Discontinue amiodarone immediately

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Time taken: 2 hrs 20 mins 5 secs

Work Smart Session - MRCP Part 1

Question: 88 of 100

A 75-year-old man with a history of anterior MI is taking amiodarone 400 mg/day for history of VT. He has a prolonged QT interval on his ECG.

What is the most appropriate management?

(Please select 1 option)

○	Admit to hospital for monitoring
◉	Atenolol ✕ Incorrect answer selected
○	Change amiodarone to flecainide
○	Continue with amiodarone
○	Discontinue amiodarone immediately ← This is the correct answer

In iatrogenic long QT, which is what this is likely to be, it is safer to stop the offending drug rather than add further drugs on board (for example, beta-blockers even though atenolol is used for long QT).

Flecainide is clearly contraindicated in this situation (CAST study).

Next question

Remove Tag Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 2 hrs 20 mins 5 secs

Work Smart Session - MRCP Part 1

Question: 89 of 100

A 60-year-old man had a myocardial infarction (MI) six weeks ago.

He is taking aspirin 75 mg/day and metoprolol 50 mg 2/day.

During a routine follow-up exercise test he has a 20 beat run of non-sustained VT. He achieved stage 4 of the Bruce protocol and 92% of his target heart rate. The non-sustained VT occurred halfway through stage 2. ST segments were normal during the study.

What is the definitive investigation?

(Please select 1 option)

○	Coronary angiography
○	Echocardiogram
○	Electrophysiological study (EPS)
○	Thallium exercise scan
○	24 hour Holter monitor

Submit answer | Skip question | Tag Question | Remove question

○	Coronary angiography
○	Echocardiogram
◉	Electrophysiological study (EPS) ✓ Correct
○	Thallium exercise scan
○	24 hour Holter monitor

Post MI ventricular tachycardia (VT) is most commonly due to scar tissue. It may also be related to ischaemia, but no signs of ischaemia were induced.

The definitive investigation would be EPS due to the fact that if this were scar-related VT the site could be localised and even possibly ablated. If not, then an implantable cardio-defibrillator (ICD) implantation may be warranted on MADIT criteria, if left ventricular (LV) dysfunction exists.

Angiography plus thallium may inform us of significant coronary artery disease (CAD) but not offer us a solution to the problem.

An echocardiogram would not be of much use apart from assessing LV function, although in this patient one might assume that LV function is pretty good achieving stage 4 of Bruce protocol, thus an echocardiogram, although required, would not be the definitive test and would be down on the selection list.

There is no need for Holter as the VT has already been recorded.

The reference for MADIT is AmJCardiol 1997;79 (suppl 6A):16-7. It was stopped early in 1996 by the steering committee due to extremely positive results in the ICD group. As a consequence it was only published in abstract form. However, MADIT-2 published in the NEJM (Ref: N Engl J Med 2002; 346:877-883, Mar 21, 2002) showed a 5.6% 20 month absolute survival benefit in patients with LV dysfunction (EF<30%), post MI, treated prophylactically with an ICD.

Work Smart Session - MRCP Part 1

Time taken: 12 mins 21 secs

Question: 8 of 100

A 60-year-old man presented with a rash over his forearms, shins and face when he visited cardiology clinic in the summer.

Which of the following medications is the most likely to be associated with this photosensitive rash?

(Please select 1 option)

○	Atenolol
◉	Bendroflumethiazide ✓ Correct
○	Clopidogrel
○	Digoxin
○	Ezetimibe

Photosensitivity is a common adverse effect and the cardiology drugs affected include amiodarone and thiazide diuretics.

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin 2 receptor blockers (A2RBs) commonly cause rashes some of which appear to be photosensitive.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 12 mins 21 secs

Question: 9 of 100

Which of the following mechanisms best explains the action of fibrates?

(Please select 1 option)

○	Activation of PPAR-alpha
○	Bile acid sequestration
○	Decreases hepatic cholesterol synthesis
○	Increases peroxisomal beta-oxidation of fatty acids
○	Inhibits cholesterol absorption

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Time taken: 2 hrs 21 mins 24 secs

Work Smart Session - MRCP Part 1

Question: 90 of 100

A 75-year-old lady presents with sudden breathlessness and palpitations.

On examination, she was observed to have an irregular heart beat with rate of 140 bpm, BP 98/64 mmHg and normal heart sounds. On auscultation of the chest, fine basal crepitations are heard.

An ECG confirms atrial fibrillation (AF) and an old inferior myocardial infarction. She is anticoagulated with heparin and given diuretics. Her heart rate remains rapid.

What is the most appropriate management of the lady's AF?

(Please select 1 option)

- DCCV
- IV amiodarone
- IV beta-blocker
- IV digoxin
- Oral quinidine therapy

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

What is the most appropriate management of the lady's AF?

(Please select 1 option)

◉	DCCV ✓ Correct
○	IV amiodarone
○	IV beta-blocker
○	IV digoxin
○	Oral quinidine therapy

The key to this question is that the patient has clinical signs of pulmonary oedema with fast AF and hypotension.

In this age group AF is poorly tolerated and often leads to pulmonary oedema even in the presence of a relatively normal left ventricle (LV).

NICE have published guidance on the treatment of AF.

The primary aim here should be rate control which is best achieved with direct current cardioversion (DCCV) in this situation.

Digoxin even when used intravenously is suggested to have too slow an onset of action to merit its use.

Beta-blockers can also be used but due to the fact that they are negatively inotropic may complicate the acute pulmonary oedema.

Emergency DCCV is required as there is haemodynamic compromise (low BP).

Reference:

M Bilal Iqbal, Anil K Taneja, Gregory Y H Lip, and Marcus Flather. Recent developments in atrial fibrillation. BMJ, Jan 2005;330:238-243

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 2 hrs 22 mins 38 secs

Work Smart Session - MRCP Part 1

Question: 91 of 100

A 17-year-old girl was found collapsed and drowsy.

Her 12-lead ECG showed a sinus tachycardia of 120 beats per minute with a corrected QT interval of 500 ms (normal <470).

Which of the following drugs is the most likely cause of her presentation?

(Please select 1 option)

○	Amphetamine
○	Diphenhydramine
○	Glue sniffing
○	Methadone
○	Methanol

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Question: 91 of 100

A 17-year-old girl was found collapsed and drowsy.

Her 12-lead ECG showed a sinus tachycardia of 120 beats per minute with a corrected QT interval of 500 ms (normal <470).

Which of the following drugs is the most likely cause of her presentation?

(Please select 1 option)

○	Amphetamine
○	Diphenhydramine ← This is the correct answer
○	Glue sniffing
◉	Methadone ✕ Incorrect answer selected
○	Methanol

You are given here the option of choosing between two drugs that can possibly cause prolongation of QT - diphenhydramine and methadone.

However, bearing in mind that she has collapsed and is drowsy with a tachycardia, the most likely option is diphenhydramine as the tachycardia is more typical.

Many drugs can cause a prolonged QT interval. More here.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 2 hrs 23 mins 4 secs

Work Smart Session - MRCP Part 1

Question: 92 of 100

In Down syndrome, which is the most common congenital heart defect?

(Please select 1 option)

- A. Atrial septal defect
- B. Atrioventricular septal defect
- C. Patent ductus arteriosus
- D. Tetralogy of Fallot
- E. Ventricular septal defect

Submit answer | Skip question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 2 hrs 23 mins 31 secs

Work Smart Session - MRCP Part 1

Question: 92 of 100

In Down syndrome, which is the most common congenital heart defect?

(Please select 1 option)

○	A. Atrial septal defect
◉	B. Atrioventricular septal defect ✓ Correct
○	C. Patent ductus arteriosus
○	D. Tetralogy of Fallot
○	E. Ventricular septal defect

50% of Down syndrome births have congenital heart disease.

Defects in order of decreasing frequency are: B, E, C, D and A.

Next question

Tag Question Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 2 hrs 23 mins 31 secs

Work Smart Session - MRCP Part 1

Question: 93 of 100

A 65-year-old was advised to start oral digoxin at a dose of 250 µg daily. His physician explained that the full effect of this treatment would not be apparent for at least a week.

Which one of the following pharmacokinetic variables did the physician use to give this explanation?

(Please select 1 option)

- ○ Bioavailablity
- ○ Half life
- ○ Plasma protein binding
- ○ Renal clearance
- ○ Volume of distribution

Submit answer | Skip question | Remove Tag | Remove question

Time taken: 2 hrs 25 mins 19 secs

Work Smart Session - MRCP Part 1

Question: 93 of 100

A 65-year-old was advised to start oral digoxin at a dose of 250 µg daily. His physician explained that the full effect of this treatment would not be apparent for at least a week.

Which one of the following pharmacokinetic variables did the physician use to give this explanation?

(Please select 1 option)

◉	Bioavailablity ✗ Incorrect answer selected
○	Half life ← This is the correct answer
○	Plasma protein binding
○	Renal clearance
○	Volume of distribution

Digoxin follows first order kinetics and has a half life of 1.6 days in a patient with normal renal function.

65% of the drug absorbed remains in the system after one day.

Subsequent doses gradually accumulate until a steady state is achieved after four to five days.

Next question

Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 2 hrs 25 mins 19 secs

Work Smart Session - MRCP Part 1

Question: 94 of 100

A 55-year-old man presents with gynaecomastia. He is receiving treatment for heart failure and gastro-oesophageal reflux.

Which of the following drug he takes is most likely to be responsible for his gynaecomastia?

(Please select 1 option)

- Amitryptiline
- Carvedilol
- Furosemide
- Omeprazole
- Ramipril

Submit answer | Skip question | Tag Question | Remove question

A 55-year-old man presents with gynaecomastia. He is receiving treatment for heart failure and gastro-oesophageal reflux.

Which of the following drug he takes is most likely to be responsible for his gynaecomastia?

(Please select 1 option)

○	Amitryptiline
○	Carvedilol
○	Furosemide
◉	Omeprazole ✓ Correct
○	Ramipril

Like cimetidine, omeprazole is associated with gynaecomastia.

The other agents are not associated.

Other causes of gynaecomastia include

- spironolactone
- amiloride
- to a lesser extent eplerenone
- digoxin
- luteinising hormone-releasing hormone (LHRH) analogues
- finasteride.

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 2 hrs 26 mins 44 secs

Work Smart Session - MRCP Part 1

Question: 95 of 100

On discovering an unconscious patient in a pre-hospital environment basic life support needs to be considered.

Which of the following statements is correct?

(Please select 1 option)

- Cross infection with hepatitis B may occur during CPR
- On confirming an arrest, a ratio of 30 compressions to 2 ventilations should be adopted at all times
- On confirming an arrest, one minute of CPR should be performed before leaving the patient and getting help
- Rapid assessment of the airway and breathing is our primary objective
- Two effective rescue breaths should be given once apnoea is confirmed

Submit answer | Skip question | Tag Question | Remove question

	On confirming an arrest, one minute of CPR should be performed before leaving the patient and getting help
	Rapid assessment of the airway and breathing is our primary objective
	Two effective rescue breaths should be given once apnoea is confirmed

Assessing the environment to see if it is safe to approach is the first priority when considering providing aid to an unconscious patient. You do not want to become a casualty yourself.

Cardiopulmonary resuscitation (CPR) related infections are extremely rare, although tuberculosis, human immunodeficiency virus (HIV) and *Neisseria meningitidis* have all been recorded.

Most of the 15 cases were due to bacterial agents and the three HIV infections were from major cutaneous wound contamination.

No case reports of hepatitis B have been recorded (Ann Int Med 1998;129(10):813-828).

Once it has been confirmed that the patient is not breathing you must get help or alert the emergency services, even if this means leaving the patient (this is especially important in a pre-hospital environment).

However, if the patient is an infant or child, a victim of trauma, a near drowning or if drug or alcohol intoxication is likely, then one minute of CPR should be performed before going for help.

The new ALS guidelines (pdf) correct ratio of compressions to ventilations is 30:2 regardless of the number of rescuers present.

Further reading:
Adult Basic Life Support (pdf) Resuscitation Council (UK)

Next question

Tag Question | Remove question

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 2 hrs 28 mins 12 secs

Work Smart Session - MRCP Part 1

Question: 96 of 100

Which of the following infections is least likely to cause myocarditis?

(Please select 1 option)

- Chagas disease
- Coxsackie virus
- Diphtheria
- Syphilis
- Toxoplasmosis

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 2 hrs 28 mins 54 secs

Work Smart Session - MRCP Part 1

Question: 97 of 100

A 23-year-old male presents with a deep vein thrombosis (DVT). He has no past medical history but his mother has suffered from deep vein thromboses.

Which of the following is likely to be found on haematological assessment?

(Please select 1 option)

- Antithrombin deficiency
- Factor V (FV) Leiden mutation
- Lupus anticoagulant
- Protein C deficiency
- Protein S deficiency

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 2 hrs 30 mins 8 secs

Work Smart Session - MRCP Part 1

Question: 98 of 100

A 34-year-old male presents with episodes of breathlessness on exertion. Examination reveals a loud P2 and fixed splitting of the second sound.

Which of the following may be responsible for these signs?

(Please select 1 option)

○	47 XXY karyotype
○	Excess maternal alcohol consumption
○	Homocystinuria
○	Maternal chicken pox infection
○	Maternal thalidomide therapy

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 2 hrs 33 mins 24 secs

Work Smart Session - MRCP Part 1

Question: 98 of 100

A 34-year-old male presents with episodes of breathlessness on exertion. Examination reveals a loud P2 and fixed splitting of the second sound.

Which of the following may be responsible for these signs?

(Please select 1 option)

○	47 XXY karyotype
○	Excess maternal alcohol consumption ← This is the correct answer
○	Homocystinuria
◉	Maternal chicken pox infection ✕ Incorrect answer selected
○	Maternal thalidomide therapy

Fetal alcohol syndrome, Down syndrome and congenital rubella syndrome are associated with an atrial septal defect (ASD) with a loud second sound plus fixed splitting, as described in this case.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 2 hrs 33 mins 24 secs

Work Smart Session - MRCP Part 1

Question: 99 of 100

Which of the following anti-arrhythmic drugs may be used in the treatment of long QT syndrome?

(Please select 1 option)

- Amiodarone
- Atenolol
- Flecainide
- Propafenone
- Sotalol

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

EN 11:34 PM 3/1/2011

Question: 99 of 100

Which of the following anti-arrhythmic drugs may be used in the treatment of long QT syndrome?

(Please select 1 option)

○	Amiodarone
◉	Atenolol ✓ Correct
○	Flecainide
○	Propafenone
○	Sotalol

Beta-blockers are the mainstay of treatment in long QT syndrome.

The most commonly used drugs are propranolol and nadolol, but metoprolol and atenolol are also used.

Implantable cardioverter-defibrillators are the most effective treatment in high risk cases.

The others drugs may produce a prolongation of the QT interval, exacerbating risk of polymorphic ventricular tachycardia (VT) and torsades de pointes.

Further reading:
QT Drug Lists by Risk Groups Arizona Cert
Long QT Interval ECG library

Next question

Tag Question | Remove question

EN 11:35 PM 3/1/2011

Work Smart Session - MRCP Part 1

Time taken: 12 mins 56 secs

Question: 9 of 100

Which of the following mechanisms best explains the action of fibrates?

(Please select 1 option)

○	Activation of PPAR-alpha ← This is the correct answer
◉	Bile acid sequestration ✕ Incorrect answer selected
○	Decreases hepatic cholesterol synthesis
○	Increases peroxisomal beta-oxidation of fatty acids
○	Inhibits cholesterol absorption

The effect of fibrates on the metabolism of triglyceride-rich lipoproteins is due to a peroxisome proliferator activating receptor (PPAR)-alpha-dependent stimulation of lipoprotein lipase and of apolipoprotein (apo)A-V and to an inhibition of apoC-III expression, whereas the increase in plasma high density lipoprotein (HDL)-cholesterol depends partly on an overexpression of apoA-I and apoA-II. Drugs Today (Barc). 2006 Jan;42(1):39-64

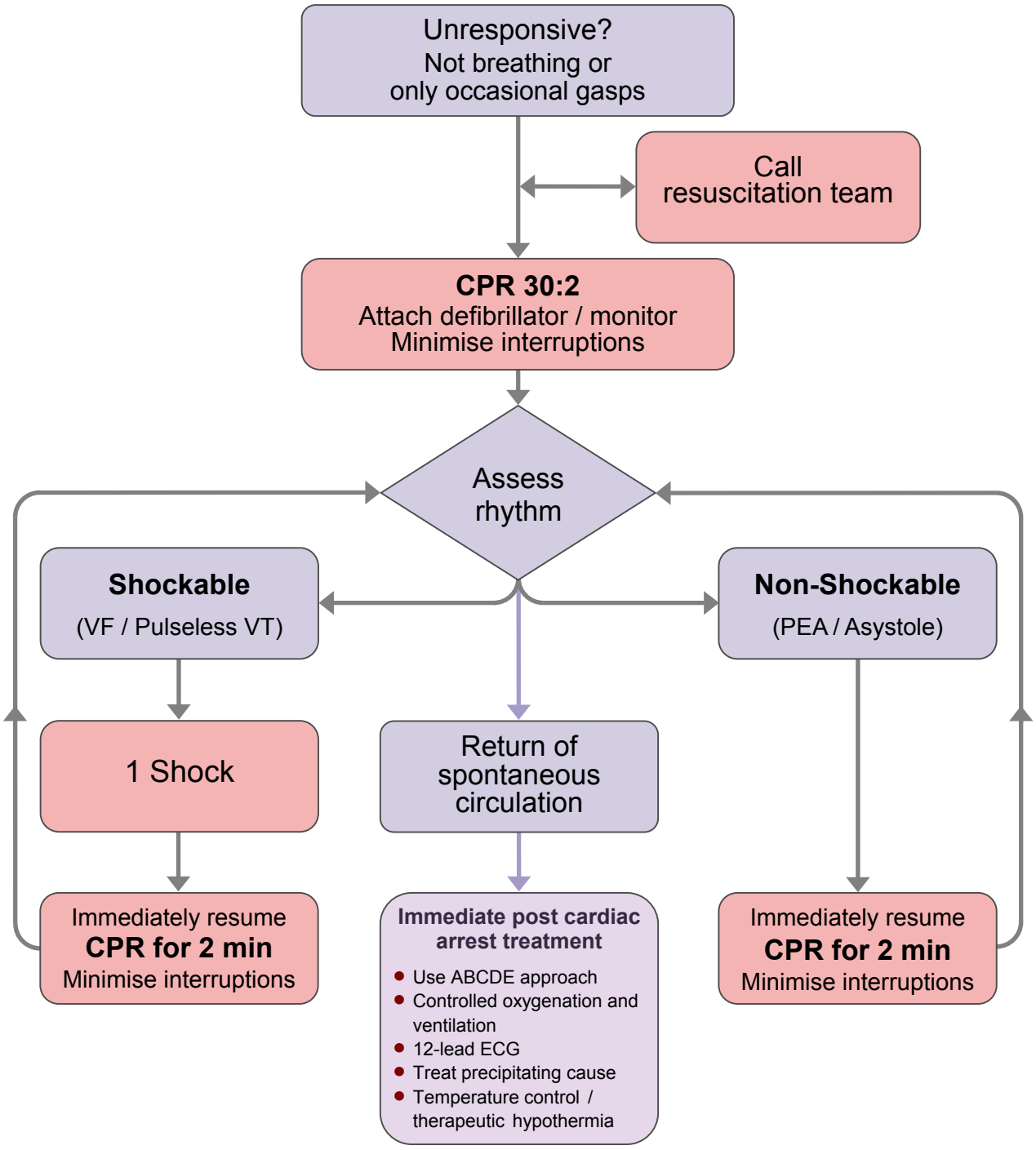
Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

2010 Resuscitation Guidelines

Resuscitation Council (UK)

Adult Advanced Life Support



During CPR

- Ensure high-quality CPR: rate, depth, recoil
- Plan actions before interrupting CPR
- Give oxygen
- Consider advanced airway and capnography
- Continuous chest compressions when advanced airway in place
- Vascular access (intravenous, intraosseous)
- Give adrenaline every 3-5 min
- Correct reversible causes

Reversible Causes

- Hypoxia
- Hypovolaemia
- Hypo- / hyperkalaemia / metabolic
- Hypothermia
- Thrombosis - coronary or pulmonary
- Tamponade - cardiac
- Toxins
- Tension pneumothorax

Questions Set : REF64340 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF64340
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken:

Question: 1 of 100

Regarding gamma glutamyl transferase (GGT), which of the follwoing statements is false?

(Please select 1 option)

- **A** GGT in serum originates mainly from the liver
- **B** GGT is a sensitive marker of alcohol intake
- **C** GGT levels are higher in patients of African ancestry
- **D** Most of the GGT in a cell is contained in the cell membrane
- **E** Renal tissue has the highest concentration of the GGT enzyme

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
100%

Questions Set : REF38768 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF38768
Page Safety Tools

Work Smart Session - MRCP Part 1

Time taken: 15 mins 29 secs

Question: 10 of 100

A 20-year-old woman was referred for investigation of iron deficiency anaemia. Her mother died aged 28 years from colonic carcinoma complicating Peutz-Jegher syndrome.

Which is the most likely mode of inheritance of Peutz-Jegher syndrome?

(Please select 1 option)

- Autosomal dominant
- Autosomal recessive
- Mitochondrial
- Polygenic
- X linked dominant

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
100%

Questions Set : REF1822 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF1822
Page Safety Tools

Dashboard
Questions
Scores
Community
Help
Shop

Work Smart Session - MRCP Part 1

Time taken: 5 hrs 20 mins 28 secs

Question: 100 of 100

Which molecule is produced in the nucleus, matures in the cytoplasm, binds to the ribosome and initiates protein synthesis?

(Please select 1 option)

- Messenger RNA
- Ribosomal RNA
- RNA nucleotide
- RNA polymerase
- Transfer RNA

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
115%

Questions Set : REF1822 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF1822
Page
Safety
Tools

Question: 100 of 100

Which molecule is produced in the nucleus, matures in the cytoplasm, binds to the ribosome and initiates protein synthesis?

(Please select 1 option)

◉	Messenger RNA ✓ Correct
○	Ribosomal RNA
○	RNA nucleotide
○	RNA polymerase
○	Transfer RNA

Protein synthesis consists of two phases.

Transcription is where one strand of the deoxyribonucleic acid (DNA) double helix is used as a template by ribonucleic acid (RNA) polymerase to synthesise messenger RNA from RNA nucleotides.

The mRNA then migrates into the cytoplasm maturing, for example, by the splicing of non-coding sequences.

Translation occurs when the ribosome binds to mRNA at the start codon and transfer RNA brings amino acids into position along the mRNA template.

The ribosome moves from codon to codon along the mRNA producing a polypeptide sequence.

Finish

Tag Question

Remove question

Done
Internet | Protected Mode: Off
115%

Questions Set : REF38768 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF38768
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 16 mins 18 secs

Question: 10 of 100

A 20-year-old woman was referred for investigation of iron deficiency anaemia. Her mother died aged 28 years from colonic carcinoma complicating Peutz-Jegher syndrome.

Which is the most likely mode of inheritance of Peutz-Jegher syndrome?

(Please select 1 option)

◉	Autosomal dominant ✓ Correct
○	Autosomal recessive
○	Mitochondrial
○	Polygenic
○	X linked dominant

Peutz-Jegher syndrome is a condition characterised by perioral pigmentation and numerous hamartomas of the bowel.

Originally it was assumed that these did not predispose to malignancy but studies now suggest the contrary.

The condition is autosomal dominant.

Next question

Tag Question

Remove question

Show tools

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
100%

Questions Set : REF36545 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF36545
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 16 mins 18 secs

Question: 11 of 100

A clinical trial assessing a new lipid lowering therapy for stroke allocates 1000 patients to active treatment and another 1000 patients to placebo.

Results demonstrate that the number needed to treat (NNT) is 20 for the prevention of the primary end-point.

Which of the following best describes the results?

(Please select 1 option)

- 20 patients in the treatment group were protected from stroke
- 20 extra patients in the placebo group had a stroke
- For 1000 patients treated with active therapy, there would be 20 fewer strokes
- For 1000 patients treated with active therapy, there would be 50 fewer strokes
- For every 1000 patients treated with active therapy there would be 100 fewer strokes

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
100%

Questions Set : REF36545 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites | Suggested Sites | Get More Add-ons
Questions Set : REF36545
Page | Safety | Tools

Work Smart Session - MRCP Part 1

Time taken: 30 mins 19 secs

Question: 11 of 100

A clinical trial assessing a new lipid lowering therapy for stroke allocates 1000 patients to active treatment and another 1000 patients to placebo.

Results demonstrate that the number needed to treat (NNT) is 20 for the prevention of the primary end-point.

Which of the following best describes the results?

(Please select 1 option)

○	20 patients in the treatment group were protected from stroke
○	20 extra patients in the placebo group had a stroke
◉	For 1000 patients treated with active therapy, there would be 20 fewer strokes ✕ Incorrect answer selected
○	For 1000 patients treated with active therapy, there would be 50 fewer strokes ← This is the correct answer
○	For every 1000 patients treated with active therapy there would be 100 fewer strokes

This prevention study for stroke reveals that 20 patients need to be treated to prevent one event.

Thus if you treat a 1000 patients then you will expect to have 50 fewer strokes.

Next question | Tag Question | Remove question

Show tools

Done
Internet | Protected Mode: On
100%

Questions Set : REF36493 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF36493
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 30 mins 19 secs

Question: 12 of 100

There is presently no known effective treatment for a chronic disease.

A new treatment is known to be effective in animal models and shows promise in short-term studies in patients. There are some theoretical concerns regarding possible hepato- and bone marrow toxicity although, thus far, no toxicity has been observed in studies.

What is the most appropriate next step in the drug's development?

(Please select 1 option)

- A case control study
- An open study
- A randomised double-blind placebo-controlled study
- A randomised single-blind placebo-controlled study
- No further studies should be done and drug development should be stopped

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
100%

Questions Set : REF36493 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF36493
Page Safety Tools

There is presently no known effective treatment for a chronic disease.

A new treatment is known to be effective in animal models and shows promise in short-term studies in patients. There are some theoretical concerns regarding possible hepato- and bone marrow toxicity although, thus far, no toxicity has been observed in studies.

What is the most appropriate next step in the drug's development?

(Please select 1 option)

◉	A case control study ✕ Incorrect answer selected
○	An open study
○	A randomised double-blind placebo-controlled study ← This is the correct answer
○	A randomised single-blind placebo-controlled study
○	No further studies should be done and drug development should be stopped

It appears that the drug has undergone animal testing and we can surmise that it has also been tested on normal volunteers (phase 1) as we are told that it has been tried in short-term studies of patients (phase 2).

After this testing process comes phase 3 studies - broad clinical trials designed to determine whether the drug is of clinical benefit in the disease state.

In particular you wish to know whether the drug is effective or not and you wish to know its safety.

A double-blind placebo-controlled study would be best placed to provide this information.

Next question Tag Question Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
100%

Questions Set : REF36469 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites | Suggested Sites | Get More Add-ons
Questions Set : REF36469
Page | Safety | Tools

Work Smart Session - MRCP Part 1

Time taken: 32 mins 53 secs

Question: 13 of 100

In a trial of a new drug the following results were obtained:

	Improved	Not improved
Treatment group	44	16
Placebo group	36	26

Which of the following statements regarding the statistical analysis or interpretation of the trial is true?

(Please select 1 option)

- A Student *t*-test could be used
- Pearson's co-efficient of linear regression would be an appropriate significance test
- The data could be evaluated using the chi-squared test
- The numbers are too small to draw any conclusions
- The results so obviously show the benefit of treatment that statistical analysis is not required

Submit answer | Skip question | Tag Question | Remove question

Questions.aspx
Internet | Protected Mode: On
100%

Questions Set : REF36469 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF36469
Page Safety Tools

	Improved	Not improved
Treatment group	44	16
Placebo group	36	26

Which of the following statements regarding the statistical analysis or interpretation of the trial is true?

(Please select 1 option)

- A Student *t*-test could be used
- Pearson's co-efficient of linear regression would be an appropriate significance test
- The data could be evaluated using the chi-squared test ✓ Correct
- The numbers are too small to draw any conclusions
- The results so obviously show the benefit of treatment that statistical analysis is not required

These data would be ideal for a chi-squared test. It is a 2 x 2 contingency table for which there is a special Chi-squared formula that gives a value that can be looked up in a table giving the p value.

The Student *t*-test cannot be used as we are comparing proportions not means.

Pearson's co-efficient cannot be calculated as there is no linear regression to plot.

Nothing is ever so obvious that no statistical analysis is needed, surely?

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
100%

Questions Set : REF36455 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF36455 Chi Square Statistics
Page Safety Tools

Dashboard
Questions
Scores
Community
Help
Shop

Work Smart Session - MRCP Part 1

Time taken: 35 mins 6 secs

Question: 14 of 100

Which of the following regarding the anatomy of the heart is true?

(Please select 1 option)

- The aortic valve is tricuspid
- The ascending aorta is entirely outside the pericardial sac
- The left atrial appendage is identified readily by transthoracic echocardiography
- The right atrium is posterior to the left atrium
- The right branch of the pulmonary artery lies anterior to the ascending aorta

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
100%

Questions Set : REF36455 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF36455
Chi Square Statistics
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 36 mins 18 secs

Question: 14 of 100

Which of the following regarding the anatomy of the heart is true?

(Please select 1 option)

- (●) The aortic valve is tricuspid ✓ Correct
- ( ) The ascending aorta is entirely outside the pericardial sac
- ( ) The left atrial appendage is identified readily by transthoracic echocardiography
- ( ) The right atrium is posterior to the left atrium
- ( ) The right branch of the pulmonary artery lies anterior to the ascending aorta

The right branch of the pulmonary artery lies posterior to the ascending aorta.

The ascending aorta lies completely within the pericardium as does the pulmonary trunk.

The left atrium is the most posterior chamber of the heart; the right atrium is just anterior and to the right of the left atrium.

The left atrial appendage is not readily seen on transthoracic echocardiography and requires transoesophageal echocardiography.

Next question | Tag Question | Remove question

Done
Internet | Protected Mode: On
100%

Questions Set : REF36447 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
File Edit View Favorites Tools Help
Favorites Suggested Sites Get More Add-ons
Questions Set : REF36447 Chi Square Statistics
Page Safety Tools

Work Smart Session - MRCP Part 1

Time taken: 36 mins 18 secs

Question: 15 of 100

Concerning neurofibromatosis type 1 (NF1), which one of the following statements is true?

(Please select 1 option)

- Bilateral acoustic neuromas are common
- Clinical severity in individuals is similar in a given family
- New mutations occur rarely
- Pigmented spots on the iris are a characteristic feature
- The diagnosis is likely if two café au lait patches are present

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
100%

Questions Set : REF36447 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF36447
Chi Square Statistics
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 38 mins 25 secs

Question: 15 of 100

Concerning neurofibromatosis type 1 (NF1), which one of the following statements is true?

(Please select 1 option)

○	Bilateral acoustic neuromas are common
○	Clinical severity in individuals is similar in a given family
○	New mutations occur rarely
◉	Pigmented spots on the iris are a characteristic feature ✓ Correct
○	The diagnosis is likely if two café au lait patches are present

Lisch nodules of the iris are present in more than 90% of patients.

Bilateral acoustic neuromas are a hallmark feature of neurofibromatosis type 2.

Expressivity of the gene is highly variable and members of the same family usually show wide differences in clinical symptoms.

NF1 is one of the most common autosomal dominant conditions. However almost half of all cases give no family history and are new mutations. The mutation rate is estimated to be 1:10,000 gametes.

The diagnosis is suggested by six or more café au lait macules (spots), each over 5 mm in diameter in prepubescent individuals and over 15 mm in post pubertal individuals.

Next question | Tag Question | Remove question

Done
Internet | Protected Mode: On
100%

Questions Set : REF36398 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF36398
Chi Square Statistics
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 38 mins 25 secs

Question: 16 of 100

Which of the following statements is true about immunological reactions?

(Please select 1 option)

- Angio-neurotic oedema is the most severe form of type I reaction
- Deficiencies in the terminal components of complement increase the risk of meningococcal disease
- Graves' disease is caused by a type IV reaction
- Serum sickness is caused by a type II reaction
- Urticaria usually responds to cimetidine

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
100%

Questions Set : REF36398 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF36398
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 40 mins 47 secs

Question: 16 of 100

Which of the following statements is true about immunological reactions?

(Please select 1 option)

- Angio-neurotic oedema is the most severe form of type I reaction
- Deficiencies in the terminal components of complement increase the risk of meningococcal disease ✓ Correct
- Graves' disease is caused by a type IV reaction
- Serum sickness is caused by a type II reaction
- Urticaria usually responds to cimetidine

Serum sickness is due to circulating antibody-antigen complexes (type III).

Graves' disease is due to stimulating antibody (type V).

The most severe variety of type I reaction is anaphylaxis, with angio-oedema an intermediate reaction associated with wheeze and swelling of the lips and severe urticaria. These reactions are mediated by histamine 1 receptor stimulation.

Congenital C1 inhibitor deficiency is also caused by hereditary angio-oedema. Deficiencies in C1r, s, and 2-4 result in vasculitides; while deficiencies in C2, 3 and 5-8 are associated with an increased risk of septicaemia.

Copyright © 2002 Dr Colin Melville

Next question | Tag Question | Remove question

Show to
Done
Internet | Protected Mode: On
100%

Questions Set : REF36296 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF36296
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 40 mins 47 secs

Question: 17 of 100

Which of the following statements concerning abnormalities of the haemoglobin molecule is true?

(Please select 1 option)

- **A** Alpha thalassaemia is due to a deficiency of beta-chain production
- **B** HbS is caused by a single base mutation on the beta-chain
- **C** Genes for the alpha and beta chains are located on the same chromosome
- **D** In thalassaemia, persistence of HbF is an adverse prognostic sign
- **E** Oligonucleotide probes may assist in the diagnosis of haemoglobinopathies in adolescents

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Internet | Protected Mode: On
100%

Questions Set : REF36296 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF36296
Page Safety Tools

Work Smart Session - MRCP Part 1

Time taken: 42 mins 13 secs

Question: 17 of 100

Which of the following statements concerning abnormalities of the haemoglobin molecule is true?

(Please select 1 option)

- **A** Alpha thalassaemia is due to a deficiency of beta-chain production ✕ Incorrect answer selected
- **B** HbS is caused by a single base mutation on the beta-chain ← This is the correct answer
- **C** Genes for the alpha and beta chains are located on the same chromosome
- **D** In thalassaemia, persistence of HbF is an adverse prognostic sign
- **E** Oligonucleotide probes may assist in the diagnosis of haemoglobinopathies in adolescents

A Alpha thalassaemia is due to abnormalities of the alpha chain. Persistence of HbF has survival advantages in severely affected subjects.

C Alpha is located on 16, beta on 11.

E Hb electrophoresis are used in the adult, rather than oligonucleotide probes as used in the fetus.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
100%

Questions Set : REF36279 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF36279
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 42 mins 13 secs

Question: 18 of 100

Which of the following is true of BCG vaccination?

(Please select 1 option)

- **A** Is a killed polysaccharide antigen vaccine
- **B** Is contraindicated in neonates
- **C** Is presently routinely offered in the UK at age 16 years
- **D** Provides protection against leprosy
- **E** Should be given to all children who have a strongly positive tuberculin test

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
100%

Questions Set : REF36279 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF36279
Page Safety Tools

Work Smart Session - MRCP Part 1

Time taken: 43 mins 26 secs

Question: 18 of 100

Which of the following is true of BCG vaccination?

(Please select 1 option)

- A Is a killed polysaccharide antigen vaccine
- B Is contraindicated in neonates
- C Is presently routinely offered in the UK at age 16 years
- **D Provides protection against leprosy** ✓ Correct
- E Should be given to all children who have a strongly positive tuberculin test

A The BCG vaccine is an attenuated strain; it provides approximately 70% protection.

B BCG vaccine may given to newborns at high risk of exposure.

C BCG is given at comprehensive school entry (age 11-13).

D It has also found a use in stimulating the immune system for the treatment of some cancers.

E It should not be given to these children. A low reactivity Heaf test (grade 0-1) should be documented before administration.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
100%

Questions Set : REF33712 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF33712
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 43 mins 26 secs

Question: 19 of 100

A 17-year-old primigravida complains of constipation and arthralgia at 28 weeks' gestation.

A number of biochemical investigations are performed, but which of these are clinically significant?

(Please select 1 option)

- Detectable urinary human chorionic gonadotrophin
- Free thyroxine 8.9 pmol/l (9-22)
- Prolactin of 1000 mU/l (<450)
- Serum alkaline phosphatase of 350 iu/l (50-110)
- Serum corrected calcium 2.89 mmol/l (2.2-2.6)

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
100%

Questions Set : REF33712 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF33712
Page Safety Tools

Work Smart Session - MRCP Part 1

Time taken: 46 mins 29 secs

Question: 19 of 100

A 17-year-old primigravida complains of constipation and arthralgia at 28 weeks' gestation.

A number of biochemical investigations are performed, but which of these are clinically significant?

(Please select 1 option)

○	Detectable urinary human chorionic gonadotrophin
◉	Free thyroxine 8.9 pmol/l (9-22) ✕ Incorrect answer selected
○	Prolactin of 1000 mU/l (<450)
○	Serum alkaline phosphatase of 350 iu/l (50-110)
○	Serum corrected calcium 2.89 mmol/l (2.2-2.6) ← This is the correct answer

This patient has symptoms suggestive of hypercalcaemia, which are clinically significant.

Free thyroxine (T_4) is at the lower end of the normal range which is often the case in pregnancy and thyroid-stimulating hormone (TSH) is a better guide of thyroid function.

Hyperprolactinaemia is a normal finding in pregnancy, as is detectable urinary human chorionic gonadotrophin.

It is also normal for serum alkaline phosphatase to rise by up to four times normal due to increased placental production.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
100%

Questions Set : REF64340 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF64340
Page Safety Tools

Work Smart Session - MRCP Part 1

Time taken: 1 mins 53 secs

Question: 1 of 100

Regarding gamma glutamyl transferase (GGT), which of the follwoing statements is false?

(Please select 1 option)

- A GGT in serum originates mainly from the liver
- B GGT is a sensitive marker of alcohol intake ← This is the correct answer
- C GGT levels are higher in patients of African ancestry
- D Most of the GGT in a cell is contained in the cell membrane ✕ Incorrect answer selected
- E Renal tissue has the highest concentration of the GGT enzyme

GGT is an enzyme which transfers a gamma glutamyl group between substances, especially between amino acids. It is found in many different types of tissue with the highest levels to be found in the proximal renal tubules. Serum GGT appears to come mostly from the liver and hepatobiliary system. GGT levels are higher in patients of African ancestry - the reason for this is unclear. Most of the GGT in the cell is incorporated into the cell membrane although some is also to be found in the cytoplasm. It may also be involve in transporting glutamyl-containing peptides across the cell membrane.

GGT is often used as a marker for alcohol intake but it is not sensitive or specific in this role. Some patients with heavy alcohol intake will have a GGT within the reference range and there are many causes of an elevated GGT - not just alcohol. GGT can be elevated with many drugs and toxins, cholestasis, viral hepatitis and pancreatitis. In some patients with acute myocardial infarction, GGT can raise after 3-4 days. The highest levels of GGT are usually seen with hepatobiliary disease.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A
Done
Internet | Protected Mode: On
100%

Questions Set : REF64332 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx?id=629485&ws=true
Favorites Suggested Sites Get More Add-ons
Questions Set : REF64332
Page Safety Tools

Work Smart Session - MRCP Part 1

Time taken: 1 mins 53 secs

Question: 2 of 100

Oxygen-requiring metabolic reactions occur predominantly in which type of liver cells?

(Please select 1 option)

- **A** Ito (Stellate) cells
- **B** Zone 1 hepatocytes
- **C** Kupffer cells
- **D** Zone 2 hepatocytes
- **E** Zone 3 hepatocytes

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
100%

Questions Set : REF30338 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF30338
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 46 mins 29 secs

Question: 20 of 100

Which of the following determines the primary mechanical properties of skin?

(Please select 1 option)

- Dermis
- Stratum basale
- Stratum corneum
- Stratum granulosum
- Subcutaneous tissue

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
100%

Questions Set : REF30338 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites | Suggested Sites | Get More Add-ons
Questions Set : REF30338
Page | Safety | Tools

Dashboard
Questions
Scores
Community
Help
Shop

Work Smart Session - MRCP Part 1

Time taken: 47 mins

Question: 20 of 100

Which of the following determines the primary mechanical properties of skin?

(Please select 1 option)

- Dermis
- Stratum basale
- Stratum corneum ✓ Correct
- Stratum granulosum
- Subcutaneous tissue

The stratum corneum is the last layer and provides a mechanical barrier to the skin and therefore determines the mechanical functions of the skin. The hands and feet have thick stratum corneum as compared to the lips and eyelids. The thicker the stratum corneum is the more protection there is for the skin.

The dermis also has some factor to play with its elastic fibres and fibrous tissue.

The rest of the layers are also important but the mechanical properties are primarily determined by the stratum corneum.

Next question | Tag Question | Remove question

Show tools
Done
Internet | Protected Mode: On
100%

Questions Set : REF30217 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF30217
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 47 mins

Question: 21 of 100

Which of the following is true of autosomal dominant breast cancer?

(Please select 1 option)

- Autosomal dominant breast cancer affects females but not males
- BRCA 2 mutations increase the risk of prostate cancer
- Females with the BRCA1 mutation will develop breast cancer
- It accounts for nearly half of all breast cancer cases in the United States
- Penetrance is close to 100%, with nearly all gene carriers developing breast cancer by age 80

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
100%

Questions Set : REF30217 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites | Suggested Sites | Get More Add-ons
Questions Set : REF30217
Page | Safety | Tools

Dashboard
Questions
Scores
Community
Help
Shop

Work Smart Session - MRCP Part 1

Time taken: 48 mins 1 secs

Question: 21 of 100

Which of the following is true of autosomal dominant breast cancer?

(Please select 1 option)

- Autosomal dominant breast cancer affects females but not males
- BRCA 2 mutations increase the risk of prostate cancer ← This is the correct answer
- Females with the BRCA1 mutation will develop breast cancer
- It accounts for nearly half of all breast cancer cases in the United States
- (●) Penetrance is close to 100%, with nearly all gene carriers developing breast cancer by age 80 ✕ Incorrect answer selected

An estimated 5-10% of breast cancers are inherited.

Autosomal dominant inheritance is the main means of inheritance and the BRCA1 and BRCA2 mutations are two such genes.

BRCA1 is also associated with increased risk of pancreatic cancer, and BRCA2 is associated with pancreatic cancer, prostate cancer and melanoma.

It is important to remember that inheritance of these mutations leads to an increased risk of developing a malignancy, not the certainty of developing a malignancy.

Next question | Tag Question | Remove question

Show tools

Done
Internet | Protected Mode: On
100%

Questions Set : REF29721 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF29721
Page Safety Tools

Question: 22 of 100

A study reports on the results of a large study of the primary prevention of stroke in a diabetic population using a new antiplatelet agent versus aspirin.

The results of the study reveal that over a five year period the incidence of stroke in the aspirin treated group is 3%, compared to a rate of 1.5% in the group treated with the new antiplatelet agent (p <0.001).

What is the relative risk reduction in stroke associated with the new drug?

(Please select 1 option)

○	1.5%
○	15%
○	30%
◉	40% ✕ Incorrect answer selected
○	50% ← This is the correct answer

The relative risk reduction is an important calculation for the interpretation of publications.

In this case there is an absolute risk reduction of 1.5% (3 - 1.5%) in stroke afforded by the new agent compared with aspirin yet the relative risk reduction is 1.5 / 3 = 50%.

That is 50% fewer strokes may be prevented by the use of the newer agent compared with aspirin although this would be the equivalent of 15 per 1000 patients treated (30 strokes expected / 1000 patients treated with aspirin but only 15 with the new drug).

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
100%

Questions Set : REF28454 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF28454
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 50 mins 52 secs

Question: 23 of 100

A 52-year-old man has been referred to the outpatient clinic due to deteriorating renal function.

A diagnosis of adult polycystic kidney disease (APKD) is made.

His family history reveals that his mother died of a stroke at the age of 50, and that his father is still alive. He is concerned regarding the inheritance of the disorder.

What is the probability that his son will inherit it?

(Please select 1 option)

- 0%
- 25%
- 50%
- 75%
- 100%

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Questions.aspx
Internet | Protected Mode: On
100%

Questions Set : REF28454 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF28454
Page
Safety
Tools

A 52-year-old man has been referred to the outpatient clinic due to deteriorating renal function.

A diagnosis of adult polycystic kidney disease (APKD) is made.

His family history reveals that his mother died of a stroke at the age of 50, and that his father is still alive. He is concerned regarding the inheritance of the disorder.

What is the probability that his son will inherit it?

(Please select 1 option)

○	0%
○	25%
◉	50% ✓ Correct
○	75%
○	100%

APKD is an autosomal dominant condition and typically presents between the ages of 30-50.

Patients develop deteriorating renal function and associated hypertension.

As well as renal cysts, they may also have hepatic and berry aneurysms (maternal history may be highly relevant here).

The chance of passing this condition to his son is 50%.

Next question

Tag Question

Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
100%

Questions Set : REF27758 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx?id=629485&ws=true
Favorites Suggested Sites Get More Add-ons
Questions Set : REF27758 Home - Windows Live
Page Safety Tools

Work Smart Session - MRCP Part 1

Time taken: 52 mins 7 secs

Question: 24 of 100

A 53-year-old male presents with a three month history of polyuria with polydipsia.

Which of the following measurements would confirm a diagnosis of diabetes mellitus?

(Please select 1 option)

- A fasting plasma glucose of 6.5 mmol/L
- A fasting plasma glucose of 7.5 mmol/l
- A plasma glucose of 10 mmol/l at the end of an oral glucose tolerance test
- A random glucose of 10.5 mmol/l
- A urine dipstick analysis showing +++ glucose

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Internet | Protected Mode: On 100%

Questions Set : REF27758 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx?id=629485&ws=true
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF27758
Hotmail - dr.zahir2009@h...
Page
Safety
Tools

Dashboard
Questions
Scores
Community
Help
Shop

Work Smart Session - MRCP Part 1

Time taken: 53 mins 40 secs

Question: 24 of 100

A 53-year-old male presents with a three month history of polyuria with polydipsia.

Which of the following measurements would confirm a diagnosis of diabetes mellitus?

(Please select 1 option)

- A fasting plasma glucose of 6.5 mmol/L
- A fasting plasma glucose of 7.5 mmol/l ✓ Correct
- A plasma glucose of 10 mmol/l at the end of an oral glucose tolerance test
- A random glucose of 10.5 mmol/l
- A urine dipstick analysis showing +++ glucose

Diabetes mellitus is diagnosed on the basis of symptoms plus a random glucose above 11.1 mmol/l or fasting plasma glucose above 7 mmol/l or the two hour oral glucose tolerance test (OGTT).

Impaired glucose tolerance would be indicated by a post OGTT plasma glucose between 7.7 and 11.1 or a fasting plasma glucose between 6.1 and 7.

Next question | Tag Question | Remove question

Show tools

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Internet | Protected Mode: On
100%

Questions Set : REF22746 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF22746 XE - Universal Currency Co... Connecting...
Page Safety Tools

Work Smart Session - MRCP Part 1

Time taken: 53 mins 40 secs

Question: 25 of 100

Mutation in which of the following is associated with Ehler-Danlos syndrome?

(Please select 1 option)

- Collagen type 1 gene
- FGFR3 gene
- Fibrillin- gene
- FMR-1 gene
- Type II procollagen gene

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Waiting for http://my.onexamination.com/Assessment/Questions.aspx?id=629485&ws=true...
Internet | Protected Mode: On
100%

Questions Set : REF22746 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF22746 XE: (EUR/GBP) Euro to Unit... Yahoo!
Page Safety Tools

Collagen type 1 gene ← This is the correct answer

FGFR3 gene

Fibrillin- gene

FMR-1 gene ✕ Incorrect answer selected

Type II procollagen gene

Mutations in the following genes cause Ehlers-Danlos syndrome:

- ADAMTS2
- COL1A1
- COL1A2
- COL3A1
- COL5A1
- COL5A2
- PLOD1
- TNXB.

Ehlers-Danlos occurs in 1:5000 people world-wide.

In view of the wide number of mutations that can cause Ehlers-Danlos syndrome, this is a very heterogeneous condition.

FGFR3 is implicated in achondroplasia; fibrillin gene in Marfan's syndrome; and FMR-1 gene fragile X mental retardation 1.

Next question Tag Question Remove question

Internet | Protected Mode: On 100%

Questions Set : REF22742 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF22742 XE - Universal Currency Co... فيديو كليب بيان تنحي مبارك | أ...
Page Safety Tools

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 19 secs

Question: 26 of 100

A new rapid test is developed for the screening of leptospirosis.

Blood from 100 patients was analysed by the gold standard laboratory technique and by the new method. There were 20 positive results with the gold standard technique but there were 40 positive results using the new technique. The new technique correctly identified all cases that were later confirmed with the gold standard technique.

Approximately which of the following values reflects the positive predictive value of the new technique?

(Please select 1 option)

- 33%
- 50%
- 66%
- 75%
- 90%

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Waiting for http://my.onexamination.com/Assessment/Questions.aspx...
Internet | Protected Mode: On 100%

Questions Set : REF22742 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF22742 XE: (GBP/SDG) United King... فيديو كليب بيان تنحي مبارك | أ...
Page Safety Tools

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 5 mins 42 secs

Question: 26 of 100

A new rapid test is developed for the screening of leptospirosis.

Blood from 100 patients was analysed by the gold standard laboratory technique and by the new method. There were 20 positive results with the gold standard technique but there were 40 positive results using the new technique. The new technique correctly identified all cases that were later confirmed with the gold standard technique.

Approximately which of the following values reflects the positive predictive value of the new technique?

(Please select 1 option)

◉	33% ✕ Incorrect answer selected
○	50% ← This is the correct answer
○	66%
○	75%
○	90%

The positive predictive value is number of true positives/(no of true positives + false positives).

In the new technique there were 20 true positives and 20 false positives.

Thus the positive predictive value is 20/ (20 + 20) = 50%.

Next question | Tag Question | Remove question

Internet | Protected Mode: On 100%

Questions Set : REF22544 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF22544 Connecting... XE: (GBP/SDG) United King...
Page Safety Tools

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 5 mins 42 secs

Question: 27 of 100

Which of the following statements regarding the internal jugular vein and relations is true?

(Please select 1 option)

- Lies lateral to the common carotid artery
- Originates at the carotid canal
- Passes behind the clavicle to join the superior vena cava
- Passes posterior to the subclavian artery
- Receives a lymphatic trunk at its union with the external jugular vein.

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Internet | Protected Mode: On 100%

Questions Set : REF22544 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF22544 | Internet Explorer cannot di... | XE: (GBP/SDG) United King...
Page Safety Tools

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 10 mins 38 secs

Question: 27 of 100

Which of the following statements regarding the internal jugular vein and relations is true?

(Please select 1 option)

○	Lies lateral to the common carotid artery ← This is the correct answer
○	Originates at the carotid canal
○	Passes behind the clavicle to join the superior vena cava
◉	Passes posterior to the subclavian artery ✕ Incorrect answer selected
○	Receives a lymphatic trunk at its union with the external jugular vein.

The internal jugular vein originates at the jugular foramen.

It initially lies posterior to the carotid artery as it descends in the carotid sheath it lies lateral first to the internal then the common carotid artery within the carotid sheath.

It passes anterior to the subclavian artery to join the subclavian vein and then form the brachiocephalic vein; the left and right brachiocephalic veins unite to form the superior vena cava.

The internal jugular vein receives a lymphatic trunk at its union with the subclavian vein.

The external jugular vein drains into the subclavian vein.

Next question | Tag Question | Remove question

Done
Internet | Protected Mode: On
100%

Questions Set : REF22008 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF22008
Connecting...
XE: (GBP/SDG) United King...
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 10 mins 38 secs

Question: 28 of 100

In a study of elderly patients with atrial fibrillation, patients receiving warfarin (n= 6000), 6% had strokes or died as a consequence of stroke, whereas in subjects treated with aspirin (n = 8000), 9 % had strokes or death from a stroke over the three year study period (p=0.001). The risk of stroke in an untreated population with atrial fibrillation over this time was 12%.

Which of the following percentages is the approximate annual incidence of stroke in the treated population in this study?

(Please select 1 option)

- 2.6%
- 3.3%
- 5.5%
- 6.9%
- 7.7%

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Internet | Protected Mode: On
100%

Questions Set : REF22008 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF22008 XE: (GBP/SDG) United King...
Page Safety Tools

In a study of elderly patients with atrial fibrillation, patients receiving warfarin (n= 6000), 6% had strokes or died as a consequence of stroke, whereas in subjects treated with aspirin (n = 8000), 9 % had strokes or death from a stroke over the three year study period (p=0.001). The risk of stroke in an untreated population with atrial fibrillation over this time was 12%.

Which of the following percentages is the approximate annual incidence of stroke in the treated population in this study?

(Please select 1 option)

○	2.6% ← This is the correct answer
◉	3.3% ✕ Incorrect answer selected
○	5.5%
○	6.9%
○	7.7%

One needs to calculate the incidence as follows:

In the group treated with warfarin there were 360 strokes (6% of 6000).

In the aspirin treated group there were 720 strokes (9% of 8000).

Thus, there are 1080 strokes amongst the treated population (n=14000) over a three year time period.

Therefore there are 360 strokes annually in the treated group (14000) giving an annual incidence of stroke of approx 2.6%

Note: remember to divide by three since the study lasted three years and the figures given are for the three years incidence rates.

Next question Tag Question Remove question

Done
Internet | Protected Mode: On
100%

Questions Set : REF22006 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF22006 XE: (GBP/SDG) United King...
Page Safety Tools

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 13 mins 40 secs

Question: 29 of 100

In a study of 26,000 females, 1300 subjects were found to have either overt or subclinical hypothyroidism. Within this group, the risk of demonstrating either overt or subclinical hypothyroidism was therefore 5%.

What is the best descriptive term of this 5% risk?

(Please select 1 option)

- Absolute risk
- Incidence
- Prevalence
- Relative risk
- Specificity

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
100%

Questions Set : REF22006 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites | Suggested Sites | Get More Add-ons
Questions Set : REF22006 | XE: (GBP/SDG) United King...
Page | Safety | Tools

Dashboard
Questions
Scores
Community
Help
Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 24 mins 42 secs

Question: 29 of 100

In a study of 26,000 females, 1300 subjects were found to have either overt or subclinical hypothyroidism. Within this group, the risk of demonstrating either overt or subclinical hypothyroidism was therefore 5%.

What is the best descriptive term of this 5% risk?

(Please select 1 option)

- ○ Absolute risk
- ◉ Incidence ✕ Incorrect answer selected
- ○ Prevalence ← This is the correct answer
- ○ Relative risk
- ○ Specificity

This is the risk of either subclinical or overt hypothyroidism in a female population at any specific time which is the prevalence. This is defined as the rate of a disorder in a specified population at a specified time.

Incidence refers to the number of new cases of a disorder developing over a specific time.

Next question | Tag Question | Remove question

Show tools

Done
Internet | Protected Mode: On
100%

Questions Set : REF64332 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx?id=629485&ws=true
Favorites Suggested Sites Get More Add-ons
Questions Set : REF64332
Page Safety Tools

A Ito (Stellate) cells

B Zone 1 hepatocytes ← This is the correct answer

C Kupffer cells ✕ Incorrect answer selected

D Zone 2 hepatocytes

E Zone 3 hepatocytes

The liver is made up of many small subunits called acini. Each acinus has a dual blood supply from firstly, a branch of the hepatic artery (oxygen rich) and secondly, a branch of the portal vein (solute rich). The blood from these flows though the hepatic sinusoids which allow quite free movement of solutes and oxygen from the blood cells into the hepatocytes. Eventually the blood joins a venule and drains into the hepatic vein and back to the systemic circulation.

Hepatocytes near the hepatic arterial supply and portal vein supply (periportal region) are called zone 1 hepatocytes. Zone 3 hepatocytes are furthest from the arterial supply and closest to the branch of the hepatic vein (perivenular region). Zone 2 hepatocytes are in the middle.

Zone 1 hepatocytes receive an oxygen-rich, solute-rich supply which makes them highly metabolically active, but more at risk of damage through the effects of toxins coming from the gut. Most of the highly-oxygen-requiring reactions occur here, including the electron transport chains, Krebs' cycle, fatty acid oxidation and urea synthesis. Zones 2 and 3 receive less oxygen and tend to be involved in reactions requiring little or no oxygen, such as glycolysis.

Ito cells store fats and Vitamin A and are involved in production of connective tissue. In liver disease, they are thought to be fundamental in the development of fibrosis and cirrhosis.

Kupffer cells are part of the reticuloendothelial system and are specialised macrophages. They are involved in the breakdown of haemoglobulin and the removal of haem for further metabolism in the hepatocytes. Kupffer cells also have a role in immunity.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
100%

Questions Set : REF64163 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF64163
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 2 mins 58 secs

Question: 3 of 100

A patient with multiple drug resistant (MDR) TB is receiving prolonged treatment with moxifloxacin. Which side effect is likely to occur as a result of prolonged administration?

(Please select 1 option)

- **A** Achilles tendinitis
- **B** Hepatotoxicity
- **C** Nephrotoxicity
- **D** Peripheral neuropathy
- **E** Retinopathy

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
100%

Questions Set : REF21343 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites | Suggested Sites | Get More Add-ons
Questions Set : REF21343 | XE: (GBP/SDG) United King...
Page | Safety | Tools

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 24 mins 42 secs

Question: 30 of 100

A new test is developed for the diagnosis of HIV.

Blood from 10,000 patients was analysed by the gold standard technique and by the new method. There were 100 positive results with the gold standard technique but there were 150 positive results using the new technique.

Approximately which of the following values reflects the positive predictive value of the new technique?

(Please select 1 option)

- 33%
- 50%
- 66%
- 75%
- 90%
- It cannot be determined

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

http://my.onexamination.com/GoToShop.aspx
Internet | Protected Mode: On
100%

Questions Set : REF21343 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF21343 XE - Universal Currency Co...
Page Safety Tools

A new test is developed for the diagnosis of HIV.

Blood from 10,000 patients was analysed by the gold standard technique and by the new method. There were 100 positive results with the gold standard technique but there were 150 positive results using the new technique.

Approximately which of the following values reflects the positive predictive value of the new technique?

(Please select 1 option)

○	33%
○	50%
◉	66% ✕ Incorrect answer selected
○	75%
○	90%
○	It cannot be determined ← This is the correct answer

The positive predictive value is number of true positives/(no of true positives + false positives).

There are 100 people tested positive with gold standard. However, we don't know how many of these are tested positive and how many are tested negative by the new techniques. Similarly, we don't know the number of people tested positive or negative aby the gold standard mong the 150 people tested positive by the new technique. Therefore, the number of true positives and false positives and hence the positive predictive value cannot be determined.

Next question Tag Question Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

http://my.onexamination.com/GoToShop.aspx
Internet | Protected Mode: On 100%

Questions Set : REF21340 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF21340 XE: (GBP/SDG) United King...
Page Safety Tools

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 27 mins 48 secs

Question: 31 of 100

Mutation in which of the following is associated with Marfan's syndrome?

(Please select 1 option)

- Collagen type 1 gene
- Collagen type 5 gene
- Fibrillin-1 gene
- FMR-1 gene
- Type II procollagen gene

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Waiting for http://my.onexamination.com/Assessment/Questions.aspx...
Internet | Protected Mode: On
100%
EN
07:51 ص
2/10/2011

Questions Set : REF21340 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF21340
Page Safety Tools

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 28 mins 29 secs

Question: 31 of 100

Mutation in which of the following is associated with Marfan's syndrome?

(Please select 1 option)

○	Collagen type 1 gene
○	Collagen type 5 gene
◉	Fibrillin-1 gene ✓ Correct
○	FMR-1 gene
○	Type II procollagen gene

Mutation in the fibrillin-1 gene is thought to be responsible for Marfan's syndrome.

In Marfan's syndrome the lack of normal fibrillin-1 leads to overactivity of transforming growth factor type beta (TGF-b) in the wall of the aorta and the heart valves, leading to damage and destruction to the connective tissue which weakens that aortic wall and heart valves causing them to stretch.

Type 1 collagen gene defects are found in osteogenesis imperfecta and type 3 in Ehlers-Danlos syndrome.

Type II procollagen defect is found in hereditary spodyloarthropathy.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A
Internet | Protected Mode: On 100%

Questions Set : REF20763 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF20763
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 28 mins 29 secs

Question: 32 of 100

A large multi-centre secondary prevention study reports a reduction in the annual incidence of recurrent subarachnoid haemorrhage from 10% in a medically treated group versus 6% in the group treated with medical therapy plus radiological intervention ($p<0.005$). The additional cost of the new treatment is £3000 per patient.

In the first year of treatment, what would be the predicted additional cost of preventing a single recurrent subarachnoid haemorrhage?

(Please select 1 option)

- ○ £3000
- ○ £12000
- ○ £30000
- ○ £75000
- ○ £90000

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Internet | Protected Mode: On
100%

Questions Set : REF20763 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF20763
Page Safety Tools

Question: 32 of 100

A large multi-centre secondary prevention study reports a reduction in the annual incidence of recurrent subarachnoid haemorrhage from 10% in a medically treated group versus 6% in the group treated with medical therapy plus radiological intervention ($p<0.005$). The additional cost of the new treatment is £3000 per patient.

In the first year of treatment, what would be the predicted additional cost of preventing a single recurrent subarachnoid haemorrhage?

(Please select 1 option)

○	£3000
◉	£12000 ✕ Incorrect answer selected
○	£30000
○	£75000 ← This is the correct answer
○	£90000

This study shows that annual rate of recurrent subarachnoid haemorrhage is reduced from 10% to 6%.

Therefore, if you treated 100 patients for one year you would expect 10 patients with subarachnoid haemorrhage in the medically treated group versus six patients in the medical plus radiological intervention group - a reduction of four patients per hundred.

Therefore you would need to treat 25 patients (4/100) to expect one less case of subarachnoid haemorrhage.

Thus the extra cost of this would be 25 x 3000 = £75000.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
100%

Questions Set : REF19924 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF19924
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 33 mins 24 secs

Question: 33 of 100

Where does RNA splicing occur?

(Please select 1 option)

- Cytoplasm
- Endoplasmic reticulum
- Mitochondria
- Nucleus
- Ribosome

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
120%

Questions Set : REF19924 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF19924
Page Safety Tools

Question: 33 of 100

Where does RNA splicing occur?

(Please select 1 option)

○	Cytoplasm
○	Endoplasmic reticulum
○	Mitochondria
○	Nucleus ← This is the correct answer
◉	Ribosome ✕ Incorrect answer selected

Coding sequence is interrupted by non-coding sequences.

Removal of the introns in RNA transcript modification is called RNA splicing.

Splicing occurs in the nucleus before transport to the cytoplasm.

Exons are expressed sequences: these sequences are those present in mature mRNA.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
120%

Questions Set : REF19922 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF19922
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 35 mins 1 secs

Question: 34 of 100

Which of the following is typically elevated in Gaucher's disease?

(Please select 1 option)

- Acid phosphatase
- Alkaline phosphatase
- Amylase
- Glucocerebrosidase
- Lipase

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
120%

Questions Set : REF19922 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF19922
Page
Safety
Tools

Question: 34 of 100

Which of the following is typically elevated in Gaucher's disease?

(Please select 1 option)

◉	Acid phosphatase ✓ Correct
○	Alkaline phosphatase
○	Amylase
○	Glucocerebrosidase
○	Lipase

Gaucher's disease is the most frequent of the lysosomal storage diseases.

The condition is usually due to a catalytic deficiency of glucocerebrosidase. It is accompanied by many ill-understood plasma and metabolic abnormalities. These include a polyclonal immunoglobulin response that may progress to monoclonal gammopathy, amyloidosis, or even frank myeloma.

Low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol fractions are abnormal in the plasma.

Some lysosomal enzymes are elevated including tartrate-resistant acid phosphatase, hexosaminidase, and a human chitinase, chitotriosidase. This latter enzyme has proved to be very useful for monitoring Gaucher's disease activity in response to treatment and may reflect the severity of the disease.

Done
Internet | Protected Mode: On
120%

Questions Set : REF19619 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF19619
Page
Safety
Tools

Question: 35 of 100

In a study of 1000 subjects with adrenal incidental tumours a new serological marker for adrenal carcinoma was assessed against formal histology.

The following results were obtained:

	Test positive	Test negative
Histology positive	40	10
Histology negative	50	900

To what does the specificity approximate?

(Please select 1 option)

- 50%
- 60%
- 70%
- 80%
- 90%

Submit answer | Skip question | Tag Question | Remove question

Done
Internet | Protected Mode: On
120%

Questions Set : REF19619 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF19619
Page
Safety
Tools

Histology positive	40	10
Histology negative	50	900

To what does the specificity approximate?

(Please select 1 option)

○	50%
○	60%
○	70%
◉	80% ✕ Incorrect answer selected
○	90% ← This is the correct answer

Sensitivity relates to the probability that the person with a disease will be correctly identified with the disease.

Therefore in this study 50 subjects have adrenal carcinoma of whom 40 are correctly identified with the disease giving a sensitivity of 80%.

The specificity is the probability that a person without the disease will be correctly identified by the test.

In this case there are 950 subjects without adrenal carcinoma of whom 900 were identified by the test - giving a specificity of ~95%.

Summary of sensitivity and specificity as defined by contingency tables.

Next question

Tag Question

Remove question

Done
Internet | Protected Mode: On
110%

Questions Set : REF17839 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF17839
http://my.onexamination....
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 39 mins 46 secs

Question: 36 of 100

Which of the following has been shown to increase the risk of prostate cancer?

(Please select 1 option)

- Caucasian race
- Exposure to cadmium
- Family history of colon cancer
- Low intake of animal fats
- Occupational exposure to dust

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
110%

Questions Set : REF17839 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF17839
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 40 mins 58 secs

Question: 36 of 100

Which of the following has been shown to increase the risk of prostate cancer?

(Please select 1 option)

○	Caucasian race
◉	Exposure to cadmium ✓ Correct
○	Family history of colon cancer
○	Low intake of animal fats
○	Occupational exposure to dust

Black ethnicity is associated with a higher risk of prostate cancer than white.

A family history of breast cancer increases the risk of prostate cancer, as does a family history of prostate cancer.

An occupation in farming also seems to increase the risk of prostate cancer.

High intake of animal fats, and low selenium intake, as well as exposure to radiation and cadmium all increase the risk of prostate cancer.

Next question

Tag Question

Remove question

Show to
© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A
Done
Internet | Protected Mode: On
110%

Questions Set : REF14853 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF14853
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 40 mins 58 secs

Question: 37 of 100

A 45-year-old female attends clinic complaining of tiredness. She is hypothyroid and takes thyroxine 150 micrograms daily.

Which of the following is the most useful test for assessing the appropriateness of thyroid hormone replacement in primary hypothyroidism?

(Please select 1 option)

- Free T3 and T4 concentrations
- Skin biopsy
- Thyroid binding globulin
- Total T3 and T4
- TSH

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
110%

Questions Set : REF14853 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF14853
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 41 mins 51 secs

Question: 37 of 100

A 45-year-old female attends clinic complaining of tiredness. She is hypothyroid and takes thyroxine 150 micrograms daily.

Which of the following is the most useful test for assessing the appropriateness of thyroid hormone replacement in primary hypothyroidism?

(Please select 1 option)

○	Free T3 and T4 concentrations
○	Skin biopsy
○	Thyroid binding globulin
○	Total T3 and T4
◉	TSH ✓ Correct

Thyroid-stimulating hormone (TSH) has been recognised as an exquisitely sensitive indicator of thyroid status.

A normal TSH result suggests adequate thyroid hormone replacement and euthyroidism.

Similarly elevated TSH with normal thyroid hormone concentrations would suggest poor compliance and suppressed TSH with normal high thyroxine (T4) suggests over-replacement.

Show to
Done
Internet | Protected Mode: On
110%

Questions Set : REF13176 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF13176
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 41 mins 51 secs

Question: 38 of 100

Which of the following is most likely to be reversible following venesection in a 45-year-old male with haemochromatosis?

(Please select 1 option)

- Arthropathy
- Cardiomyopathy
- Cirrhosis
- Diabetes mellitus
- Hypopituitarism

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
110%

Questions Set : REF13176 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF13176
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 42 mins 22 secs

Question: 38 of 100

Which of the following is most likely to be reversible following venesection in a 45-year-old male with haemochromatosis?

(Please select 1 option)

- Arthropathy
- Cardiomyopathy ✓ Correct
- Cirrhosis
- Diabetes mellitus
- Hypopituitarism

Disorders that are potentially reversible in haemochromatosis include the dermal pigmentation and cardiomyopathy.

Similarly there are improvements in liver function tests.

However, diabetes, cirrhosis, hypogonadism and arthropathy are usually irreversible.

Next question | Tag Question | Remove question

Done
Internet | Protected Mode: On
110%

Questions Set : REF11679 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF11679
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 42 mins 22 secs

Question: 39 of 100

It has been suggested that cystic fibrosis (CF) (autosomal recessive) has a high prevalence in some populations because heterozygotes are resistant to the effects of chloride-secreting diarrhoea. This is best described as an example of:

(Please select 1 option)

- Gene flow
- Genetic drift
- Linkage disequilibrium
- Mutation
- Natural selection

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
110%

Questions Set : REF11679 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF11679
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 43 mins 30 secs

Question: 39 of 100

It has been suggested that cystic fibrosis (CF) (autosomal recessive) has a high prevalence in some populations because heterozygotes are resistant to the effects of chloride-secreting diarrhoea. This is best described as an example of:

(Please select 1 option)

- Gene flow
- Genetic drift
- Linkage disequilibrium
- Mutation
- Natural selection ✓ Correct

Natural selection is the likely explanation as it appears that heterozygous for CF may offer some protection against diarrhoeal illnesses particularly typhoid.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
110%

Questions Set : REF64163 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF64163
Page Safety Tools

Work Smart Session - MRCP Part 1

Time taken: 4 mins 8 secs

Question: 3 of 100

A patient with multiple drug resistant (MDR) TB is receiving prolonged treatment with moxifloxacin. Which side effect is likely to occur as a result of prolonged administration?

(Please select 1 option)

- **A** Achilles tendinitis ← This is the correct answer
- **B** Hepatotoxicity
- **C** Nephrotoxicity
- **D** Peripheral neuropathy ✕ Incorrect answer selected
- **E** Retinopathy

This is an idiosyncratic reaction associated with prolonged use of quinolones.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
100%

Questions Set : REF64158 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF64158
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 4 mins 8 secs

Question: 4 of 100

What is the mechanism of action of glycopeptides (e.g. vancomycin)?

(Please select 1 option)

- **A** Cell wall inhibition
- **B** Inhibition of protein synthesis (translation)
- **C** Inhibition of protein synthesis (transcription)
- **D** Inhibition of folic acid metabolism
- **E** Interference with DNA replication

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
100%

Questions Set : REF11676 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF11676
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 43 mins 30 secs

Question: 40 of 100

Which is a likely explanation for the high prevalence of cystic fibrosis in European populations?

(Please select 1 option)

- Heterozygotes may have an advantage because of increased resistance to cholera.
- Inbreeding is common among Europeans.
- Many different mutations can cause cystic fibrosis.
- Most of the disease genes are hidden in heterozygotes.
- The locus has a high mutation rate.

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
110%

Questions Set : REF11676 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF11676
Page Safety Tools

Which is a likely explanation for the high prevalence of cystic fibrosis in European populations?

(Please select 1 option)

◉	Heterozygotes may have an advantage because of increased resistance to cholera. ✓ Correct
○	Inbreeding is common among Europeans.
○	Many different mutations can cause cystic fibrosis.
○	Most of the disease genes are hidden in heterozygotes.
○	The locus has a high mutation rate.

The prevalence of the cystic fibrosis gene at around 1 in 20 of the population would suggest that this provides some evolutionary survival advantage. Like sickle cell trait offering a survival advantage to malaria, it is believed that the cystic fibrosis gene offers a possible survival advantage against cholera and enteropathogenic bacteria.

"Cholera opens chloride channels, letting chloride and water leave cells. The CFTR protein does just the opposite, closing chloride channels and trapping salt and water in cells, which dries out mucus and other secretions. A person with CF cannot contract cholera, because the toxin cannot open the chloride channels in the small intestine.

Carriers of CF enjoy the mixed blessing of a balanced polymorphism. They do not have enough abnormal chloride channels to cause the labored breathing and clogged pancreas of cystic fibrosis, but they do have enough of a defect to prevent the cholera from taking hold. During the devastating cholera epidemics that have peppered history, individuals carrying mutant CF alleles had a selective advantage, and they disproportionately transmitted those alleles to future generations. However, because CF arose in Western Europe and cholera in Africa, perhaps an initial increase in CF herterozygosity was a response to a different diarrheal infection." (Read more about balanced polymorphism).

Done
Internet | Protected Mode: On
110%

Questions Set : REF10154 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF10154
Page
Safety
Tools

Dashboard
Questions
Scores
Community
Help
Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 44 mins 53 secs

Question: 41 of 100

A 65-year-old man with a history of myocardial infarction four years earlier was admitted with sudden onset shortness of breath, decreasing exercise tolerance and pedal oedema.

He takes lansoprazole, aspirin, furosemide and lisinopril.

Which of the following laboratory tests would identify the reason for his acute presentation?

(Please select 1 option)

- Brain natriuretic peptide (BNP)
- Clotting screen
- C reactive protein
- Full blood count
- Urea and electrolytes

Submit answer | Skip question | Tag Question | Remove question

Questions.aspx
Internet | Protected Mode: On
110%

Questions Set : REF10154 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF10154
Page Safety Tools

A 65-year-old man with a history of myocardial infarction four years earlier was admitted with sudden onset shortness of breath, decreasing exercise tolerance and pedal oedema.

He takes lansoprazole, aspirin, furosemide and lisinopril.

Which of the following laboratory tests would identify the reason for his acute presentation?

(Please select 1 option)

◉	Brain natriuretic peptide (BNP) ✓ Correct
○	Clotting screen
○	C reactive protein
○	Full blood count
○	Urea and electrolytes

This patient has features of heart failure which appear to be related to underlying ischaemic heart disease.

BNP is synthesised in the cardiac ventricles and correlates with left ventricle (LV) pressure, degree of dyspnoea, and state of neurohormonal modulation. Thus BNP is the first potential marker for heart failure.

Measurement of plasma BNP concentration is evolving as a very efficient and cost effective mass screening technique for identifying patients with various cardiac abnormalities regardless of etiology and degree of LV systolic dysfunction.

Next question Tag Question Remove question

Done
Internet | Protected Mode: On
110%

Questions Set : REF10061 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF10061
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 45 mins 55 secs

Question: 42 of 100

A patient presents with acute promyelocytic leukaemia (APL).

What is the likely mechanism underlying leukaemogenesis?

(Please select 1 option)

- ○ Aberrant fusion of 2 genes
- ○ Impaired protein degradation
- ◉ Over expression of cellular oncogene
- ○ Post-translational modification
- ○ Telomere shortening

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Internet | Protected Mode: On
110%

Questions Set : REF10061 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites | Suggested Sites | Get More Add-ons
Questions Set : REF10061
Page | Safety | Tools

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 47 mins 18 secs

Question: 42 of 100

A patient presents with acute promyelocytic leukaemia (APL).

What is the likely mechanism underlying leukaemogenesis?

(Please select 1 option)

○	Aberrant fusion of 2 genes ← This is the correct answer
○	Impaired protein degradation
◉	Over expression of cellular oncogene ✕ Incorrect answer selected
○	Post-translational modification
○	Telomere shortening

In APL one of the retinoic acid receptor genes, RARA, is fused to PML in the great majority of patients as a result of the chromosomal translocation t(15; 17).

Next question | Tag Question | Remove question

Done
Internet | Protected Mode: On
110%

Questions Set : REF8847 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF8847
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 47 mins 18 secs

Question: 43 of 100

A publication reports the outcome of a new statin therapy in a placebo controlled primary prevention of ischaemic heart disease in a diabetic population.

1000 patients were randomised to receive the new therapy and 1000 allocated to placebo. The study was completed over a five year period.

In the placebo group there were 150 myocardial infarcts (MI) and in the group treated with the new statin there were 100 infarcts.

What is the relative risk reduction of MI afforded by statin therapy?

(Please select 1 option)

- ○ 15%
- ○ 25%
- ○ 33%
- ○ 40%
- ○ 50%

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
110%

Questions Set : REF8847 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF8847
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Question: 43 of 100

A publication reports the outcome of a new statin therapy in a placebo controlled primary prevention of ischaemic heart disease in a diabetic population.

1000 patients were randomised to receive the new therapy and 1000 allocated to placebo. The study was completed over a five year period.

In the placebo group there were 150 myocardial infarcts (MI) and in the group treated with the new statin there were 100 infarcts.

What is the relative risk reduction of MI afforded by statin therapy?

(Please select 1 option)

○	15%
◉	25% ✕ Incorrect answer selected
○	33% ← This is the correct answer
○	40%
○	50%

There are 50 fewer MIs in the treated group than the placebo treated group, hence 50/150=33%.

The relative risk reduction provides information regarding the efficacy of a therapy and what reduction in risk may be expected when treating subjects rather then just having data relating to the significance of the data.

Done
Internet | Protected Mode: On
110%

Questions Set : REF8279 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF8279
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 49 mins 30 secs

Question: 44 of 100

A 17-year-old female presents after taking an overdose of her grandmother's medication.

Investigations revealed a serum potassium of 6 mmol/L (3.5-4.9).

Which one of the following drugs is the most likely cause of this abnormality?

(Please select 1 option)

- Aspirin
- Digoxin
- Fluoxetine
- Omeprazole
- Propranolol

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Questions.aspx
Internet | Protected Mode: On
110%

Questions Set : REF8279 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF8279
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 51 mins 6 secs

Question: 44 of 100

A 17-year-old female presents after taking an overdose of her grandmother's medication.

Investigations revealed a serum potassium of 6 mmol/L (3.5-4.9).

Which one of the following drugs is the most likely cause of this abnormality?

(Please select 1 option)

○	Aspirin
○	Digoxin
○	Fluoxetine
○	Omeprazole
◉	Propranolol ✓ Correct

Betablockers, particularly propranolol, in overdose can cause hyperkalaemia by transmembrane shifts. It is useful to think of the opposite - beta-agonists such as salbutamol are far more widely known to cause hypokalaemia.

Overdose of digoxin therapy most commonly manifests as rhythm disturbance and may be exacerbated by hyper- or hypokalaemia.

Salicylate overdose causes metabolic acidosis and respiratory alkalosis.

Done
Internet | Protected Mode: On
110%

Questions Set : REF8260 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF8260
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 51 mins 6 secs

Question: 45 of 100

A 28-year-old man presented with hypertension.

On examination he had palpable kidneys and abdominal ultrasound shows bilaterally enlarged cystic kidneys.

Which one of the following conditions is most likely to be present in this patient?

(Please select 1 option)

- Mitral stenosis
- Nail dystrophy
- Polycythaemia
- Short stature
- Testicular atrophy

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Questions.aspx
Internet | Protected Mode: On
110%

Questions Set : REF8260 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF8260
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 52 mins 41 secs

Question: 45 of 100

A 28-year-old man presented with hypertension.

On examination he had palpable kidneys and abdominal ultrasound shows bilaterally enlarged cystic kidneys.

Which one of the following conditions is most likely to be present in this patient?

(Please select 1 option)

○	Mitral stenosis
○	Nail dystrophy
◉	Polycythaemia ✓ Correct
○	Short stature
○	Testicular atrophy

The most likely diagnosis here is adult polycystic kidney disease, which is associated with valvular heart abnormalities, incompetence and aneurysms of the cerebral circulation.

However, it is also associated with excessive erythropoietin production and polycythaemia.

Next question

Tag Question

Remove question

Done
Internet | Protected Mode: On
110%

Questions Set : REF7558 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF7558
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 52 mins 41 secs

Question: 46 of 100

A 25-year-old female wishes to start a family but she is concerned as her 50-year-old mother had adult polycystic kidney disease.

Examination reveals no specific abnormalities.

Which is the most appropriate screening test for polycystic kidney disease in this woman?

(Please select 1 option)

- Genetic linkage analysis
- Intravenous urogram
- Isotope renography
- Renal ultrasound
- Urinalysis

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
110%

Questions Set : REF7558 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF7558
Page Safety Tools

Intravenous urogram

Isotope renography

Renal ultrasound ✓ Correct

Urinalysis

The answer lies between renal ultrasound and genetic linkage analysis. Polycystic kidney disease is an autosomal dominant disorder. Mutations in at least three different genes can lead to autosomal dominant polycystic disease (APKD).

1. PKD-1 on chromosome 16: 85% of cases. Polycystin 1 is an integral membrane glycoprotein involved in cell/matrix interactions
2. PKD-2 on chromosome 4: 10% of cases. Polycystin 2 which may associate with polycystin 1 through a common signalling pathway
3. A third gene mutation is known but its exact chromosomal location is not.

Diagnosis is made by multiple bilateral renal cysts and a positive family history.

Genetic linkage studies: Can exclude or make the diagnosis in younger patients. Requires blood from at least two affected family members.

Ultrasonography:

- In PKD 1 families, age related diagnostic criteria are used: two cysts in under 30 years age group.
- At least two cysts in each kidney in 30-59 years. Four cysts in each kidney for over 60 years.

CT: More sensitive than USS and may aid in diagnosis in younger patients.

MR angiography: In patients with a family history of intracranial aneurysm - to screen for cerebral aneurysms.

Next question Tag Question Remove question

Done Internet | Protected Mode: On 110%

Questions Set : REF6922 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF6922
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 53 mins 40 secs

Question: 47 of 100

In a trial of statin therapy in the secondary prevention of ischaemic heart disease, therapy is shown to reduce cardiovascular mortality from 12% to 8% over the five years duration of the study.

In comparison with standard therapy, what is the number of patients that need to be treated to prevent one death over five years?

(Please select 1 option)

- 5
- 10
- 20
- 25
- 50

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
110%

Questions Set : REF6922 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF6922
Page
Safety
Tools

Question: 47 of 100

In a trial of statin therapy in the secondary prevention of ischaemic heart disease, therapy is shown to reduce cardiovascular mortality from 12% to 8% over the five years duration of the study.

In comparison with standard therapy, what is the number of patients that need to be treated to prevent one death over five years?

(Please select 1 option)

○	5
○	10
◉	20 ✕ Incorrect answer selected
○	25 ← This is the correct answer
○	50

The drug has reduced the risk of death post myocardial infarction (MI) by 4% over five years.

Therefore if 100 people were treated we could expect the prevention of four deaths.

Therefore in order to prevent one death, 25 individuals would need to treated.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Internet | Protected Mode: On
110%

Questions Set : REF6889 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF6889
Page Safety Tools

Dashboard
Questions
Scores
Community
Help
Shop

A 79-year-old woman presents with mild dyspnoea and confusion. Of note in her past medical history was a one year history of Raynaud's phenomenon.

On examination her pulse was 118 beats per minute, she had a blood pressure of 122/88 mmHg and she had a small ulcer on her right big toe.

Auscultation of her chest revealed bibasal crackles and she had mild ankle oedema.

Her investigations show:

Haemoglobin	9.5 g/dl	(11.5-16.5)
White cell count	3.5 x 10^9/l	(4-11)
Platelet count	110 x 10^9/l	(150-400)
Serum total protein	120 g/l	(61-76)

Serum immunoglobulins:

IgA	0.8 g/l	(0.8-3.0)
IgG	15 g/l	(6.0-13.0)
IgM	70 g/l	(0.4-2.5)

Which of the following complications is she likely to develop?

(Please select 1 option)

- Acute renal failure

Done
Internet | Protected Mode: On
110%

Questions Set : REF6889 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
File Edit View Favorites Tools Help
Favorites Suggested Sites Get More Add-ons
Questions Set : REF6889
Page Safety Tools

White cell count	3.5 x 10^9/l	(4-11)
Platelet count	110 x 10^9/l	(150-400)
Serum total protein	120 g/l	(61-76)

Serum immunoglobulins:

IgA	0.8 g/l	(0.8-3.0)
IgG	15 g/l	(6.0-13.0)
IgM	70 g/l	(0.4-2.5)

Which of the following complications is she likely to develop?

(Please select 1 option)

- Acute renal failure
- Atypical pneumonia
- Erythema repens gyratum
- Hyperviscosity syndrome
- Pathological bone fracture

Submit answer | Skip question | Tag Question | Remove question

Done
Internet | Protected Mode: On
110%

Questions Set : REF6889 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF6889
Page Safety Tools

○	Hyperviscosity syndrome ← This is the correct answer
◉	Pathological bone fracture ✕ Incorrect answer selected

This elderly woman has a very raised IgM level, pancytopenia, Raynaud's phenomenon and a foot ulcer.

The most likely diagnosis here is Waldenström's macroglobulinaemia (WM). WM refers to a condition that presents in the seventh or eighth decade of life.

It is characterised by the presence of a high level of a macroglobulin (immunoglobulin M [IgM]), elevated serum viscosity and the presence of a lymphoplasmacytic infiltrate in the bone marrow, resulting in pancytopenias.

Raynaud's phenomenon may herald the onset of this condition and is due to cryoglobulinaemia.

The monoclonal IgM causes

- Hyperviscosity syndrome
- Cryoglobulinaemia types 1 and 2
- Coagulation abnormalities
- Polyneuropathies
- Cold agglutinin disease and anaemia
- Primary amyloidosis
- Tissue deposition of amorphous IgM in skin, the gastrointestinal tract, kidneys, and other organs.

Next question Remove Tag Remove question

Done Internet | Protected Mode: On 110%

Questions Set : REF6382 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites | Suggested Sites | Get More Add-ons
Questions Set : REF6382
Page | Safety | Tools

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 5 mins 47 secs

Question: 49 of 100

A 51-year-old woman presented with nocturia and pruritis vulvae.

Investigations revealed:

Urine dipstick analysis	glucose 2%

Which one of he following would most reliably confirm a diagnosis of diabetes mellitus?

(Please select 1 option)

- 50 g oral glucose tolerance test
- Elevated glycated haemoglobin concentration
- Fasting plasma glucose of 6.7 mmol/L (3.0-6.0)
- Random plasma glucose of 8.3 mmol/L
- Two hour post-prandial plasma glucose of 12 mmol/L (<11.1)

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd. All rights reserved. Terms and conditions Privacy policy
Done
Internet | Protected Mode: On
110%

Questions Set : REF6382 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF6382
Page Safety Tools

Investigations revealed:

Urine dipstick analysis	glucose 2%

Which one of he following would most reliably confirm a diagnosis of diabetes mellitus?

(Please select 1 option)

- ○ 50 g oral glucose tolerance test
- ○ Elevated glycated haemoglobin concentration
- ○ Fasting plasma glucose of 6.7 mmol/L (3.0-6.0)
- ○ Random plasma glucose of 8.3 mmol/L
- ◉ Two hour post-prandial plasma glucose of 12 mmol/L (<11.1) ✓ Correct

The post-prandial glucose gives an equivalent to the 75 g glucose tolerance test which would be one of the investigations of choice in this patient.

None of the other results listed here formally confirm the diagnosis of type 2 diabetes.

Next question Tag Question Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
110%

Questions Set : REF64158 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF64158
Page Safety Tools

Dashboard
Questions
Scores
Community
Help
Shop

Work Smart Session - MRCP Part 1

Time taken: 5 mins 4 secs

Question: 4 of 100

What is the mechanism of action of glycopeptides (e.g. vancomycin)?

(Please select 1 option)

- **A** Cell wall inhibition ✓ Correct
- **B** Inhibition of protein synthesis (translation)
- **C** Inhibition of protein synthesis (transcription)
- **D** Inhibition of folic acid metabolism
- **E** Interference with DNA replication

Glycopeptides inhibit cell wall synthesis through steric hindrance of peptidoglycans, components of the bacterial cell wall.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
100%

Questions Set : REF59843 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF59843
Page Safety Tools

Work Smart Session - MRCP Part 1

Time taken: 5 mins 4 secs

Question: 5 of 100

The CAPRIE study looked at whether aspirin or clopidogrel was most appropriate in patients at increased risk of cardiovascular disease to prevent the MACE composite endpoint, which consists of stroke, MI or cardiovascular death, re-hospitalisation or bleeding.

A substudy looked at 3,866 patients with a history of diabetes and found an event rate of 17.7% for patients taking aspirin, versus 15.6% for patients taking clopidogrel.

What is the number needed to treat (NNT) to prevent one event for patients taking clopidogrel versus aspirin?

(Please select 1 option)

- 2.1
- 15.6/17.7
- 100/2.1
- 100/15.6
- 100/17.7

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
100%

Questions Set : REF6367 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF6367
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 6 mins 41 secs

Question: 50 of 100

A letter to a medical journal suggested that an established antidepressant may cause photosensitivity. The manufacturer wished to set up a study to determine rapidly and efficiently whether this was a true association.

Which one of the following techniques is most appropriate?

(Please select 1 option)

- A dose ranging study
- A case control study
- A double blind, randomised, placebo controlled study
- A meta-analysis
- A sequential trial

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
110%

Questions Set : REF6367 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF6367
Page
Safety
Tools

○	A double blind, randomised, placebo controlled study
◉	A meta-analysis ✓ Correct
○	A sequential trial

A sequential trial is one in which the data are analysed after each participant's results become available, and the trial continues until a clear benefit is seen in one of the comparison groups, or it is unlikely that any difference will emerge.

The main advantage of sequential trials is that they will be shorter than fixed length trials when there is a large difference in the effectiveness of the interventions being compared. Their use is restricted to conditions where the outcome of interest is known relatively quickly.

In a case control study, patients who have developed a disease are identified and their past exposure to aetiological factors is compared with that of controls who do not have the disease.

A double-blind randomised placebo controlled study does not seem appropriate in this case, and a dose-ranging study would be used in the early stages of drug development to identify common side effects, perhaps toxicity, and threshold efficacy doses.

The most appropriate study would probably be a meta-analysis. This is because:

- the drug is in the market place
- large studies will have taken place in order for it to obtain its license the data are available relatively rapidly (compared with the other options in this question)
- the analysis could be carried out efficiently (cheaply if one were being cynical), and
- the results of the trial would also be available rapidly.

Next question
Tag Question
Remove question
Done
Internet | Protected Mode: On
110%

Questions Set : REF6313 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF6313 Welcome to Facebook — ...
Page Safety Tools

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 7 mins 35 secs

Question: 51 of 100

A 17-year-old girl presents with a two week history of urticaria.

Over the last couple of days she has been aware of new lesions occurring on a daily basis.

Which one of the following statements is most likely to be correct?

(Please select 1 option)

- She is likely to have an associated asthma
- She is likely to have taken penicillin recently
- She is unlikely to have any identifiable trigger factor
- The lesions will be present for at least 24 hours
- There is likely to be a nut allergy

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Questions.aspx
Internet | Protected Mode: On
110%

Questions Set : REF6313 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF6313 Facebook
Page Safety Tools

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 8 mins 42 secs

Question: 51 of 100

A 17-year-old girl presents with a two week history of urticaria.

Over the last couple of days she has been aware of new lesions occurring on a daily basis.

Which one of the following statements is most likely to be correct?

(Please select 1 option)

◉	She is likely to have an associated asthma ✕ Incorrect answer selected
○	She is likely to have taken penicillin recently
○	She is unlikely to have any identifiable trigger factor ← This is the correct answer
○	The lesions will be present for at least 24 hours
○	There is likely to be a nut allergy

The commonest form of urticaria is idiopathic and there is no identifiable trigger.

Peanut allergy and penicillin may cause urticarial rashes but there is usually an associated specific history of contact with the allergen.

Urticarial lesions last less than 24 hours usually.

Next question Tag Question Remove question

Show to
Waiting for http://my.onexamination.com/Assessment/Questions.aspx...
Internet | Protected Mode: On
110%

Questions Set : REF6066 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF6066 Yahoo! مكتوب
Page Safety Tools

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 8 mins 42 secs

Question: 52 of 100

Which of the following organelles contains enzymes responsible for the digestion of constituents of cells and tissues?

(Please select 1 option)

- Endoplasmic reticulum
- Golgi apparatus
- Lysosomes
- Microtubules
- Mitochondria

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Internet | Protected Mode: On 110%

Questions Set : REF6066 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF6066 تسجيل الدخول إلى Yahoo!
Page Safety Tools

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 9 mins 25 secs

Question: 52 of 100

Which of the following organelles contains enzymes responsible for the digestion of constituents of cells and tissues?

(Please select 1 option)

○	Endoplasmic reticulum
○	Golgi apparatus
◉	Lysosomes ✓ Correct
○	Microtubules
○	Mitochondria

The lysosomes contain the enzymes and molecules such as oxidases, free radical etc. responsible for the breakdown of intracellular components. Micortubules are involved in mitotic processes and intracellular transportation. The mitochondria produce energy for cellular functions.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Internet | Protected Mode: On 110%

Questions Set : REF5696 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx?id=629485&ws=true
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF5696
Demonoid.me
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 9 mins 25 secs

Question: 53 of 100

Which of the following hormones acts through cyclic AMP as the second messenger?

(Please select 1 option)

- Insulin
- Oestradiol
- PTH
- TRH
- Triiodothyronine

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Internet | Protected Mode: On
110%

Questions Set : REF5696 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx?id=629485&ws=true
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF5696
Page
Safety
Tools

○	Oestradiol
◉	PTH ✓ Correct
○	TRH
○	Triiodothyronine

Unlike steroids (progesterone, testosterone, oestradiol and cortisol) other ionic hormones such as:

- Adrenaline
- Growth hormone-releasing hormone (GHRH)
- Glucagon
- Luteinising hormone (LH)
- Follicle stimulating hormone (FSH)
- Parathyroid hormone (PTH)
- Thyroid-stimulating hormone (TSH)

are unable to pass the plasma membrane acting upon cell surface receptors and then through cyclic adenosine monophosphate (cAMP) as the second messenger.

Insulin acts through mitogen-activated protein (MAP) kinase pathway, as does growth hormone (GH) and prolactin.

- Thyroid releasing hormone (TRH)
- Gonadatrophin-releasing hormone (GnRH)
- Antidiuretic hormone (ADH)

Done
Internet | Protected Mode: On
110%

Questions Set : REF5696 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx?id=629485&ws=true
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF5696
Page
Safety
Tools

Unlike steroids (progesterone, testosterone, oestradiol and cortisol) other ionic hormones such as:

- Adrenaline
- Growth hormone-releasing hormone (GHRH)
- Glucagon
- Luteinising hormone (LH)
- Follicle stimulating hormone (FSH)
- Parathyroid hormone (PTH)
- Thyroid-stimulating hormone (TSH)

are unable to pass the plasma membrane acting upon cell surface receptors and then through cyclic adenosine monophosphate (cAMP) as the second messenger.

Insulin acts through mitogen-activated protein (MAP) kinase pathway, as does growth hormone (GH) and prolactin.

- Thyroid releasing hormone (TRH)
- Gonadatrophin-releasing hormone (GnRH)
- Antidiuretic hormone (ADH)

act through calcium/phosphoinositide.

Nitric oxide and atrial natriuretic peptide (ANP) act through cyclic guanosine monophosphate (cGMP).

Triiodothyronine (T3) acts by binding to intracellular receptors.

Done
Internet | Protected Mode: On
110%

Questions Set : REF5693 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx?id=629485&ws=true
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF5693
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 10 mins 38 secs

Question: 54 of 100

Which one of the following conditions is a polygenic disorder?

(Please select 1 option)

- Amyotrophic lateral sclerosis (ALS)
- Congenital adrenal hyperplasia (CAH)
- Friedreich's ataxia
- Huntington's disease
- Klinefelter's syndrome

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
110%

Questions Set : REF5527 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF5527
RealPlayer
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 11 mins 16 secs

Question: 55 of 100

A 75-year-old female presents with an acute stroke and is noted to have a partial left homonymous hemianopia, a mild left hemiparesis and left hemisensory inattention.

Where on the right is the most likely area of infarction?

(Please select 1 option)

- Frontal lobe
- Medial temporal lobe
- Occipital lobe
- Parietal lobe
- Thalamus

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
110%

Questions Set : REF5527 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF5527
RealPlayer
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 11 mins 16 secs

Question: 55 of 100

A 75-year-old female presents with an acute stroke and is noted to have a partial left homonymous hemianopia, a mild left hemiparesis and left hemisensory inattention.

Where on the right is the most likely area of infarction?

(Please select 1 option)

- Frontal lobe
- Medial temporal lobe
- Occipital lobe
- Parietal lobe
- Thalamus

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
110%

Questions Set : REF5527 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF5527
Torrent list - Demonoid
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 13 mins 16 secs

Question: 55 of 100

A 75-year-old female presents with an acute stroke and is noted to have a partial left homonymous hemianopia, a mild left hemiparesis and left hemisensory inattention.

Where on the right is the most likely area of infarction?

(Please select 1 option)

- ○ Frontal lobe
- ○ Medial temporal lobe
- ○ Occipital lobe
- ◉ Parietal lobe ✓ Correct
- ○ Thalamus

Sensory inattention is caused by parietal lobe pathology.

Occipital lobe stroke usually causes isolated homonymous hemianopia.

Thalamic and frontal lobe infarcts do not cause visual field defects.

Next question

Tag Question

Remove question

Internet | Protected Mode: Off
110%

Questions Set : REF5356 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF5356
Torrent list - Demonoid
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 13 mins 16 secs

Question: 56 of 100

Which of the following statements regarding CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) is correct?

(Please select 1 option)

- It is associated with an abnormality of the X chromosome
- It may present with migraine
- Computerised tomography (CT) of the brain is diagnostic
- Death usually occurs in infancy
- The thalami are usually spared

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

http://my.onexamination.com/GoToShop.aspx
Internet | Protected Mode: Off
110%

Questions Set : REF5356 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF5356
Torrent list - Demonoid
Page
Safety
Tools

- It may present with migraine ✓ Correct
- Computerised tomography (CT) of the brain is diagnostic
- Death usually occurs in infancy
- The thalami are usually spared

CADASIL is a diffuse disease of small arteries, predominantly in the brain.

- It starts during mid adulthood and is characterised by:
-
- recurrent ischaemic events (transient or permanent)
- attacks of migraine with aura
- severe mood disorders
- sub-cortical dementia and
- a wide spread leukoencephalopathy on magnetic resonance imaging (MRI).
-
- CT brain is not diagnostic. Characteristic MRI changes include T2 .weighted hyperintensity of the periventricular white matter.
-
- A family history is almost always present, as it is an autosomal dominant condition, located to chromosome 19.
-
- Infarcts are subcortical, and the thalami and basal ganglia are usually involved.

Done
Internet | Protected Mode: Off
110%

Questions Set : REF5354 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF5354
Page Safety Tools

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 17 mins 23 secs

Question: 57 of 100

Which of the following statements regarding B-type natriuretic peptide (BNP), is correct?

(Please select 1 option)

- BNP augments sodium reabsorption in the kidney
- BNP causes arterial and venous smooth muscle vasodilatation
- BNP is synthesised predominantly in the cerebrovascular circulation
- BNP synthesis is decreased by thyroid hormone
- The stimulus for BNP release is increased ventricular pressure load

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Internet | Protected Mode: Off 110%

Questions Set : REF5280 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx?id=629485&ws=true
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF5280
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 23 mins 46 secs

Question: 58 of 100

A new publication describes a new test for cystic fibrosis.

You want to know what proportion of patients with cystic fibrosis would be correctly identified by this new test.

Which one of the following values would identify this?

(Please select 1 option)

- Accuracy
- Negative predictive value
- Positive predictive value
- Sensitivity
- Specificity

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Internet | Protected Mode: Off
110%

Questions Set : REF5280 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx?id=629485&ws=true
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF5280
Page
Safety
Tools

Question: 58 of 100

A new publication describes a new test for cystic fibrosis.

You want to know what proportion of patients with cystic fibrosis would be correctly identified by this new test.

Which one of the following values would identify this?

(Please select 1 option)

○	Accuracy
○	Negative predictive value
○	Positive predictive value
◉	Sensitivity ✓ Correct
○	Specificity

The proportion of patients with the disease who would be identified by the new test is the sensitivity. This refers to the proportion with the disease who truly have cystic fibrosis and are identified as such by the test.

Positive predictive value refers to the percent of people having a positive test who actually have the disease interpreted in conjunction to the prevalence of the disease (true positives/true positives+false positives).

Next question

Tag Question

Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
110%

Questions Set : REF5210 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF5210
Page Safety Tools

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 27 mins 25 secs

Question: 59 of 100

These are the blood gas results obtained in a 20-year-old female admitted to hospital.

Hydrogen ion concentration	35 nmol/l	(35-45)
pH	7.45	(7.36-7.44)
pCO_2	6.8 kPa	(4.7-6.0)
Bicarbonate	32 mmol/l	(20-28)

Which one of the following is a recognised cause of this acid-base disorder?

(Please select 1 option)

- Amitriptyline overdose
- Cushing's syndrome
- Hepatic failure
- Pregnancy
- Salicylate poisoning

Submit answer | Skip question | Tag Question | Remove question

Done
Internet | Protected Mode: Off
110%

Questions Set : REF5210 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF5210
Page
Safety
Tools

○	Cushing's syndrome
○	Hepatic failure
○	Pregnancy ← This is the correct answer
◉	Salicylate poisoning ✕ Incorrect answer selected

This patient has a mild metabolic alkalosis with what appears to be respiratory compensation as reflected by the elevated pCO_2.

Amitriptyline overdose is associated with acidosis as is salicylate poisoning.

Hepatic failure usually presents with acidosis.

This type of picture is associated with:

- prolonged vomiting (as in pregnancy)
- diarrhoea
- diuretic therapy
- Cushing's syndrome
- those receiving high dose corticosteroids.

With no other information provided for this case, common things being common, one should select pregnancy as the best answer for a 20-year-old female.

Next question | Tag Question | Remove question

Done
Internet | Protected Mode: Off
110%

Questions Set : REF59843 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF59843
Page Safety Tools

A substudy looked at 3,866 patients with a history of diabetes and found an event rate of 17.7% for patients taking aspirin, versus 15.6% for patients taking clopidogrel.

What is the number needed to treat (NNT) to prevent one event for patients taking clopidogrel versus aspirin?

(Please select 1 option)

○	2.1
○	15.6/17.7
○	100/2.1 ← This is the correct answer
◉	100/15.6 ✕ Incorrect answer selected
○	100/17.7

The number needed to treat to prevent one specified outcome event is 100 divided by the absolute risk reduction, in this case 17.7-15.6%= 2.1%. This equals 48, meaning that 48 patients need to be treated with clopidogrel versus aspirin to prevent one stroke, MI cardiovascular death, bleed or hospitalisation.

For many studies now, papers quote the number needed to harm. This uses the same principle to establish the difference in absolute risk of an adverse event occurring between two treatment strategies, calculating a number needed to harm by dividing 100 by the absolute risk.

Calculation of both number needed to treat and number needed to harm for a new therapy allows clinicians to establish net clinical benefit.

Further reading:
Comparative Benefits of Clopidogrel and Aspirin in High-Risk Patient Populations (pdf) Arch Intern Med. 2004;164:2106-2110

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
100%

Questions Set : REF59820 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF59820
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 7 mins 52 secs

Question: 6 of 100

You are reviewing the results of a clinical trial of a new agent for treating type 2 diabetes mellitus. There are a number of analyses presented as part of the study.

Which of the following would be considered the most robust?

(Please select 1 option)

- All patients who took one dose of medication
- Intention to treat
- One month completer
- Per protocol
- Trial completer

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
100%

Questions Set : REF5207 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF5207
Page
Safety
Tools

Dashboard
Questions
Scores
Community
Help
Shop

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 29 mins 4 secs

Question: 60 of 100

An 18-year-old male is diagnosed with Becker's muscular dystrophy.

Which of the following statements concerning the genetics of the condition is correct?

(Please select 1 option)

- His brothers will all be affected
- His daughters will have a 50% chance of being carriers
- His daughters' sons will have a 50% chance of having the disease
- His sons will be carriers of the condition
- His sons' children will have a 50% chance of having the disease

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
110%

Questions Set : REF5207 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF5207
Page Safety Tools

Dashboard
Questions
Scores
Community
Help
Shop

An 18-year-old male is diagnosed with Becker's muscular dystrophy.

Which of the following statements concerning the genetics of the condition is correct?

(Please select 1 option)

○	His brothers will all be affected
○	His daughters will have a 50% chance of being carriers
◉	His daughters' sons will have a 50% chance of having the disease ✓ Correct
○	His sons will be carriers of the condition
○	His sons' children will have a 50% chance of having the disease

Becker's muscular dystrophy is an X-linked condition and so 50% of males will be affected in a family.

His sons will get the X chromosome from his wife and so will not be carriers but all his daughters will be carriers.

However, his daughters' sons will consequently have a 50% chance of inheriting the disease as all his daughters are carriers and there is a one in two chance (50:50) of passing the gene onto their sons.

On the other hand his sons who are not affected do not pass on the condition.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
110%

Questions Set : REF5149 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx?id=629485&ws=true
Favorites Suggested Sites Get More Add-ons
Questions Set : REF5149
Page Safety Tools

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 30 mins 6 secs

Question: 61 of 100

Which of the following would invalidate the use of the unpaired *t* test in the comparison of mean drug concentrations between two groups of subjects?

(Please select 1 option)

- Insufficient statistical power
- Non-normal distribution of data
- Small sample size
- Small standard error
- Unequal sample sizes in both groups

Submit answer | Skip question | Tag Q

© 2011 BMJ Publishing Group Ltd . All rights reserved . Te

Avira
Guard: Malware found
Date/Time: 07/03/32, 07:20:07 ص
Type: Detection
A virus or unwanted program 'DR/Monder.436224' was found in file 'D:\Vuze Downloads\...\Activator.exe'.
Access to this file was denied.
Please select a further action:
Help
Remove Details

Done
Internet | Protected Mode:

Questions Set : REF5149 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx?id=629485&ws=true
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF5149
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 31 mins 11 secs

Question: 61 of 100

Which of the following would invalidate the use of the unpaired *t* test in the comparison of mean drug concentrations between two groups of subjects?

(Please select 1 option)

○	Insufficient statistical power
◉	Non-normal distribution of data ✓ Correct
○	Small sample size
○	Small standard error
○	Unequal sample sizes in both groups

The *t* test can only be used for parametric (normally distributed) data.

Insufficient statistical power as a consequence of numbers recruited would not invalidate the results of a *t* test.

It is probable that the results would be unlikely to show any difference with too few subjects, although it is possible that if the differences were large then irrespective of prior power calculations differences might be seen.

Next question | Tag Question | Remove question

Show to
Done
Internet | Protected Mode: Off
110%

Questions Set : REF5039 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF5039
Page
Safety
Tools

Dashboard
Questions
Scores
Community
Help
Shop

A 60-year-old male is brought to casualty in the early hours of the morning after being found unconscious in the street.

On examination, he was drowsy but localised to painful stimuli. There was no evidence of head injury or meningism.

Investigations revealed:

Sodium	134 mmol/l	(137-144)
Potassium	4.0 mmol/l	(3.5-4.9)
Urea	4.0 mmol/l	(2.5-7.5)
Creatinine	80 µmol/l	(60-110)
Glucose	4.5 mmol/l	(3.0-6.0)
Chloride	100 mmol/l	(95-107)
Bicarbonate	25 mmol/l	(20-28)
Plasma osmolality	385 mosmol/kg	(278-305)

What is the most likely explanation for his presentation?

(Please select 1 option)

- ○ Diazepam poisoning
- ○ Ethanol poisoning
- ○ Methanol poisoning

Done
Internet | Protected Mode: Off
110%

Questions Set : REF5039 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
File Edit View Favorites Tools Help
Favorites Suggested Sites Get More Add-ons
Questions Set : REF5039
Page Safety Tools

On examination, he was drowsy but localised to painful stimuli. There was no evidence of head injury or meningism.

Investigations revealed:

Sodium	134 mmol/l	(137-144)
Potassium	4.0 mmol/l	(3.5-4.9)
Urea	4.0 mmol/l	(2.5-7.5)
Creatinine	80 µmol/l	(60-110)
Glucose	4.5 mmol/l	(3.0-6.0)
Chloride	100 mmol/l	(95-107)
Bicarbonate	25 mmol/l	(20-28)
Plasma osmolality	385 mosmol/kg	(278-305)

What is the most likely explanation for his presentation?

(Please select 1 option)

- Diazepam poisoning
- Ethanol poisoning
- Methanol poisoning
- Phenobarbitone poisoning
- Phenytoin poisoning

Done
Internet | Protected Mode: Off
110%

Questions Set : REF5039 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF5039
Page Safety Tools

Bicarbonate	25 mmol/l	(20-28)
Plasma osmolality	385 mosmol/kg	(278-305)

What is the most likely explanation for his presentation?

(Please select 1 option)

- Diazepam poisoning
- Ethanol poisoning ← This is the correct answer
- Methanol poisoning ✕ Incorrect answer selected
- Phenobarbitone poisoning
- Phenytoin poisoning

This gent is intoxicated.

He has a normal acid base balance, slight hyponatraemia reflecting dilution, and very high osmolality reflecting the presence of ethanol.

Methanol would produce an acidosis.

Diazepam is not an osmolyte nor would the other agents produce this picture.

Next question Tag Question Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A
Done Internet | Protected Mode: Off 110%

Questions Set : REF4820 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF4820
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 35 mins 54 secs

Question: 63 of 100

Which of the following statements concerning iron metabolism is correct?

(Please select 1 option)

- Approximately 0.1% of body iron circulates in the plasma
- Approximately 90% of dietary iron is absorbed in the intestine
- The main route of excretion is the liver
- The serum ferritin concentration is reduced characteristically following surgery
- The transferrin content of intestinal mucosal cells is high when body iron stores are high

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
110%

Questions Set : REF4820 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF4820
Page Safety Tools

Question: 65 of 100

Which of the following statements concerning iron metabolism is correct?

(Please select 1 option)

○	Approximately 0.1% of body iron circulates in the plasma ← This is the correct answer
◉	Approximately 90% of dietary iron is absorbed in the intestine ✕ Incorrect answer selected
○	The main route of excretion is the liver
○	The serum ferritin concentration is reduced characteristically following surgery
○	The transferrin content of intestinal mucosal cells is high when body iron stores are high

Approximately 4 mg of iron circulate within the plasma with a total body iron store of 3-4 g (2500 mg in the RBCs, 500 mg in liver, 500 mg in macrophages and about 500 mg in muscle).

From an intake of approximately 6 mg/1000 kcal of dietary iron only 15% is bioavailable.

The majority of iron contained within the RBCs is metabolised and re-utilised but 1 mg per day is lost through the gut.

Ferritin, the plasma protein responsible for binding iron, is an acute phase reactant protein and increases in inflammatory conditions following surgery.

Transferrin is a glycoprotein responsible for internal iron exchange and the content within mucosal cells is naturally low in haemochromatosis with high saturation.

Next question | Tag Question | Remove question

Done
Internet | Protected Mode: Off
110%

Questions Set : REF4813 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF4813
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 38 mins 24 secs

Question: 64 of 100

A 65-year-old woman presented with a malabsorption syndrome.

She had a past history of radiotherapy for cervical cancer.

Small intestine biopsy reveals

- villous atrophy and crypt hypertrophy

- chronic inflammatory cell infiltrate of the lamina propria together with

- increase in intra-epithelial lymphocytes.

What is the most likely diagnosis?

(Please select 1 option)

○	Bacterial overgrowth
○	Coeliac disease
○	Crohn's disease
○	Mesenteric ischaemia
○	Radiation enteropathy

Done
Internet | Protected Mode: Off
110%

Questions Set : REF4813 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF4813
Page
Safety
Tools

- increase in intra-epithelial lymphocytes.

What is the most likely diagnosis?

(Please select 1 option)

○	Bacterial overgrowth
◉	Coeliac disease ✓ Correct
○	Crohn's disease
○	Mesenteric ischaemia
○	Radiation enteropathy

Do not be put off by the description of the case; these histological features are typical of coeliac disease with

- villous atrophy

- crypt hyperplasia/hypertrophy

- inflammatory infiltrate of the lamina propria and

- intra-epithelial lymphocytes.

Useful serology includes anti-TTG antibodies which would be expected in over 90% of cases.

Treatment of this case would therefore entail gluten-free diet.

Next question
Tag Question
Remove question
Done
Internet | Protected Mode: Off
110%

Questions Set : REF4562 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF4562
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 49 mins 16 secs

Question: 65 of 100

A 43-year-old man has had vague malaise for three weeks.

Physical examination is normal, except for a blood pressure of 150/95 mmHg and pitting oedema of the legs to the knees.

Dipstick urinalysis shows no glucose, blood, ketones, nitrite, or urobilinogen, and the microscopic urinalysis reveals no RBC/hpf and only 1 WBC/hpf. Additional laboratory testing reveals a 24 hour urine protein of 4.1 gm. His serum creatinine is 350 µmol/L (60-110) with urea of 30 mmol/L (2.5-7.5). His hepatitis B surface antigen is positive.

Which of the following conditions is he most likely to have?

(Please select 1 option)

- Acute tubular necrosis
- Diabetic nephropathy
- Membranous glomerulonephritis
- Post-streptococcal glomerulonephitis
- Systemic lupus erythematosus

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
110%

Questions Set : REF4482 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx?id=629485&ws=true
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF4482
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 3 hrs 8 mins 1 secs

Question: 66 of 100

A new diagnostic test for malabsorption has been analysed and the results have yielded the following 2x2 contingency table.

	Disease present	
test result	yes	no
+ve	0.9	0.1
-ve	0.2	0.8

Applying this test to a case of chronic diarrhoea from a patient group where the prevalence of malabsorption is known to be 20% (probability = 0.2) what is the probability of a patient having malabsorption if they have a positive test?

(Please select 1 option)

- 0.16
- 0.24
- 0.48
- 0.64
- 0.8

Submit answer | Skip question | Tag Question | Remove question

Internet | Protected Mode: Off
110%

Questions Set : REF4482 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx?id=629485&ws=true
Favorites Suggested Sites Get More Add-ons
Questions Set : REF4482
Page Safety Tools

0.8 ✕ Incorrect answer selected

This is tough but the College are putting more and more Evidence Based Medicine Questions into the exam. This question tests understanding of pre-test and post-test odds, likelihood ratios, sensitivity and specificity. The calculation is as follows.

Sensitivity = 0.9/(0.9 + 0.2) = 0.818

Specificity = 0.8 / (0.1 + 0.8) = 0.889

Likelihood ratio for a postivie test (LR+) = 0.818 / (1 - 0.889) = 7.2

Pre-test **odds** = 0.2 / (1 - 0.2) = 0.25

Post-test odds = pre-test odds X LR+ = 0.25 X 7.2 = 1.8

Post-test **probability** = 1.8 / (1.8 + 1) = 0.64

	Disease present	
test result	yes	no
+ve	true positive (A)	false positive (B)
-ve	false negative (C)	true negative (D)

Done
Internet | Protected Mode: Off
110%

Questions Set : REF4481 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF4481
Page Safety Tools

Dashboard
Questions
Scores
Community
Help
Shop

Work Smart Session - MRCP Part 1

Time taken: 3 hrs 11 mins 6 secs

Question: 67 of 100

A study of a new chemotherapy drug for lung cancer is reported in a medical journal. The authors state that with the new agent the five year mortality rate was 60%. Without treatment the five year mortality rate was 80%.

Which of the following represents the absolute risk reduction using this treatment?

(Please select 1 option)

- ○ 10%
- ○ 20%
- ○ 25%
- ◉ 33%
- ○ 40%

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Waiting for http://my.onexamination.com/Assessment/Questions.aspx...
Internet | Protected Mode: Off
110%

Questions Set : REF4481 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF4481
Page Safety Tools

Which of the following represents the absolute risk reduction using this treatment?

(Please select 1 option)

○	10%
○	20% ← This is the correct answer
○	25%
◉	33% ✕ Incorrect answer selected
○	40%

The absolute risk reduction is an important figure and should always be quoted instead of the the relative risk reduction.

Examples: If a drug reduces the incidence of heart attacks from 10% to 5% then:

- The control event rate (CER) is 10%
- The experimental event rate (EER) is 5%
- The relative risk reduction (RRR) is 50%
- The absolute risk reduction (ARR) is 5%
- The number needed to treat (NNT) is 100% / 5% = 20.

Next question Tag Question Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done Internet | Protected Mode: Off 110%

Questions Set : REF4472 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF4472
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 3 hrs 23 mins 52 secs

Question: 68 of 100

Concerning complete atrioventricular septal defects which one of the following statements is true?

(Please select 1 option)

- Are seen frequently in patients with trisomy 21
- Frequently have aortic valve (AV) insufficiency
- Have a normal mitral valve structure
- Include a coronary sinus atrial septal defect (ASD)
- Include a perimembranous ventricular septal defect

Submit answer | Skip question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
110%

Questions Set : REF4472 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF4472
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 3 hrs 25 mins 10 secs

Question: 68 of 100

Concerning complete atrioventricular septal defects which one of the following statements is true?

(Please select 1 option)

◉	Are seen frequently in patients with trisomy 21 ✓ Correct
○	Frequently have aortic valve (AV) insufficiency
○	Have a normal mitral valve structure
○	Include a coronary sinus atrial septal defect (ASD)
○	Include a perimembranous ventricular septal defect

Partial AV canal defects or ostium primum ASDs are seen in Down syndrome.

Sinus venous defects seem to be rare in Down syndrome.

Possibly 50% of children with Down syndrome have a cardiac defect.

Further reading:
Cardiac defects in Down syndrome

Done
Internet | Protected Mode: Off
110%

Questions Set : REF4471 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites | Suggested Sites | Get More Add-ons
Questions Set : REF4471
Page | Safety | Tools

Work Smart Session - MRCP Part 1

Time taken: 3 hrs 25 mins 10 secs

Question: 69 of 100

You are asked to see a patient in the intensive care unit who is short of breath and tachycardic to rule out a cardiac cause of her symptoms.

A right heart catheter reveals that the mixed venous O_2 saturation is 70%; the pulmonary capillary wedge O_2 saturation is 97%. The haemoglobin is normal and the patient is afebrile.

Which of the following is the most appropriate statement that could be applied to her features?

(Please select 1 option)

- Her cardiac output is decreased
- Her cardiac output is normal
- Her heart is normal
- She has high-output failure
- She is in shock due to a non-cardiac cause

Submit answer | Skip question | Remove question

Done
Internet | Protected Mode: Off
110%

Questions Set : REF4471 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF4471
Page Safety Tools

You are asked to see a patient in the intensive care unit who is short of breath and tachycardic to rule out a cardiac cause of her symptoms.

A right heart catheter reveals that the mixed venous O_2 saturation is 70%; the pulmonary capillary wedge O_2 saturation is 97%. The haemoglobin is normal and the patient is afebrile.

Which of the following is the most appropriate statement that could be applied to her features?

(Please select 1 option)

- Her cardiac output is decreased
- Her cardiac output is normal ✓ Correct
- Her heart is normal
- She has high-output failure
- She is in shock due to a non-cardiac cause

The right heart and wedge catheters show normal saturations, the latter suggesting that she has good pulmonary oxygenation and so these features would argue against any failure.

Decreased or high output failure would certainly argue against shock of any sort; therefore, one cannot go as far as to say that she has a normal heart, so the best response (by a process of elimination) is that she has a normal output.

Next question Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

(1 item remaining) Waiting for http://my.onexamination.com/Assessment/Questions.aspx...
Internet | Protected Mode: Off 110%

Questions Set : REF59820 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF59820
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 9 mins 29 secs

Question: 6 of 100

You are reviewing the results of a clinical trial of a new agent for treating type 2 diabetes mellitus. There are a number of analyses presented as part of the study.

Which of the following would be considered the most robust?

(Please select 1 option)

○	All patients who took one dose of medication
○	Intention to treat ← This is the correct answer
○	One month completer
◉	Per protocol ✕ Incorrect answer selected
○	Trial completer

The intention to treat (ITT) analysis contains all the patients randomised to a particular therapy regardless of whether they received it or not. ITT is considered to be the analysis which is least subject to bias.

Completer analyses, whether they took one dose of medication, one month of medication or completed the study, are subject to degrees of bias.

A per protocol analysis may exclude patients who suffered an event but then did not follow the protocol accurately, for example, a patient treated with the diabetes agent who was admitted to hospital, but missed one to two doses of medication.

Next question | Tag Question | Remove question

Done
Internet | Protected Mode: On
100%

Questions Set : REF55631 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF55631
Page Safety Tools

Work Smart Session - MRCP Part 1

Time taken: 9 mins 29 secs

Question: 7 of 100

A 62-year-old man who has recently had his medication for hypertension altered presents with flushing, stridor, shortness of breath and hypotension.

He comes to the emergency department and receives intravenous hydrocortisone, intramuscular adrenaline, and intravenous antihistamine. After a slow recovery he is discharged home for planned review at the allergy clinic.

Which of the following medications is most likely to be responsible for his presentation?

(Please select 1 option)

- Amlodipine
- Atenolol
- Bendroflumethiazide
- Doxazosin
- Ramipril

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
100%

Questions Set : REF4441 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF4441
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 3 hrs 27 mins 12 secs

Question: 70 of 100

The pulmonary vascular system is different from the systemic circulation in that the pulmonary system demonstrates which of the following?

(Please select 1 option)

- High pressures, high flow rates, highly compliant vessels
- High pressures, high flow rates, low compliance vessels
- Low pressures, high flow rates, high compliance vessels
- Low pressures, low flow rates, high compliance vessels
- Low pressures, low flow rates, low compliance vessels

Submit answer | Skip question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
110%

Questions Set : REF4441 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF4441
Page Safety Tools

Dashboard
Questions
Scores
Community
Help
Shop

Work Smart Session - MRCP Part 1

Time taken: 3 hrs 28 mins 34 secs

Question: 70 of 100

The pulmonary vascular system is different from the systemic circulation in that the pulmonary system demonstrates which of the following?

(Please select 1 option)

- High pressures, high flow rates, highly compliant vessels
- High pressures, high flow rates, low compliance vessels
- Low pressures, high flow rates, high compliance vessels ✗ Incorrect answer selected
- Low pressures, low flow rates, high compliance vessels ← This is the correct answer
- Low pressures, low flow rates, low compliance vessels

The normal pulmonary circulation is characterised by low pressures, low flow rates, high compliance vessels.

Next question | Remove question

Show tools

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

(1 item remaining) Downloading picture http://my.onexamination.com/SidePortalTab.aspx?state=inactive&theme=&text=Comment:
Internet | Protected Mode: Off
110%

Questions Set : REF4427 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF4427
Page Safety Tools

A 60-year-old man was diagnosed last year with adenocarcinoma of the lung and a 4 cm mass lesion was treated with a right lower lobectomy.

He now has an abdominal CT scan that reveals scattered hepatic mass lesions and hilar lymphadenopathy. For several weeks, he has had increasing malaise.

His results show

Urinalysis	Protein +++
24 hour urine protein	2.7 g/24hr
Serum urea	30 mmol/L (2.5-7.5)
Serum creatinine	450 µmol/L (60-110)

A renal biopsy shows focal deposition of IgG and C3 with a granular pattern.

What is the most likely diagnosis?

(Please select 1 option)

- Goodpasture's syndrome
- Membranous glomerulonephritis
- Minimal change glomerulonephritis
- Nodular glomerulosclerosis
- Rapidly progressive glomerulonephritis

Done
Internet | Protected Mode: Off
110%

Questions Set : REF4427 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF4427
Page Safety Tools

Urinalysis	Protein +++
24 hour urine protein	2.7 g/24hr
Serum urea	30 mmol/L (2.5-7.5)
Serum creatinine	450 µmol/L (60-110)

A renal biopsy shows focal deposition of IgG and C3 with a granular pattern.

What is the most likely diagnosis?

(Please select 1 option)

- ○ Goodpasture's syndrome
- ○ Membranous glomerulonephritis ← This is the correct answer
- ○ Minimal change glomerulonephritis
- ○ Nodular glomerulosclerosis
- ◉ Rapidly progressive glomerulonephritis ✕ Incorrect answer selected

Most cases of membranous GN are idiopathic, but in some patients there is a history of an infection or a malignancy (usually lung) with antigenemia.

Next question Tag Question Remove question

Internet | Protected Mode: Off 110%

Questions Set : REF4426 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF4426
Page
Safety
Tools

Dashboard
Questions
Scores
Community
Help
Shop

A 15-year-old girl was seen by her family physician because of increasing lethargy. She had a recent history of the "flu".

Biochemistry tests show that she has renal impairement.

Serum sodium	140 mmol/L (137-144)
Serum potassium	4.2 mmol/L (3.5-4.9)
Serum urea	28 mmol/L (2.5-7.5)
Serum creatinine	280 µmol/L (60-110)

Her condition does not improve after several weeks on corticosteroid therapy, so a renal biopsy is performed. The biopsy demonstrates the presence of segmental sclerosis of 3 of 10 glomeruli identified in the biopsy specimen.

Immunofluorescence studies and electron microscopy do not reveal evidence for immune deposits.

What is the most appropriate advice to give regarding her condition?

(Please select 1 option)

- She has an underlying malignancy
- She may require a renal transplant in 10 years
- She will improve if she loses weight
- She will likely develop a restrictive lung disease
- She will probably improve with additional corticosteroid therapy

Done
Internet | Protected Mode: Off
110%

Questions Set : REF4426 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF4426
Page Safety Tools

Shop

Serum urea	28 mmol/L (2.5-7.5)
Serum creatinine	280 µmol/L (60-110)

Her condition does not improve after several weeks on corticosteroid therapy, so a renal biopsy is performed. The biopsy demonstrates the presence of segmental sclerosis of 3 of 10 glomeruli identified in the biopsy specimen.

Immunofluorescence studies and electron microscopy do not reveal evidence for immune deposits.

What is the most appropriate advice to give regarding her condition?

(Please select 1 option)

- She has an underlying malignancy
- **She may require a renal transplant in 10 years** ✓ Correct
- She will improve if she loses weight
- She will likely develop a restrictive lung disease
- She will probably improve with additional corticosteroid therapy

The findings point to focal segmental glomerulosclerosis (FSGS) which leads to chronic renal failure in half of cases.

The lack of resolution with corticosteroid therapy and the progression to chronic renal failure is what sets FSGS apart from minimal change disease.

Next question | Tag Question | Remove question

Done
Internet | Protected Mode: Off
110%

Questions Set : REF4366 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF4366
Page
Safety
Tools

Question: 73 of 100

A 44-year-old man has had no major medical problems throughout his life, except for arthritis pain involving all extremities for the past couple of years.

He has had worsening orthopnoea and ankle oedema in the past six months. He is afebrile. There is no chest pain. A chest x ray shows cardiomegaly with both enlarged left and right heart borders, along with pulmonary oedema.

Laboratory test findings include:

Sodium	139 mmol/l	(137-144)
Potassium	4.3 mmol/l	(3.5-4.9)
Urea	7 mmol/l	(2.5-7.5)
Creatinine	95 µmol/l	(60-110)
Glucose	8.6 mmol/l	(3.0-6.0)

Which of the following additional laboratory test findings is he most likely to have?

(Please select 1 option)

- Anti-centromere antibody titre of 1:320
- Erythrocyte sedimentation rate of 79 mm/hr
- Haemoglobin of 10.7 g/dl with MCV of 72 fl
- Serum ferritin of 3400 pmol/l
- Spherocytes in his peripheral blood smear

Internet | Protected Mode: Off
100%

Questions Set : REF4366 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF4366
Page
Safety
Tools

Which of the following additional laboratory test findings is he most likely to have?

(Please select 1 option)

○	Anti-centromere antibody titre of 1:320
○	Erythrocyte sedimentation rate of 79 mm/hr
○	Haemoglobin of 10.7 g/dl with MCV of 72 fl
◉	Serum ferritin of 3400 pmol/l ✓ Correct
○	Spherocytes in his peripheral blood smear

He has findings of a cardiomyopathy with right and left heart failure. Hereditary haemochromatosis (HHC) is suspected with a serum ferritin greater than 1000 and confirmed by genetic testing.

Hereditary haemochromatosis is characterised by diabetes, congestive cardiac failure (CCF), pseudogout and slate-grey skin.

"HHC is an autosomal recessive condition and in 90% of cases in the United Kingdom (UK) the condition is owing to homozygosity for the C282Y mutation in the HFE gene. A second mutation in the HFE gene, H63D, can cause the disease when in the presence of a single C282Y mutation (the so-called 'compound heterozygote' state). These mutations are common in people of Northern European origin with a carrier frequency of the C282Y mutation of one in 10-17, in the UK, suggesting a prevalence of people homozygous for the C282Y mutation of between one in 100 and one in 280.

"If HHC becomes symptomatic by mid-life, a general practitioner (GP) with a list size of 2,000 patients should have approximately four cases. In our experience most GPs claim to have never seen a case. Herein lies the conundrum: is HHC far more common than is currently recorded in clinical records and death registers because it is not being diagnosed, or does significant disease not develop in a large proportion of C282Y homozygotes and compound heterozygotes?"

Further reading:
Hereditary haemochromatosis: never seen a case? (pdf) Br J Gen Pract. 2001 May; 51(466): 347-348.

Done
Internet | Protected Mode: Off
100%

Questions Set : REF4336 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF4336
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 3 hrs 38 mins 14 secs

Question: 74 of 100

Which of the following is found in subjects acclimatised to life at high altitudes?

(Please select 1 option)

- Increased mean corpuscular haemoglobin concentration
- Increased pulmonary artery pressure
- Periodic respiration
- Reduced airway resistance
- Reduced cardiac output

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
100%

Questions Set : REF4336 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF4336
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 3 hrs 39 mins 35 secs

Question: 74 of 100

Which of the following is found in subjects acclimatised to life at high altitudes?

(Please select 1 option)

◉	Increased mean corpuscular haemoglobin concentration ✗ Incorrect answer selected
○	Increased pulmonary artery pressure ← This is the correct answer
○	Periodic respiration
○	Reduced airway resistance
○	Reduced cardiac output

Discriminating question!

Acclimatisation results in increased Hb with erythrocytosis.

Periodic respiration is a feature of non-acclimatisation.

Respiration is normal when subjects are acclimatised to altitude as is cardiac output.

Done
Internet | Protected Mode: Off
110%

Questions Set : REF4245 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF4245
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 3 hrs 39 mins 35 secs

Question: 75 of 100

Which of the following statements is true of Xenotransplantation?

(Please select 1 option)

- Has not yet been performed in humans
- Is characterised by a vigorous early cell-mediated immune response
- Is the transfer of organs between species
- Is the transfer of tissue grown in-vitro
- Requires a close HLA match

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
110%

Questions Set : REF4245 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF4245
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 3 hrs 40 mins 43 secs

Question: 75 of 100

Which of the following statements is true of Xenotransplantation?

(Please select 1 option)

- Has not yet been performed in humans
- Is characterised by a vigorous early cell-mediated immune response
- Is the transfer of organs between species ✓ Correct
- Is the transfer of tissue grown in-vitro
- Requires a close HLA match

Xenotransplantation is the transfer of organs between species - particularly the transfer of animal organs to humans. Compare this with allotransplantation which is the transfer of organs within the same species.

There have already been several documented cases of xenotransplantation - baboon heart, chimpanzee kidneys.

A close human leukocyte antigen (HLA) match is not possible of course, unless a transgenic species is used that express human major histocompatability complexes (HLA).

Early immune response is humoral - immunoglobulin M (IgM).

Next question | Tag Question | Remove question

Show tod
Done
Internet | Protected Mode: Off
110%

Questions Set : REF4207 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF4207
Page
Safety
Tools

Dashboard
Questions
Scores
Community
Help
Shop

Work Smart Session - MRCP Part 1

Time taken: 3 hrs 40 mins 43 secs

Question: 76 of 100

Adequate randomisation can be assumed in which of the following circumstances?

(Please select 1 option)

- All consecutive patients attending a tertiary referral centre
- A sample based on a family cluster
- A sample of those judged to be appropriate for inclusion in the study
- A sample using healthy volunteers
- A stratified random sample

Submit answer | Skip question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
110%

Questions Set : REF4207 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF4207
Page Safety Tools

A stratified random sample ← This is the correct answer

The actual patients included in the study often differ substantially from what was initially intended. This dramatically alters one's interpretation of a study.

The target population includes all those with a given disease, and is seldom fully accessible. The accessible population available for study may be biased in time or place.

It is important to randomise when selecting a sample which is supposed to represent the target population. In simple randomisation, every member of the population is numbered, and a random sample is selected.

In a stratified random sample, groups of interest are identified, and then randomisation occurs within those groups.

In systematic sampling a "periodic" approach is used. This is not really random and is open to alteration and bias.

In a cluster sample, a natural grouping of population is used (such as a family), but this may well be unrepresentative of the whole population.

Classic errors in randomisation are:

- Consecutive sampling, which may well not be representative if the study time is short.
- Convenience sampling: strong potential for bias, with volunteers generally healthier than others.
- Judgmental sample: including those that you want only. The potential for systematic error is enormous.

© 2002 Dr Colin Melville

Next question Tag Question Remove question

Done Internet | Protected Mode: Off 110%

Questions Set : REF4205 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF4205
Page
Safety
Tools

Dashboard
Questions
Scores
Community
Help
Shop

Work Smart Session - MRCP Part 1

Time taken: 3 hrs 41 mins 40 secs

Question: 77 of 100

Which of the following conditions is most likely to be detectable by growth monitoring?

(Please select 1 option)

- Hyperthyroidism
- Hypothyroidism
- Insulin dependent diabetes mellitus
- Pseudohypoparathyroidism
- XYY syndrome

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
110%

Questions Set : REF4205 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF4205
Page Safety Tools

(Please select 1 option)

○	Hyperthyroidism
○	Hypothyroidism ← This is the correct answer
○	Insulin dependent diabetes mellitus
○	Pseudohypoparathyroidism
◉	XYY syndrome ✕ Incorrect answer selected

Benefits of growth monitoring include:

Early detection of conditions such as:

- Hypothyroidism
- Growth hormone insufficiency
- Syndromes: Turner, Russell-Silver, Noonan's, skeletal dysplasias
- Growth impairment, for example, coeliac disease, inflammatory bowel disease or chronic renal failure
- Intracranial tumours
- Short normal children
- Children with short stature
- Health promotion: impaired growth may be associated with child abuse or neglect for example
- Focus of interest for parents.

Public health aspects:

Done
Internet | Protected Mode: Off
110%

Questions Set : REF4205 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF4205
Page
Safety
Tools

XYY syndrome ✕ Incorrect answer selected

Benefits of growth monitoring include:

Early detection of conditions such as:

- Hypothyroidism
- Growth hormone insufficiency
- Syndromes: Turner, Russell-Silver, Noonan's, skeletal dysplasias
- Growth impairment, for example, coeliac disease, inflammatory bowel disease or chronic renal failure
- Intracranial tumours
- Short normal children
- Children with short stature
- Health promotion: impaired growth may be associated with child abuse or neglect for example
- Focus of interest for parents.

Public health aspects:

- Secular trend of increasing growth
- Linking growth patterns in fetal life and early infancy with adult patterns of disease
- Link between height and social circumstances.

Copyright © 2002 Dr Colin Melville

Done
Internet | Protected Mode: Off
110%

Questions Set : REF4193 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF4193
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 3 hrs 42 mins 26 secs

Question: 78 of 100

Which of the following suggests a diagnosis of Hurler's syndrome rather than Hunter's syndrome?

(Please select 1 option)

- Cardiomyopathy
- Cloudy cornea
- Mental retardation
- Skeletal abnormalities
- X linked inheritance

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
110%

Questions Set : REF4193 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF4193
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 3 hrs 43 mins 30 secs

Question: 78 of 100

Which of the following suggests a diagnosis of Hurler's syndrome rather than Hunter's syndrome?

(Please select 1 option)

◉	Cardiomyopathy ✕ Incorrect answer selected
○	Cloudy cornea ← This is the correct answer
○	Mental retardation
○	Skeletal abnormalities
○	X linked inheritance

Hunter's syndrome (MPS-2) is of X linked inheritance. The corneas are clear. The skeletal involvement tends to be mild with no gibbous present, though scoliosis is often found.

Mental retardation and heart involvement are less severe than in Hurler's syndrome.

Hurler's syndrome (MPS-1) is autosomal recessive in inheritance and is associated with cloudy cornea. There is severe mental retardation, and gibbous deformation of the spine is characteristic. There is the characteristic coarse facies with hepatosplenomegaly.

Copyright © 2002 Dr Colin Melville

Next question

Tag Question

Remove question

Done
Internet | Protected Mode: Off
110%

Questions Set : REF4136 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF4136
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 3 hrs 43 mins 30 secs

Question: 79 of 100

Which of the following micro-organisms is generally sensitive to benzylpenicillin?

(Please select 1 option)

- *Bordetella pertussis*
- *Cryptococcus neoformans*
- *Legionella pneumophila*
- *Mycoplasma pneumoniae*
- *Streptococcus Pneumonaie*

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
110%

Questions Set : REF4136 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF4136
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 3 hrs 44 mins 8 secs

Question: 79 of 100

Which of the following micro-organisms is generally sensitive to benzylpenicillin?

(Please select 1 option)

- *Bordetella pertussis*
- *Cryptococcus neoformans*
- *Legionella pneumophila*
- *Mycoplasma pneumoniae*
- ◉ *Streptococcus Pneumonaie* ✓ Correct

Penicillin binds to specific penicillin-binding proteins (PBP's) in the cell wall, mainly of gram positive organisms.

Penicillin resistance is usually due to production of altered PBPs or beta-lactamases which leave the...

Penicillin is mainly useful for group A Strep., Group B Strep., meningococcal and pneumococcal infections, though anthrax are also sensitive.

Pneumococci with modified PBPs are an increasing problem.

Copyright © 2002 Dr Colin Melville

Next question | Tag Question | Remove question

Done
Internet | Protected Mode: Off
110%

Questions Set : REF55631 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF55631
Page Safety Tools

A 62-year-old man who has recently had his medication for hypertension altered presents with flushing, stridor, shortness of breath and hypotension.

He comes to the emergency department and receives intravenous hydrocortisone, intramuscular adrenaline, and intravenous antihistamine. After a slow recovery he is discharged home for planned review at the allergy clinic.

Which of the following medications is most likely to be responsible for his presentation?

(Please select 1 option)

- Amlodipine
- Atenolol
- Bendroflumethiazide
- Doxazosin
- Ramipril ✓ Correct

This man has presented with anaphylaxis.

Whilst angio-oedema may be hereditary or idiopathic, it is also associated with use of both ACE inhibitors and angiotensin receptor blockers (ARB). Given that he has recently increased his anti-hypertensive medication, presentation with angio-oedema associated with ACE inhibitor therapy seems the most likely explanation.

He should cease ramipril therapy and not commence either ACE inhibitors or ARBs in the future.

Further reading:
Anaphylaxis algorithm (pdf) Resuscitation Council (UK)

Next question Tag Question Remove question

Done
Internet | Protected Mode: On
100%

Questions Set : REF55104 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF55104
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 11 mins 22 secs

Question: 8 of 100

A 34-year-old man with polycystic kidney disease attends the transplant clinic with his 19-year-old brother.

His most recent creatinine has been measured at 342 µmol/l, and he is on several anti-hypertensive drugs and erythropoietin injections to maintain his haemoglobin, which was recently measured as 10.4 g/l.

On examination his BP is 149/87 mmHg. Other findings are consistent with chronic renal failure. His father had end stage renal failure for some years before his death.

Which of the following most accurately reflects the chances of his brother being able to donate a kidney to him?

(Please select 1 option)

- 0%
- 25%
- 33%
- 50%
- 100%

Submit answer | Skip question | Tag Question | Remove question

Done
Internet | Protected Mode: On
100%

Questions Set : REF4101 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF4101
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 3 hrs 44 mins 8 secs

Question: 80 of 100

Metabolic alkalosis is characteristically found in which of the following?

(Please select 1 option)

- An infusion of sodium chloride
- Ileostomy
- Mineralocorticoid deficiency
- Pyloric stenosis
- Salicylate poisoning

Submit answer | Skip question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
110%

Questions Set : REF4101 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF4101
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 3 hrs 45 mins 8 secs

Question: 80 of 100

Metabolic alkalosis is characteristically found in which of the following?

(Please select 1 option)

- An infusion of sodium chloride
- Ileostomy
- Mineralocorticoid deficiency
- (●) Pyloric stenosis ✓ Correct
- Salicylate poisoning

Pyloric stenosis is associated with vomiting and the loss of stomach content - hence a metabolic alkalosis.

Normal saline has a pH of 5 and may produce a mild metabolic acidosis with significant infusions.

Ileostomy may be associated with a loss of bicarbonate ions and hence acidosis.

Mineralocorticoid excess (Conn's syndrome) is also associated with a metabolic alkalosis.

Salicylates are themselves acidic and produce a metabolic acidosis.

Next question | Tag Question | Remove question

Show to
Done
Internet | Protected Mode: Off
110%

Questions Set : REF4100 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx?id=629485&ws=true
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF4100
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 3 hrs 46 mins 21 secs

Question: 81 of 100

Which of the following is true regarding chromosomes?

(Please select 1 option)

- Down syndrome is most commonly due to an extra copy of chromosome 21 inherited from the father
- A fetus with triploidy will have 47 chromosomes
- Heterochromatin is mostly composed of active genes
- **The normal human karyotype contains 22 pairs of autosomes** ✓ Correct
- Telomeres provide the point of attachment to the mitotic spindle

The human karyotype consists of 22 pairs of autosomes and 1 pair of sex chromosomes.

Down syndrome is most commonly due to trisomy of C21 with the majority a consequence of non-disjunction within the ovum.

Trisomy results in 47 chromosomes whereas triploidy is the presence of three complete sets of chromosomes instead of two in all cells.

Heterochromatin is of little genetic significance containing mostly inactivated genes.

Telomeres are the distal extremities of the chromosomal arms but the centromeres provide the point of attachment to the mitotic spindle.

Next question | Tag Question | Remove question

Done
Internet | Protected Mode: Off
110%

Questions Set : REF4087 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx?id=629485&ws=true
Favorites Suggested Sites Get More Add-ons
Questions Set : REF4087
Page Safety Tools

Work Smart Session - MRCP Part 1

Time taken: 3 hrs 46 mins 21 secs

Question: 82 of 100

Which of the following is activated by cholera toxin?

(Please select 1 option)

- Adenylate cyclase
- Guanlyate cyclase
- Peroxisome proliferator receptor (PPAR) gamma
- Sodium/potassium ATPase
- The glucose-sodium transporter

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

(1 item remaining) Waiting for http://my.onexamination.com/Assessment/Questions.aspx?id=629485&ws=true...
Internet | Protected Mode: Off
110%

Questions Set : REF4087 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx?id=629485&ws=true
Favorites Suggested Sites Get More Add-ons
Questions Set : REF4087
Page Safety Tools

Dashboard
Questions
Scores
Community
Help
Shop

Work Smart Session - MRCP Part 1

Time taken: 3 hrs 46 mins 50 secs

Question: 82 of 100

Which of the following is activated by cholera toxin?

(Please select 1 option)

- (●) Adenylate cyclase ✓ Correct
- ( ) Guanlyate cyclase
- ( ) Peroxisome proliferator receptor (PPAR) gamma
- ( ) Sodium/potassium ATPase
- ( ) The glucose-sodium transporter

Cholera toxin activates adenylate cyclase with generation of cyclic adenosine monophosphate (cAMP).

Next question | Tag Question | Remove question

Show tools

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
110%

Questions Set : REF4069 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF4069
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 3 hrs 46 mins 50 secs

Question: 83 of 100

Which of the following would be expected following distal occlusion of the posterior cerebral artery?

(Please select 1 option)

- Cerebellar ataxia
- Contralateral hemiplegia
- Dysarthria
- Homonymous hemianopia
- Palatal palsy

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
110%

Questions Set : REF4069 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF4069
Page Safety Tools

Dashboard
Questions
Scores
Community
Help
Shop

Work Smart Session - MRCP Part 1

Time taken: 3 hrs 47 mins 38 secs

Question: 83 of 100

Which of the following would be expected following distal occlusion of the posterior cerebral artery?

(Please select 1 option)

- (●) Cerebellar ataxia ✗ Incorrect answer selected
- ( ) Contralateral hemiplegia
- ( ) Dysarthria
- ( ) Homonymous hemianopia ← This is the correct answer
- ( ) Palatal palsy

Distal (peripheral territory) posterior cerebral artery stroke, homonymous hemianopia (often upper quadrantic), cortical blindness, verbal dyslexia without agraphia, hemivisual neglect, visual hallucinations(Harrisons).

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
110%

Questions Set : REF4061 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF4061
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 3 hrs 47 mins 38 secs

Question: 84 of 100

Which of the following is a typical feature of farmer's lung?

(Please select 1 option)

- Basal crackles
- Eosinophilia
- Haemoptysis
- Increased pCO2
- Positive serum paraproteins

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
110%

Questions Set : REF4061 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF4061
Page
Safety
Tools

Which of the following is a typical feature of farmer's lung?

(Please select 1 option)

○	Basal crackles ← This is the correct answer
○	Eosinophilia
○	Haemoptysis
○	Increased pCO2
◉	Positive serum paraproteins ✕ Incorrect answer selected

Farmer's lung is the commonest occupational extrinsic allergic alveolitis, due to thermophillic actinomycetes. Crackles are typically heard at the bases.

Eosinophilia can be seen but is not typical.

Immunoglobulin levels are frequently elevated but not a paraprotein.

P02 may be decreased particularly with exercise.

A restrictive pattern on LF studies is seen.

(Dr Shu Ho)

Next question

Tag Question

Remove question

Done
Internet | Protected Mode: Off
110%

Questions Set : REF4058 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF4058
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 3 hrs 48 mins 21 secs

Question: 85 of 100

A study of the intellectually handicapped was performed.

The 112 subjects, put through program A showed an increase in their mean IQ score of 6 points.

The 115 subjects, put through program B showed an increase in their mean IQ score of 4.

The p value was >0.05 .

Which of the following is true?

(Please select 1 option)

- a. The numbers are too large for a Student t-test
- b. The study demonstrates the usefulness of program A
- c. The distribution of individual values is not important
- d. Even though the difference between the means is not significant it would be appropriate to calculate confidence intervals
- f. The above results would be found by chance in less than 1:20

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
110%

Questions Set : REF4058 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF4058
Page Safety Tools

The 112 subjects, put through program A showed an increase in their mean IQ score of 6 points.

The 115 subjects, put through program B showed an increase in their mean IQ score of 4.

The p value was >0.05 .

Which of the following is true?

(Please select 1 option)

○	a. The numbers are too large for a Student t-test
○	b. The study demonstrates the usefulness of program A
○	c. The distribution of individual values is not important
◉	d. Even though the difference between the means is not significant it would be appropriate to calculate confidence intervals ✓ Correct
○	f. The above results would be found by chance in less than 1:20

a. The t-test could be used in the comparison of data and the larger the sample size the more meaningful the data.

b. A is no more useful than B or even simply repeating an IQ test?

c+d. This gives us an idea of the distribution of the data. Confidence intervals may provide more meaningful data concerning the study.

e. The chances are greater than 1 in 20 as P is greater than 0.05.

Done
Internet | Protected Mode: Off
110%

Questions Set : REF4032 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF4032
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 3 hrs 50 mins 40 secs

Question: 86 of 100

Which one of the following is true concerning antidiuretic hormone (ADH)?

(Please select 1 option)

- Carbamazepine potentiates its release
- Ethanol potentiates its release
- It circulates in the blood bound to neurohypophysin
- It is a cyclic octapeptide
- It is synthesised in the posterior pituitary

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
110%

Questions Set : REF4032 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF4032
Page Safety Tools

Question: 86 of 100

Which one of the following is true concerning antidiuretic hormone (ADH)?

(Please select 1 option)

○	Carbamazepine potentiates its release ← This is the correct answer
◉	Ethanol potentiates its release ✕ Incorrect answer selected
○	It circulates in the blood bound to neurohypophysin
○	It is a cyclic octapeptide
○	It is synthesised in the posterior pituitary

ADH is a nonapeptide manufactured in the paraventricular and supra-optic nuclei of the hypothalamus and released from the posterior pituitary.

It acts on the collecting ducts improving water permeability and hence water retention.

Carbamazepine as well as other agents such as thiazides and selective serotin reuptake inhibitors (SSRIs) may potentiate its release.

Ethanol usually inhibits release.

http://acbrown.com/kidney/Lectures/RnWatr/RnWatrAntiTrmn.htm

Done
Internet | Protected Mode: Off
115%

Questions Set : REF4027 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF4027
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 3 hrs 52 mins 2 secs

Question: 87 of 100

Which of the following is a feature of pseudohypoparathyroidism?

(Please select 1 option)

- Increased urinary phosphate and cAMP with PTH infusion
- Low serum calcium and high serum phosphate
- Low serum calcium and low serum phosphate
- Low serum PTH
- Shortened second and third metacarpals

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
115%

Questions Set : REF4027 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF4027
Page Safety Tools

Question: 87 of 100

Which of the following is a feature of pseudohypoparathyroidism?

(Please select 1 option)

- Increased urinary phosphate and cAMP with PTH infusion
- Low serum calcium and high serum phosphate ✓ Correct
- Low serum calcium and low serum phosphate
- Low serum PTH
- Shortened second and third metacarpals

The biochemistry shows a hypocalcaemia with hyperphosphataemia being usual but elevated parathyroid hormone (PTH) due to resistance to PTH.

This is due to mutation of the PTH receptor with abnormality of the Gsalpha subunit with reduced cyclic adenosine monophosphate (cAMP) production following a PTH infusion.

There are associated phenotypic signs including short stature, low IQ and shortened fourth and fifth metacarpals.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd. All rights reserved. Terms and conditions Privacy policy

Done
Internet | Protected Mode: Off
115%

Questions Set : REF2351 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF2351
Page
Safety
Tools

Dashboard
Questions
Scores
Community
Help
Shop

Work Smart Session - MRCP Part 1

Time taken: 3 hrs 53 mins 13 secs

Question: 88 of 100

An Afro-Carribean male aged 48 years presents with gradual onset of exertional dyspnoea, non-productive cough, malaise, weight loss and polyarthralgia.

Schirmer's test indicates a dry eye. x Ray of the hand shows punched out osteopenic lesions.

Which of the following investigations is unlikely to be helpful in establishing the diagnosis of this condition?

(Please select 1 option)

- Quantitative immunoglobulins.
- Serum calcium
- Serum phosphorus
- Thallium scan
- Urea and electrolytes

Submit answer | Skip question | Tag Question | Remove question

Done
Internet | Protected Mode: Off
115%

Questions Set : REF2351 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF2351 IBS treatment - Google Sea... Irritable Bowel Syndrome (... Internet Explorer cannot di...
Page Safety Tools

Schirmer's test indicates a dry eye. x Ray of the hand shows punched out osteopenic lesions.

Which of the following investigations is unlikely to be helpful in establishing the diagnosis of this condition?

(Please select 1 option)

○	Quantitative immunoglobulins.
○	Serum calcium
○	Serum phosphorus
◉	Thallium scan ✓ Correct
○	Urea and electrolytes

This condition is sarcoidosis. Serum calcium, serum phosphorus, chem7 and chem 20 and quantitative immunoglobulins are all used in establishing the diagnosis. Gallium scan is helpful in sarcoidosis. (Radiology of extrathoracic sarcoid ...)

Gallium scan vs. Thallium scan.

Gallium scan (radioactive ^{67}Ga) is used to detect inflammation - such as in inflammatory disorders or malignancy.

Thallium (radioactive ^{201}Tl) is a potassium analogue and is used to demonstrate areas of poor perfusion. It is particularly used in cardiology to detect areas of ischaemia.

Next question Tag Question Remove question

Internet | Protected Mode: Off 115%

Questions Set : REF2349 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites | Suggested Sites | Get More Add-ons
Questions Set : REF2349 | IBS treatment - Google Sea... | Irritable Bowel Syndrome (... | loperamide Oral : Uses, Sid...
Page | Safety | Tools

Work Smart Session - MRCP Part 1

Time taken: 4 hrs 1 mins 12 secs

Question: 89 of 100

Gaucher's disease is associated with the deficiency of:

(Please select 1 option)

- Arylsulphatase-A
- B- Glucosidase
- Hexosaminidase A
- Iduronidase
- Sphingomyelinase

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Internet | Protected Mode: Off | 115%

Questions Set : REF2349 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF2349
Page
Safety
Tools

Question: 89 of 100

Gaucher's disease is associated with the deficiency of:

(Please select 1 option)

○	Arylsulphatase-A
◉	B- Glucosidase ✓ Correct
○	Hexosaminidase A
○	Iduronidase
○	Sphingomyelinase

Hexosaminidase A deficiency is associated with Tay-Sachs disease.

Sphingomyelinase deficiency is associated with Niemann-Pick disease.

Arylsulphatase-A deficiency is associated with metachromic leucodystrophy.

Iduronidase deficiency is associated with Hurler's syndrome.

Next question

Tag Question

Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Waiting for http://my.onexamination.com/Assessment/Questions.aspx...
Internet | Protected Mode: Off
115%

Questions Set : REF55104 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF55104
Page
Safety
Tools

A 34-year-old man with polycystic kidney disease attends the transplant clinic with his 19-year-old brother.

His most recent creatinine has been measured at 342 µmol/l, and he is on several anti-hypertensive drugs and erythropoietin injections to maintain his haemoglobin, which was recently measured as 10.4 g/l.

On examination his BP is 149/87 mmHg. Other findings are consistent with chronic renal failure. His father had end stage renal failure for some years before his death.

Which of the following most accurately reflects the chances of his brother being able to donate a kidney to him?

(Please select 1 option)

◉	0% ✕ Incorrect answer selected
○	25%
○	33%
○	50% ← This is the correct answer
○	100%

Polycystic kidney disease (PCKD) carries an autosomal dominant inheritance pattern. As such, with one affected parent, each child has a 50% chance of inheriting the PCKD gene.

Whilst ultrasound is very sensitive in detection of PCKD in patients over 20, in those under 20 it is not 100% accurate.

It may not seem immediately obvious to consider a family member as a potential donor, but they may be a valuable source for a kidney in this situation.

Next question

Tag Question | Remove question

Done
Internet | Protected Mode: On
100%

Questions Set : REF48176 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF48176
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 14 mins 37 secs

Question: 9 of 100

Which of the following arteries are branches of the axillary artery?

(Please select 1 option)

- Inferior ulnar collateral artery
- Internal thoracic artery
- Profunda brachi artery
- Subscapular artery
- Superior ulnar collateral artery

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
100%

Questions Set : REF2348 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF2348
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 4 hrs 3 mins 42 secs

Question: 90 of 100

Are the following true regarding leukotrienes?

(Please select 1 option)

- Are formed from the cyclo-oxygenase pathway
- Are synthesised by fibroblasts
- Decrease vascular permeability
- Leukotriene D4 has been identified as SRS-A which causes bronchial wall smooth muscle relaxation
- Stimulate mucus secretion

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Internet | Protected Mode: Off
115%

Questions Set : REF2348 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF2348
Page Safety Tools

(Please select 1 option)

○	Are formed from the cyclo-oxygenase pathway
○	Are synthesised by fibroblasts
○	Decrease vascular permeability
○	Leukotriene D4 has been identified as SRS-A which causes bronchial wall smooth muscle relaxation
◉	Stimulate mucus secretion ✓ Correct

Leukotrienes are synthesised by leucocytes.

They are mediators of allergic reaction.

They increase vascular permeability and attract neutrophils and eosinophils to inflammatory sites.

Leukotrienes are synthesised via the lipoxygenase pathway.

Leukotriene D4 has been identified as SRS-A which causes bronchial wall and intestinal smooth muscle contraction (not dilatation).

Leukotrienes also stimulate mucus production, an important consideration in the pathophysiology of bronchial asthma.

Next question Tag Question Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
115%

Questions Set : REF2173 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF2173
Page
Safety
Tools

Dashboard
Questions
Scores
Community
Help
Shop

Work Smart Session - MRCP Part 1

Time taken: 4 hrs 5 mins 43 secs

Question: 91 of 100

Restriction enzymes:

(Please select 1 option)

- Are involved in cell cycle arrest
- Cut DNA
- Degrade DNA
- Join two pieces of DNA together
- Synthesise DNA

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
115%

Questions Set : REF2173 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF2173
Page Safety Tools

Dashboard
Questions
Scores
Community
Help
Shop

Work Smart Session - MRCP Part 1

Time taken: 4 hrs 6 mins 51 secs

Question: 91 of 100

Restriction enzymes:

(Please select 1 option)

- Are involved in cell cycle arrest
- Cut DNA ← This is the correct answer
- Degrade DNA
- Join two pieces of DNA together
- Synthesise DNA ✕ Incorrect answer selected

Restriction enzymes cut deoxyribonucleic acid (DNA) at sequences specific for each restriction enzyme; they are vital tools for molecular biology and molecular genetic research.

Next question | Tag Question | Remove question

Show tools

© 2011 BMJ Publishing Group Ltd. All rights reserved. Terms and conditions Privacy policy A A A

Done
Internet | Protected Mode: Off
115%

Questions Set : REF2171 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF2171
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 4 hrs 6 mins 51 secs

Question: 92 of 100

Which of the following is a glycoprotein hormone?

(Please select 1 option)

- Cortisol
- Growth hormone releasing hormone
- Oxytocin
- Thyrotropin (TSH)
- Thyrotropin releasing hormone (TRH)

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
115%

Questions Set : REF2171 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF2171
Page
Safety
Tools

Dashboard
Questions
Scores
Community
Help
Shop

Work Smart Session - MRCP Part 1

Time taken: 4 hrs 7 mins 49 secs

Question: 92 of 100

Which of the following is a glycoprotein hormone?

(Please select 1 option)

- Cortisol
- Growth hormone releasing hormone
- Oxytocin
- Thyrotropin (TSH) ✓ Correct
- Thyrotropin releasing hormone (TRH)

Thyrotropin is glycosylated, cortisol is a steroid hormone and the others are peptide hormones/neuropeptides which as a group are rarely glycosylated.

Next question | Tag Question | Remove question

Show tools

© 2011 BMJ Publishing Group Ltd. All rights reserved. Terms and conditions Privacy policy

Done
Internet | Protected Mode: Off
115%

Questions Set : REF2032 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF2032
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 4 hrs 7 mins 49 secs

Question: 93 of 100

Which of the following would be most in keeping with a diagnosis of polymyalgia rheumatica (PMR)?

(Please select 1 option)

- Erythema nodosum
- Increased alkaline phosphatase
- Raised creatine kinase (CK)
- Shoulder and pelvic girdle pain in a 40-year-old man
- Sudden loss of vision in one eye

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
115%

Questions Set : REF2032 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF2032
Page Safety Tools

Question: 93 of 100

Which of the following would be most in keeping with a diagnosis of polymyalgia rheumatica (PMR)?

(Please select 1 option)

○	Erythema nodosum
○	Increased alkaline phosphatase ← This is the correct answer
○	Raised creatine kinase (CK)
◉	Shoulder and pelvic girdle pain in a 40-year-old man ✕ Incorrect answer selected
○	Sudden loss of vision in one eye

Liver enzymes are elevated in most patients.

Visual disturbances are suggestive of temporal arteritis not PMR, and are due to ischaemic changes in ciliary arteries (optic neuritis/infarction) and less commonly due to central artery occlusion.

Raised CK occurs in polymyositis.

PMR is rare before the age of 50 years.

Next question Tag Question Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
115%

Questions Set : REF1993 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF1993
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 4 hrs 14 mins 29 secs

Question: 94 of 100

Are the following true concerning anti-neutrophilic cytoplasmic autoantibodies?

(Please select 1 option)

- ANCA positive glomerulonephritis characteristically causes nephrotic syndrome
- Cause neutropenia in SLE
- Increased in systemic lupus erythematosus (SLE)
- Positive only in Wegener's syndrome associated with renal disease
- Present in inflammatory bowel disease

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
115%

Questions Set : REF1879 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF1879
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 4 hrs 18 mins 18 secs

Question: 95 of 100

A 17-year-old female is affected by an inherited disorder. She has two brothers who are unaffected. She has two sisters both are affected. Her father is affected but not her mother.

Which of the following modes of inheritance is the best explanation?

(Please select 1 option)

- Autosomal dominant
- Autosomal recessive
- Mitochondrial
- X-linked dominant
- X-linked recessive

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Questions.aspx
Internet | Protected Mode: Off
115%

Questions Set : REF1879 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF1879
Page Safety Tools

Help

Shop

(Please select 1 option)

○	Autosomal dominant
○	Autosomal recessive
○	Mitochondrial
◉	X-linked dominant ✓ Correct
○	X-linked recessive

This is a tricky question and the crucial part is recognising that X-linked dominant conditions are transmitted by a father to all his daughters and that, on balance, this is a better explanation of the genetics than the tenuous assertion that an autosomal dominant condition has by chance affected three daughters but neither of two sons.

X-linked dominant disorders are rare (for example, vitamin D-resistant rickets). They affect both sexes but females more than males.

All children of a homozygous mother are affected.

Half the sons and half the daughters inherit the disorder from an affected mother with the trait.

An affected father passes the disease to all his daughters but none of his sons - as in this example.

Next question Tag Question Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Waiting for http://my.onexamination.com/Assessment/Questions.aspx...
Internet | Protected Mode: Off 115%

Questions Set : REF1878 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF1878
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 5 hrs 15 mins 26 secs

Question: 96 of 100

Which of the following disorders is characterised by an autosomal dominant mode of inheritance?

(Please select 1 option)

- Beta-thalassaemia
- Cystic fibrosis
- Marfan syndrome
- Wilson's disease
- Xeroderma pigmentosa

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
115%

Questions Set : REF1878 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF1878
Page
Safety
Tools

Dashboard
Questions
Scores
Community
Help
Shop

Work Smart Session - MRCP Part 1

Time taken: 5 hrs 16 mins 19 secs

Question: 96 of 100

Which of the following disorders is characterised by an autosomal dominant mode of inheritance?

(Please select 1 option)

- Beta-thalassaemia
- Cystic fibrosis
- Marfan syndrome ✓ Correct
- Wilson's disease
- Xeroderma pigmentosa

All the others are autosomal recessive of course.

Next question | Tag Question | Remove question

Show tools

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
115%

Questions Set : REF1872 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF1872
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 5 hrs 16 mins 19 secs

Question: 97 of 100

Apoptosis is the process of programmed cell death and occurs in cells that have damaged DNA.

A mediator of this process is a tumour suppressor gene that inhibits mitosis and promotes apoptosis.

This gene is which of the following?

(Please select 1 option)

- BCL-2
- Caspases
- Fas (CD95)
- p53
- Ras

Submit answer | Skip question | Tag Question | Remove question

Done
Internet | Protected Mode: Off
115%

Questions Set : REF1872 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF1872
Page Safety Tools

Question: 97 of 100

Apoptosis is the process of programmed cell death and occurs in cells that have damaged DNA.

A mediator of this process is a tumour suppressor gene that inhibits mitosis and promotes apoptosis.

This gene is which of the following?

(Please select 1 option)

○	BCL-2
○	Caspases
○	Fas (CD95)
◉	p53 ✓ Correct
○	Ras

BCL-2 is an inhibitor of apoptosis.

Fas is a cell receptor and caspases are present in all cells; both promote apoptosis but are not tumour suppressor genes.

Ras is an oncogene.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
115%

Questions Set : REF1841 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF1841
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 5 hrs 17 mins 32 secs

Question: 98 of 100

A plasmid is best described as:

(Please select 1 option)

- A recombinant section of DNA
- A small viral particle
- Bacterial DNA separate from the chromosome
- Consisting of multiple copies of a single gene
- Having multiple origins of replication

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
115%

Questions Set : REF1841 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF1841
Page
Safety
Tools

◉	A small viral particle ✕ Incorrect answer selected
○	Bacterial DNA separate from the chromosome ← This is the correct answer
○	Consisting of multiple copies of a single gene
○	Having multiple origins of replication

Plasmids are circular molecules of bacterial deoxyribonucleic acid (DNA) separate from the bacterial chromosome.

They are usually:

- small

- consisting of a few thousand base pairs

- carry one or a few genes, and

- have a single origin of replication.

Genes on plasmids with multiple copies are usually expressed at higher levels.

In nature these genes often encode for proteins such as those needed for bacterial resistance.

Plasmids can be used to clone genes by splicing a particular gene into a plasmid and then allowing the bacteria to multiply - this is then called recombinant plasmid DNA.

Next question

Tag Question

Remove question

Done
Internet | Protected Mode: Off
115%

Questions Set : REF1823 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF1823
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 5 hrs 19 mins 18 secs

Question: 99 of 100

Transcription RNA (tRNA) has three bases specific for a particular amino acid with which it binds to messenger RNA (mRNA).

Which of the following is this specific area of tRNA?

(Please select 1 option)

- Anticodon
- Codon
- Exon
- Intron
- Transposon

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
115%

Questions Set : REF1823 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF1823
Page
Safety
Tools

Question: 99 of 100

Transcription RNA (tRNA) has three bases specific for a particular amino acid with which it binds to messenger RNA (mRNA).

Which of the following is this specific area of tRNA?

(Please select 1 option)

○	Anticodon ← This is the correct answer
◉	Codon ✕ Incorrect answer selected
○	Exon
○	Intron
○	Transposon

mRNA has codons which are bound by the anticodons on tRNA during translation of protein synthesis.

Exons are coding sequences in the mRNA and introns are areas of unknown function.

Transposons are genetic sequences that have been transposed from one part of DNA to another.

Next question

Tag Question

Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
115%

Questions Set : REF48176 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF48176
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 15 mins 29 secs

Question: 9 of 100

Which of the following arteries are branches of the axillary artery?

(Please select 1 option)

- Inferior ulnar collateral artery
- Internal thoracic artery
- Profunda brachi artery
- Subscapular artery ✓ Correct
- Superior ulnar collateral artery

The internal thoracic artery arises from the subclavian artery.

The inferior and superior ulnar collateral arteries and the profunda brachii are branches of the brachial artery.

The subscapular artery arises from the axillary and is its largest branch, eventually anastomosing with the lateral thoracic and intercostal arteries.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
100%

Questions Set : REF59810 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
File Edit View Favorites Tools Help
Favorites Suggested Sites Get More Add-ons
Questions Set : REF59810
Page Safety Tools

Work Smart Session - MRCP Part 1

Time taken:

Question: 1 of 82

A 17-year-old man comes to the clinic. He has recently returned from a holiday to Spain with his friends and is very disappointed with the quality of his tan, as there appear to be large depigmented areas on the skin of his abdomen and on his back. He says the areas are itchy.

On examination you confirm the depigmentation, and there is superficial scaling over the areas.

Which of the following is the most appropriate treatment?

(Please select 1 option)

- Oral antifungals
- Oral corticosteroids
- Reassurance
- Topical antifungals
- Topical corticosteroids

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

(2 items remaining) Downloading picture http://roicharger.com/btn_bsearch.png...
Internet | Protected Mode: Off
100%

Questions Set : REF36345 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF36345
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 21 mins 38 secs

Question: 10 of 82

Which of the following is true regarding diabetic foot ulceration?

(Please select 1 option)

- Autonomic neuropathy results in increased resting blood flow
- Callus formation at pressure areas is an important predictor of ulceration
- Plantar ulceration is most commonly due to atherosclerosis
- Skin infection is the most common initiating event in ulceration
- Radiography can readily distinguish between Charcot's joint and osteomyelitis

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Internet | Protected Mode: Off
110%

Questions Set : REF36345 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF36345
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 33 mins 29 secs

Question: 10 of 82

Which of the following is true regarding diabetic foot ulceration?

(Please select 1 option)

○	Autonomic neuropathy results in increased resting blood flow
○	Callus formation at pressure areas is an important predictor of ulceration ← This is the correct answer
○	Plantar ulceration is most commonly due to atherosclerosis
◉	Skin infection is the most common initiating event in ulceration ✕ Incorrect answer selected
○	Radiography can readily distinguish between Charcot's joint and osteomyelitis

Callus formation at pressure areas is an important predictor of potential ulceration.

Plantar ulceration is usually a consequence of neuropathy.

Minor skin trauma is probably the most common initiating event.

Blood flow is often decreased with autonomic neuropathy hence sympathectomy may be performed to improve skin blood flow.

It is difficult to distinguish radiographically between Charcot's joint and osteomyelitis.

Next question

Remove Tag

Remove question

Done
Internet | Protected Mode: Off
110%

Questions Set : REF30338 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF30338
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 33 mins 29 secs

Question: 11 of 82

Which of the following determines the primary mechanical properties of skin?

(Please select 1 option)

- Dermis
- Stratum basale
- Stratum corneum
- Stratum granulosum
- Subcutaneous tissue

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
110%

Questions Set : REF30338 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF30338
Page Safety Tools

Work Smart Session - MRCP Part 1

Time taken: 34 mins 8 secs

Question: 11 of 82

Which of the following determines the primary mechanical properties of skin?

(Please select 1 option)

- Dermis
- Stratum basale
- Stratum corneum ✓ Correct
- Stratum granulosum
- Subcutaneous tissue

The stratum corneum is the last layer and provides a mechanical barrier to the skin and therefore determines the mechanical functions of the skin. The hands and feet have thick stratum corneum as compared to the lips and eyelids. The thicker the stratum corneum is the more protection there is for the skin.

The dermis also has some factor to play with its elastic fibres and fibrous tissue.

The rest of the layers are also important but the mechanical properties are primarily determined by the stratum corneum.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
110%

Questions Set : REF29690 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF29690
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 34 mins 8 secs

Question: 12 of 82

A 43-year-old female presents with a weepy, erythematous rash mainly affecting the forehead, scalp, neck and upper back.

Three days earlier she had used red hair dye at home to self-administer 'highlights'.

What is the likely diagnosis?

(Please select 1 option)

- Acne rosacea
- Contact allergic dermatitis
- Eczema
- Psoriasis
- Seborrhoeic dermatitis

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
110%

Questions Set : REF29690 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF29690
Page
Safety
Tools

What is the likely diagnosis?

(Please select 1 option)

○	Acne rosacea
◉	Contact allergic dermatitis ✓ Correct
○	Eczema
○	Psoriasis
○	Seborrhoeic dermatitis

Hair dye contains substances which may induce contact allergic dermatitis.

This type of reaction is typical for this sort of time scale, and is an example of a type IV, or delayed, hypersensitivity reaction.

Sensitisation occurs on initial exposure to the allergen and 'memory' T-cells proliferate in lymphoid tissue. Subsequent exposure to allergen induces activation of the T-lymphocytes and an inflammatory response.

Hairdressing chemicals are a very common cause of contact allergic dermatitis, a disorder which is very common amongst the hairdressing community.

A lady at this age is unlikely to present with a new, previously undiagnosed case of eczema.

Acne rosacea is usually a disorder of the skin on the cheeks and nose.

Next question

Tag Question | Remove question

Done
Internet | Protected Mode: Off
110%

Questions Set : REF22745 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx?id=644011&ws=true
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF22745
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 36 mins 33 secs

Question: 13 of 82

During a follow-up visit at an asthma clinic a 38-year-old female complains of the appearance of a mole.

Which of the following characteristics of the lesion would raise suspicion that it is a malignant melanoma?

(Please select 1 option)

- Lesion has irregular outline
- Lesion is deeply pigmented
- Lesion is present on face
- Lesion is raised
- Lesion is 6 mm in diameter

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Questions.aspx?id=644011&ws=true
Internet | Protected Mode: Off
110%

Questions Set : REF22745 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx?id=644011&ws=true
Favorites Suggested Sites Get More Add-ons
Questions Set : REF22745
Page Safety Tools

During a follow-up visit at an asthma clinic a 38-year-old female complains of the appearance of a mole.

Which of the following characteristics of the lesion would raise suspicion that it is a malignant melanoma?

(Please select 1 option)

◉	Lesion has irregular outline ✓ Correct
○	Lesion is deeply pigmented
○	Lesion is present on face
○	Lesion is raised
○	Lesion is 6 mm in diameter

The mnemonic of ABCDE regarding characteristics of a melanoma are as follows:

- A - Asymmetry - one half of the lesion does not match the other half
- B - Border irregularity
- C - Colour variegation - pigmentation is not uniform
- D - Diameter- a diameter 7 mm warrants investigation although changes in size are also important
- E - Evolution - evolving size or changes in characteristics such as nodules.

Next question Tag Question Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
110%

Questions Set : REF22633 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF22633
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 37 mins 48 secs

Question: 14 of 82

A 47-year-old woman presented with a history several years of dysphagia, hard calcified nodules in the fingers, and cold hands. Examination revealed calcified nodules, sclerodactyly and facial telangiectasia.

Which one of the following antibodies is most likely to be found in the blood?

(Please select 1 option)

- Anticardiolipin
- Anticentromere
- Anti-DNA antibodies
- Antimitochondrial
- Antimyeloperoxidase

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
110%

Questions Set : REF22633 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF22633
Page
Safety
Tools

(Please select 1 option)

○	Anticardiolipin
◉	Anticentromere ✓ Correct
○	Anti-DNA antibodies
○	Antimitochondrial
○	Antimyeloperoxidase

This patient has CREST syndrome which consists of

Calcinosis

Raynaud's phenomenon

(o)**E**sophageal dysmotility

Sclerodactyly

Telangiectasia.

It is a limited form of scleroderma with less involvement of internal organs and is better referred to as 'cutaneous limited systemic sclerosis'.

Next question

Tag Question

Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
110%

Questions Set : REF21801 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF21801
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 41 mins 9 secs

Question: 15 of 82

A 59-year-old patient of South Asian origin presents with a widespread blistering rash.

Which of the following features would be consistent with a diagnosis of pemphigus?

(Please select 1 option)

- Acanthosis
- Blisters arising within the subepidermal area
- IgA antibodies
- Oral involvement
- Treatment with methotrexate

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Internet | Protected Mode: Off
110%

Questions Set : REF21801 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF21801
Page Safety Tools

Question: 15 of 82

A 59-year-old patient of South Asian origin presents with a widespread blistering rash.

Which of the following features would be consistent with a diagnosis of pemphigus?

(Please select 1 option)

○	Acanthosis
○	Blisters arising within the subepidermal area
○	IgA antibodies
◉	Oral involvement ✓ Correct
○	Treatment with methotrexate

Pemphigus is associated with loss of intercellular cohesion in the lower part of the epidermis, leading to acantholysis (separation of keratinocytes). Pemphigus is classically associated with flaccid blistering, and often with immunoglobulin (Ig)G antibodies.

Treatment may be successful with azathioprine.

Pemphigoid is associated with subepidermal bullae.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
110%

Questions Set : REF21341 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF21341
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 56 mins 12 secs

Question: 16 of 82

A 33-year-old female attends her GP concerned regarding a mole.

Which of the following characteristics of the lesion would raise suspicion that it is a malignant melanoma?

(Please select 1 option)

- Lesion has irregular edge
- Lesion is 5 mm in diameter
- Lesion is pigmented uniformly
- Lesion is present on face
- Lesion is smoothly raised

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
110%

Questions Set : REF21341 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF21341
Page Safety Tools

A 33-year-old female attends her GP concerned regarding a mole.

Which of the following characteristics of the lesion would raise suspicion that it is a malignant melanoma?

(Please select 1 option)

◉	Lesion has irregular edge ✓ Correct
○	Lesion is 5 mm in diameter
○	Lesion is pigmented uniformly
○	Lesion is present on face
○	Lesion is smoothly raised

The mnemonic of ABCDE regarding characteristics of a melanoma are as follows:

- A - Asymmetry - one half of the lesion does not match the other half
- B - Border irregularity
- C - Colour variegation - pigmentation is not uniform
- D - Diameter- a diameter 7 mm warrants investigation although changes in size are also important
- E - Evolution - evolving size or changes in characteristics such as nodules.

Next question Tag Question Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
110%

Questions Set : REF20325 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF20325
Page Safety Tools

Work Smart Session - MRCP Part 1

Time taken: 56 mins 52 secs

Question: 17 of 82

A 16-year-old boy presents with scaly patches on his scalp. Examination reveals well-circumscribed, circular areas of hair loss, 2-5 cm in diameter with scaling and raised margins. There is no scarring.

What is the most likely cause in this patient?

(Please select 1 option)

- Discoid lupus erythematosus
- Lichen planus
- Morphoea
- Systemic lupus erythematosus
- Tinea capitis

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
110%

Questions Set : REF20325 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF20325
Page
Safety
Tools

○	Morphoea
○	Systemic lupus erythematosus
◉	Tinea capitis ✓ Correct

This patient has non-scarring alopecia due to invasion of hairs by dermatophytes, most commonly *Trichophyton tonsurans*.

The most common causes of non-scarring alopecia include:

- Telogen effluvium
- Androgenetic alopecia
- Alopecia areata
- Tinea capitis
- Traumatic alopecia.

Less commonly, non-scarring alopecia is associated with lupus erythematosus and secondary syphilis.

Scarring alopecia is more frequently the result of a primary cutaneous disorder such as:

- Lichen planus
- Folliculitis decalvans
- Cutaneous lupus
- Linear scleroderma (morphoea).

Next question | Tag Question | Remove question

Done
Internet | Protected Mode: Off
110%

Questions Set : REF20324 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF20324
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 58 mins 33 secs

Question: 18 of 82

A 22-year-old man consults his GP complaining of redness and itching on his face and hands.

He has regularly visited another GP for similar complaints within the last two years and has been signed off on sick leave from employment as a builder. He is in receipt of benefits and reports that he is in the process of making an insurance claim for loss of earnings.

He says that there was one ointment that cured the problem but he had not been able to find any proprietary medication that works. Examination showed no skin lesions and no apparent rash.

What is the most likely diagnosis?

(Please select 1 option)

- Conversion disorder
- Delusional disorder
- Malingering
- Munchausen syndrome
- Obsessive compulsive disorder

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Internet | Protected Mode: Off
110%

Questions Set : REF20324 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF20324
Page Safety Tools

builder. He is in receipt of benefits and reports that he is in the process of making an insurance claim for loss of earnings.

He says that there was one ointment that cured the problem but he had not been able to find any proprietary medication that works. Examination showed no skin lesions and no apparent rash.

What is the most likely diagnosis?

(Please select 1 option)

- Conversion disorder
- Delusional disorder
- Malingering ✓ Correct
- Munchausen syndrome
- Obsessive compulsive disorder

In somatoform disorders, both illness production and motivation are unconscious drives.

In malingering, as suggested here, the patient consciously fakes or claims to have a disorder in order to attain a specific gain (for example, financial).

Münchausen syndrome is manifested by a chronic history of multiple hospital admissions and willingness to receive invasive procedures.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
110%

Questions Set : REF20304 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF20304
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 5 mins 53 secs

Question: 19 of 82

A 45-year-old teacher presents six weeks after he returns from a hiking holiday in South America with a shallow, painless ulcer of the nose.

What is the likely diagnosis?

(Please select 1 option)

- *Fusobacterium ulcerans*
- Leishmaniasis
- Squamous cell carcinoma
- Trichomoniasis
- Trypanosomiasis

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Questions.aspx
Internet | Protected Mode: Off
110%

Questions Set : REF20304 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF20304
Page Safety Tools

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 6 mins 37 secs

Question: 19 of 82

A 45-year-old teacher presents six weeks after he returns from a hiking holiday in South America with a shallow, painless ulcer of the nose.

What is the likely diagnosis?

(Please select 1 option)

- *Fusobacterium ulcerans*
- Leishmaniasis ✓ Correct
- Squamous cell carcinoma
- Trichomoniasis
- Trypanosomiasis

The likely diagnosis, given the history, is cutaneous leishmaniasis. Lesion pain and pruritis may be present in cutaneous leishmaniasis, but are not typical.

Diagnosis is by histologic section with staining for amastigotes. *Leishmania braziliensis* is the likely pathogen which is spread by sandfly bites in endemic areas.

Fusobacteria cause the tropical ulcer, an intensely painful, shallow ulcer.

Next question | Tag Question | Remove question

Done
Internet | Protected Mode: Off
110%

Questions Set : REF59810 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF59810
Page Safety Tools

Work Smart Session - MRCP Part 1

Time taken: 2 mins 16 secs

Question: 1 of 82

A 17-year-old man comes to the clinic. He has recently returned from a holiday to Spain with his friends and is very disappointed with the quality of his tan, as there appear to be large depigmented areas on the skin of his abdomen and on his back. He says the areas are itchy.

On examination you confirm the depigmentation, and there is superficial scaling over the areas.

Which of the following is the most appropriate treatment?

(Please select 1 option)

- Oral antifungals
- Oral corticosteroids
- Reassurance
- Topical antifungals ✓ Correct
- Topical corticosteroids

This patient has clinical findings which are typical of those seen in pityriasis versicolor, caused by a fungus known as *Malassezia furfur*. This causes more of a problem in hot weather, is present on the skin of the trunk, and leads to the depigmentation seen here.

Topical antifungals are the treatment of choice; if the depigmentation is extensive, a systemic compound like fluconazole may be used.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A
Internet | Protected Mode: Off 100%

Questions Set : REF56461 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF56461
Page Safety Tools

Shop

Hb	11.9 g/dl	(13.5-18)
WCC	8.9 x 10^9/l Eosinophilia	(4-11)
PLT	203 x 10^9/l	(150-400)
Na	139 mmol/l	(135-146)
K	6.1 mmol/l	(3.5-5)
Cr	382 mmol/l	(79-118)
Urine protein	++	
Blood	-	
White cells	-	

Which of the following is the most likely diagnosis?

(Please select 1 option)

- ○ Acute tubular necrosis
- ○ Churg-Strauss syndrome
- ◉ Interstitial nephritis
- ○ Membranous nephropathy
- ○ Pyelonephritis

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Waiting for http://my.onexamination.com/Assessment/Questions.aspx...
Internet | Protected Mode: Off
100%

Questions Set : REF20219 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF20219
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 6 mins 37 secs

Question: 20 of 82

A 25-year-old female presents with concerns regarding the unsightly appearance of her toe nails.

They have a whitish discolouration extending up the nail bed in a number of the toes of both feet. They are entirely painless and she is otherwise well.

What is the most appropriate treatment?

(Please select 1 option)

- Oral fluconazole
- Oral terbinafine
- Topical benzoic acid
- Topical fluconazole
- Topical terbinafine

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
110%

Questions Set : REF20219 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF20219
Page Safety Tools

A 25-year-old female presents with concerns regarding the unsightly appearance of her toe nails.

They have a whitish discolouration extending up the nail bed in a number of the toes of both feet. They are entirely painless and she is otherwise well.

What is the most appropriate treatment?

(Please select 1 option)

○	Oral fluconazole
◉	Oral terbinafine ✓ Correct
○	Topical benzoic acid
○	Topical fluconazole
○	Topical terbinafine

This young woman has typical features of fungal nail infection - onychomycosis - and the most appropriate treatment is oral antifungals as topical antifungals may be effective for one or two nails but not where there are a number affected.

Further reading:
Guidelines for treatment of onychomycosis (pdf) British Journal of Dermatology 2003; 148: 402-410.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Questions.aspx
Internet | Protected Mode: Off
110%
EN
02:14
2/16/2011

Questions Set : REF20145 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF20145
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 7 mins 48 secs

Question: 21 of 82

A 40-year-old female presents with a long history of excessive localised armpit sweating. She finds the problem embarrassing and has problems staining clothes. She has tried antiperspirants without relief.

Which is the most appropriate treatment that you would offer this patient?

(Please select 1 option)

- Amitriptyline
- Axillary surgery
- Botulinum toxin injection
- Propantheline
- Topical aluminium salts

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
110%

Questions Set : REF20145 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF20145
Page Safety Tools

A 40-year-old female presents with a long history of excessive localised armpit sweating. She finds the problem embarrassing and has problems staining clothes. She has tried antiperspirants without relief.

Which is the most appropriate treatment that you would offer this patient?

(Please select 1 option)

- Amitriptyline
- Axillary surgery
- Botulinum toxin injection ✓ Correct
- Propantheline
- Topical aluminium salts

This woman has primary hyperhidrosis which can be quite psychologically disabling.

In this case the most appropriate treatment would be botulinum toxin injection to each axilla. This treatment is licensed for use and would be the preferred treatment before aluminium salts, as antiperspirants have failed.

Similarly, antimuscarinics are associated with systemic side effects that may prove intolerable and their efficacy is really not proven.

Pharmacological approaches should be tried before surgery.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
110%

Questions Set : REF14937 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF14937
Page Safety Tools

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 9 mins 17 secs

Question: 22 of 82

A 20-year-old female with a history of systemic lupus erythematosus (SLE) presents with symmetrical reticulated violaceous patches involving both lower limbs, which become more prominent in cold weather.

Which of the following is the likely diagnosis?

(Please select 1 option)

- Erythema ab igne
- Erythema marginatum
- Erythema nodosum
- Livedo reticularis
- Pyoderma gangrenosum

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
110%

Questions Set : REF14937 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF14937
Page
Safety
Tools

(Please select 1 option)

- Erythema ab igne
- Erythema marginatum
- Erythema nodosum
- Livedo reticularis ✓ Correct
- Pyoderma gangrenosum

Livedo reticularis is due to dilation of capillary blood vessels and stagnation of blood within these vessels, producing a mottled discolouration of the skin.

It is described as being reticular (net-like), cyanotic, cutaneous discolouration surrounding pale central areas. It occurs mostly on the legs, arms and trunk and is more pronounced in cold weather.

Mostly it is idiopathic, or secondary to:

- malignancy
- vasculitis
- SLE
- cancer
- cholesterol embolisation.

Next question

Tag Question

Remove question

Internet | Protected Mode: Off
110%

Questions Set : REF10135 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF10135
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 10 mins 9 secs

Question: 23 of 82

An 82-year-old lady had a history of a red facial rash and has suffered with venous eczema of the legs. She was treated for acne rosacea.

On examination, she was noted to have blue-grey discolouration of both legs.

What drug is most likely to have caused this?

(Please select 1 option)

- Amiodarone
- Ciprofloxacin
- Doxycycline
- Minocycline
- Oxytetracycline

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
110%

Questions Set : REF10135 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF10135
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 11 mins 26 secs

Question: 23 of 82

An 82-year-old lady had a history of a red facial rash and has suffered with venous eczema of the legs. She was treated for acne rosacea.

On examination, she was noted to have blue-grey discolouration of both legs.

What drug is most likely to have caused this?

(Please select 1 option)

- Amiodarone
- Ciprofloxacin
- Doxycycline
- Minocycline ✓ Correct
- Oxytetracycline

This patient has developed skin pigmentation in her venous eczema due to treatment of her acne rosacea.

Tetracyclines are the most appropriate treatment of acne rosacea and the most likely of these to cause this bluish grey skin pigmentation in the legs is minocycline.

Next question | Tag Question | Remove question

Done
Internet | Protected Mode: Off
110%
EN
02:23
2/16/2011

Questions Set : REF9123 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF9123
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 11 mins 26 secs

Question: 24 of 82

A 22-year-old female presents with a six month history of increasing fatigue and arthralgia of the wrists and ankles. More recently, she has also noted a symmetrical rash on her cheeks and some hair loss.

What is the most likely diagnosis?

(Please select 1 option)

- Dermatomyositis
- Hypothyroidism
- Porphyria cutanea tarda
- Scleroderma
- Systemic lupus erythematosus (SLE)

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
110%

Questions Set : REF9123 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF9123
Page
Safety
Tools

(Please select 1 option)

○	Dermatomyositis
○	Hypothyroidism
○	Porphyria cutanea tarda
○	Scleroderma
◉	Systemic lupus erythematosus (SLE) ✓ Correct

This woman has clinical features consistent with systemic lupus erythematosus. She gives a history of fatigue which occurs in almost all SLE patients. Arthralgia and arthritis are the most common presenting manifestations of SLE typically affecting the small joints of the hands, wrists and knees. The symmetrical rash is the classical butterfly rash that occurs in a malar distribution. Alopecia is common and may be diffuse or patchy.

In dermatomyositis there is proximal, symmetrical muscle weakness that progresses over weeks to months. The typical lilac papular rash occurs over the dorsum of the metacarpophalangeal (Gottron's papules), elbows and knees.

Hypothyroidism does not result in a symmetrical facial rash.

The initial symptoms of scleroderma tend to be non-specific and may consist of fatigue, weakness and musculoskeletal complaints. Raynaud's phenomenon is an early symptom. Skin changes include telangiectasia, hyper- and hypo-pigmentation.

Sarcoidosis can present acutely with arthritis and erythema nodosum.

Next question | Tag Question | Remove question

Done
Internet | Protected Mode: Off
110%

Questions Set : REF9121 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx?id=644011&ws=true
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF9121
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 13 mins 6 secs

Question: 25 of 82

A 31-year-old female presents with red scaly plaques on her cheeks, forehead and sides of the neck. On close inspection of the lesions there was plugging of some hair follicles with keratin and atrophy of the skin.

What is the most likely diagnosis?

(Please select 1 option)

- Atopic eczema
- Discoid lupus erythematosus
- Polymorphic light eruption
- Porphyria cutanea tarda
- Psoriasis

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Internet | Protected Mode: Off
110%

Questions Set : REF9121 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx?id=644011&ws=true
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF9121
Page
Safety
Tools

(Please select 1 option)

○	Atopic eczema
○	Discoid lupus erythematosus ← This is the correct answer
○	Polymorphic light eruption
○	Porphyria cutanea tarda
◉	Psoriasis ✕ Incorrect answer selected

This woman has discoid lupus erythematosus.

Lesions are discrete plaques, often erythematous, covered by scales that extend into dilated hair follicles. These lesions most typically occur on the face, scalp, in the pinnae, behind the ears and on the neck. They can exist in areas not exposed to the sun.

The lesions can progress, with active indurated erythema at the periphery. Central atrophic scarring is characteristic.

Amiodarone phototoxicity results in blue-grey skin pigmentation in sun-exposed areas.

In eczema dryness and lichenification are predominant features.

Psoriasis commonly appears as inflamed lesions covered with a silvery white scale.

Polymorphic light eruption is characterised by recurrent, abnormal, delayed reactions to sunlight, ranging from erythematous papules, papulovesicles, and plaques to erythema multiforme-like lesions on sunlight-exposed surfaces.

Next question

Tag Question
Remove question

Done
Internet | Protected Mode: Off
110%

Questions Set : REF8283 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF8283
Page Safety Tools

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 14 mins 47 secs

Question: 26 of 82

A 22-year-old female is referred with symmetrical, depigmented areas on the arms and legs but has been otherwise quite well.

Which one of the following diseases is most likely to be associated with her skin disease?

(Please select 1 option)

- Diabetes mellitus
- Hypoparathyroidism
- Pernicious anaemia
- Scleroderma
- Systemic lupus erythematosus (SLE)

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
110%

Questions Set : REF8283 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF8283
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 15 mins 27 secs

Question: 26 of 82

A 22-year-old female is referred with symmetrical, depigmented areas on the arms and legs but has been otherwise quite well.

Which one of the following diseases is most likely to be associated with her skin disease?

(Please select 1 option)

- Diabetes mellitus
- Hypoparathyroidism
- Pernicious anaemia ✓ Correct
- Scleroderma
- Systemic lupus erythematosus (SLE)

She has vitiligo and consequently is 15 times more likely to be suffering from an additional autoimmune condition. Although hypoparathyroidism may be an associated autoimmune condition, pernicious anaemia occurs more frequently.

Vitiligo may be a component of the polyglandular autoimmune syndrome which includes type 1 diabetes, autoimmune adrenal insufficiency and autoimmune thyroid disease.

SLE causes post-inflammatory hypopigmentation and scleroderma is not associated.

Next question | Tag Question | Remove question

Done
Internet | Protected Mode: Off
110%

Questions Set : REF6364 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF6364
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 15 mins 27 secs

Question: 27 of 82

A 17-year-old pregnant female attends antenatal clinic and is noted to have scattered small, raised lesions on her trunk and axillary freckles.

She was not aware of any of her family members having these lesions.

What is the likely mode of inheritance of this condition?

(Please select 1 option)

- Autosomal dominant
- Autosomal recessive
- Trinucleotide repeating
- X-linked dominant
- X-linked recessive

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Questions.aspx
Internet | Protected Mode: Off
110%

Questions Set : REF6364 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF6364
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 17 mins 3 secs

Question: 27 of 82

A 17-year-old pregnant female attends antenatal clinic and is noted to have scattered small, raised lesions on her trunk and axillary freckles.

She was not aware of any of her family members having these lesions.

What is the likely mode of inheritance of this condition?

(Please select 1 option)

◉	Autosomal dominant ✓ Correct
○	Autosomal recessive
○	Trinucleotide repeating
○	X-linked dominant
○	X-linked recessive

This patient has neurofibromatosis with axillary freckling and neurofibromas.

This is usually inherited as autosomal dominant, although it may arise from a sporadic new mutation of the NF1 gene.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
110%

Questions Set : REF6363 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF6363
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 17 mins 3 secs

Question: 28 of 82

A 22-year-old female returns from a fortnight holiday in Cyprus with a tan and numerous scaly hypopigmented lesions on the neck and upper trunk.

What is the most likely diagnosis?

(Please select 1 option)

- Chronic plaque psoriasis
- Discoid eczema
- Pityriasis rosea
- Pityriasis versicolor
- Seborrhoeic dermatitis

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
110%

Questions Set : REF6363 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF6363
Page Safety Tools

A 22-year-old female returns from a fortnight holiday in Cyprus with a tan and numerous scaly hypopigmented lesions on the neck and upper trunk.

What is the most likely diagnosis?

(Please select 1 option)

- Chronic plaque psoriasis
- Discoid eczema
- Pityriasis rosea
- **Pityriasis versicolor** ✓ Correct
- Seborrhoeic dermatitis

Pityriasis versicolor is caused by a superficial fungal infection with *Pityrosporum ovale*.

It usually presents as slightly scaly hypopigmented lesions. Growth is encouraged by an increase in temperature and suntan oils, and is most commonly seen after a sun holiday.

Chronic plaque psoriasis, discoid eczema and seborrhoeic dermatitis have distinct appearance and distribution.

Pityriasis rosea usually starts with a herald patch followed by small scaly lesions following the rib lines.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
110%

Questions Set : REF6362 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites | Suggested Sites | Get More Add-ons
Questions Set : REF6362 | Pityriasis Versicolor | Healt...
Page | Safety | Tools

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 17 mins 43 secs

Question: 29 of 82

A 52-year-old female presents with blistering of the hands and arms which deteriorates during the summer. She is otherwise well and drinks approximately 20 units of alcohol weekly.

Examination of her skin revealed erosions and scarring on the backs of her hands and forearms, and some mild hirsutism.

Which one of the following is the most likely diagnosis?

(Please select 1 option)

- Acute intermittent porphyria
- Erythropoietic protoporphyria
- Pemphigoid
- Porphyria cutanea tarda (PCT)
- Subacute lupus erythematous (LE)

Submit answer | Skip question | Tag Question | Remove question

Done | Internet | Protected Mode: Off | 110%

Questions Set : REF6362 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF6362
Page Safety Tools

A 52-year-old female presents with blistering of the hands and arms which deteriorates during the summer. She is otherwise well and drinks approximately 20 units of alcohol weekly.

Examination of her skin revealed erosions and scarring on the backs of her hands and forearms, and some mild hirsutism.

Which one of the following is the most likely diagnosis?

(Please select 1 option)

- Acute intermittent porphyria
- Erythropoietic protoporphyria
- Pemphigoid
- **Porphyria cutanea tarda (PCT)** ✓ Correct
- Subacute lupus erythematous (LE)

The history of photosensitive eruption, hypertrichosis and milia formation (keratin-containing cysts) are characteristic of PCT.

Acute intermittent porphyria usually causes intermittent neurological and abdominal problems.

Subacute LE can cause erythema and scarring, but in a patient with increased alcohol intake and hypertrichosis the most likely diagnosis is PCT.

Erythropoietic protoporphyria patients get pain and erythema on exposure to sunlight.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
110%

Questions Set : REF56461 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF56461
Page Safety Tools

Urine protein	++
Blood	-
White cells	-

Which of the following is the most likely diagnosis?

(Please select 1 option)

- Acute tubular necrosis
- Churg-Strauss syndrome
- Interstitial nephritis ✓ Correct
- Membranous nephropathy
- Pyelonephritis

The rapid onset of renal failure, coupled with a rash and eosinophilia is highly suspicious of a diagnosis of interstitial nephritis as a result of exposure to non-steroidal or amoxicillin.

Whilst eosinophilia is not usually seen in interstitial nephritis as a result of NSAIDs, it is seen in penicillin induced interstitial nephritis.

CT scanning and ultrasound are the main imaging modalities, with IVU being rarely used now. Renal biopsy is definitive in cases where the diagnosis is in doubt.

Resolution of renal failure usually begins after the causative agent is discontinued.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
100%

Questions Set : REF56302 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF56302
Page Safety Tools

Work Smart Session - MRCP Part 1

Question: 3 of 82

A 45-year-old man is referred to the dermatology clinic, with an intensely itchy, red, scaling rash which affects his scalp predominantly and is worse in spring and winter time. He also has a patch on his chest and around his beard.

On examination he has a severe scalp rash with crusting and scaling of skin.

Investigations show

Haemoglobin	13.1 g/dl	(13.5-18)
White cell count	5.9 x 10^9/l	(4-10)
Platelets	192 x 10^9/l	(150-400)
Sodium	139 mmol/l	(134-143)
Potassium	4.3 mmol/l	(3.5-5)
Creatinine	101 µmol/l	(60-120)
Scalp biopsy	Hyperkeratosis, acanthosis and focal spongiosis	

He tells you he cares most about his scalp.

Which of the following is the most appropriate first line treatment for him?

(Please select 1 option)

- Coal tar shampoo
- Ketoconazole shampoo

Done
Internet | Protected Mode: Off
100%

Questions Set : REF56302 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF56302
Page Safety Tools

Investigations show

Haemoglobin	13.1 g/dl	(13.5-18)
White cell count	5.9 x 10^9/l	(4-10)
Platelets	192 x 10^9/l	(150-400)
Sodium	139 mmol/l	(134-143)
Potassium	4.3 mmol/l	(3.5-5)
Creatinine	101 µmol/l	(60-120)
Scalp biopsy	Hyperkeratosis, acanthosis and focal spongiosis	

He tells you he cares most about his scalp.

Which of the following is the most appropriate first line treatment for him?

(Please select 1 option)

- Coal tar shampoo
- Ketoconazole shampoo
- Oral prednisolone
- Tacrolimus ointment
- Topical betamethasone

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A
Internet | Protected Mode: Off 100%

Questions Set : REF6317 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites | Suggested Sites | Get More Add-ons
Questions Set : REF6317
Page | Safety | Tools

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 19 mins 39 secs

Question: 30 of 82

A 33-year-old female is admitted with erythema multiforme (EM) and erythematous lesions of the mouth and eyes.

Which one of the following drugs may account for her presentation?

(Please select 1 option)

- Diazepam
- Fluoxetine
- Mebeverine
- Oral contraceptive
- Sulfasalazine

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
110%

Questions Set : REF6317 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites | Suggested Sites | Get More Add-ons
Questions Set : REF6317
Page | Safety | Tools

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 20 mins 27 secs

Question: 30 of 82

A 33-year-old female is admitted with erythema multiforme (EM) and erythematous lesions of the mouth and eyes.

Which one of the following drugs may account for her presentation?

(Please select 1 option)

- ○ Diazepam
- ○ Fluoxetine
- ○ Mebeverine
- ○ Oral contraceptive
- ◉ Sulfasalazine ✓ Correct

Any drug or infection can trigger EM but sulfasalazine and sulpha-group drugs are well reported as causes of EM and Stevens-Johnson syndrome.

Next question | Tag Question | Remove question

Show tools

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
110%

Questions Set : REF6316 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF6316
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 20 mins 27 secs

Question: 31 of 82

A 25-year-old female presents with red crusted lesions around the mouth and finger pulps, three months after having had small bowel resection for Crohn's disease.

What is the most likely cause of her skin condition?

(Please select 1 option)

- Nicotinamide deficiency
- Pyridoxine deficiency
- Thiamine deficiency
- Vitamin B_{12} deficiency
- Zinc deficiency

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
110%

Questions Set : REF6316 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF6316
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 22 mins 36 secs

Question: 31 of 82

A 25-year-old female presents with red crusted lesions around the mouth and finger pulps, three months after having had small bowel resection for Crohn's disease.

What is the most likely cause of her skin condition?

(Please select 1 option)

- ○ Nicotinamide deficiency
- ○ Pyridoxine deficiency
- ○ Thiamine deficiency
- ○ Vitamin B_{12} deficiency
- ◉ Zinc deficiency ✓ Correct

Zinc deficiency can lead to acrodermatitis which presents with perioral dermatitis, acral involvement and sometimes alopecia.

The features of this patient who had bowel resection suggest zinc deficiency.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
110%

Questions Set : REF6315 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF6315
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 22 mins 36 secs

Question: 32 of 82

A 16-year-old girl is seen in clinic as she is concerned due to areas of hair loss on the scalp.

Past medical history includes atopic eczema and she has a number of depigmented areas on her hands.

What is the most likely diagnosis?

(Please select 1 option)

- Alopecia areata
- Hypothyroidism
- Seborrhoeic dermatitis
- Systemic lupus erythematosus
- Trichotillomania

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Questions.aspx
Internet | Protected Mode: Off
110%

Questions Set : REF6315 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF6315
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 23 mins 26 secs

Question: 32 of 82

A 16-year-old girl is seen in clinic as she is concerned due to areas of hair loss on the scalp.

Past medical history includes atopic eczema and she has a number of depigmented areas on her hands.

What is the most likely diagnosis?

(Please select 1 option)

◉	Alopecia areata ✓ Correct
○	Hypothyroidism
○	Seborrhoeic dermatitis
○	Systemic lupus erythematosus
○	Trichotillomania

This girl has a combination of vitiligo and alopecia areata which can co-exist and have similar autoimmune aetiology.

Discrete areas of hair loss and normal texture on the scalp are highly suggestive of alopecia areata.

Next question

Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
110%

Questions Set : REF6314 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF6314
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 23 mins 26 secs

Question: 33 of 82

A 70-year-old female presents with a four month history of a dry, pruritic rash affecting the upper back and shins.

What is the most appropriate initial management of this patient?

(Please select 1 option)

- Avoidance of contact irritants
- Emollients
- Skin biopsy
- Take a detailed history to ascertain contact allergen
- Topical corticosteroids

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
110%

Questions Set : REF6314 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF6314
Page Safety Tools

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 24 mins 8 secs

Question: 33 of 82

A 70-year-old female presents with a four month history of a dry, pruritic rash affecting the upper back and shins.

What is the most appropriate initial management of this patient?

(Please select 1 option)

○	Avoidance of contact irritants
○	Emollients ← This is the correct answer
○	Skin biopsy
◉	Take a detailed history to ascertain contact allergen ✕ Incorrect answer selected
○	Topical corticosteroids

This lady is likely to have asteatotic eczema which is a common problem and will improve just with plain emollients.

Xerotic skin is commoner in the elderly population especially in the winter months due to the dry heat from central heating.

All the other suggestions may be appropriate in a patient resistant to first line treatment but the first line is to try emollients.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
110%

Questions Set : REF6313 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF6313
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 24 mins 8 secs

Question: 34 of 82

A 17-year-old girl presents with a two week history of urticaria.

Over the last couple of days she has been aware of new lesions occurring on a daily basis.

Which one of the following statements is most likely to be correct?

(Please select 1 option)

- She is likely to have an associated asthma
- She is likely to have taken penicillin recently
- She is unlikely to have any identifiable trigger factor
- The lesions will be present for at least 24 hours
- There is likely to be a nut allergy

Submit answer | Skip question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

http://my.onexamination.com/GoToShop.aspx
Internet | Protected Mode: Off
110%

Questions Set : REF6313 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF6313
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 25 mins 23 secs

Question: 34 of 82

A 17-year-old girl presents with a two week history of urticaria.

Over the last couple of days she has been aware of new lesions occurring on a daily basis.

Which one of the following statements is most likely to be correct?

(Please select 1 option)

- She is likely to have an associated asthma ✗ Incorrect answer selected
- She is likely to have taken penicillin recently
- She is unlikely to have any identifiable trigger factor ← This is the correct answer
- The lesions will be present for at least 24 hours
- There is likely to be a nut allergy

The commonest form of urticaria is idiopathic and there is no identifiable trigger.

Peanut allergy and penicillin may cause urticarial rashes but there is usually an associated specific history of contact with the allergen.

Urticarial lesions last less than 24 hours usually.

Next question | Remove Tag | Remove question

Done
Internet | Protected Mode: Off
110%
EN
02:43 P
2/16/2011

Questions Set : REF6312 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF6312
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 25 mins 23 secs

Question: 35 of 82

A 36-year-old female presents with raised erythematous tender lesions on both legs which have developed since she had a throat infection two weeks ago.

Which one of the following investigations is most likely to establish the diagnosis?

(Please select 1 option)

- Anti-streptolysin-O titre (ASOT)
- Chest x ray
- Throat swab cultured for bacteria
- Mantoux test
- Throat swab cultured for viruses

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Internet | Protected Mode: Off
110%

Questions Set : REF6312 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF6312
Page Safety Tools

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 26 mins 16 secs

Question: 35 of 82

A 36-year-old female presents with raised erythematous tender lesions on both legs which have developed since she had a throat infection two weeks ago.

Which one of the following investigations is most likely to establish the diagnosis?

(Please select 1 option)

○	Anti-streptolysin-O titre (ASOT) ← This is the correct answer
◉	Chest x ray ✕ Incorrect answer selected
○	Throat swab cultured for bacteria
○	Mantoux test
○	Throat swab cultured for viruses

This lady presents with tender lesions two weeks after a sore throat.

This is most likely to be post-streptococcal erythema nodosum and ASOT is most likely to confirm this.

Next question

Remove Tag Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Show tool

Internet | Protected Mode: Off 110%

Questions Set : REF6311 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF6311
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 26 mins 16 secs

Question: 36 of 82

A 41-year-old female presents with a six month history of a pruritic vesicular-papular rash on the elbows, knees and buttocks associated with numerous blistering eruptions and excoriations.

Her GP has prescribed topical steroid therapy but this has not helped.

What is the most likely diagnosis?

(Please select 1 option)

- Atopic eczema (dermatitis)
- Dermatitis herpetiformis (DH)
- Lichen planus
- Psoriasis
- Scabies

Submit answer | Skip question | Tag Question | Remove question

http://my.onexamination.com/Assessment/WorkHard.aspx
Internet | Protected Mode: Off
110%

Questions Set : REF6311 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF6311
Page
Safety
Tools

A 41-year-old female presents with a six month history of a pruritic vesicular-papular rash on the elbows, knees and buttocks associated with numerous blistering eruptions and excoriations.

Her GP has prescribed topical steroid therapy but this has not helped.

What is the most likely diagnosis?

(Please select 1 option)

○	Atopic eczema (dermatitis)
◉	Dermatitis herpetiformis (DH) ✓ Correct
○	Lichen planus
○	Psoriasis
○	Scabies

This patient presents with pruritic vesicles on her elbows, knees and buttocks which have not responded to topical steroids. This is the classical presentation of DH.

Atopic dermatitis usually is flexural and responds to topical steroids.

Henoch-Schönlein purpura is a form of vasculitis.

In scabies there are burrows and in psoriasis the rash consists of plaques with silvery scales.

Next question

Tag Question

Remove question

Done
Internet | Protected Mode: Off
110%

Questions Set : REF5880 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF5880
Page Safety Tools

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 29 mins 7 secs

Question: 37 of 82

A 17-year-old boy is diagnosed with scabies.

Which of the following statements regarding scabies is correct?

(Please select 1 option)

- Is best treated by salicylate emulsion
- It can be spread by a droplet infection
- It causes itchiness in the skin even where there is no obvious lesion to be seen
- It is caused by *Staphylococcus aureus*
- Typically affects the face

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
110%

Questions Set : REF5880 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF5880
Page Safety Tools

○	Is best treated by salicylate emulsion
○	It can be spread by a droplet infection
○	It causes itchiness in the skin even where there is no obvious lesion to be seen ← This is the correct answer
○	It is caused by *Staphylococcus aureus*
◉	Typically affects the face ✕ Incorrect answer selected

Scabies is an infestation of the skin with the microscopic mite *Sarcoptes scabei*. Infestation is common, found worldwide, and affects people of all races and social classes.

Scabies spreads rapidly under crowded conditions where there is frequent skin-to-skin contact between people, such as in hospitals, institutions, child-care facilities, and nursing homes.

Scabies can spread by direct, prolonged, skin-to-skin contact, with a person already infested with scabies. Contact must be prolonged (a quick handshake or hug will usually not spread infestation).

Infestation is easily spread to sexual partners and household members. Infestation may also occur by sharing clothing, towels, and bedding.

Scabies is characterised by papular-like irritations, burrows or rash of the skin, especially:

- the webbing between the fingers

- the skin folds on the wrist, elbow, or knee

- the penis

Done
Internet | Protected Mode: Off
110%

Questions Set : REF5880 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF5880
Page
Safety
Tools

Scabies spreads rapidly under crowded conditions where there is frequent skin-to-skin contact between people, such as in hospitals, institutions, child-care facilities, and nursing homes.

Scabies can spread by direct, prolonged, skin-to-skin contact, with a person already infested with scabies. Contact must be prolonged (a quick handshake or hug will usually not spread infestation).

Infestation is easily spread to sexual partners and household members. Infestation may also occur by sharing clothing, towels, and bedding.

Scabies is characterised by papular-like irritations, burrows or rash of the skin, especially:

- the webbing between the fingers

- the skin folds on the wrist, elbow, or knee

- the penis

- the breast or

- shoulder blades.

A number of treatments are available for scabies, including:

- permethrin ointment

- benzyl benzoate and

- oral ivermectin for resistant cases.

Antihistamines and calamine lotion may be used to alleviate itching.

Internet | Protected Mode: Off
110%

Questions Set : REF5549 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx?id=644011&ws=true
Favorites Suggested Sites Get More Add-ons
Questions Set : REF5549
Page Safety Tools

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 30 mins 12 secs

Question: 38 of 82

A 15-year-old boy was treated with permethrin cream for scabies infestation.

On follow-up three weeks later he was found to have continuing infestation.

What is the most likely reason for this?

(Please select 1 option)

- Facial skin was not treated
- Non-disposal of underwear
- Other household members were not treated
- The organism is resistant to permethrin
- The treatment was not repeated as prescribed

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Internet | Protected Mode: Off 110%

Questions Set : REF5549 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx?id=644011&ws=true
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF5549
Page
Safety
Tools

A 15-year-old boy was treated with permethrin cream for scabies infestation.

On follow-up three weeks later he was found to have continuing infestation.

What is the most likely reason for this?

(Please select 1 option)

○	Facial skin was not treated
○	Non-disposal of underwear
◉	Other household members were not treated ✓ Correct
○	The organism is resistant to permethrin
○	The treatment was not repeated as prescribed

Scabies is an intensely pruritic and highly contagious infestation of the skin acquired through close personal contact.

A delayed type IV hypersensitivity reaction to the mites, their eggs, or excreta occurs approximately 30 days after infestation and is responsible for the intense pruritus that is the hallmark of the disease.

All household members and close personal contacts should be treated whether or not they are symptomatic and patients should be re-examined two weeks after treatment to evaluate effectiveness.

Treatment failures are uncommon. Recurrence of the eruption usually means re-infection has occurred.

Next question

Tag Question

Remove question

Done
Internet | Protected Mode: Off
110%

Questions Set : REF5353 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF5353
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 31 mins 5 secs

Question: 39 of 82

In the treatment of psoriasis, which of the following statements is correct?

(Please select 1 option)

- Etanercept is not effective in psoriatic arthritis
- Infliximab is associated with tuberculosis
- PUVA is ineffective
- Retinoids are the most useful monotherapy in psoriatic patients
- Vitamin D analogues are associated with cutaneous atrophy

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
110%

Questions Set : REF5353 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
File Edit View Favorites Tools Help
Favorites Suggested Sites Get More Add-ons
Questions Set : REF5353
Page Safety Tools

In the treatment of psoriasis, which of the following statements is correct?

(Please select 1 option)

○	Etanercept is not effective in psoriatic arthritis
◉	Infliximab is associated with tuberculosis ✓ Correct
○	PUVA is ineffective
○	Retinoids are the most useful monotherapy in psoriatic patients
○	Vitamin D analogues are associated with cutaneous atrophy

Psoralen and ultraviolet light (PUVA) is an effective treatment for psoriasis, but has been related to increased risk of squamous cell carcinoma, and possibly malignant melanoma.

Retinoids are most effective in combination therapy, especially with ultraviolet B (UVB) phototherapy and PUVA.

Part of the attraction of vitamin D analogues over steroids is that they do not cause cutaneous atrophy, whereas steroids do.

The recombinant tumour necrosis factor and receptor fusion protein, etanercept, has demonstrated considerable beneficial effects on psoriatic arthropathy in placebo controlled, double blind studies.

Infliximab is associated with tuberculosis, by reactivation of latent disease. Thus it is advised that patients who are to be treated with infliximab are tuberculin tested, and if required, receive chest radiography.

Next question | Tag Question | Remove question

Done
Internet | Protected Mode: Off
110%

Questions Set : REF56302 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF56302
Page
Safety
Tools

Creatinine	101 µmol/l	(60-120)
Scalp biopsy	Hyperkeratosis, acanthosis and focal spongiosis	

He tells you he cares most about his scalp.

Which of the following is the most appropriate first line treatment for him?

(Please select 1 option)

- (●) Coal tar shampoo ✕ Incorrect answer selected
- ( ) Ketoconazole shampoo ← This is the correct answer
- ( ) Oral prednisolone
- ( ) Tacrolimus ointment
- ( ) Topical betamethasone

This man has seborrhoeic dermatitis which tends to affect hair bearing areas of skin with the scalp the worst affected.

It is thought that, at least in part, the activity of activated T cells may be enhanced by an increased reservoir of *Malassezia* yeasts. As such, regular washing of the hair with a ketoconazole based shampoo has been shown to reduce the severity of the condition.

Topical corticosteroids have been shown to hasten recovery, but may be associated with a rebound effect and rapid recurrence of the rash when they are withdrawn.

Coal tar shampoo and topical tacrolimus are alternate treatments.

Next question
Tag Question
Remove question
Done
Internet | Protected Mode: Off
100%

Questions Set : REF56298 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF56298
Page Safety Tools

Question: 4 of 82

A 31-year-old woman comes to the dermatology clinic complaining that a mole on her forearm has changed shape, enlarging to nearly three quarters of a centimetre in diameter, and although it was previously homogeneous in colour, parts of it have now become a very dark black.

She has no significant past medical history but admits to significant use of tanning beds and having spent a few years living in California.

Investigations show

Haemoglobin	13.0 g/dl	(13.5-18)
White cell count	5.4 x 10^9/l	(4-10)
Platelets	200 x 10^9/l	(150-400)
ESR	11 mm/hr	(1-20)
Sodium	139 mmol/l	(134-143)
Potassium	4.2 mmol/l	(3.5-5)
Creatinine	110 µmol/l	(60-120)

Excision biopsy: 5 mm thick lesion, no ulceration.

Which of the following features is most associated with a poor prognosis in this patient?

(Please select 1 option)

- (●) Depth of the melanoma lesion
- ( ) Female sex

Internet | Protected Mode: Off 100%

Questions Set : REF56298 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF56298
Page
Safety
Tools

Investigations show

Haemoglobin	13.0 g/dl	(13.5-18)
White cell count	5.4 x 10^9/l	(4-10)
Platelets	200 x 10^9/l	(150-400)
ESR	11 mm/hr	(1-20)
Sodium	139 mmol/l	(134-143)
Potassium	4.2 mmol/l	(3.5-5)
Creatinine	110 µmol/l	(60-120)

Excision biopsy: 5 mm thick lesion, no ulceration.

Which of the following features is most associated with a poor prognosis in this patient?

(Please select 1 option)

- (●) Depth of the melanoma lesion
- ( ) Female sex
- ( ) Her age
- ( ) Lack of ulceration
- ( ) Significant exposure to sun beds

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Internet | Protected Mode: Off
100%

Questions Set : REF5352 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF5352
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 31 mins 43 secs

Question: 40 of 82

Which of the following statements regarding psoriasis is most true?

(Please select 1 option)

- Ciclosporin is ineffective in the treatment of psoriasis
- Diagnosis requires histological confirmation
- Guttate psoriasis often arises after staphylococcal infection
- T-cells play a prominent role in the pathogenesis of psoriasis
- Twin studies have identified no genetic basis for psoriasis

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
110%

Questions Set : REF5352 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF5352
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 32 mins 22 secs

Question: 40 of 82

Which of the following statements regarding psoriasis is most true?

(Please select 1 option)

○	Ciclosporin is ineffective in the treatment of psoriasis
○	Diagnosis requires histological confirmation
◉	Guttate psoriasis often arises after staphylococcal infection ✕ Incorrect answer selected
○	T-cells play a prominent role in the pathogenesis of psoriasis ← This is the correct answer
○	Twin studies have identified no genetic basis for psoriasis

Diagnosis of psoriasis is based on clinical observation of sharply demarcated, erythematous, scaling plaques, and rarely requires biopsy.

Streptococcal infection is associated with precipitation and recurrence of guttate psoriasis.

Ciclosporin is a major inhibitor of T cell activation, and, given that T cells are central to the pathogenesis of psoriasis, is very effective treatment in psoriasis.

Genetic studies have led most experts to believe that psoriasis is the result of multiple genetic factors interacting with environmental stimuli. Genetic factors also seem to contribute to the clinical manifestations of the disease, for example, age of onset and severity of disease.

Next question

Remove Tag

Remove question

Done
Internet | Protected Mode: Off
110%

Questions Set : REF5351 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF5351
Page Safety Tools

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 32 mins 22 secs

Question: 41 of 82

Which of the following statements regarding psoriasis is correct?

(Please select 1 option)

- 1% of patients have associated psoriatic arthropathy
- Guttate psoriasis is the most common form of the disease
- Psoriasis is more common at lower geographical altitudes
- Psoriatic arthropathy precedes cutaneous lesions in roughly 20% of cases
- The prevalence in the United Kingdom is 10%

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
110%

Questions Set : REF5351 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF5351
Page Safety Tools

○	1% of patients have associated psoriatic arthropathy
○	Guttate psoriasis is the most common form of the disease
○	Psoriasis is more common at lower geographical altitudes
◉	Psoriatic arthropathy precedes cutaneous lesions in roughly 20% of cases ✓ Correct
○	The prevalence in the United Kingdom is 10%

The prevalence of psoriasis is reported as between 0.5 and 4.6%.

For reasons which may be explained by the filtering of ultraviolet B (UVB) light, psoriasis is more common at higher altitudes.

The commonest form of psoriasis is plaque psoriasis, making up approximately 80% of cases (guttate -10%, erythrodermic - 3%, pustular - 3%).

Studies report:

- A 5-42% prevalence of psoriatic arthropathy in patients with cutaneous psoriasis and
- Arthropathy precedes cutaneous lesions in 20%
- Cutaneous lesions precede joint disease in 60-70% and
- They occur simultaneously in 10-20%.

Next question Tag Question Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
110%

Questions Set : REF5286 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF5286
Page
Safety
Tools

Dashboard
Questions
Scores
Community
Help
Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 32 mins 59 secs

Question: 42 of 82

A 69-year-old woman presented with an ulcer over the left ankle, which had developed over the previous nine months. She had a history of right deep vein thrombosis (DVT) five years previously.

On examination she had a superficial slough-based ulcer, 6 cm in diameter, over the medial malleolus with no evidence of cellulitis.

Which one of the following is the most appropriate next investigation?

(Please select 1 option)

- Ankle-brachial pressure index
- Bacteriological swab of the ulcer
- Bilateral lower limb arteriogram
- Right leg venogram
- Venous duplex ultrasound scan

Submit answer | Skip question | Tag Question | Remove question

Internet | Protected Mode: Off
110%

Questions Set : REF5286 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF5286
Page
Safety
Tools

Which one of the following is the most appropriate next investigation?

(Please select 1 option)

◉	Ankle-brachial pressure index ✓ Correct
○	Bacteriological swab of the ulcer
○	Bilateral lower limb arteriogram
○	Right leg venogram
○	Venous duplex ultrasound scan

It has been reported that venous ulcerations are the most common type of ulcer affecting the lower extremities. The probable underlying cause of venous congestion, which may promote ulceration, is venous insufficiency.

The treatment of venous ulceration is control of oedema, treating any infection, and compression. However, compressive dressings or devices should not be applied if the arterial circulation is impaired.

It is thus important to identify any arterial disease, and ankle-brachial pressure index is a simple way of doing this. One may then progress to lower limb arteriogram if indicated.

There is no clinical sign of infection, and although a bacterial swab would help to rule out pathogens within the ulcer, arterial insufficiency is the more important issue.

If there is a clinical suspicion of DVT then duplex (or rarely a venogram) is indicated to decide on the indication for warfarin.

Done
Internet | Protected Mode: Off
110%

Questions Set : REF5190 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF5190
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 34 mins 17 secs

Question: 43 of 82

A 35-year-old woman presents with a facial rash which had been present for one year.

On examination she had erythematous, scaly, indurated plaques on both cheeks with areas of scarring alopecia. Hyperkeratosis over dilated hair follicles was also seen.

What is the diagnosis?

(Please select 1 option)

- Acne rosacea
- Discoid lupus erythematosus
- Impetigo
- Lupus pernio
- Psoriasis

Submit answer | Skip question | Tag Question | Remove question

Done
Internet | Protected Mode: Off
110%

Questions Set : REF5190 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF5190
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 35 mins 39 secs

Question: 43 of 82

A 35-year-old woman presents with a facial rash which had been present for one year.

On examination she had erythematous, scaly, indurated plaques on both cheeks with areas of scarring alopecia. Hyperkeratosis over dilated hair follicles was also seen.

What is the diagnosis?

(Please select 1 option)

- Acne rosacea
- Discoid lupus erythematosus ✓ Correct
- Impetigo
- Lupus pernio
- Psoriasis

The patient has discoid lupus as suggested by the indurated plaques on cheeks, the scarring alopecia and hyperkeratosis over the hair follicles.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
110%

Questions Set : REF5138 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF5138
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 35 mins 39 secs

Question: 44 of 82

A 24-year-old female attends clinic complaining of numerous depigmented areas on the arms and legs.

Which of the following diseases is most likely to accompany this skin condition?

(Please select 1 option)

- Addison's disease
- Hypoparathyroidism
- Pernicious anaemia
- Systemic lupus erythematosus
- Tuberous sclerosis

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
110%

Questions Set : REF5138 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF5138
Page Safety Tools

A 24-year-old female attends clinic complaining of numerous depigmented areas on the arms and legs.

Which of the following diseases is most likely to accompany this skin condition?

(Please select 1 option)

○	Addison's disease
○	Hypoparathyroidism
◉	Pernicious anaemia ✓ Correct
○	Systemic lupus erythematosus
○	Tuberous sclerosis

The suggested diagnosis is vitiligo which is associated with numerous autoimmune conditions including, in order of frequency:

1. Autoimmune hypothyroidism
2. Pernicious anaemia
3. Alopecia areata
4. Addison's disease.

It is associated with both type 1 and 2 autoimmune polyendocrine syndromes but these are much rarer than the former diagnoses.

Next question Tag Question Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
110%

Questions Set : REF5123 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites | Suggested Sites | Get More Add-ons
Questions Set : REF5123
Page | Safety | Tools

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 36 mins 8 secs

Question: 45 of 82

An 18-year-old woman attends antenatal clinic 12 weeks into her pregnancy where the doctor incidentally notes numerous small lumps over her trunk and freckles in her axillae.

She reported that none of her relatives had any similar features.

What is the most likely diagnosis?

(Please select 1 option)

- Acanthosis nigricans
- Dysplastic naevus syndrome
- Mastocytosis
- Neurofibromatosis
- Tuberous sclerosis

Submit answer | Skip question | Tag Question | Remove question

Done
Internet | Protected Mode: Off
110%

Questions Set : REF5123 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF5123
Page Safety Tools

○	Acanthosis nigricans
○	Dysplastic naevus syndrome
○	Mastocytosis
◉	Neurofibromatosis ✓ Correct
○	Tuberous sclerosis

The patient is likely to have neurofibromatosis (NF1).

To be given the diagnosis of NF1, an individual must have at least two of the following features. Some people with NF1 have only two, while others can have several of these features:

- Six or more café-au-lait spots, or coffee-coloured birthmarks, each measuring over an inch in adults (1/4 inch in children)
- Two of more neurofibromas or a plexiform neurofibroma
- Freckles under the arm or in the groin region
- A tumour of the nerve to the eye called an optic glioma
- Two or more spots on the iris of the eye called Lisch nodules
- A problem of one of the bones such as bowing of a leg, with or without a fracture
- A parent, brother, sister, or child with NF1.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
110%

Questions Set : REF5122 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF5122
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 36 mins 51 secs

Question: 46 of 82

A 55-year-old woman presents with a non-pruritic rash that had developed over the last two months. Examination revealed several, circular, erythematous, raised, smooth-surfaced lesions of variable size from 1-5 cm in diameter on the elbows, extensor aspects of the forearms and knuckles.

What is the most likely diagnosis?

(Please select 1 option)

- Eczema
- Granuloma annulare
- Psoriasis
- Tinea corporis
- Urticaria

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
110%

Questions Set : REF5122 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF5122
Page
Safety
Tools

What is the most likely diagnosis?

(Please select 1 option)

○	Eczema
○	Granuloma annulare ← This is the correct answer
○	Psoriasis
◉	Tinea corporis ✕ Incorrect answer selected
○	Urticaria

The history of non-itchy, circular, raised, smooth-surfaced lesions on the elbows, extensor aspects of the forearms and knuckles and the raised borders are suggestive of granuloma annulare.

Discoid eczema tends to be scaly and pruritic in nature.

Psoriasis typically has a silvery scale and can be pruritic.

Urticaria lasts a few hours and is pruritic.

Tinea corporis is a fungal infection and is typically scaly and pruritic in nature.

The most likely answer is therefore granuloma annulare. This can be associated with diabetes.

Next question

Remove Tag

Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
110%

Questions Set : REF5121 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
File Edit View Favorites Tools Help
Favorites Suggested Sites Get More Add-ons
Questions Set : REF5121
Page Safety Tools

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 38 mins 37 secs

Question: 47 of 82

A 70-year-old woman complained of a rash that had developed over a month. She had otherwise been fit and well. On examination, there were numerous tense, fluid filled blisters over the trunk and limbs, but no mucosal involvement was evident.

What is the most likely diagnosis?

(Please select 1 option)

- Dermatitis herpetiformis
- Erythema multiforme
- Herpes simplex
- Pemphigoid
- Pemphigus vulgaris

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Internet | Protected Mode: Off 110%

Questions Set : REF5121 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF5121
Page Safety Tools

numerous tense, fluid filled blisters over the trunk and limbs, but no mucosal involvement was evident.

What is the most likely diagnosis?

(Please select 1 option)

○	Dermatitis herpetiformis
○	Erythema multiforme
○	Herpes simplex
○	Pemphigoid ← This is the correct answer
◉	Pemphigus vulgaris ✕ Incorrect answer selected

The patient presents with tense blisters on her arms, trunk and legs. She is otherwise well and there is no mucosal involvement. This is typical of bullous pemphigoid.

Dermatitis herpetiformis presents with itchy excoriated areas in the elbows knees and buttocks.

Erythema multiforme presents with characteristic target lesions.

Herpes simplex is vesicular and in generalised cases the patient is likely to be unwell.

Pemphigus presents with superficial erosions and usually there is mucosal involvement.

Next question Remove Tag Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
110%
EN
02:16 P
2/16/2011

Questions Set : REF5120 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF5120
Page Safety Tools

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 39 mins 35 secs

Question: 48 of 82

A 60-year-old woman presents with raised, erythematous lesions on the limbs and blistering in the mouth and eyes. She had been taking a number of drugs prescribed by her GP.

Which may be responsible for her presentation?

(Please select 1 option)

- Nifedipine
- Paracetamol
- Paroxetine
- Prednisolone
- Sulphasalazine

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Internet | Protected Mode: Off 110%

Questions Set : REF5120 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF5120
Page
Safety
Tools

Sulphasalazine ✓ Correct

This is a typical case of Stevens-Johnson syndrome.

Stevens-Johnson syndrome (SJS) is an immune-complex-mediated hypersensitivity complex that is a severe expression of erythema multiforme. It is now known also as erythema multiforme major.

SJS typically involves the skin and the mucous membranes. While minor presentations may occur, significant involvement of:

- oral
- nasal
- eye
- vaginal
- urethral
- gastrointestinal (GI)
- lower respiratory tract mucous membranes

may develop in the course of the illness.

GI and respiratory involvement may progress to necrosis.

SJS is a serious systemic disorder with the potential for severe morbidity and even death.

The drugs most closely associated with causing Stevens-Johnson syndrome are:

- antibacterials

Done
Internet | Protected Mode: Off
110%

Questions Set : REF5120 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF5120
Page
Safety
Tools

SJS typically involves the skin and the mucous membranes. While minor presentations may occur, significant involvement of:

- oral
- nasal
- eye
- vaginal
- urethral
- gastrointestinal (GI)
- lower respiratory tract mucous membranes

may develop in the course of the illness.

GI and respiratory involvement may progress to necrosis.

SJS is a serious systemic disorder with the potential for severe morbidity and even death.

The drugs most closely associated with causing Stevens-Johnson syndrome are:

- antibacterials
- sulfonamides
- anticonvulsants (oxicam)
- non-steroidal anti-inflammatory agents (piroxicam and tenoxicam)
- chlormezanone
- allopurinol.

Done
Internet | Protected Mode: Off
110%

Questions Set : REF5119 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF5119
Page
Safety
Tools

Dashboard
Questions
Scores
Community
Help
Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 40 mins 18 secs

Question: 49 of 82

A 65-year-old female who has a history of long-standing psoriasis and heavy alcohol intake, presents with a severe exacerbation of psoriasis. She was admitted and received topical therapy and over the month of her admission, her gamma-GT concentration had fallen from 400 U/L to 150 U/L (4-35).

Six weeks after discharge she was seen in outpatients where her psoriasis remained under control, but she complained of generalised hair loss.

What is the most likely cause for her hair loss?

(Please select 1 option)

- Alopecia areata
- Iron deficiency
- Telogen effluvium
- Thiamine deficiency
- Trichotillomania

Submit answer | Skip question | Tag Question | Remove question

Done
Internet | Protected Mode: Off
110%

Questions Set : REF5119 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF5119
Page
Safety
Tools

Shop

What is the most likely cause for her hair loss?

(Please select 1 option)

◉	Alopecia areata ✕ Incorrect answer selected
○	Iron deficiency
○	Telogen effluvium ← This is the correct answer
○	Thiamine deficiency
○	Trichotillomania

In a normal healthy person's scalp about 85% of the hair follicles are actively growing hair and 15% are resting.

If there is some shock to the system, as many as 70% of the scalp hairs can be precipitated into a resting state, thus reversing the usual ratio. Typical precipitants include illnesses, operations, accidents and childbirth.

The resting scalp hairs, now in the form of club hairs, remain firmly attached to the hair follicles at first. It is only about two months after the shock that the new hairs coming up through the scalp push out the 'dead' club hairs and increased hair fall is noticed. Thus, paradoxically, with this type of hair loss, hair fall is a sign of hair regrowth.

As the new hair first comes up through the scalp and pushes out the dead hair a fine fringe of new hair is often evident along the forehead hairline. At first the fall of club hairs is profuse and a general thinning of the scalp hair may become evident but after several months a peak is reached and hair fall begins to lessen, gradually tapering back to normal over six to nine months.

As the hair fall tapers off the scalp thickens back up to normal, but recovery may be incomplete in some cases.

Next question

Remove Tag | Remove question

Done
Internet | Protected Mode: Off
110%

Questions Set : REF56298 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF56298
Page Safety Tools

Sodium	139 mmol/l	(134-143)
Potassium	4.2 mmol/l	(3.5-5)
Creatinine	110 µmol/l	(60-120)

Excision biopsy: 5 mm thick lesion, no ulceration.

Which of the following features is most associated with a poor prognosis in this patient?

(Please select 1 option)

- (●) Depth of the melanoma lesion ✓ Correct
- ( ) Female sex
- ( ) Her age
- ( ) Lack of ulceration
- ( ) Significant exposure to sun beds

Survival is strongly correlated with depth of melanoma at the point of diagnosis, with lesions over 4 mm thick being associated with a particularly poor outcome.

Other predictors of a poor outcome include increasing age and male sex.

Ulceration of the lesion also implies greater risk of metastases. For lesions over 4 mm thick with ulceration, five year survival is less than 50%.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
100%

Questions Set : REF55635 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF55635
Page Safety Tools

Work Smart Session - MRCP Part 1

Time taken: 14 mins 12 secs

Question: 5 of 82

A 38-year-old woman has erythematous plaques with hyperpigmentation at the edge and central hypopigmentation. Serological tests are unremarkable and the patient is diagnosed with discoid lupus.

Which of the following therapeutic strategies is most appropriate initially?

(Please select 1 option)

- Cyclophosphamide
- Dapsone
- Methotrexate
- Oral prednisolone
- Sun protective measures

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Internet | Protected Mode: Off 100%

Questions Set : REF5118 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites | Suggested Sites | Get More Add-ons
Questions Set : REF5118
Page | Safety | Tools

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 42 mins 47 secs

Question: 50 of 82

A 20-year-old male presents with extensive, coalescing, hypopigmented, slightly scaly lesions on his back and chest.

The rash had been present for two years and had gradually become more extensive. He had otherwise been in good health. The lesions were not symptomatic but he was concerned about their appearance.

What is the most appropriate treatment for his condition?

(Please select 1 option)

- Aciclovir cream
- Ketoconazole cream
- Nystatin cream
- Oral itraconazole
- Oral terbinafine

Submit answer | Skip question | Tag Question | Remove question

Done
Internet | Protected Mode: Off
110%

Questions Set : REF5118 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF5118
Page
Safety
Tools

(Please select 1 option)

○	Aciclovir cream
◉	Ketoconazole cream ✓ Correct
○	Nystatin cream
○	Oral itraconazole
○	Oral terbinafine

The patient presents with an asymptomatic eruption on his trunk. The lesions are scaly, hypopigmented and are not associated with any systemic disease. This is characteristic of pityriasis versicolor, which is caused by the unicellular yeast *Pityrosporum ovale* and *Pityrosporum orbiculare*. The yeast is lipophilic and is encouraged by an increase in environmental temperature, thus many patients notice that the condition begins after a summer vacation.

It is a disorder of the healthy, but the immunocompromised are at risk.

The condition is asymptomatic and appears pale in comparison to the normal skin. The fungus affects the melanocytes hence the hypo-pigmentation.

The treatment options include topical imidazole creams, selenium sulphide shampoo and, if not responding to topical treatment, oral itraconazole 200 mg once a day for seven days.

In this patient the topical treatment should be tried first.

Next question

Tag Question

Remove question

Done
Internet | Protected Mode: Off
110%

Questions Set : REF5111 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF5111
Page
Safety
Tools

Dashboard
Questions
Scores
Community
Help
Shop

A 63-year-old man presents with recurrent gradually increasing shortness of breath over the last few weeks.

His chest x ray is shown:

Done
Internet | Protected Mode: Off
110%

Questions Set : REF5111 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF5111
Page
Safety
Tools

On examination his hands showed the following:

Done
Internet | Protected Mode: Off
110%

Questions Set : REF5111 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF5111
Page
Safety
Tools

What is the diagnosis?

(Please select 1 option)

- Chronic mucocutaneous candidiasis
- Iron deficiency
- Ochronosis
- Polychondritis
- Yellow nail syndrome

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
110%

Questions Set : REF5111 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF5111
Page
Safety
Tools

What is the diagnosis?

(Please select 1 option)

○	Chronic mucocutaneous candidiasis
○	Iron deficiency
○	Ochronosis
○	Polychondritis
◉	Yellow nail syndrome ✓ Correct

This is yellow nail syndrome where the nails are yellow, thickened, curved, stop growing and may become detached from the nail bed.

Associated findings include lymphoedema, bronchiectasis and pleural effusions.

Internet | Protected Mode: Off
110%

Questions Set : REF4716 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF4716
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 50 mins 51 secs

Question: 52 of 82

A 68-year-old woman presents with a two month history of a widespread pruritic rash.

Examination reveals widespread erythema with several small blisters containing straw-coloured fluid and one or two larger serosanguineous blisters.

What is the most likely diagnosis?

(Please select 1 option)

- Bullous impetigo
- Bullous pemphigoid
- Insect bite
- Scabies
- Urticarial vasculitis

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
110%

Questions Set : REF4716 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF4716
Page Safety Tools

(Please select 1 option)

○	Bullous impetigo
◉	Bullous pemphigoid ✓ Correct
○	Insect bite
○	Scabies
○	Urticarial vasculitis

Pemphigoid, erythema multiforme and herpes are the commonest causes of a blistering rash.

The history above is a classic description of bullous pemphigoid (BP).

Immunoglobulin (Ig)G autoantibodies bind to the skin basement membrane in patients with BP. The binding of antibodies at the basement membrane activates complement and inflammatory mediators.

Activation of the complement system is thought to play a critical role in attracting inflammatory cells to the basement membrane. These inflammatory cells are postulated to release proteases, which degrade hemidesmosomal proteins and lead to blister formation.

Eosinophils are characteristically present in blisters as demonstrated by histopathologic analysis, although their presence is not an absolute diagnostic criterion.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
110%

Questions Set : REF4638 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx?id=644011&ws=true
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF4638
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 52 mins 4 secs

Question: 53 of 82

A 26-year-old male epileptic is admitted with temperature and rash.

Over the last one week a rash has developed and he has become increasingly ill. Recently he has had some problems with epileptic control and has commenced carbamazepine with valproate.

Examination reveals an unwell patient with a temperature of 39°C, a diffuse erythematous, painful rash with evidence of some lateral sliding of these erythematous areas on palpation.

There is also blistering and inflammation of the oral cavity.

What is the likely diagnosis?

(Please select 1 option)

- Erythema elevatum diutinum
- Exfoliative dermatitis
- Pustular psoriasis
- Toxic epidermal necrolysis
- Toxic shock syndrome

Submit answer | Skip question | Tag Question | Remove question

Done
Internet | Protected Mode: Off
110%

Questions Set : REF4638 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx?id=644011&ws=true
Favorites Suggested Sites Get More Add-ons
Questions Set : REF4638
Page Safety Tools

○	Pustular psoriasis
◉	Toxic epidermal necrolysis ✓ Correct
○	Toxic shock syndrome

This patient's presentation and clinical description suggests a diagnosis of toxic epidermal necrolysis (TEN) due to carbamazepine therapy.

TEN is a severe mucocutaneous exfoliative disease with an uncertain pathogenesis and a high mortality rate.

It is difficult to say whether it is another variant of Stevens-Johnson syndrome and treatment of both are similar.

It is often idiopathic but may be associated with:

- viral infections

- leukaemia

- lymphoma and

- drugs (in particular sulphonamides and anticonvulsants).

The suggested association with carbamazipine in this case makes toxic shock syndrome due to *Staph. aureus* remote, which like pustular psoriasis would not be expected to affect the mucous membranes.

Next question Tag Question Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done Internet | Protected Mode: Off 110%

Questions Set : REF4430 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF4430
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 54 mins 39 secs

Question: 54 of 82

An 18-year-old woman presents with red, tender lumps on her shins and arthralgia.

Chest x ray shows bilateral hilar lymphadenopathy and clear lung fields. A clinical diagnosis of sarcoidosis is made.

Which one of the following is the most appropriate management plan?

(Please select 1 option)

- 24 hour urinary calcium measurement
- Follow up appointment with chest x ray in three months
- Mediastinoscopy and lymph node biopsy
- Skin biopsy
- Thoracic CT scan

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Questions.aspx
Internet | Protected Mode: Off
110%

Questions Set : REF4430 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF4430
Page Safety Tools

Chest x ray shows bilateral hilar lymphadenopathy and clear lung fields. A clinical diagnosis of sarcoidosis is made.

Which one of the following is the most appropriate management plan?

(Please select 1 option)

○	24 hour urinary calcium measurement
◉	Follow up appointment with chest x ray in three months ✓ Correct
○	Mediastinoscopy and lymph node biopsy
○	Skin biopsy
○	Thoracic CT scan

This is also known as Löfgren's syndrome (a benign form of sarcoidosis).

The presentation of erythema nodosum-arthropathy-bilateral hilar lymphadenopathy syndrome is so characteristic that histological diagnosis is not necessary.

The prognosis is excellent with less than 10% having persistent disease.

With less characteristic presentations, positive biopsies are needed.

Mediastinoscopy is the method of choice for anterior mediastinal nodes.

Next question Tag Question Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
110%

Questions Set : REF4389 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF4389
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 55 mins 22 secs

Question: 55 of 82

A young woman has acne and is taking oral medication. She develops polyarthritis and has raised liver enzyme tests.

Investigations show:

AST	95 U/l	(1-31)
ALT	170 U/l	(5-35)
Bilirubin	16 µmol/l	(1-22)
Antinuclear antibodies	Strongly positive at 1/20 Negative at 1/640	

Which of the following drugs is she most likely to have been prescribed?

(Please select 1 option)

- Erythromycin
- Isotretinoin
- Minocycline
- Oxytetracycline
- Trimethoprim

Done
Internet | Protected Mode: Off
110%

Questions Set : REF4389 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF4389
Page Safety Tools

ALT	170 U/l	(5-35)
Bilirubin	16 µmol/l	(1-22)
Antinuclear antibodies	Strongly positive at 1/20 Negative at 1/640	

Which of the following drugs is she most likely to have been prescribed?

(Please select 1 option)

- Erythromycin
- Isotretinoin
- Minocycline ✓ Correct
- Oxytetracycline
- Trimethoprim

Except trimethoprim, all other drugs listed above are used in the treatment of acne. All of these can cause hepatotoxicity.

Erythromycin usually causes cholestasis.

Minocycline can cause drug induced systemic lupus erythematosus (SLE).

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
110%

Questions Set : REF4388 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF4388
Page Safety Tools

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 57 mins 49 secs

Question: 56 of 82

A 58-year-old man has a history of obesity, gastro-oesophageal reflux disease, low back pain and IHD.

He presents with large, itchy weals over the trunk and limbs and a sensation of tightness in the throat.

Which one of the following drugs is the most likely to have triggered this skin eruption?

(Please select 1 option)

- Aspirin
- GTN (nitrate) spray
- Omeprazole
- Paracetamol
- Simvastatin

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
110%

Questions Set : REF4388 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF4388
Page Safety Tools

Question: 56 of 82

A 58-year-old man has a history of obesity, gastro-oesophageal reflux disease, low back pain and IHD.

He presents with large, itchy weals over the trunk and limbs and a sensation of tightness in the throat.

Which one of the following drugs is the most likely to have triggered this skin eruption?

(Please select 1 option)

◉	Aspirin ✓ Correct
○	GTN (nitrate) spray
○	Omeprazole
○	Paracetamol
○	Simvastatin

In hypersensitive patients, aspirin can cause

- angioedema
- bronchospasm
- urticaria (skin rashes).

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
110%

Questions Set : REF4323 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF4323
Page Safety Tools

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 58 mins 59 secs

Question: 57 of 82

A 38-year-old female presents with red target lesions confined to the hands and is diagnosed with erythema multiforme.

Which of the following could be the cause?

(Please select 1 option)

- Cytomegalovirus infection
- Group B streptococci
- Langerhan's cells histiocytosis
- Penicillin V
- *Ureaplasma urealyticum*

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
110%

Questions Set : REF4323 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF4323
Page
Safety
Tools

○	Cytomegalovirus infection
◉	Group B streptococci ✕ Incorrect answer selected
○	Langerhan's cells histiocytosis
○	Penicillin V ← This is the correct answer
○	*Ureaplasma urealyticum*

Potential causes of erythema multiforme include:

1. Infections

- Viruses: herpes simplex 1 and 2, hepatitis B, Epstein-Barr virus (EBV), enteroviruses
- Small agents: *Mycoplasma pneumoniae*
- Bacteria: Group A Streptococcus, eosina
- Other: *Mycobacterium tuberculosis*, histoplasma, coccidioides.

2. Neoplasia

- Leukaemia
- Lymphoma.

3. Antibiotics

- Penicillins, sulphonamides, isoniazid, tetracycline.

4. Anticonvulsants

Done
Internet | Protected Mode: Off
110%

Questions Set : REF4323 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF4323
Page
Safety
Tools

2. Neoplasia

- Leukaemia
- Lymphoma.

3. Antibiotics

- Penicillins, sulphonamides, isoniazid, tetracycline.

4. Anticonvulsants

- Phenytoin, phenobarbitone, carbamazepine.

5. Other

- Aspirin
- Radiation therapy
- Etoposide
- NSAIDs
- Sunlight
- Pregnancy.

Next question

Tag Question

Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
110%

Questions Set : REF4280 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF4280
Page Safety Tools

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 59 mins 58 secs

Question: 58 of 82

A 50-year-old man presented in the summer complaining of itching and blistering of his hands and forehead.

On examination there were small areas of excoriation on the backs of his hands.

What is the most likely diagnosis?

(Please select 1 option)

- Dermatitis herpetiformis
- Lupus erythematosus
- Pemphigoid
- Pemphigus
- Porphyria cutanea tarda (PCT)

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Questions.aspx
Internet | Protected Mode: Off
110%

Questions Set : REF4280 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF4280
Page Safety Tools

A 50-year-old man presented in the summer complaining of itching and blistering of his hands and forehead.

On examination there were small areas of excoriation on the backs of his hands.

What is the most likely diagnosis?

(Please select 1 option)

- ○ Dermatitis herpetiformis
- ○ Lupus erythematosus
- ○ Pemphigoid
- ○ Pemphigus
- ◉ Porphyria cutanea tarda (PCT) ✓ Correct

The distribution of the lesions suggests a photosensitive element.

Both lupus erythematosus and PCT are associated with a photosensitive elements, however this is more typical of PCT.

PCT causes blistering of the hands and the forehead which usually heal with small scar and milia formation.

It is also associated with an excessive alcohol intake.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd. All rights reserved. Terms and conditions Privacy policy
Done
Internet | Protected Mode: Off
110%

Questions Set : REF4275 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF4275
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 58 secs

Question: 59 of 82

A previously fit 30-year-old female presents with a four day history of intractable pruritus and urticaria.

What is the most appropriate initial management?

(Please select 1 option)

- Chlorpheniramine
- Prednisolone
- Ranitidine
- Topical hydrocortisone
- Topical mepyramine

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
110%

Questions Set : REF4275 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF4275
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 1 mins 49 secs

Question: 59 of 82

A previously fit 30-year-old female presents with a four day history of intractable pruritus and urticaria.

What is the most appropriate initial management?

(Please select 1 option)

○	Chlorpheniramine ← This is the correct answer
○	Prednisolone
○	Ranitidine
◉	Topical hydrocortisone ✕ Incorrect answer selected
○	Topical mepyramine

Urticaria is a common condition and usually responds very well to systemic antihistamines which are the correct first line treatment.

Oral steroids can be given for severe cases but only as a last resort.

Topical steroids/topical antihistamines have no effect.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
110%

Questions Set : REF55635 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF55635
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 15 mins 16 secs

Question: 5 of 82

A 38-year-old woman has erythematous plaques with hyperpigmentation at the edge and central hypopigmentation. Serological tests are unremarkable and the patient is diagnosed with discoid lupus.

Which of the following therapeutic strategies is most appropriate initially?

(Please select 1 option)

- ○ Cyclophosphamide
- ○ Dapsone
- ○ Methotrexate
- ◉ Oral prednisolone ✕ Incorrect answer selected
- ○ Sun protective measures ← This is the correct answer

Discoid lupus is photosensitive and so avoiding the sun with protective clothing and sunscreens, and changing behaviour is important.

Topical or intradermal steroids and hydroxychloroquine are useful therapies to prevent scarring and new lesions appearing. The latter are less effective if patients continue to smoke.

If these treatments are ineffective, second line drugs such as methotrexate, azathioprine, or thalidomide may be used.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
100%

Questions Set : REF55626 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF55626
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 15 mins 16 secs

Question: 6 of 82

A 15-year-old boy comes to the dermatology clinic as his parents are concerned about some changes they have noticed in his skin. He is from a travelling community, and as such his parents have previously shunned medical services.

On examination you notice that he has a number of facial and periungual fibromata. He also has a number of hypomelanotic areas (at least four) on examination of his skin. You also notice gingival fibromata and pitting of his tooth enamel on examination of his mouth.

On which chromosome is the abnormality associated with this disease likely to be found?

(Please select 1 option)

- Chromosome 2
- Chromosome 6
- Chromosome 9
- Chromosome 11
- Chromosome 12

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Questions.aspx
Internet | Protected Mode: Off
100%

Questions Set : REF4274 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites | Suggested Sites | Get More Add-ons
Questions Set : REF4274
Page | Safety | Tools

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 1 mins 49 secs

Question: 60 of 82

A 74-year-old man with a thirty year history of psoriasis presented with generalised erythroderma of three days duration.

Examination reveals him to be shivering but otherwise well. He was treated as an in-patient with emollients and attention to fluid replacement and temperature control but failed to improve after five days.

What is the most appropriate next treatment?

(Please select 1 option)

- Oral hydroxychloroquine
- Oral methotrexate
- Oral prednisolone
- Topical coal tar
- Topical dithranol

Submit answer | Skip question | Tag Question | Remove question

Done
Internet | Protected Mode: Off
110%

Questions Set : REF4274 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF4274
Page Safety Tools

Examination reveals him to be shivering but otherwise well. He was treated as an in-patient with emollients and attention to fluid replacement and temperature control but failed to improve after five days.

What is the most appropriate next treatment?

(Please select 1 option)

◉	Oral hydroxychloroquine ✕ Incorrect answer selected
○	Oral methotrexate ← This is the correct answer
○	Oral prednisolone
○	Topical coal tar
○	Topical dithranol

Erythroderma is an emergency as patients are susceptible to profound dehydration, infection and hypothermia.

Methotrexate would be the only correct treatment for someone with erythrodermic psoriasis.

Steroids could lead to unstable pustular psoriasis and would not generally work.

Hydroxychloroquine has little effect on psoriasis.

Topical coal tar and dithranol are good treatments for chronic plaque psoriasis but are highly irritant and would make the erythroderma much more inflamed and deteriorate his condition.

Next question Tag Question Remove question

Done
Internet | Protected Mode: Off
110%

Questions Set : REF4273 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF4273
Page Safety Tools

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 3 mins 35 secs

Question: 61 of 82

A 40-year-old female presents with a six month history of pruritic papules, vesicles and excoriations on the elbows, knees, buttocks and scalp.

Her GP has prescribed topical betamethasone therapy which has been unhelpful.

What is the most likely diagnosis?

(Please select 1 option)

- Atopic dermatitis (eczema)
- Dermatitis herpetiformis (DH)
- Henoch-Schönlein purpura (HSP)
- Psoriasis
- Scabies

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
110%

Questions Set : REF4273 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF4273
Page Safety Tools

Her GP has prescribed topical betamethasone therapy which has been unhelpful.

What is the most likely diagnosis?

(Please select 1 option)

○	Atopic dermatitis (eczema)
◉	Dermatitis herpetiformis (DH) ✓ Correct
○	Henoch-Schönlein purpura (HSP)
○	Psoriasis
○	Scabies

The question describes the characteristic distribution of the lesions of dermatitis herpetiformis.

DH is one of the immunobullous conditions and characteristically has very intensely pruritic vesicles. It is not usually responsive to topical steroids, but would respond well to dapsone. It is associated with gluten sensitivity and coeliac disease.

Atopic eczema is non-vesicular and would respond to potent topical steroids.

HSP is a purpuric rash and is non-pruritic.

Scabies usually affect the extremities and rarely affect above the neck line. It does not cause papules and vesicles.

Next question Tag Question Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
110%

Questions Set : REF4272 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF4272
Page Safety Tools

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 4 mins 50 secs

Question: 62 of 82

A 75-year-old female presents with chronic leg ulceration which is a consequence of venous insufficiency.

Which one of the following is the most appropriate management?

(Please select 1 option)

- Appropriate systemic antibiotic in preparation for skin grafting
- Compression bandaging
- Improve the venous return by limb elevation
- Skin biopsy to exclude neoplasm
- Vein surgery exclusion of neoplasm by skin biopsy

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
110%

Questions Set : REF4272 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF4272
Page Safety Tools

Dashboard
Questions
Scores
Community
Help
Shop

A 75-year-old female presents with chronic leg ulceration which is a consequence of venous insufficiency.

Which one of the following is the most appropriate management?

(Please select 1 option)

- Appropriate systemic antibiotic in preparation for skin grafting
- (●) Compression bandaging ✓ Correct
- Improve the venous return by limb elevation
- Skin biopsy to exclude neoplasm
- Vein surgery exclusion of neoplasm by skin biopsy

Venous ulcers are secondary to venous stasis and chronic stretching vessel of the vein walls of the superficial veins.

These eventually become thinner and ulcerate.

The only treatment shown in studies to be beneficial for this condition would be to compress the superficial venous using a four layer compression bandage.

The patient should always have their Doppler's and ABPI (ankle brachial pulse index) prior to compression. This should be greater than 1.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
110%

Questions Set : REF4252 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF4252
Page Safety Tools

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 5 mins 33 secs

Question: 63 of 82

A 30-year-old woman presents with a skin rash. On applying pressure to an unaffected area of skin it was relatively easy to induce trauma.

Increased fragility of the skin is characteristic of which of the following conditions?

(Please select 1 option)

- Acute intermittent porphyria
- Epidermolysis bullosa
- Neurofibromatosis
- Pseudo-xanthoma elasticum
- Tuberous sclerosis

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
110%

Questions Set : REF4252 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF4252
Page Safety Tools

Increased fragility of the skin is characteristic of which of the following conditions?

(Please select 1 option)

○	Acute intermittent porphyria
○	Epidermolysis bullosa ← This is the correct answer
○	Neurofibromatosis
◉	Pseudo-xanthoma elasticum ✕ Incorrect answer selected
○	Tuberous sclerosis

Increased skin fragility is seen in a number of disorders and is used as a clinical test in bullous disorders (Nikolsky's sign).

Other causes include

- pemphigus vulgaris
- porphyria cutanea tarda
- drug reactions (especially pseudoporphyria).

Other causes of increased skin fragility (not associated with bullae) include long term corticosteroid therapy, Ehlers-Danlos syndrome and scurvy (vitamin C deficiency).

Next question Remove Tag Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A
Internet | Protected Mode: Off 110%

Questions Set : REF4232 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF4232
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 6 mins 24 secs

Question: 64 of 82

Which of the following is a feature of hereditary haemorrhagic telangiectasia?

(Please select 1 option)

- A good response to oestrogen therapy
- Cerebral arteriovenous malformations
- GI haemorrhage is the usual presenting feature
- Telangiectasia of the mucous membranes, but not the skin
- Tendency of lesions to become less obvious with age

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
110%

Questions Set : REF4232 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF4232
Page Safety Tools

Help

Shop

	Cerebral arteriovenous malformations ← This is the correct answer
◉	GI haemorrhage is the usual presenting feature ✕ Incorrect answer selected
	Telangiectasia of the mucous membranes, but not the skin
	Tendency of lesions to become less obvious with age

Hereditary Haemorrhagic Telangiectasia (HHT) is a multisystem vascular dysplasia characterised by the presence of multiple arteriovenous malformations (AVMs) that lack intervening capillaries and result in direct connections between arteries and veins. Small AVMs, called telangiectases, close to the surface of skin and mucous membranes often rupture and bleed.

The most common clinical manifestations are spontaneous and recurrent epistaxis and multiple telangiectases, which commonly appear on the lips, face, tongue or hands in adulthood. A minority of individuals with HHT have symptomatic GI bleeding, which most commonly begins after age 50 years. Large AVMs often cause symptoms when they occur in the brain or lung; complications from bleeding or shunting may be sudden and catastrophic.

In HHT there may also be pulmonary AVMs.

Epistaxis, not gastrointestinal (GI) haemorrhage, is the usual presenting feature.

Lesions become more obvious with age and affect mucous membranes as well as skin.

Oestrogen therapy is sometimes advocated but the effect, if any, is small.

Next question

Remove Tag Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
110%

Questions Set : REF4172 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF4172
Page Safety Tools

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 7 mins 10 secs

Question: 65 of 82

Which is true regarding eczema herpeticum?

(Please select 1 option)

- Is invariably fatal if untreated
- Is more severe in reactivation disease
- Is typically associated with a high fever for over a week
- Only a single crop of vesicles usually appear
- Usually has an indolent onset

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
110%

Questions Set : REF4172 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF4172
Page Safety Tools

Question: 65 of 82

Which is true regarding eczema herpeticum?

(Please select 1 option)

○	Is invariably fatal if untreated
○	Is more severe in reactivation disease
◉	Is typically associated with a high fever for over a week ✓ Correct
○	Only a single crop of vesicles usually appear
○	Usually has an indolent onset

Eczema herpeticum is the result of primary infection of eczematous skin with *Herpes simplex* virus (HSV). The severity varies from mild to fatal.

There is usually an abrupt onset with crops appearing over seven to nine days. These may become coalesced. Typically, the child has a high fever for seven days, and recurrent attacks can occur.

Death can result from physiological disturbances (loss of fluid electrolytes and protein through the skin) or dissemination of the virus to brain and other organs or from secondary bacterial sepsis.

© 2002 Dr Colin Melville

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
110%

Questions Set : REF4169 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF4169
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 8 mins 2 secs

Question: 66 of 82

A 16-year-old boy presents with erythema nodosum.

Which of the following should be considered?

(Please select 1 option)

- Cytomegalovirus infection
- Kawasaki disease
- Reiter's disease
- Toxoplasmosis
- Ulcerative colitis

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
110%

Questions Set : REF4169 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF4169
Page Safety Tools

Toxoplasmosis

Ulcerative colitis ← This is the correct answer

Erythema nodosum is characterised by painful, indurated, shiny, red, hot, elevated nodules 1-3 cm diameter particularly on the shins. There may be associated fever, malaise, and arthralgia ± hilar adenopathy.

Over a period of days they become violaceous, then dull purple, then fade like a large bruise without residual ulceration or scar. There may be crops over three to six weeks.

They are uncommon under the age of six, and are commoner in females than males.

Causes include:

1. *Infections*
   - Bacteria: Streptococci, leptospirosis, cat-scratch disease, psittacosis, yersinia.
   - Viruses: EBV.
2. *Other*
   - TB, tularaemia, histoplasmosis, coccidioidomycosis.
3. *Drugs*
   - Sulphonamides, oral contraceptive pill.
4. *Systemic diseases*
   - SLE, vasculitis, regional enteritis, ulcerative colitis, Behçet syndrome.

© 2002 Dr Colin Melville

Done
Internet | Protected Mode: Off
110%

Questions Set : REF4167 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF4167
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 8 mins 35 secs

Question: 67 of 82

Which statement regarding tinea capitis is correct?

(Please select 1 option)

- It causes patches that fluoresce dull green under Wood's lamp
- It is effectively treated with topical nystatin ointment
- It is most commonly caused by the fungus Microsporum canis
- It often results in permanent alopecia
- Its presence should suggest immunological deficiency

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
110%

Questions Set : REF4167 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF4167
Page Safety Tools

(Please select 1 option)

- It causes patches that fluoresce dull green under Wood's lamp ← This is the correct answer
- It is effectively treated with topical nystatin ointment
- It is most commonly caused by the fungus Microsporum canis ✕ Incorrect answer selected
- It often results in permanent alopecia
- Its presence should suggest immunological deficiency

Tinea capitis is a dermatophyte infection of the scalp most often caused by *Trichophyton tonsurans*, and occasionally by *Microsporum canis*. It is commonest in areas of socio-economic deprivation.

M. canis is a zoophilic species acquired from cats and dogs. There is initially a small papule at the base of the hair follicle which spreads peripherally forming a scaly circular plaque (ringworm) within which there are brittle, broken infected hairs (exclamation mark hairs).

Confluent patches of alopecia develop and there may be pruritis. Sometimes a severe inflammatory response produces an elevated boggy granulomatous mass (kerion), studded with sterile pustules. There may be fever and regional lymphadenopathy, and occasionally permanent scarring and alopecia may result.

The crusted patches fluoresce dull green under Wood's light. Microscopic examination of a potassium hydroxide (KOH) preparation shows tiny spores and the fungi may be grown in Sabouraud medium with antibiotics.

Oral griseofulvin for two to three months is required, or ketoconazole for resistant cases.

© 2002 Dr Colin Melville

Done
Internet | Protected Mode: Off
110%

Questions Set : REF4165 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF4165
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 9 mins 17 secs

Question: 68 of 82

Which of the following suggests a diagnosis of molluscum contagiosum rather than chickenpox?

(Please select 1 option)

- Absence of erythema surrounding lesions
- Lesions disappearing within a month
- Positive contact history
- Presence of macules and papules
- Presence of pruritis

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
110%

Questions Set : REF4165 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF4165
Page
Safety
Tools

Question: 68 of 82

Which of the following suggests a diagnosis of molluscum contagiosum rather than chickenpox?

(Please select 1 option)

◉	Absence of erythema surrounding lesions ✓ Correct
○	Lesions disappearing within a month
○	Positive contact history
○	Presence of macules and papules
○	Presence of pruritis

Molluscum contagiosum is caused by a deoxyribonucleic acid (DNA) pox virus.

The lesions are small, skin coloured papules with central umbilication. There is little surrounding inflammation and they may be spread following scratching to other sites.

Chickenpox lesions in the early stages may be mistaken for molluscum. However, the presence of associated macules and later vesicles and pustules help to differentiate them.

These lesions also affect the mucus membranes, and usually disappear within a few weeks, while molluscum can persist for up to a year.

© 2002 Dr Colin Melville

Next question

Tag Question

Remove question

Done
Internet | Protected Mode: Off
110%

Questions Set : REF4050 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF4050
Page Safety Tools

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 10 mins 3 secs

Question: 69 of 82

A 26-year-old man is noted to have cyanosis of the lower limbs and clubbing of the toes but not the fingers.

Which of the following statements is true?

(Please select 1 option)

- He has coarctation of the aorta
- He has Eisenmenger's syndrome
- He has had a Blalock shunt operation
- He is likely to have a loud continuous 'machinery' murmur below the left clavicle
- He is likely to need urgent surgery

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
110%

Questions Set : REF4050 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF4050
Page Safety Tools

(Please select 1 option)

◉	He has coarctation of the aorta ✕ Incorrect answer selected
○	He has Eisenmenger's syndrome ← This is the correct answer
○	He has had a Blalock shunt operation
○	He is likely to have a loud continuous 'machinery' murmur below the left clavicle
○	He is likely to need urgent surgery

This is the differential cyanosis of a reversed patent ductus arteriosus (PDA). There is a right-left shunt from the pulmonary artery to the aorta just distal to the left subclavian artery.

Coarctation causes radiofemoral delay. It may be associated with PDA but there is no suggestion in this patient.

Continuous machinery murmur is the classic murmur of PDA but when the shunt reverses (as in patients with a large PDA and/or pulmonary disease) the murmur becomes softer and shorter.

When Eisenmenger's syndrome has developed surgery is associated with a very high mortality.

A Blalock shunt (anastomosis of subclavian artery to pulmonary artery) used to be performed for Fallot's tetralogy and leads to a weak left radial pulse.

Next question Remove Tag Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Internet | Protected Mode: Off 110%

Questions Set : REF55626 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF55626
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Question: 6 of 82

A 15-year-old boy comes to the dermatology clinic as his parents are concerned about some changes they have noticed in his skin. He is from a travelling community, and as such his parents have previously shunned medical services.

On examination you notice that he has a number of facial and periungual fibromata. He also has a number of hypomelanotic areas (at least four) on examination of his skin. You also notice gingival fibromata and pitting of his tooth enamel on examination of his mouth.

On which chromosome is the abnormality associated with this disease likely to be found?

(Please select 1 option)

○	Chromosome 2
◉	Chromosome 6 ✕ Incorrect answer selected
○	Chromosome 9 ← This is the correct answer
○	Chromosome 11
○	Chromosome 12

This boy has tuberous sclerosis, which is inherited in autosomal dominant fashion, with responsible defects having been identified on both chromosome 9 and chromosome 16. These chromosomes carry codes for hamartin and tuberin, protein gene products which are responsible for regulation of cell growth.

Most of the tumours which are produced in tuberous sclerosis are hamartomas, and various phenotypes of the disease occur, with some parents of patients having much more subtle features than those seen in their children.

Next question

Remove Tag | Remove question

Done
Internet | Protected Mode: Off
100%

Questions Set : REF51394 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF51394
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 17 mins 6 secs

Question: 7 of 82

A nurse presents with severe swelling around the mouth following her lunch.

She was treated for suspected anaphylaxis and on further questioning she says that previously she has had an itchy rash on her hands after wearing latex gloves.

Which of the following fruit is the most likely to have been in her lunch to explain this reaction?

(Please select 1 option)

- Apple
- Banana
- Gooseberry
- Pineapple
- Star fruit

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Internet | Protected Mode: Off
100%

Questions Set : REF4049 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF4049
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 11 mins 19 secs

Question: 70 of 82

Which of the following is true of cutaneous anthrax?

(Please select 1 option)

- Causes a black eschar which overlies pus
- Is very likely to occur in subjects exposed to anthrax spores
- Lesions are associated with marked oedema
- Lesions are usually painful and tender
- Mortality is approximately 20% despite antibiotic therapy

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
110%

Questions Set : REF4049 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF4049
Page Safety Tools

Question: 70 of 82

Which of the following is true of cutaneous anthrax?

(Please select 1 option)

- ○ Causes a black eschar which overlies pus
- ○ Is very likely to occur in subjects exposed to anthrax spores
- ◉ Lesions are associated with marked oedema ✓ Correct
- ○ Lesions are usually painful and tender
- ○ Mortality is approximately 20% despite antibiotic therapy

Anthrax is caused by *Bacillus anthracis* a Gram-positive rod.

Cutaneous anthrax is caused by direct contact of the bacteria into an open wound (usually touching an infected animal). Cutaneous anthrax is associated with a black eschar without pus, tends to be painless and to have widespread oedema.

Without antibiotics mortality is of the order of 20%, but with antibiotics, mortality is low, which contrasts with pulmonary anthrax.

Further reading:
Cutaneous Anthrax Management Algorithm American Academy of Dermatology

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
110%

Questions Set : REF4047 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF4047
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 12 mins

Question: 71 of 82

Which of the following concerning leg ulcers is correct?

(Please select 1 option)

- Diuretics have been shown to improve ulcer healing when associated with oedema
- In diabetic ulcers, the dressing should be left in situ for no more than one week
- Large gravitational ulcers are always painful
- Treating superficial infection with antibiotics has been shown to be beneficial
- Ulcers caused by arterial disease are typically treated by compression bandaging

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
110%

Questions Set : REF4047 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF4047
Page Safety Tools

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 12 mins 55 secs

Question: 71 of 82

Which of the following concerning leg ulcers is correct?

(Please select 1 option)

- Diuretics have been shown to improve ulcer healing when associated with oedema
- In diabetic ulcers, the dressing should be left in situ for no more than one week ← This is the correct answer
- Large gravitational ulcers are always painful
- Treating superficial infection with antibiotics has been shown to be beneficial ✕ Incorrect answer selected
- Ulcers caused by arterial disease are typically treated by compression bandaging

Diuretics may reduce oedema but have not been demonstrated per se to reduce healing time.

Gravitational ulcers are not usually painful.

If there are no obvious features of surrounding cellulitis, antibiotic therapy is usually unnecessary and has not been shown to improve healing in superficial infection which is common in ulceration.

Next question | Remove Tag | Remove question

Show tool

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Questions.aspx
Internet | Protected Mode: Off
110%

Questions Set : REF4026 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF4026
Page
Safety
Tools

Dashboard
Questions
Scores
Community
Help
Shop

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 12 mins 55 secs

Question: 72 of 82

Which of the following is a recognised feature of psoriasis?

(Please select 1 option)

- Angular stomatitis
- Iridocyclitis
- Koebner phenomenon
- Loss of hair
- Response to chloroquine

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
110%

Questions Set : REF4026 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF4026
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 13 mins 20 secs

Question: 72 of 82

Which of the following is a recognised feature of psoriasis?

(Please select 1 option)

- ○ Angular stomatitis
- ○ Iridocyclitis
- ◉ Koebner phenomenon ✓ Correct
- ○ Loss of hair
- ○ Response to chloroquine

Psoriasis is associated with a dermopathy and arthropathy which may range from mild distal interphalangeal joint involvement with nail pitting to severe arthritis mutilans.

A Koebner phenomenon refers to outbreak of a skin eruption following minor trauma and is a feature of psoriasis.

Psoriatic arthropathy may be associated with an anterior uveitis.

Chloroquine may produce a severe attack of psoriasis.

Next question

Tag Question

Remove question

Show to
Done
Internet | Protected Mode: Off
110%

Questions Set : REF4023 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF4023
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 13 mins 20 secs

Question: 73 of 82

Which of the following concerning pityriasis rosea is correct?

(Please select 1 option)

- It is characterised by flat scaly patches
- It is due to a fungal infection
- It is frequently associated with oro-genital itching
- May be preceded by intense itching
- Tends to recur after apparent cure

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
110%

Questions Set : REF4023 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF4023
Page Safety Tools

(Please select 1 option)

○	It is characterised by flat scaly patches ← This is the correct answer
○	It is due to a fungal infection
◉	It is frequently associated with oro-genital itching ✕ Incorrect answer selected
○	May be preceded by intense itching
○	Tends to recur after apparent cure

Pityriasis rosea is a rash that can occur at any age, but it occurs most commonly in people between the ages of 10 and 35 years.

It may be set off by a viral infection but does not appear to be contagious; herpes viruses six and seven have most often been associated with pityriasis rosea. It is not caused by a fungus.

It is not related to foods, medicines, or stress. It most often affects teenagers or young adults.

The condition often begins as a large single pink patch on the chest or back. This patch may be scaly and is called a 'herald' or 'mother' patch.

Within a week or two, more pink patches, sometimes hundreds of them, appear on the body and on the arms and legs. Patches may also occur on the neck, and though rare, the face.

The oval patches follow the line of the ribs like a fir tree. They have a dry surface and may have an inner circlet of scaling.

Next question Remove Tag Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
110%

Questions Set : REF4012 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx?id=644011&ws=true
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF4012
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 14 mins 12 secs

Question: 74 of 82

Which of the following may be responsible for an acute relapse of systemic lupus erythematosus (SLE) in a 38-year-old female?

(Please select 1 option)

- Hydralazine therapy
- Pregnancy
- Progesterone only contraceptive pill
- Salmeterol therapy
- Winter holiday in Lapland

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
110%

Questions Set : REF4012 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx?id=644011&ws=true
Favorites Suggested Sites Get More Add-ons
Questions Set : REF4012
Page Safety Tools

- Pregnancy ✓ Correct
- Progesterone only contraceptive pill
- Salmeterol therapy
- Winter holiday in Lapland

Some physiological and environmental factors affect the periods of deterioration and of remission in systemic lupus erythematosus.

These factors include hormone replacement therapy (HRT) and particularly the oral contraceptive, pregnancy and infection. It would not be expected with the progesterone only oral contraceptive.

You would expect to find virtually no sun on a winter holiday in Lapland (Arctic circle)!

A number of drugs (hydralazine, procainamide, isoniazid, chlorpromazine, D-penicillamine and methyldopa) can result in drug-induced lupus in predisposed individuals.

This can be differentiated from the idiopathic SLE on genetic and immunologic grounds.

Furthermore,

- it is mild and reversible on stopping the drug
- renal disease and double stranded anti-DNA are rare (although antibodies specific for histones may be present)
- the sex ratio is equal.

These drugs do not cause deterioration in patients with SLE.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd. All rights reserved. Terms and conditions Privacy policy

Done
Internet | Protected Mode: Off
100%

Questions Set : REF3989 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF3989
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 14 mins 37 secs

Question: 75 of 82

A 43-year-old woman with atopic dermatitis (atopic eczema) presented with an acute generalised exacerbation of her disease.

She was admitted to hospital but failed to improve with emollients, topical betamethasone 17-valerate and oral antihistamine.

Which one of the following drugs is the most appropriate treatment?

(Please select 1 option)

- Acitretin
- Amoxicillin
- Cyclosporin
- Colchicine
- Dapsone

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
105%

Questions Set : REF3989 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites | Suggested Sites | Get More Add-ons
Questions Set : REF3989
Page | Safety | Tools

A 43-year-old woman with atopic dermatitis (atopic eczema) presented with an acute generalised exacerbation of her disease.

She was admitted to hospital but failed to improve with emollients, topical betamethasone 17-valerate and oral antihistamine.

Which one of the following drugs is the most appropriate treatment?

(Please select 1 option)

○	Acitretin
○	Amoxicillin
○	Cyclosporin ← This is the correct answer
○	Colchicine
◉	Dapsone ✕ Incorrect answer selected

Cyclosporin is a well used drug in the treatment of atopic dermatitis (AD). It is usually at doses of 2-5 mg/kg.

The pathophysiology of AD is complex but the T lymphocytes are involved and it is known that there is an increased production of cytokines particularly IL -4.

Cyclosporin is a suppressor of T cells and in that respect works very well in atopic dermatitis and psoriasis. The side effects of hypertension and renal toxicity limit its use.

These patients are seen monthly to have their blood pressure and urea and electrolytes (U&E) checked.

Next question | Tag Question | Remove question

Done
Internet | Protected Mode: Off
105%

Questions Set : REF3794 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF3794
Page Safety Tools

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 19 mins 42 secs

Question: 76 of 82

A 22-year-old woman complains of haemoptysis, abdominal pains and pyrexia for a month.

She is admitted to hospital and found to be apyrexial and not distressed. There are numerous crusted, linear lesions on her forearms.

What is the most likely diagnosis?

(Please select 1 option)

- Acute intermittent porphyria
- Factitious disorder
- Systemic lupus erythematosus
- TB
- Wegener's granulomatosis

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
105%

Questions Set : REF3794 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF3794
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 23 mins 54 secs

Question: 76 of 82

A 22-year-old woman complains of haemoptysis, abdominal pains and pyrexia for a month.

She is admitted to hospital and found to be apyrexial and not distressed. There are numerous crusted, linear lesions on her forearms.

What is the most likely diagnosis?

(Please select 1 option)

○	Acute intermittent porphyria
◉	Factitious disorder ✓ Correct
○	Systemic lupus erythematosus
○	TB
○	Wegener's granulomatosis

The history is very vague and the patient has no clinical features other than a rash which sounds typical of dermatitis artifacta.

The crusted lesions on the forearms suggest artefacta as this is the most typical site for these lesions.

Porphyria may be expected to have vesicles on sun exposed regions, face, arms and legs.

Next question

Tag Question

Remove question

Show to

© 2011 BMJ Publishing Group Ltd. All rights reserved. Terms and conditions Privacy policy

Done
Internet | Protected Mode: Off
105%

Questions Set : REF2761 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF2761
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 23 mins 54 secs

Question: 77 of 82

A 40-year-old man presented with pityriasis versicolor.

What is the most appropriate treatment?

(Please select 1 option)

- Methotrexate
- Oral terbinafine
- Phototherapy with ultraviolet light (UVB)
- Psoralen with ultraviolet light (PUVA) therapy
- Topical selenium sulphide

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
105%
EN
02:11 P
2/16/2011

Questions Set : REF2761 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF2761
Page Safety Tools

Dashboard
Questions
Scores
Community
Help
Shop

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 25 mins 16 secs

Question: 77 of 82

A 40-year-old man presented with pityriasis versicolor.

What is the most appropriate treatment?

(Please select 1 option)

○	Methotrexate
○	Oral terbinafine
○	Phototherapy with ultraviolet light (UVB)
◉	Psoralen with ultraviolet light (PUVA) therapy ✕ Incorrect answer selected
○	Topical selenium sulphide ← This is the correct answer

Pityriasis versicolor (also called tinea versicolor) is a skin lesion caused by a fungus called *Malassezia furfur*.

The treatment is topical selenium sulphide. Oral itraconazole is also effective.

Next question | Remove Tag | Remove question

Show tools

© 2011 BMJ Publishing Group Ltd. All rights reserved. Terms and conditions Privacy policy

Done
Internet | Protected Mode: Off
105%

Questions Set : REF2757 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF2757
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 25 mins 16 secs

Question: 78 of 82

What is the most common presenting feature of porphyria cutanea tarda?

(Please select 1 option)

- Acute blistering crises affecting the trunk and limbs
- Acute redness and swelling following sun exposure
- Erythroderma
- Generalised hypertrichosis
- Skin fragility and blistering affecting the hands, face and scalp

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
105%

Questions Set : REF2757 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites | Suggested Sites | Get More Add-ons
Questions Set : REF2757
Page | Safety | Tools

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 26 mins 22 secs

Question: 78 of 82

What is the most common presenting feature of porphyria cutanea tarda?

(Please select 1 option)

- Acute blistering crises affecting the trunk and limbs
- Acute redness and swelling following sun exposure
- Erythroderma
- Generalised hypertrichosis
- Skin fragility and blistering affecting the hands, face and scalp ✓ Correct

Porphyria cutanea tarda (PCT) is a term that encompasses a group of related disorders, all of which arise from deficient activity of the haeme-synthetic enzyme uroporphyrinogen decarboxylase (URO-D) in the liver.

The porphyrins produced in PCT are photoactive molecules that absorb light energy strongly in the visible violet spectrum. Photoexcited porphyrins in the skin mediate oxidative damage to biomolecular targets, causing cutaneous photosensitivity reactions.

The most common presenting sign of PCT is fragility of sunexposed skin after mechanical trauma, leading to erosions and bullae, worst on dorsal hands, forearms and face.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A
Internet | Protected Mode: Off
105%

Questions Set : REF2755 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx?id=644011&ws=true
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF2755
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 26 mins 22 secs

Question: 79 of 82

Deficiency of which one of the following trace elements is implicated as a cause of cardiomyopathy?

(Please select 1 option)

- Chromium
- Copper
- Manganese
- Selenium
- Zinc

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
105%

Questions Set : REF42931 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF42931
Page Safety Tools

Work Smart Session - MRCP Part 1

Time taken: 18 mins 46 secs

Question: 8 of 82

A 51-year-old male presents with a rash that has been present intermittently over the last two years. On examination there is a symmetrical rash over the cheeks, nose and chin, with multiple papules and pustules.

What is the most appropriate therapy for this patient?

(Please select 1 option)

- Flucloxacillin
- Hydroxychloroquine
- Isotretinoin
- Oxytetracycline
- Prednisolone

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
100%

Questions Set : REF2755 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx?id=644011&ws=true
Favorites Suggested Sites Get More Add-ons
Questions ... passmedicine.... passmedicine.... passmedicine.... passmedicine.... passmedicine.... passmedicine.... passmedicine....
Page Safety Tools

Dashboard
Questions
Scores
Community
Help
Shop

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 31 mins 11 secs

Question: 80 of 82

Deficiency of which one of the following trace elements is implicated as a cause of cardiomyopathy?

(Please select 1 option)

- Chromium
- Copper
- Manganese
- Selenium ✓ Correct
- Zinc

Selenium deficiency is one of the reversible causes of dilated cardiomyopathy.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Show tools

Internet | Protected Mode: Off 105%

Questions Set : REF1958 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions ... passmedicine.... passmedicine.... passmedicine.... passmedicine.... passmedicine.... passmedicine.... passmedicine....
Page Safety Tools

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 31 mins 11 secs

Question: 81 of 82

A 23-year-old obese female with known tuberculosis presents with ulcerating nodules on the back of her legs.

Which of the following is the most likely diagnosis?

(Please select 1 option)

- Erythema induratum (EI)
- Erythema marginatum
- Erythema nodosum
- Lupus pernio
- Lupus vulgaris

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
105%

Questions Set : REF1958 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questio... passmedici... passmedici... passmedici... passmedici... passmedici... passmedici... passmedici... passmedici...
Page Safety Tools

(Please select 1 option)

○	Erythema induratum (EI) ← This is the correct answer
○	Erythema marginatum
○	Erythema nodosum
○	Lupus pernio
◉	Lupus vulgaris ✕ Incorrect answer selected

EI is a form of panniculitis characterised by chronic, recurrent, tender, subcutaneous, and sometimes ulcerated nodules on the lower legs that may also appear elsewhere.

Females are more frequently affected, with a female:male ratio of 7:1 and it is more frequent in younger females.

It is found in association with tuberculosis.

Another possibility although not provided in the stems is pyoderma gangrenosum.

On the other hand, lupus vulgaris is a chronic, progressive and destructive form of cutaneous tuberculosis in patients with a moderate or high degree of immunity. It occurs more commonly in females than in males.

The classical lesions consist of reddish-brown plaques not nodules. The lesions progress by peripheral extension and central healing, atrophy and scarring. The areas of predilection are head and neck (80%), followed by arms, legs, then trunk.

This rash is not the typical description of erythema marginatum (finer rash) or multiforme (blisters, targets).

Lupus pernio occurs in association with sarcoid.

Internet | Protected Mode: Off 105%

Questions Set : REF1860 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questio... passmedici... passmedici... passmedici... passmedici... passmedici... passmedici... passmedici... passmedici...
Page Safety Tools

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 34 mins 34 secs

Question: 82 of 82

A 24-year-old female presents with vague frontal headaches and visual disturbance.

She has a past history of acne for which she is receiving treatment. Examination reveals her to be obese with a blood pressure of 110/70 mmHg. There is absence of the central retinal vein pulsation on fundoscopic examination.

Which of the following drugs account for these findings?

(Please select 1 option)

- Ampicillin
- Dianette
- Erythromycin
- Isotretinoin
- Topical tetracycline

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
105%

Questions Set : REF42931 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF42931
Page Safety Tools

Work Smart Session - MRCP Part 1

Time taken: 20 mins 7 secs

Question: 8 of 82

A 51-year-old male presents with a rash that has been present intermittently over the last two years. On examination there is a symmetrical rash over the cheeks, nose and chin, with multiple papules and pustules.

What is the most appropriate therapy for this patient?

(Please select 1 option)

- Flucloxacillin
- Hydroxychloroquine
- Isotretinoin
- Oxytetracycline ✓ Correct
- Prednisolone

The description is that of acne rosacea particularly in view of the distribution, duration and absence of any other features. The most appropriate treatment is a tetracycline.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
100%

Questions Set : REF36447 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF36447
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 20 mins 7 secs

Question: 9 of 82

Concerning neurofibromatosis type 1 (NF1), which one of the following statements is true?

(Please select 1 option)

- Bilateral acoustic neuromas are common
- Clinical severity in individuals is similar in a given family
- New mutations occur rarely
- Pigmented spots on the iris are a characteristic feature
- The diagnosis is likely if two café au lait patches are present

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
100%

Questions Set : REF36447 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF36447
Page Safety Tools

Question: 9 of 82

Concerning neurofibromatosis type 1 (NF1), which one of the following statements is true?

(Please select 1 option)

- Bilateral acoustic neuromas are common
- Clinical severity in individuals is similar in a given family
- New mutations occur rarely
- Pigmented spots on the iris are a characteristic feature ✓ Correct
- The diagnosis is likely if two café au lait patches are present

Lisch nodules of the iris are present in more than 90% of patients.

Bilateral acoustic neuromas are a hallmark feature of neurofibromatosis type 2.

Expressivity of the gene is highly variable and members of the same family usually show wide differences in clinical symptoms.

NF1 is one of the most common autosomal dominant conditions. However almost half of all cases give no family history and are new mutations. The mutation rate is estimated to be 1:10,000 gametes.

The diagnosis is suggested by six or more café au lait macules (spots), each over 5 mm in diameter in prepubescent individuals and over 15 mm in post pubertal individuals.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: Off
100%

Work Smart Session - MRCP Part 1

Time taken:

Question: 1 of 100

A 40-year-old man is admitted to the Emergency Department after being involved in a house fire. He is extremely drowsy but you notice on examining him that he seems well perfused, with his cheeks looking almost pink. His BP is 100/60 and his pulse is 95 and regular. Blood gas analysis reveals a CO level of 12% and a metabolic acidosis with a pH of 7.15.

Which of the following is the most appropriate next intervention?

(Please select 1 option)

- **A** Hyperbaric oxygen
- **B** IV mannitol
- **C** IV sodium bicarbonate
- **D** 100% oxygen by mask
- **E** Nebulised salbutamol

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 37 mins 19 secs

Question: 10 of 100

A 50-year-old woman is found to have reversed splitting of the second heart sound.

This is found in which one of the following conditions?

(Please select 1 option)

- Atrial septal (AS) defect
- Mild aortic regurgitation
- Patent ductus arteriosus
- Right bundle branch block (RBBB)
- Ventricular septal defect (VSD)

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 5 hrs 37 mins 17 secs

Question: 100 of 100

A 63-year-old female presents with a one day history of confusion with headaches.

On examination she is confused, with a Glasgow Coma Scale of 13 and a temperature of 39.5°C.

She has nuchal rigidity and photophobia.

CSF examination reveals a glucose of 0.5 mmol/l (3.3-4.4), a white cell count of 2500 per mm and Gram-positive cocci in pairs.

Which of the following is correct?

(Please select 1 option)

○	A characteristic rash would be expected
○	Nerve deafness would be a common complication in this case
○	Rifampicin should be given to close contacts
○	The most likely infective organism is *Staphylococcus aureus*
○	The organism is likely to be penicillin resistant

Submit answer | Skip question | Tag Question | Remove question

She has nuchal rigidity and photophobia.

CSF examination reveals a glucose of 0.5 mmol/l (3.3-4.4), a white cell count of 2500 per mm and Gram-positive cocci in pairs.

Which of the following is correct?

(Please select 1 option)

○	A characteristic rash would be expected
◉	Nerve deafness would be a common complication in this case ✓ Correct
○	Rifampicin should be given to close contacts
○	The most likely infective organism is *Staphylococcus aureus*
○	The organism is likely to be penicillin resistant

This patient has pneumococcal meningitis, caused by the Gram-positive coccus *Strep. pneumoniae*.

This is the second commonest cause of bacterial meningitis (commonest in the elderly) and is associated with the highest mortality (20%) and highest morbidity, such as deafness which may occur in 50%.

Contacts do not require treatment and there is no rash associated with pneumococcal meningitis.

Meningococcus is Gram-negative.

Finish | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 41 mins 7 secs

Question: 10 of 100

A 50-year-old woman is found to have reversed splitting of the second heart sound.

This is found in which one of the following conditions?

(Please select 1 option)

○	Atrial septal (AS) defect
○	Mild aortic regurgitation
○	Patent ductus arteriosus ← This is the correct answer
◉	Right bundle branch block (RBBB) ✕ Incorrect answer selected
○	Ventricular septal defect (VSD)

Reversed splitting of the second heart sound occurs with reversal of the normal A2, P2 pattern.

Thus A2 may be delayed as with severe AS (not mild), and LBBB.

P2 may be early as with Wolff-Parkinson-White type B and persistent ductus arteriosus.

Atrial septal defects show wide fixed splitting, and RBBB has wide, but not fixed splitting.

Next question

Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 41 mins 7 secs

Question: 11 of 100

A 35-year-old lady presented with left-sided weakness.

She has a young family with a 5-year-old son and a 2-year-old daughter. Previously she had two spontaneous abortions. After the birth of her last child she developed a deep vein thrombosis (DVT) and received three months of anticoagulation with warfarin.

On examination she has left-sided weakness with pyramidal signs. A CT head scan showed a right middle cerebral artery territory infarct.

Which of the following is the most likely diagnosis?

(Please select 1 option)

○	Hypertension
○	Kawasaki syndrome
○	Patent foramen ovale
○	Systemic lupus erythematosus
○	Thrombotic thrombocytopaenic purpura

Submit answer | Skip question | Tag Question | Remove question

Question: 11 of 100

A 35-year-old lady presented with left-sided weakness.

She has a young family with a 5-year-old son and a 2-year-old daughter. Previously she had two spontaneous abortions. After the birth of her last child she developed a deep vein thrombosis (DVT) and received three months of anticoagulation with warfarin.

On examination she has left-sided weakness with pyramidal signs. A CT head scan showed a right middle cerebral artery territory infarct.

Which of the following is the most likely diagnosis?

(Please select 1 option)

○	Hypertension
○	Kawasaki syndrome
○	Patent foramen ovale
◉	Systemic lupus erythematosus ✓ Correct
○	Thrombotic thrombocytopaenic purpura

This patient has a prothrombotic tendency suggestive of the lupus anticoagulant with recurrent abortions, previous DVT and now she has developed a left hemiparesis.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 42 mins

Question: 12 of 100

A 59-year-old male presents with a one hour history of central crushing chest pain. He is known to be diabetic, hypertensive and is a non-smoker.

On examination his pulse rate is 90 beats/min, blood pressure 130/85 mmHg, S1 S2 are audible with no murmurs. There is no evidence of cardiac failure.

An electrocardiogram (ECG) is performed.

Which of the following would be an indication for thrombolysis?

(Please select 1 option)

○	Atrial fibrillation greater than 150 min^{-1}
○	Right bundle branch block
○	ST depression of 2 mm in leads II, III, avF
○	ST elevation of 2 mm in V4-V6
○	Supraventricular tachycardia

Submit answer | Skip question | Tag Question | Remove question

(Please select 1 option)

○	Atrial fibrillation greater than 150 min^{-1}
○	Right bundle branch block
○	ST depression of 2 mm in leads II, III, avF
◉	ST elevation of 2 mm in V4-V6 ✓ Correct
○	Supraventricular tachycardia

This patient is having an acute myocardial infarction (MI); the ECG changes of ST elevation of 2 mm in V4-V6 suggest an anterolateral MI.

Given this history and ECG changes, he should be given thrombolytic treatment, along with aspirin, heparin, beta-blockade, statin therapy and subsequent angiotensin-converting enzyme (ACE) inhibition.

ECG criteria for thrombolysis include:

- ST elevation of more than 1 mm in standard limb leads
- ST elevation more than 2 mm in anterior chest leads
- new left bundle branch block

within 24 hours of typical pain.

Evidence beyond 12 hours of pain is equivocal thrombolysis at this time; it tends to be used if there is clinical deterioration or persistent pain.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd. All rights reserved. Terms and conditions Privacy policy A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 43 mins 4 secs

Question: 13 of 100

A 54-year-old obese male with a history of angina and hypertension presents with central crushing chest pain of two hours duration.

High flow oxygen, sublingual GTN and aspirin are administered and venous access is obtained. Whilst being attached to an ECG monitor he collapses and the initial rhythm is pulseless ventricular tachycardia (VT).

Which of the following is the most appropriate immediate treatment for this man?

(Please select 1 option)

○	A ventilation to compression ratio of 30:2 should commenced
○	Continuous chest compressions should be started
○	He should be defibrillated with a 200 J (monophasic) shock
○	He should be given a praecordial thump
○	Intravenous adrenaline should be given

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

A 54 year old obese male with a history of angina and hypertension presents with central crushing chest pain of two hours duration.

High flow oxygen, sublingual GTN and aspirin are administered and venous access is obtained. Whilst being attached to an ECG monitor he collapses and the initial rhythm is pulseless ventricular tachycardia (VT).

Which of the following is the most appropriate immediate treatment for this man?

(Please select 1 option)

○	A ventilation to compression ratio of 30:2 should commenced
○	Continuous chest compressions should be started
○	He should be defibrillated with a 200 J (monophasic) shock
◉	He should be given a praecordial thump ✓ Correct
○	Intravenous adrenaline should be given

An initial praecordial thump is indicated and is more likely to be successful in converting pulseless VT to sinus rhythm, than if the rhythm was ventricular fibrillation (VF).

The appropriate compression to ventilation ratio is 30:2, which should be synchronised to allow effective ventilation, until a laryngeal mask airway (LMA) or tracheal tube is passed.

When using a monophasic defibrillator all unsynchronised shocks are 360 J.

The first dose of adrenaline is given immediately before the third 360 J (monophasic) shock.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 44 mins 13 secs

Question: 14 of 100

A 32-year-old female smoker presents with acute severe asthma. The SaO2 are 80% on 15 L of oxygen and the pO2 is 8.2kPa (10.5-13).

There is widespread expiratory wheeze throughout the chest. She is given IV hydrocortisone, 100% oxygen and 5 mg of nebulised salbutamol.

What is the next step in your management?

(Please select 1 option)

- IV augmentin
- IV magnesium
- IV potassium
- IV theophylline
- Oral prednisolone

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

○	IV magnesium ← This is the correct answer
○	IV potassium
○	IV theophylline
◉	Oral prednisolone ✕ Incorrect answer selected

This question focuses on acute treatment of asthma.

Your initial approach should be SOS - salbutamol, oxygen and steroids intravenously (IV).

In the meantime a chest x-ray (CXR) should be organised to rule out pneumothorax.

You should then consider further efforts to treat bronchoconstriction - a silent chest, or a tiring patient should suggest ITU review.

The recommended dose of magnesium is 2 g over 30 minutes. The mechanism by which it has its effect is not fully understood, but it is thought that low magnesium levels in bronchial smooth muscle favour bronchoconstriction.

IV theophylline may be considered, but magnesium would be higher on the list.

IV antibiotic may be indicated, but your initial focus should be promoting bronchodilation.

IV potassium may be required as the beta agonists push down the potassium.

Oral prednisolone can wait, as you have already given IV hydrocortisone as part of your SOS approach.

Next question | Tag Question | Remove question

Work Smart Session - MRCP Part 1

Time taken: 45 mins 33 secs

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Question: 15 of 100

A 22-year-old male is admitted wheezing with a respiratory rate of 35/min, a pulse of 120 beats per min, blood pressure 110/70 mmHg, peak expiratory flow rate <50% predicted.

The emergency medical services have administered salbutamol 5 mg (twice), ipratroprium 0.5 mg and face mask oxygen.

His arterial blood gas reveals:

pH	7.42	(7.36-7.44)
$PaCO_2$	5.0 kPa	(4.7-6.0)
PaO_2	22 kPa	(11.3-12.6)
Base excess	-2 mmol/l	(+/-2)
SpO_2	98	

Which of the following is the most appropriate action for this man?

(Please select 1 option)

- ○ Chest x ray
- ○ Intensive care referral
- ○ Ipratroprium
- ○ Magnesium 1-2 g
- ○ Oxygen 35 %

Base excess	-2 mmol/l	(+/-2)
SpO_2	98	

Which of the following is the most appropriate action for this man?

(Please select 1 option)

◉	Chest x ray ✕ Incorrect answer selected
○	Intensive care referral ← This is the correct answer
○	Ipratroprium
○	Magnesium 1-2 g
○	Oxygen 35 %

In this case the patient is showing signs of respiratory decompensation.

A normal or raised $PaCO_2$ in an asthmatic is a warning of impending respiratory failure as the patient becomes too tired to ventilate adequately and ITU need to be notified.

Administration of magnesium would be the next therapeutic measure.

A chest x ray will be helpful but should not delay in treatment and referral.

35 % oxygen is inadequate.

Next question

Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 48 mins 5 secs

Question: 16 of 100

A 22-year-old female is admitted very distressed and short of breath.

Examination reveals a respiratory rate of 35/min, a pulse of 120 beats per minute, a blood pressure 110/70 mmHg, oxygen saturations of 90% and a peak expiratory flow rate <50% predicted.

The emergency medical services have administered salbutamol 5 mg (twice) and face mask oxygen.

Which of the following is the most appropriate next action in this patient?

(Please select 1 option)

- Arterial blood gas analysis
- Intensive care referral
- Oxygen 35%
- Prednisolone 40 mg
- Salbutamol 5 mg and ipratroprium bromide 0.5 mg

Submit answer | Skip question | Tag Question | Remove question

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Which of the following is the most appropriate next action in this patient?

(Please select 1 option)

○	Arterial blood gas analysis
◉	Intensive care referral ✕ Incorrect answer selected
○	Oxygen 35%
○	Prednisolone 40 mg
○	Salbutamol 5 mg and ipratroprium bromide 0.5 mg ← This is the correct answer

According to British Thoracic Society guidelines, addition of ipratroprium would be the next step in the case of this lady with acute severe asthma.

Prednisolone would be administered shortly thereafter.

35% oxygen is inadequate and a maximal concentration should be used.

A blood gas is not essential for management particularly with the oxygen saturations of 90% although these will be performed.

Intensive care referral may well be appropriate if this lady does not improve.

Further reading:
Management of Acute Severe Asthma University of Cambridge

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 49 mins 35 secs

Question: 17 of 100

A 27-year-old lady collapses in the Emergency Department after being admitted with numerous seizures.

You obtain information from her husband that she has a past history of seizures, but has not had any for the last two years, and is well controlled on valproate.

He also informs you that she has been gaining weight recently and has also had erratic menses which the neurology clinic attribute to the valproate.

Pulse	110/min
Blood pressure	160/90 mmHg
Urinalysis	3+ proteinuria

After airway, breathing and circulation, the immediate drug therapy should be:

(Please select 1 option)

- Diazepam 10 mg
- Lorazepam 2 mg
- Magnesium 2 grams
- Nil
- Phenytoin 1000 mg

Submit answer | Skip question | Tag Question | Remove question

He also informs you that she has been gaining weight recently and has also had erratic menses which the neurology clinic attribute to the valproate.

Pulse	110/min
Blood pressure	160/90 mmHg
Urinalysis	3+ proteinuria

After airway, breathing and circulation, the immediate drug therapy should be:

(Please select 1 option)

- ◉ Diazepam 10 mg ✕ Incorrect answer selected
- ○ Lorazepam 2 mg
- ○ Magnesium 2 grams ← This is the correct answer
- ○ Nil
- ○ Phenytoin 1000 mg

This lady may well be having an epileptic fit, but why should a young woman have an elevated blood pressure and proteinuria?

In a woman of this age with raised blood pressure and proteinuria, a diagnosis of eclampsia has to be considered and the primary treatment of eclampsia is the administration of magnesium.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 51 mins 49 secs

Question: 18 of 100

A 67-year-old man with insulin-dependent diabetes with a broad complex pulseless tachyarrhythmia (with a protected airway) has been defibrillated three times.

He has just finished receiving two minutes of cardiopulmonary resuscitation (CPR) and has received adrenaline.

Which of the following is the next step in the management of the arrest?

(Please select 1 option)

- Adrenaline 1 mg
- Amiodarone 300 mg
- DC shock
- Lidocaine 100 mg
- Removal of oxygen and then DC shock

Submit answer | Skip question | Tag Question | Remove question

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 53 mins 27 secs

Question: 18 of 100

A 67-year-old man with insulin-dependent diabetes with a broad complex pulseless tachyarrhythmia (with a protected airway) has been defibrillated three times.

He has just finished receiving two minutes of cardiopulmonary resuscitation (CPR) and has received adrenaline.

Which of the following is the next step in the management of the arrest?

(Please select 1 option)

○	Adrenaline 1 mg
○	Amiodarone 300 mg ← This is the correct answer
◉	DC shock ✕ Incorrect answer selected
○	Lidocaine 100 mg
○	Removal of oxygen and then DC shock

After three DC shocks and a further cycle of two minutes of CPR the next step is amiodarone 300 mg intravenously and then a fourth shock.

If amiodarone is not available lidocaine is a suitable alternative.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 53 mins 27 secs

Question: 19 of 100

A 66-year-old man with insulin-dependent diabetes with a treated potassium of 5.4 mmol/l (3.5-5) and palpitations develops pulseless ventricular tachycardia. The anaesthetist is supporting airway and breathing.

Which of the following is the next step in his management?

(Please select 1 option)

- Adrenaline 1 mg
- Amiodarone 300 mg
- Cardiopulmonary resuscitation (CPR) 15:2 for two minutes
- Defibrillation at 150J biphasic
- Praecordial thump

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 54 mins 29 secs

Question: 19 of 100

A 66-year-old man with insulin-dependent diabetes with a treated potassium of 5.4 mmol/l (3.5-5) and palpitations develops pulseless ventricular tachycardia. The anaesthetist is supporting airway and breathing.

Which of the following is the next step in his management?

(Please select 1 option)

○	Adrenaline 1 mg
○	Amiodarone 300 mg
○	Cardiopulmonary resuscitation (CPR) 15:2 for two minutes
○	Defibrillation at 150J biphasic ← This is the correct answer
◉	Praecordial thump ✕ Incorrect answer selected

In the case of ventricular tachycardia and ventricular fibrillation immediate defibrillation is the treatment of choice.

The other options come further down the algorithm and CPR is now recommended at 30:2.

A praecordial thump can be administered immediately following a witnessed cardiac arrest.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 1 mins 47 secs

Question: 1 of 100

A 40-year-old man is admitted to the Emergency Department after being involved in a house fire. He is extremely drowsy but you notice on examining him that he seems well perfused, with his cheeks looking almost pink. His BP is 100/60 and his pulse is 95 and regular. Blood gas analysis reveals a CO level of 12% and a metabolic acidosis with a pH of 7.15.

Which of the following is the most appropriate next intervention?

(Please select 1 option)

○	**A** Hyperbaric oxygen
○	**B** IV mannitol
○	**C** IV sodium bicarbonate
◉	**D** 100% oxygen by mask ✓ Correct
○	**E** Nebulised salbutamol

The answer is D), 100% oxygen by mask. Hyperbaric oxygen is recommended by some countries including the US, although because of a lack of randomised control evidence it is not standard practice in the UK as there appears to be no significant improvement in outcome versus high flow oxygen alone. Sodium bicarbonate is not indicated, and IV mannitol is only used if there is suspicion of cerebral oedema. Key to prognosis is removal from the source of carbon monoxide as quickly as possible, and instigation of high flow oxygen treatment. At a level of 12%, long term psychological disturbance or memory loss is possible.

Next question | Tag Question | Remove question

Work Smart Session - MRCP Part 1

Time taken: 1 mins 47 secs

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Question: 2 of 100

A 16-year-old girl presented with fever, headache and photophobia.

Investigations revealed:

Cerebrospinal fluid examination

Opening pressure	260 mm H_20	(50-180)
Total protein	0.8 g/l	(0.15-0.45)
Glucose	4.2 mmol/l	(3.3-4.4)
White cell count	60 per ml	(<5)
Lymphocytes	90%	(60-70)
Plasma glucose	6.4 mmol/l	(3.0-6.0)

What is the most likely diagnosis?

(Please select 1 option)

- Bacterial meningitis
- Cryptococcal meningitis
- Tuberculosis meningitis
- Viral encephalitis
- Viral meningitis

Work Smart Session - MRCP Part 1

Time taken: 54 mins 29 secs

Question: 20 of 100

A patient has just received intravenous ceftazidime. They immediately become flushed and wheezy, with a blood pressure of 80/40 mmHg.

Which of the following is the most appropriate immediate management for this patient?

(Please select 1 option)

- Chlorphenamine 10 mg IV
- Epinephrine 0.2 ml of 1:1000 IV
- Epinephrine 0.5 mg IV
- Epinephrine 0.5 mg i.m.
- Hydrocortisone 100 mg IV

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 55 mins 26 secs

Question: 20 of 100

A patient has just received intravenous ceftazidime. They immediately become flushed and wheezy, with a blood pressure of 80/40 mmHg.

Which of the following is the most appropriate immediate management for this patient?

(Please select 1 option)

○	Chlorphenamine 10 mg IV
○	Epinephrine 0.2 ml of 1:1000 IV
○	Epinephrine 0.5 mg IV
◉	Epinephrine 0.5 mg i.m. ✓ Correct
○	Hydrocortisone 100 mg IV

Immediate treatment of anaphylaxis includes cessation of whatever caused it.

Then give oxygen, fluids and adrenaline/epinephrine 0.5 mg intra-muscularly or subcutaneously.

Checking concentrations of adrenaline is very important especially in high pressure situations. Intravenous adrenaline is potentially hazardous unless diluted appropriately.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 55 mins 26 secs

Question: 21 of 100

You are on call for hospital at night and are urgently called to a patient on the ward who is choking on a piece of steak visible in his oropharynx. He is in extremis with saturations of 87%.

Which of the following is the most appropriate immediate management for this patient?

(Please select 1 option)

- Cricothyroidotomy
- Finger sweep
- Heimlich manoeuvre
- High flow oxygen
- Removal with forceps

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

You are on call for hospital at night and are urgently called to a patient on the ward who is choking on a piece of steak visible in his oropharynx. He is in extremis with saturations of 87%.

Which of the following is the most appropriate immediate management for this patient?

(Please select 1 option)

○	Cricothyroidotomy
○	Finger sweep
◉	Heimlich manoeuvre ✓ Correct
○	High flow oxygen
○	Removal with forceps

A finger sweep is more likely to push the obstruction further into the airway and is no longer advocated.

High flow oxygen is the breathing part of A, B, C, and the airway is not clear.

Nasopharyngeal airways will not help in this situation.

Removal with forceps is potentially hazardous.

A Heimlich manoeuvre should be performed with the possibility of cricothyroidotomy in mind immediately thereafter if this procedure fails.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 55 mins 56 secs

Question: 22 of 100

A 62-year-old male with a history of ischaemic heart disease is admitted with chest pain of 13 hours' duration and some ST depression inferolaterally.

Which of the following would be the most appropriate treatment option for this patient?

(Please select 1 option)

○	IV diamorphine 10 mg
○	Oral aspirin 600 mg
○	Oral isosorbide mononitrate 30 mg
○	Oxygen 100%
○	Subcutaneous low molecular weight heparin

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

depression inferolaterally.

Which of the following would be the most appropriate treatment option for this patient?

(Please select 1 option)

○	IV diamorphine 10 mg
○	Oral aspirin 600 mg
○	Oral isosorbide mononitrate 30 mg
◉	Oxygen 100% ✕ Incorrect answer selected
○	Subcutaneous low molecular weight heparin ← This is the correct answer

The treatment approach in this patient with acute coronary syndrome is

1. aspirin 300 mg
2. try some GTN.

If this fails then

- isosorbitdinitrate (ISDN) intravenously
- diamorphine (or morphine) 2.5 mg
- 4 L oxygen and
- subcutaneous low molecular weight heparin.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

A 59-year-old man is admitted with chest pain of eight hours duration and has ST elevation in the inferior leads on his admission ECG.

An electrocardiogram from a previous clinic visit shows sinus rhythm two months ago. He has insulin-dependent diabetes mellitus and chronic renal failure.

Investigations reveal:

Fasting plasma glucose	7.4 mmol/l	(3.0-6.0)
Sodium	137 mmol/l	(137-144)
Potassium	4.4 mmol/l	(3.5-4.9)
Urea	10 mmol/l	(2.5-7.5)
Creatinine	200 µmol/l	(60-110)

Which of the following which represent an absolute contraindication to the use of thrombolysis?

(Please select 1 option)

- Allergy to penicillin
- Gastro intestinal bleeding in last three months
- History of haemorrhagic stroke
- Ischaemic stroke 12 months ago
- On warfarin therapy

Submit answer | Skip question | Tag Question | Remove question

Which of the following which represent an absolute contraindication to the use of thrombolysis?

(Please select 1 option)

○	Allergy to penicillin
○	Gastro intestinal bleeding in last three months
◉	History of haemorrhagic stroke ✓ Correct
○	Ischaemic stroke 12 months ago
○	On warfarin therapy

Absolute contraindications to thrombolysis include:

- Previous haemorrhagic stroke
- Ischaemic stroke in last six months
- Central nervous system damage or neoplasm
- Within three weeks of major surgery, head injury or major trauma
- Active internal bleeding (menses excluded) or gastro-intestinal bleeding within the past month
- Known or suspected aortic dissection
- Known bleeding disorder
- Proliferative diabetic retinopathy.

Allergy and oral anticoagulants are relative contraindications.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 59 mins 46 secs

Question: 24 of 100

A 67-year-old female is admitted with blackouts.

Her electrocardiogram shows ventricular escape with complete heart block. As you are standing there she blacks out once more. Her rhythm strip shows P wave asystole.

Which of the following would be the initial immediate treatment here after airway and breathing?

(Please select 1 option)

- Adenosine 6 mg
- Atropine 0.6 mg
- Percussion pacing
- Transcutaneous pacing
- Transvenous pacing

Submit answer | Skip question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

A 67-year-old female is admitted with blackouts.

Her electrocardiogram shows ventricular escape with complete heart block. As you are standing there she blacks out once more. Her rhythm strip shows P wave asystole.

Which of the following would be the initial immediate treatment here after airway and breathing?

(Please select 1 option)

○	Adenosine 6 mg
○	Atropine 0.6 mg
◉	Percussion pacing ✓ Correct
○	Transcutaneous pacing
○	Transvenous pacing

Adenosine and atropine are not front line agents in this scenario, particularly adenosine which blocks atrioventricular (AV) conduction; minus one mark if you elected this.

Transvenous pacing is not a fast enough intervention here.

Transcutaneous pacing is the immediate management but percussion pacing may be effective as a holding measure whilst this is instituted.

(Percussion pacing involves gentle thumping of the lower left sternal edge with the fist.)

Next question

Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 53 secs

Question: 25 of 100

A 70-year-old male presents with haematemesis and melaena.

His presenting blood pressure is 80/46 mmHg, with a heart rate of 114 bpm. He is known to have idiopathic cirrhosis, and there is mild encephalopathy.

You fluid resuscitate him with colloid, blood, FFP and dextrose.

Which of the following is the next best step in management?

(Please select 1 option)

○	Ciproflaxacin
○	Glypressin
○	Lactulose
○	OGD
○	Oral beta-blockers

Submit answer | Skip question | Tag Question | Remove question

http://my.onexamination.com/Assessment/Questions.aspx

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Shop

Which of the following is the next best step in management?

(Please select 1 option)

○	Ciproflaxacin
◉	Glypressin ✓ Correct
○	Lactulose
○	OGD
○	Oral beta-blockers

Glypressin causes splanchnic vasoconstriction, thereby restricting bleeding from varices, which is the likely cause of bleeding in this patient.

In the acute gastrointestinal bleed described above, glypressin is the best treatment to aid cardiovascular resuscitation.

Beta-blockade comes into play later in order to treat portal hypertension chronically.

Lactulose should be considered to guard against progression of encephalopathy.

Oesophagogastroduodenoscopy (OGD) should be considered, but full resuscitation and optimal medical management should be attempted in the first instance.

In the event of ascites, ciprofloxacin is used as prophylaxis against spontaneous bacterial peritonitis. This is of secondary importance here.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 2 mins 2 secs

Question: 26 of 100

A 43-year-old gentleman develops chest pain seven minutes after fibre-optic bronchoscopy.

The procedure had been performed without sedation following an intratracheal injection of 5 ml 2.5% cocaine solution and xylocaine spray to the pharynx for topical anaesthesia.

ECG showed an evolving anterior myocardial infarction.

Which of the following would you prefer for his management?

(Please select 1 option)

- Beta-blockers
- Nitrates
- Percutaneous transluminal coronary angioplasty
- Thrombolysis with rt-PA
- Thrombolysis with streptokinase

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

○	Beta-blockers
◉	Nitrates ✓ Correct
○	Percutaneous transluminal coronary angioplasty
○	Thrombolysis with rt-PA
○	Thrombolysis with streptokinase

The underlying mechanism here is vasoconstriction, not thrombosis.

Cocaine is cardiotoxic and its use has been linked to:

- coronary artery spasm
- angina
- myocardial infarction
- arrhythmias
- sudden cardiac death
- myocardial contraction bands, which might act as a substrate for arrhythmias.

It is important to avoid beta-blockers in treating cocaine-induced chest pains or acute myocardial infarctions, as this may result in unopposed 1 adrenergic action with worsening coronary spasm.

Calcium channel antagonists or nitrates should be administered as early as possible.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 3 mins 20 secs

Question: 27 of 100

A 45-year-old man is admitted with central crushing chest pain, sweating and vomiting of one hour duration.

He is conscious with a pulse rate of 100 bpm and a blood pressure of 200/125 mmHg. An ECG shows >2 mm ST elevation in leads I, II, aVL and V2-6.

CBC: normal
U & E: normal
Troponin T: 100 ng/ml

Apart from the presence of xanthelasma (+) there are no other positive findings on clinical examination.

He is given oxygen, aspirin, morphine and intravenous 5 mg atenolol.

What will you do next?

(Please select 1 option)

○	CABG
○	Nitroprusside infusion
○	PTCA
○	Thrombolysis with rt-PA
○	Thrombolysis with streptokinase

Submit answer | Skip question | Tag Question | Remove question

CBC: normal
U & E: normal
Troponin T: 100 ng/ml

Apart from the presence of xanthelasma (+) there are no other positive findings on clinical examination.

He is given oxygen, aspirin, morphine and intravenous 5 mg atenolol.

What will you do next?

(Please select 1 option)

○	CABG
○	Nitroprusside infusion
◉	PTCA ✓ Correct
○	Thrombolysis with rt-PA
○	Thrombolysis with streptokinase

This is a case of acute myocardial infarction.

Typically thrombolysis should be carried out in the absence of any contraindications. BP higher than 200/120 mmHg is one of the contraindications.

So the next appropriate management in this case is urgent angioplasty for extensive anterolateral infarction.

BP control should follow suit.

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 4 mins 47 secs

Question: 28 of 100

A 19-year-old girl has been brought to the Emergency Department by her friends following a night out at a party.

Her friends comment that she has been talking by herself about 'irrelevant things'. She seems agitated and restless.

On examination, her reflexes are increased and an electrocardiogram (ECG) demonstrates ventricular ectopics.

What kind of substance abuse do you suspect at this point?

(Please select 1 option)

- Alcohol
- Barbiturate
- Cannabis
- Ecstasy
- Glue sniffing

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

http://my.onexamination.com/Assessment/Que
Questions Set : REF20333

○	Alcohol
○	Barbiturate
◉	Cannabis ✕ Incorrect answer selected
○	Ecstasy ← This is the correct answer
○	Glue sniffing

This is a case of ecstasy overdose.

Ecstasy (3,4-methylenedioxymethamphetamine, MDMA) stimulates the central nervous system. It causes:

- Increased alertness and self-confidence
- Euphoria
- Extrovert behaviour
- Increased talkativeness with rapid speech
- Lack of desire to eat or sleep
- Tremor
- Dilated pupils
- Tachycardia
- Hypertension.

More severe intoxication is associated with:

- Excitability
- Agitation
- Paranoid delusions
- Hallucinations with violent behaviour

Hypertension.

More severe intoxication is associated with:

- Excitability
- Agitation
- Paranoid delusions
- Hallucinations with violent behaviour
- Hypertonia
- Hyperreflexia.

Convulsions, rhabdomyolysis, hyperthermia, and cardiac arrhythmias may also develop.

In severe cases of MDMA poisoning:

- Hyperthermia
- Disseminated intravascular coagulation
- Rhabdomyolysis
- Acute renal failure
- Hyponatraemia

are observed.

Hepatic damage has also been reported.

Rarely, poisoning due to amphetamines may result in intracerebral and subarachnoid haemorrhage and acute cardiomyopathy; these complications may be fatal.

Hyperthyroxinaemia may be found in chronic amphetamine users.

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 6 mins 47 secs

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Question: 29 of 100

A known case of chronic obstructive pulmonary disease (COPD) presents to the Emergency Department, distressed and cyanosed.

Arterial blood gases reveal:

pH	7.2	(7.36-7.44)
PaO_2	8.3 kPa	(11.3-12.6 kPa)
$PaCO_2$	10 kPa	(4.7-6.0 kPa)

He is given high concentration oxygen together with a salbutamol nebuliser. Intravenous hydrocortisone is also given.

The patient becomes even worse with poorer breathing effort although pulse oximetry showed SaO_2 of 93%.

What is the cause of patient's deterioration?

(Please select 1 option)

- Constriction of bronchioles in response to salbutamol nebuliser
- High concentration oxygen administration
- Pulmonary artery relaxation causing mismatch between perfusion and ventilation
- Pulmonary vein relaxation causing mismatch between perfusion and ventilation
- Reaction to IV hydrocortisone

Submit answer | Skip question | Tag Question | Remove question

pH	7.2	(7.36-7.44)
PaO_2	8.3 kPa	(11.3-12.6 kPa)
$PaCO_2$	10 kPa	(4.7-6.0 kPa)

He is given high concentration oxygen together with a salbutamol nebuliser. Intravenous hydrocortisone is also given.

The patient becomes even worse with poorer breathing effort although pulse oximetry showed SaO_2 of 93%.

What is the cause of patient's deterioration?

(Please select 1 option)

- ○ Constriction of bronchioles in response to salbutamol nebuliser
- ◉ High concentration oxygen administration ✓ Correct
- ○ Pulmonary artery relaxation causing mismatch between perfusion and ventilation
- ○ Pulmonary vein relaxation causing mismatch between perfusion and ventilation
- ○ Reaction to IV hydrocortisone

Obviously the patient was suffering from hypoxia and hypercapnia as a result of acute exacerbation of COPD.

His respiratory centre was solely stimulated by hypoxia. That is why his respiratory effort became less and the condition worsened when he was given high concentration oxygen, depriving him of hypoxic drive.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Plasma glucose	6.4 mmol/l	(3.0-6.0)

What is the most likely diagnosis?

(Please select 1 option)

○	Bacterial meningitis
○	Cryptococcal meningitis
○	Tuberculosis meningitis
○	Viral encephalitis
◉	Viral meningitis ✓ Correct

A normal cerbrospinal fluid (CSF) glucose together with

- A CSF lymphocytosis
- An increased opening pressure, and
- A raised CSF protein

are typical of a viral meningitis, which would be high on the list of differentials in patients of this age group (together with bacterial meningitis).

Further reading:
Cerebrospinal Fluid Analysis American Academy of Family Physicians

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 6 mins 14 secs

Question: 3 of 100

A 16-year-old female attends casualty 15 hours after ingesting approximately 30 g of paracetamol and 2 g of dihydrocodeine.

On examination, she is drowsy with a Glasgow coma scale of 15. Her pulse is 100 beats per minute, blood pressure is 110/66 mmHg and she has pinpoint pupils, with saturations of 96% on air.

What is the most appropriate treatment for this patient?

(Please select 1 option)

- 10% Dextrose infusion
- Activated charcoal by mouth
- Gastric lavage
- N-acetylcysteine intravenously
- Naloxone intravenously

Submit answer | Skip question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 8 mins 7 secs

Question: 30 of 100

A 52-year-old schoolteacher attends with weight loss and sweats.

She is clinically thyrotoxic with a diffuse goitre.

Subsequent investigations show:

Free T4	40 pmol/l	(9-23)
Free T3	9.8 nmol/l	(3.5-6)
TSH	6.1 mU/l	(0.5-5)

A repeat TFT is similar.

What is the most appropriate investigation for this patient?

(Please select 1 option)

- FNA of thyroid gland
- MRI scan pituitary gland
- Radio-isotope uptake scan of thyroid gland
- Repeat TFT checking for antibody interference
- Thyroid auto antibodies

Submit answer | Skip question | Tag Question | Remove question

Free T4	40 pmol/l	(9-23)
Free T3	9.8 nmol/l	(3.5-6)
TSH	6.1 mU/l	(0.5-5)

A repeat TFT is similar.

What is the most appropriate investigation for this patient?

(Please select 1 option)

- ○ FNA of thyroid gland
- ◉ MRI scan pituitary gland ✓ Correct
- ○ Radio-isotope uptake scan of thyroid gland
- ○ Repeat TFT checking for antibody interference
- ○ Thyroid auto antibodies

This patient is thyrotoxic; however, as the non-suppressed thyroid-stimulating hormone (TSH) suggests that this is due to excessive TSH production by the pituitary gland, the possibility of a thyrotroph adenoma must be pursued.

In primary hyperthyroidism the TSH should always be suppressed by negative feedback, which is not the case here.

TSH-omas are indeed very rare, but the giveaway would be the normal or elevated TSH with thyrotoxicosis.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Question: 31 of 100

A 27-year-old female presents to the surgical intake with abdominal pain and a five day history of vomiting.

Over the last three months she has also been aware of a 6 kg weight loss.

On examination, she is pale, has a temperature of 38.5°C, blood pressure of 90/60 mmHg and pulse rate of 130 in sinus rhythm. The chest is clear on auscultation but she has a diffusely tender abdomen with no guarding. Her BM reading is 2.5.

Initial biochemistry is as follows:

Sodium	124 mmol/l	(137-144)
Potassium	6.0 mmol/l	(3.5-4.9)
Urea	7.5 mmol/l	(2.5-7.5)
Creatinine	78 µmol/l	(60-110)
Glucose	2.0 mmol/l	(3.0-6.0)

What is the probable diagnosis?

(Please select 1 option)

- ○ Abdominal migraine
- ○ Acute appendicitis
- ○ Acute cholecystitis
- ○ Addison's disease
- ○ Insulinoma

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Sodium	124 mmol/l	(137-144)
Potassium	6.0 mmol/l	(3.5-4.9)
Urea	7.5 mmol/l	(2.5-7.5)
Creatinine	78 µmol/l	(60-110)
Glucose	2.0 mmol/l	(3.0-6.0)

What is the probable diagnosis?

(Please select 1 option)

- ○ Abdominal migraine
- ○ Acute appendicitis
- ○ Acute cholecystitis
- ◉ Addison's disease ✓ Correct
- ○ Insulinoma

This patient has clinical features of hypoadrenal crisis with abdominal pain and vomiting and shock with hypoglycaemia, hyponatraemia and hyperkalaemia in keeping with hypoadrenalism.

She needs emergency fluid resuscitation, steroid administration (prior to this urgent cortisol measurement), and careful search for occult infection.

One may expect to find features of Addison's disease such as oral pigmentation or other autoimmune disease.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 13 mins 11 secs

Question: 32 of 100

A 78-year-old male is brought to the Emergency Department and has a witnessed seizure in the resuscitation room.

His blood glucose is recorded as 1.0 mmol/l. He does not have diabetes, and has no other significant past medical history.

He is given 50 ml of 50% dextrose and he slowly recovers over the next one hour. A serum cortisol concentration later returns as 800 nmol/l (120-600).

Which of the following would be the most relevant investigation for this man?

(Please select 1 option)

○	Chest x ray
○	CT head scan
○	Electrocardiogram
◉	Prolonged 72 hour fast
○	Short synacthen test

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

He is given 50 ml of 50% dextrose and he slowly recovers over the next one hour. A serum cortisol concentration later returns as 800 nmol/l (120-600).

Which of the following would be the most relevant investigation for this man?

(Please select 1 option)

○	Chest x ray
○	CT head scan
○	Electrocardiogram
◉	Prolonged 72 hour fast ✓ Correct
○	Short synacthen test

The historical and biochemical evidence here suggests a diagnosis of spontaneous hypoglycaemia, and the most likely cause would be an insulinoma. However, one would wish to exclude possible drug administration and although not mentioned here, a sulphonylurea screen should be undertaken.

He has presented with symptomatic hypoglycaemia, is not diabetic and therefore should not have received insulin or a sulphonylurea.

There is nothing to suggest alcohol or drug misuse. Similarly, there is nothing to suggest sepsis.

However, to prove a diagnosis of spontaneous hypoglycaemia, a prolonged fast is required and should he develop hypoglycaemia, measurement of insulin and C-peptide will be needed to confirm the diagnosis.

The appropriate cortisol response during his hypoglycaemic episode (cortisol 800) excludes hypoadrenalism.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 17 mins 22 secs

Question: 33 of 100

A 65-year-old man is admitted from home with a community-acquired pneumonia (CAP). He has a history of skin rash to penicillin documented in his medical notes. He has adverse prognostic features and a CURB score of 4.

What would be an appropriate empirical antibiotic choice?

(Please select 1 option)

- Augmentin and clarithromycin
- Augmentin and gentamycin
- Cefotaxime and erythromycin
- Cefuroxime and metronidazole
- Ciprofloxacin and clarithromycin

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Question: 33 of 100

A 65-year-old man is admitted from home with a community-acquired pneumonia (CAP). He has a history of skin rash to penicillin documented in his medical notes. He has adverse prognostic features and a CURB score of 4.

What would be an appropriate empirical antibiotic choice?

(Please select 1 option)

○	Augmentin and clarithromycin
○	Augmentin and gentamycin
◉	Cefotaxime and erythromycin ✓ Correct
○	Cefuroxime and metronidazole
○	Ciprofloxacin and clarithromycin

Community-acquired pneumonia is most commonly caused by *Strep. pneumoniae*, hence the use of a beta-lactam antibiotic because of the increased incidence of atypical organisms such as mycoplasma. A macrolide such as erythromycin is also recommended.

Augmentin is contraindicated as it is penicillin-based.

Ciprofloxacin has poor cover against *Strep. pneumoniae* and metronidazole is used for anaerobic infections.

In this case a credible alternative for beta-lactam sensitivity is not mentioned and the best choice, because of clinical necessity since severe pneumonia can be fatal if treated with antibiotics that are not effective, is to go with the only cephalosporin and macrolide combination that is offered.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 52 mins 9 secs

Question: 34 of 100

A 38-year-old man experiences sudden deterioration after being admitted to the intensive care unit because of severe pneumococcal pneumonia and septic shock.

Arterial blood gas analysis reveals:

pH	7.2	(7.36-7.44)
PaO_2	12 kPa	(10-13.3)
$PaCO_2$	4.7 kPa	(4.7-6)
HCO_3^-	16 mmol/l	(20-28)

Which one of the following changes will be found in this patient at this time?

(Please select 1 option)

- Hyperventilation leading to the increase in CO_2 concentration
- Increase production of HCO_3-
- Increased renal excretion of HCO_3-
- Raised hydrogen ions level in the blood
- Respiratory acidosis

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 58 mins 48 secs

Question: 35 of 100

A 53-year-old man with a known history of Graves' disease presents to the emergency department with palpitations, anxiety and fine tremor of both hands.

ECG shows rapid atrial fibrillation (AF) with ventricular rate of 160 to 180/min.

His blood pressure was 110/80 mmHg.

TSH	0.01 mU/l	(0.4-5.0)
Free T4	60.3 pmol/l	(10-22)

What is the immediate management for this patient?

(Please select 1 option)

- Carbimazole
- DC cardioversion
- Digoxin
- Propanolol
- Warfarin

Submit answer | Skip question | Tag Question | Remove question

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 5 mins 26 secs

Question: 36 of 100

A middle-aged woman presents with new onset palpitations. She also commented that she had lost weight recently despite an increased appetite.

Examination reveals a goitre and a degree of exophthalmos. During physical examination, she fell unconscious. Blood pressure was 70/40 mmHg. Electrocardiogram revealed atrial fibrillation (AF) with rapid ventricular response.

What is the appropriate immediate management?

(Please select 1 option)

- Anticoagulation
- Carbimazole
- DC cardioversion
- Intravenous amiodarone
- Intravenous propanolol

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Examination reveals a goitre and a degree of exophthalmos. During physical examination, she fell unconscious. Blood pressure was 70/40 mmHg. Electrocardiogram revealed atrial fibrillation (AF) with rapid ventricular response.

What is the appropriate immediate management?

(Please select 1 option)

○	Anticoagulation
○	Carbimazole
◉	DC cardioversion ✓ Correct
○	Intravenous amiodarone
○	Intravenous propanolol

The patient is haemodynamically compromised due to AF.

The emergency management is DC cardioversion 200 J ⇒ 360 J ⇒ 360 J.

Adverse signs necessitating DC cardioversion are:

- BP ≤90 mmHg
- chest pain
- heart failure
- impaired consciousness
- heart rate ≥200 bpm.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 6 mins 38 secs

Question: 37 of 100

A 41-year-old female is brought into the Emergency Department after taking an uncertain quantity of paracetamol two hours previously and trying to hang herself.

She becomes agitated and insists that she wants to go home immediately. You judge that she is at high risk of suicide.

Which of the following is the most appropriate course of action for this patient?

(Please select 1 option)

- Ask her to sign a 'discharge against medical advice' form and let her go
- Call the duty psychiatrist, and with other staff in the Emergency Department attempt to restrain her under common law until they arrive
- Call the duty psychiatrist, but let the patient go if she insists and the duty psychiatrist does not arrive in time to see her
- Call the hospital security services, restrain her and sedate her
- Detain her under section 5(2) of the Mental Health Act

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

A 41-year-old female is brought into the Emergency Department after taking an uncertain quantity of paracetamol two hours previously and trying to hang herself.

She becomes agitated and insists that she wants to go home immediately. You judge that she is at high risk of suicide.

Which of the following is the most appropriate course of action for this patient?

(Please select 1 option)

○	Ask her to sign a 'discharge against medical advice' form and let her go
○	Call the duty psychiatrist, and with other staff in the Emergency Department attempt to restrain her under common law until they arrive ← This is the correct answer
○	Call the duty psychiatrist, but let the patient go if she insists and the duty psychiatrist does not arrive in time to see her
◉	Call the hospital security services, restrain her and sedate her ✕ Incorrect answer selected
○	Detain her under section 5(2) of the Mental Health Act

In an Emergency Department the suicidal patient who declines to be admitted for observation and treatment should be managed as follows:

- Ensure that a member of staff stays with them at all times
- Call the duty psychiatrist if they attempt to abscond before or during psychiatric assessment.

The staff of the Emergency Department have a duty under common law to restrain the patient.

If a patient who is already being nursed on a medical, surgical or obstetric ward, or in a high dependency or intensive care unit, develops a mental illness (or has an exacerbation of a pre-existing disorder), their physician or surgeon can authorise their compulsory detention for up to 72 hours under section 5(2) of the Mental Health Act.

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 8 mins 46 secs

Question: 38 of 100

A 65-year-old male is admitted with a two hour history of central chest pain associated with sweating and nausea. A myocardial infarction is suspected.

Which of the following is an indication for thrombolytic therapy?

(Please select 1 option)

- 1 mm ST elevation in leads II, III and aVF
- 1 mm ST elevation in leads V2 and V6
- 2 mm ST depression in leads V2-4
- Q waves in leads V2-4
- T wave inversion in lead V3-5

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 10 mins 28 secs

Question: 38 of 100

A 65-year-old male is admitted with a two hour history of central chest pain associated with sweating and nausea. A myocardial infarction is suspected.

Which of the following is an indication for thrombolytic therapy?

(Please select 1 option)

○	1 mm ST elevation in leads II, III and aVF ← This is the correct answer
◉	1 mm ST elevation in leads V2 and V6 ✕ Incorrect answer selected
○	2 mm ST depression in leads V2-4
○	Q waves in leads V2-4
○	T wave inversion in lead V3-5

There are two electrocardiogram (ECG) criteria for initiating thrombolysis in a patient with suspected myocardial infarction.

The first is the presence of ST elevation of at least 1 mm in the limb leads or 1 mm in contiguous chest leads on the ECG.

The second is new onset of left bundle branch block (LBBB.)

Also, there must be no compelling contra-indications to thrombolysis.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 10 mins 28 secs

Question: 39 of 100

A 45-year-old male with a long history of alcohol abuse presents with a two day history of deteriorating confusion.

On examination he is drowsy, has a temperature of 39°C, a pulse of 110 beats per minute, a small amount of ascites and has features of a left side hemiparesis.

What is the most likely diagnosis?

(Please select 1 option)

- Cerebral abscess
- Cerebro-vascular accident (CVA)
- Hepatic encephalopathy
- Subdural haematoma
- Wernicke's encephalopathy

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Question: 39 of 100

A 45-year-old male with a long history of alcohol abuse presents with a two day history of deteriorating confusion.

On examination he is drowsy, has a temperature of 39°C, a pulse of 110 beats per minute, a small amount of ascites and has features of a left side hemiparesis.

What is the most likely diagnosis?

(Please select 1 option)

◉	Cerebral abscess ✓ Correct
○	Cerebro-vascular accident (CVA)
○	Hepatic encephalopathy
○	Subdural haematoma
○	Wernicke's encephalopathy

This man with chronic alcohol abuse now presents with a fever and left hemiparesis.

The most likely diagnosis would therefore be cerebral abscess.

The fever would not itself be explained by a subdural haematoma nor would a simple CVA explain this.

Similarly, delirium tremens or encephalopathy would not be associated with the hemiparesis.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

On examination, she is drowsy with a Glasgow coma scale of 15. Her pulse is 100 beats per minute, blood pressure is 110/66 mmHg and she has pinpoint pupils, with saturations of 96% on air.

What is the most appropriate treatment for this patient?

(Please select 1 option)

○	10% Dextrose infusion
○	Activated charcoal by mouth
○	Gastric lavage
◉	N-acetylcysteine intravenously ✓ Correct
○	Naloxone intravenously

This patient has taken a significant overdose of paracetamol, and is presenting late at 15 hours.

She is at risk of hepatocellular damage and needs to be commenced on an infusion of intravenous N-acetylcysteine immediately. It is continued for 30 hours and sometimes beyond this, depending on results of prothrombin time, liver function tests, urea and electrolytes, and glucose.

Activated charcoal is given to patients presenting within one hour of overdose.

Flumazenil is reserved for reversal of benzodiazepine-induced respiratory depression.

Naloxone is used for opiate-induced respiratory depression.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 11 mins 5 secs

Question: 4 of 100

A 35-year-old business man presents with anxiety and palpitations after 'snorting' cocaine. The patient denies any prior use and has also consumed some alcohol.

On examination, he is distressed and sweating with a temperature of 38°C, pulse of 138 beats per minute (regular) and a blood pressure of 216/110 mmHg. His ECG reveals a sinus tachycardia.

Which of the following is the most appropriate initial treatment for this man?

(Please select 1 option)

- Dantrolene
- Diazepam
- Lidocaine
- Propranolol
- Verapamil

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 13 mins 12 secs

Question: 40 of 100

A 19-year-old female with type 1 diabetes is admitted with diabetic ketoacidosis.

Which of the following is most appropriate concerning the use of a bicarbonate infusion?

(Please select 1 option)

○	Bicarbonate infusion should be considered at pH less than 7
○	Commence a bicarbonate infusion with a ketone concentration above 5 mmol/l (NR les than 1)
○	Commence bicarbonate infusion with a potassium concentration above 6 mmol/l
○	Commence a bicarbonate infusion with a standard bicarbonate concentration below 5 mmol/l (NR 22-26)
○	No benefit from using a bicarbonate infusion

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 15 mins 5 secs

Question: 40 of 100

A 19-year-old female with type 1 diabetes is admitted with diabetic ketoacidosis.

Which of the following is most appropriate concerning the use of a bicarbonate infusion?

(Please select 1 option)

○	Bicarbonate infusion should be considered at pH less than 7 ← This is the correct answer
○	Commence a bicarbonate infusion with a ketone concentration above 5 mmol/l (NR les than 1)
○	Commence bicarbonate infusion with a potassium concentration above 6 mmol/l
○	Commence a bicarbonate infusion with a standard bicarbonate concentration below 5 mmol/l (NR 22-26)
◉	No benefit from using a bicarbonate infusion ✕ Incorrect answer selected

The use of bicarbonate in DKA is controversial (pdf).

However, most authorities agree that a bicarbonate infusion may be used in subjects with a severe metabolic acidosis (pH less than 7).

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 15 mins 5 secs

Question: 41 of 100

A 31-year-old female with pulmonary hypertension complains of increasing shortness of breath. She is 36 weeks gestation in her first pregnancy.

Which of the following statements is correct?

(Please select 1 option)

- Chest x ray is contraindicated
- Elevated D-dimers rule out PE
- Enoxaparin dose should be halved in pregnancy
- Nifedipine is contraindicated in pregnancy
- Risk of maternal mortality in patients with pulmonary hypertension is 30%

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Which of the following statements is correct?

(Please select 1 option)

○	Chest x ray is contraindicated
○	Elevated D-dimers rule out PE
○	Enoxaparin dose should be halved in pregnancy
◉	Nifedipine is contraindicated in pregnancy ✕ Incorrect answer selected
○	Risk of maternal mortality in patients with pulmonary hypertension is 30% ← This is the correct answer

A chest x ray is not contraindicated in pregnancy.

Any pregnant female presenting with shortness of breath should be reviewed by a senior member of the obstetric team, advice which comes from the RCOG.

Enoxaparin dose should be doubled in pregnancy, due to the increased glomerular filtration rate (GFR) in pregnancy.

D-dimers are always elevated in pregnancy, and are not helpful as a diagnostic aid, unless of course they are low (very unlikely), thereby making the clinical suspicion of pulmonary embolism (PE) low.

Nifedipine is not contraindicated in pregnancy, but should be used judiciously.

Labetalol and methyldopa are the commonest antihypertensives used in pregnancy.

Patients with pulmonary hypertension have a high mortality of at least 30% - some authors put it at 50% - seemingly highest immediately after delivery.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 16 mins 48 secs

Question: 42 of 100

A 16-year-old man is brought to the emergency department with a GCS (Glasgow coma scale) rating of 3/15.

Within 10 minutes he regained consciousness with a GCS of 15/15, is sitting up and talking.

What is he likely to have taken?

(Please select 1 option)

- Inhaled solvent glue
- Smoked heroin
- Smoked marijuana
- Snorted cocaine
- Taken ecstacy

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Question: 42 of 100

A 16-year-old man is brought to the emergency department with a GCS (Glasgow coma scale) rating of 3/15.

Within 10 minutes he regained consciousness with a GCS of 15/15, is sitting up and talking.

What is he likely to have taken?

(Please select 1 option)

○	Inhaled solvent glue ← This is the correct answer
◉	Smoked heroin ✕ Incorrect answer selected
○	Smoked marijuana
○	Snorted cocaine
○	Taken ecstacy

This patient was markedly comatose on arrival but quickly regains consciousness. This suggests a short acting (probably) inhaled anaesthetic-like agent - glue.

Marijuana would not be expected to produce this level of coma and the effects of cocaine would last much longer.

The inhaled solvents, due to their lipophilicity, are rapidly absorbed through the lungs and then quickly distributed to the brain and other organs. The effects therefore appear within minutes of inhalation.

Typical substances that are inhaled include toluene aromatic hydrocarbons and butane.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 18 mins 44 secs

Question: 43 of 100

A 21-year-old man, who has a past history of IV drug abuse, presents 12 hours after taking an overdose of 480 mg of codeine and 30 g of paracetamol.

His blood pressure is 100/60 mmHg and he has pin-point pupils.

What is the most appropriate management for this patient?

(Please select 1 option)

- 500ml 10% glucose IV over four hours
- 1 litre normal saline IV over six hours
- IV naloxone
- IV flumazenil
- Start N-acetylcysteine

Submit answer | Skip question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

A 21-year-old man, who has a past history of IV drug abuse, presents 12 hours after taking an overdose of 480 mg of codeine and 30 g of paracetamol.

His blood pressure is 100/60 mmHg and he has pin-point pupils.

What is the most appropriate management for this patient?

(Please select 1 option)

○	500ml 10% glucose IV over four hours
○	1 litre normal saline IV over six hours
○	IV naloxone
○	IV flumazenil
◉	Start N-acetylcysteine ✓ Correct

This patient presents 12 hours after taking a potentially fatally toxic dose of paracetamol.

In the circumstances provided in this question where there is an absence of data relating to pulse rate (as he is probably not in shock), respiratory rate (reflecting respiratory depression) or blood glucose, the most appropriate intervention at this 12 hour time-point would be N-acetylcysteine.

The urgency of treatment is underlined by the fact that the incidence of hepatotoxicity is worse if treatment is delayed.

Trials of N-acetylcysteine suggest that the incidence of hepatotoxicity is 1% in those treated within eight hours versus 46% in those treated after 16 hours.

Next question

Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

A 51-year-old lady presented to hospital with a two day history of malaise and headache.

On the day of admission the headache had become more intense and was associated with pain in her neck.

Her husband reported that she had also been febrile and confused at times. She had previously been well and had no significant past medical history.

On examination, she was febrile 38.1°C, looked unwell and was photophobic. Kernig's and Brudzinski's signs were positive. The fundi were normal with no evidence of papilloedema.

Following a normal CT scan a lumbar puncture was performed and CSF analysis showed:

White cells	200/mm^3	
Red cells	2/mm^3	
CSF protein	0.9 g/l	(0.15-0.45)
CSF glucose	1.6 mmol/l	(3.3-4.4)
Plasma glucose	5.3 mmol/l	(3.0-6.0)

What is the most likely causative organism?

(Please select 1 option)

- ○ *Eschericia coli*
- ○ *Listeria monocytogenes*
- ○ *Mycobacterium tuberculosis*
- ○ *Streptococcus pneumoniae*
- ○ *Streptococcus pyogenes*

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

http://my.onexamination.com/Assessment/Que
Questions Set : REF11185
Intravenous N-acetylcystine: t...

	Mycobacterium tuberculosis
◉	*Streptococcus pneumoniae* ✓ Correct
○	*Streptococcus pyogenes*

The most common causes of bacterial meningitis in persons over 50 years of age are:

1. *Streptococcus pneumoniae*
2. *Neisseria meningitidis*
3. *Listeria monocytogenes*
4. Gram-negative bacilli.

Although this question tries to establish whether candidates are aware of the most common cause of meningitis in this group, some questions in the examination give additional clues as to the cause of meningitis.

Physical examination may provide clues to the aetiology of meningitis in affected patients:

1. Morbilliform rash with pharyngitis and lymphadenopathy may suggest a viral aetiology (Epstein-Barr virus [EBV], cytomegalovirus [CMV], adenovirus, human immunodeficiency virus [HIV]).
2. Macules and petechiae that rapidly evolve into purpura suggest meningococcaemia (with or without meningitis).
3. Vesicular lesions in a dermatomal distribution suggest *Varicella zoster* virus.
4. Genital vesicles suggest *Herpes simplex* virus (HSV)-2 meningitis.
5. Sinusitis or otitis suggest direct extension into the meninges, usually with *Streptococcus pneumoniae* and *Haemophilus influenzae*.
6. Rhinorrhea or otorrhea suggest a cerebrospinal fluid (CSF) leak from a basilar skull fracture, with meningitis most commonly caused by *Streptococcus pneumoniae*.
7. Hepatosplenomegaly and lymphadenopathy suggest a systemic disease, including viral (for example, mononucleosis-like syndrome in EBV, CMV, and HIV) and fungal (for example, disseminated histoplasmosis) disease.
8. The presence of a murmur suggests infective endocarditis with secondary bacterial seeding of the meninges.
9. Evidence of parotitis is observed in some cases of mumps meningitis.

Kernig's sign (pdf)
In a supine patient, flex the hip to 90° while the knee is flexed at 90°. An attempt to further extend the knee produces pain in the hamstrings and resistance to further extension.

Brudzinski's sign (pdf)

2. *Neisseria meningitidis*
3. *Listeria monocytogenes*
4. Gram-negative bacilli.

Although this question tries to establish whether candidates are aware of the most common cause of meningitis in this group, some questions in the examination give additional clues as to the cause of meningitis.

Physical examination may provide clues to the aetiology of meningitis in affected patients:

1. Morbilliform rash with pharyngitis and lymphadenopathy may suggest a viral aetiology (Epstein-Barr virus [EBV], cytomegalovirus [CMV], adenovirus, human immunodeficiency virus [HIV]).
2. Macules and petechiae that rapidly evolve into purpura suggest meningococcaemia (with or without meningitis).
3. Vesicular lesions in a dermatomal distribution suggest *Varicella zoster* virus.
4. Genital vesicles suggest *Herpes simplex* virus (HSV)-2 meningitis.
5. Sinusitis or otitis suggest direct extension into the meninges, usually with *Streptococcus pneumoniae* and *Haemophilus influenzae*.
6. Rhinorrhea or otorrhea suggest a cerebrospinal fluid (CSF) leak from a basilar skull fracture, with meningitis most commonly caused by *Streptococcus pneumoniae*.
7. Hepatosplenomegaly and lymphadenopathy suggest a systemic disease, including viral (for example, mononucleosis-like syndrome in EBV, CMV, and HIV) and fungal (for example, disseminated histoplasmosis) disease.
8. The presence of a murmur suggests infective endocarditis with secondary bacterial seeding of the meninges.
9. Evidence of parotitis is observed in some cases of mumps meningitis.

Kernig's sign (pdf)
In a supine patient, flex the hip to 90° while the knee is flexed at 90°. An attempt to further extend the knee produces pain in the hamstrings and resistance to further extension.

Brudzinski's sign (pdf)
Passively flex the neck while the patient is in a supine position with extremities extended. This manoeuvre produces flexion of the hips in patients with meningeal irritation.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 23 mins 34 secs

Question: 45 of 100

An anxious 22-year-old female with a high respiration rate has the following arterial blood gas results:

pH	7.27	(7.36-7.44)
PCO_2	2.6KPa	(4.7-6.0)
Base deficit	12 mmol/l	

What is the interpretation of the acid-base status?

(Please select 1 option)

- Combined metabolic and respiratory acidosis
- Combined metabolic and respiratory alkalosis
- Metabolic acidosis with some compensatory respiratory alkalosis
- Respiratory acidosis with some compensatory metabolic alkalosis
- Respiratory alkalosis with some compensatory metabolic acidosis

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

An anxious 22-year-old female with a high respiration rate has the following arterial blood gas results:

pH	7.27	(7.36-7.44)
PCO_2	2.6KPa	(4.7-6.0)
Base deficit	12 mmol/l	

What is the interpretation of the acid-base status?

(Please select 1 option)

- Combined metabolic and respiratory acidosis
- Combined metabolic and respiratory alkalosis
- Metabolic acidosis with some compensatory respiratory alkalosis ← This is the correct answer
- Respiratory acidosis with some compensatory metabolic alkalosis
- (●) Respiratory alkalosis with some compensatory metabolic acidosis ✕ Incorrect answer selected

This patient has a metabolic acidosis as evidenced by a pH of 7.27 and a base deficit, which is a marker of the extent of acidosis.

The low CO_2 is a reflection of the physiological respiratory compensation which is attempting to normalise pH by clearing the acidic gas CO_2.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 26 mins 53 secs

Question: 46 of 100

A 22-year-old female develops a wheeze and extensive rash whilst eating a Chinese take-away.

On examination, she has extensive wheeze and stridor, with urticaria covering her upper and lower limbs and trunk. Her BP is 80/45 mmHg.

What is the likely diagnosis?

(Please select 1 option)

- C1 esterase deficiency
- Food poisoning
- Idiopathic urticaria
- Monosodium glutamate syndrome
- Peanut allergy

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

C1 esterase deficiency

Food poisoning

Idiopathic urticaria

Monosodium glutamate syndrome

Peanut allergy ✓ Correct

Chinese cooking uses cashew nuts in many dishes, and patients with peanut allergy may also experience an anaphylactic reaction with cashew nuts. Chinese chefs also use peanut oil in the stir fry, and this may also precipitate an allergic reaction.

An acute hypersensitivity reaction to monosodium glutamate (MSG) a preservative common in Chinese food, may give rise to the 'MSG syndrome'. This is characterised by

- a sudden onset of headache
- heartburn
- palpitations
- sweating
- swelling
- flushing of the face.

Patients may report a sense of increased facial pressure or tingling in the face. Symptoms generally start within two hours of eating foods rich in MSG. This condition is generally self-limited and will resolve. Antihistamines can be helpful in some cases.

It is extremely unlikely that this syndrome will cause shock, which is what this patient presents with given the hypotension.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 28 mins 34 secs

Question: 47 of 100

A 18-year-old female is brought to the Emergency Department unconscious after having taken an overdose.

On examination she has a Glasgow coma score of 6, a respiratory rate of eight breaths per minute, a heart rate of 52 beats per minute and her blood pressure is 84/62 mmHg. Her pupils are small but are reactive to light, muscle tone is reduced and plantar responses are flexor.

Which of the following is she most likely to have taken in overdose?

(Please select 1 option)

○	Diazepam
○	Dihydrocodeine
○	Diphenhydramine
○	Ecstasy (MDMA)
○	Methanol

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

On examination she has a Glasgow coma score of 6, a respiratory rate of eight breaths per minute, a heart rate of 52 beats per minute and her blood pressure is 84/62 mmHg. Her pupils are small but are reactive to light, muscle tone is reduced and plantar responses are flexor.

Which of the following is she most likely to have taken in overdose?

(Please select 1 option)

○	Diazepam
◉	Dihydrocodeine ✓ Correct
○	Diphenhydramine
○	Ecstasy (MDMA)
○	Methanol

Dihydrocodeine is an opiate analgesic and when taken in overdose has a number of toxic effects. It acts as a respiratory depressant leading to reduced respiratory rate. It can cause bradycardia and hypotension in large doses. Pupillary constriction is a diagnostic feature in opiate overdose.

It is also a central nervous system (CNS) depressant and therefore causes coma in overdose.

Benzodiazepines and antihistamines tend not to have the same cardiorespiratory effects as opiates.

MDMA is a stimulant and can cause delirium, convulsions and ventricular arrhythmias.

Diazepam would be less likely here due to the bradycardia and the hypotension.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 30 mins 34 secs

Question: 48 of 100

A 17-year-old male presents to the Emergency Department after an overdose of alcohol and paracetamol.

He complained of abdominal discomfort and an intravenous infusion of N-acetylcysteine was commenced. 15 minutes later he developed breathlessness, reported feeling flushed and developed a tachycardia.

Which of the following is most likely to have occurred?

(Please select 1 option)

- A disulfiram-like (antabuse) reaction has occurred
- The patient has developed pulmonary oedema
- The patient has had a panic attack
- The patient has received an overdose of N-acetylcysteine
- The patient has received N-acetylcysteine previously

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 33 mins 19 secs

Question: 49 of 100

A 55-year-old homeless male was found stuporous and smelling of alcohol.

Observations in the emergency department reveal a core temperature of 34°C, a pulse of 50 bpm and blood pressure of 116/80 mmHg. Dipstick urine analysis shows blood +++.

Some of his investigations are listed:

Creatinine	320 µmol/l	(60-110)
Gamma GT	40 U/l	(10-40)
AST	550 U/l	(1-40)
LDH	1500 U/l	(10-250)

Urine microscopy no cells or organisms.

What is the most likely cause of the raised serum creatinine concentration?

(Please select 1 option)

- ○ Chronic renal failure
- ○ Dehydration
- ○ Hypothermia
- ○ Paracetamol poisoning
- ○ Rhabdomyolysis

LDH	1500 U/l	(10-250)

Urine microscopy no cells or organisms.

What is the most likely cause of the raised serum creatinine concentration?

(Please select 1 option)

- ○ Chronic renal failure
- ○ Dehydration
- ○ Hypothermia
- ○ Paracetamol poisoning
- ◉ Rhabdomyolysis ✓ Correct

The elevated serum creatinine is most likely due to rhabdomyolysis as the patient was found unconscious, is hypothermic, and is likely to have sustained muscle injury.

The latter is confirmed by an elevated aspartate aminotransferase and lactate dehydrogenase (LDH) but the normal gamma-glutamyl transpeptidase (GGT) argues against these being released from the liver.

Rhabdomyolysis is strongly suggested by the fact that urinalysis is strongly positive for blood, whereas urine microscopy is negative for red blood cells.

The positive urinalysis is caused by myoglobin, a muscle protein released during muscle damage; this appears in the urine and can cause acute renal failure.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Community
- Help
- Shop

Which of the following is the most appropriate initial treatment for this man?

(Please select 1 option)

○	Dantrolene
○	Diazepam ← This is the correct answer
○	Lidocaine
◉	Propranolol ✕ Incorrect answer selected
○	Verapamil

Cocaine abuse is quite common and neurological and cardiovascular side effects predominate. Delirium, hyperthermia, dysrrhythmias, as well as myocardial and cerebral infarctions are reported.

In this patient, the first consideration should be attention to airway, breathing and circulation (ABC) and also to remove any residual cocaine from the nares.

Generally, the toxic effects of cocaine are short lived and relate to sympathetic stimulation, in this case with tachycardia, pyrexia and hypertension.

The most appropriate treatment would be an intravenous (IV) benzodiazepine such as diazepam, which relieves the sympathetic adrenergic overdrive and would be expected to relieve these features including the hypertension.

If further treatment is required, IV nitrates can be used and are particularly useful for associated coronary artery spasm.

Beta-blockers should be avoided as they may depress cardiac output, which may exacerbate the depressive effect of cocaine.

Next question | Remove Tag | Remove question

Work Smart Session - MRCP Part 1

Time taken: 16 mins 55 secs

Question: 5 of 100

A 24-year-old law student attends with visual loss affecting the right eye. She reports a constant headache for the last three months, and absence of menses for six months.

On examination her visual acuity in the right eye is 6/24, with slight constriction of the temporal field in that eye but she has no other neurological deficit. She is afebrile and haemodynamically stable.

What is the diagnosis?

(Please select 1 option)

- Glaucoma
- Migraine
- Multiple sclerosis
- Pituitary tumour
- Pregnancy

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 37 mins 28 secs

Question: 50 of 100

A 16-year-old girl presents with an acute exacerbation of asthma.

On examination her respiratory rate was 30 per minute, her heart rate was 120 beats per minute and a peak expiratory flow rate (PEFR) was 30% of the predicted value.

Her blood gas analysis on air shows:

PaO_2	9 kPa	(11.3-12.6)
$PaCO_2$	3.5 kPa	(4.7-6.0)

After the administration of oxygen and corticosteroids what is the most appropriate next step in management?

(Please select 1 option)

- Intravenous aminophylline
- Intravenous salbutamol
- Ipratropium bromide via oxygen-driven nebuliser
- Salbutamol via oxygen-driven nebuliser
- Salmeterol via breath-actuated inhaler

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

On examination her respiratory rate was 30 per minute, her heart rate was 120 beats per minute and a peak expiratory flow rate (PEFR) was 30% of the predicted value.

Her blood gas analysis on air shows:

PaO_2	9 kPa	(11.3-12.6)
$PaCO_2$	3.5 kPa	(4.7-6.0)

After the administration of oxygen and corticosteroids what is the most appropriate next step in management?

(Please select 1 option)

- ○ Intravenous aminophylline
- ○ Intravenous salbutamol
- ○ Ipratropium bromide via oxygen-driven nebuliser
- ◉ Salbutamol via oxygen-driven nebuliser ✓ Correct
- ○ Salmeterol via breath-actuated inhaler

This patient has severe asthma as revealed by the low PEFR, low $P0_2$ and signs.

The next stage in the management is the administration of nebulised beta 2 agonists with supplementation of high flow oxygen (minimum of 6 l/minute). Beta 2 agonists can be administered in 15-30 minute intervals if required.

Intravenous therapy with beta 2 agonists should only be used if inhaled therapies cannot be reliably administered.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 39 mins 57 secs

Question: 51 of 100

A 72-year-old man presented following three episodes of transient loss of consciousness not associated with chest pain. There was a previous history of an anterior myocardial infarction.

On examination his blood pressure was 140/80 mmHg and the apex beat was diffuse in character and displaced to the left. There were no neurological signs.

The ECG showed sinus rhythm with occasional ventricular extrasystoles, deep anterior Q waves and ST segment elevation in leads V2 - V6, without reciprocal depression.

Which one of the following would be the most appropriate initial course of action?

(Please select 1 option)

- Administer tissue plasminogen activator
- Arrange an electroencephalogram
- Arrange immediate computerised tomography (CT) brain scan
- Observe in the coronary care unit
- Proceed to coronary arteriography

Submit answer | Skip question | Tag Question | Remove question

On examination his blood pressure was 140/80 mmHg and the apex beat was diffuse in character and displaced to the left. There were no neurological signs.

The ECG showed sinus rhythm with occasional ventricular extrasystoles, deep anterior Q waves and ST segment elevation in leads V2 - V6, without reciprocal depression.

Which one of the following would be the most appropriate initial course of action?

(Please select 1 option)

◉	Administer tissue plasminogen activator ✕ Incorrect answer selected
○	Arrange an electroencephalogram
○	Arrange immediate computerised tomography (CT) brain scan
○	Observe in the coronary care unit ← This is the correct answer
○	Proceed to coronary arteriography

The history suggests that this man has persistent ST elevation in the anterior leads, with a previous history of anterior myocardial infarction due to left ventricular (LV) aneurysm. The blackouts are cardiac syncope due to rhythm disturbance. An ECHO would quickly support the diagnosis but, because of the risk of sudden death, observation on CCU is required.

The loss of consciousness is likely to be due to recurrent arrhythmic episodes or vertebrobasilar transient ischaemic attacks (TIAs), as a result of embolisation of an LV thrombus.

The most important investigation for this patient whom you suspect has arrhythmic episodes would be telemetry/24 hour monitoring, and hence observation on the coronary care unit (CCU) is appropriate.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 3 hrs 16 mins 10 secs

Question: 52 of 100

A 17-year-old woman presented six hours after taking 30 g of paracetamol.

Which of the following factors is most likely to predict an increased risk of hepatotoxicity from the paracetamol?

(Please select 1 option)

- Anorexia nervosa
- Consumption of 20 units of alcohol since taking the paracetamol
- Gilbert's disease
- Ingestion of amitriptyline with the paracetamol
- Smoking 20 cigarettes per day

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 3 hrs 19 mins 33 secs

Question: 52 of 100

A 17-year-old woman presented six hours after taking 30 g of paracetamol.

Which of the following factors is most likely to predict an increased risk of hepatotoxicity from the paracetamol?

(Please select 1 option)

◉	Anorexia nervosa ✓ Correct
○	Consumption of 20 units of alcohol since taking the paracetamol
○	Gilbert's disease
○	Ingestion of amitriptyline with the paracetamol
○	Smoking 20 cigarettes per day

High risk groups in paracetamol overdose include:

- malnourished patients (anorexia nervosa/bulimia nervosa)
- patients taking enzyme inducing drugs (e.g. carbamazepine, phenytoin, rifampicin and St John's wort)
- patients with induced liver enzymes due to chronic ethanol abuse
- human immunodeficiency virus (HIV) positive patients.

See review in *Clinical Medicine* Vol 3 No **2** 2003.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 3 hrs 19 mins 33 secs

Question: 53 of 100

A 64-year-old woman presented 10 hours after ingestion of 12 g of quinine sulphate.

Which of the following is the most common characteristic clinical feature in this situation?

(Please select 1 option)

- Blindness
- Bradycardia
- Hyperacusis
- Hyperglycaemia
- Hypotension

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 3 hrs 20 mins 34 secs

Question: 54 of 100

A 30-year-old woman becomes anuric 24 hours after a difficult laparoscopic cholecystectomy.

Investigations reveal:

Serum urea	9.2 mmol/l	(2.5-7.5)
Serum creatinine	120 micro mol/l	(60-110)

The blood pressure is 90/50 mmHg.

What is the next single most appropriate course of action in the management of the anuria?

(Please select 1 option)

- 1 L normal saline intravenously as fast as possible.
- Commence intravenous low-dose dopamine
- Give an 80 mg intravenous bolus of furosemide
- Give 500 ml intravenous plasma expander over 4 hours
- Urgent renal ultrasound

Dashboard
Questions
Scores
Community
Help
Shop

(Please select 1 option)

◉	1 L normal saline intravenously as fast as possible. ✓ Correct
○	Commence intravenous low-dose dopamine
○	Give an 80 mg intravenous bolus of furosemide
○	Give 500 ml intravenous plasma expander over 4 hours
○	Urgent renal ultrasound

This question is dealing with postoperative acute renal failure. This what you might find on the morning ward round and wonder why the problem was not picked up during the night.

Note that even when the glomerular filtration rate is zero, the serum creatinine tends not to rise faster than 200 micro mol/l per day - so the patient's creatinine of 120 micro mol/l may be the beginning of established renal failure.

Immediate management consists of restoring the circulation as quickly as possible; debate still continues whether it is better to use colloid or crystalloid.

In this case it would seem to be more appropriate to use 1 L of normal saline as the time scale for plasma expander is too long.

If urine output and renal function recover as soon as intravascular volume is restored, the diagnosis of pre-renal uraemia is made; if they do not then the diagnosis is acute tubular necrosis (ATN).

In a seemingly previously cardiovascularly-well 30-year-old with hypotension, giving 1 L over a short time will not precipitate any problems.

There is little evidence to suggest that loop diuretics and dopamine are effective in the treatment of ATN.

The next problem is to find out why the patient was hypotensive after surgery.....

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 3 hrs 22 mins 2 secs

Question: 55 of 100

A 16-year-old male is brought to emergency admissions with alcohol intoxication. An initial electrocardiogram (ECG) reveals atrial fibrillation (AF) but a repeat ECG after 12 hours when he has sobered up, shows sinus rhythm. An echocardiogram is normal.

What is the most appropriate management for this patient?

(Please select 1 option)

- Aspirin for 3 months
- Bisoprolol for 3 months
- Lifestyle advice
- Sotalol for one month
- Warfarin for one month

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

A 16-year-old male is brought to emergency admissions with alcohol intoxication. An initial electrocardiogram (ECG) reveals atrial fibrillation (AF) but a repeat ECG after 12 hours when he has sobered up, shows sinus rhythm. An echocardiogram is normal.

What is the most appropriate management for this patient?

(Please select 1 option)

○	Aspirin for 3 months
○	Bisoprolol for 3 months
◉	Lifestyle advice ✓ Correct
○	Sotalol for one month
○	Warfarin for one month

Excessive alcohol is a recognised cause for atrial fibrillation and is the likely cause here as the rhythm has reverted to sinus after 12 hours. There is also no evidence of structural heart disease as the echocardiogram was normal.

Therefore this patient needs advice regarding moderation of alcohol consumption and needs to be warned of the toxic effects that alcohol can have on the heart and other organs.

There is no indication for short term aspirin.

Atenolol provides rate control, which is not an issue.

Sotalol/amiodarone and flecainide can be used in paroxysmal AF.

Short term warfarin is used for 4-6 weeks prior to elective cardioversion to protect against embolic complications.

Work Smart Session - MRCP Part 1

Time taken: 3 hrs 27 mins 9 secs

Question: 57 of 100

A 72-year-old man with type 2 diabetes mellitus presented following the sudden onset of palpitations.

An ECG revealed rapid atrial fibrillation. He was commenced on amiodarone but the atrial fibrillation persisted.

Which of the following has been shown to be of greatest benefit in reducing his future risk of vascular events?

(Please select 1 option)

- Anticoagulation
- Aspirin
- Continuation of amiodarone
- DC cardioversion
- Digoxin

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 3 hrs 27 mins 9 secs

Question: 57 of 100

A 72-year-old man with type 2 diabetes mellitus presented following the sudden onset of palpitations.

An ECG revealed rapid atrial fibrillation. He was commenced on amiodarone but the atrial fibrillation persisted.

Which of the following has been shown to be of greatest benefit in reducing his future risk of vascular events?

(Please select 1 option)

- Anticoagulation
- Aspirin
- Continuation of amiodarone
- DC cardioversion
- Digoxin

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 3 hrs 30 mins 2 secs

Question: 58 of 100

An 18-year-old female presents with an acute exacerbation of asthma associated with a chest infection. She is unable to complete a sentence and her peak flow rate was 35% of her normal level.

She is treated with high flow oxygen, nebulised bronchodilators and oral steroids but this is associated with little change in her condition.

Which of the following treatments, given intravenously, would be the most appropriate for this patient?

(Please select 1 option)

- Aminophylline
- Augmentin
- Hydrocortisone
- Magnesium
- Salbutamol

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 3 hrs 30 mins 2 secs

Question: 58 of 100

An 18-year-old female presents with an acute exacerbation of asthma associated with a chest infection. She is unable to complete a sentence and her peak flow rate was 35% of her normal level.

She is treated with high flow oxygen, nebulised bronchodilators and oral steroids but this is associated with little change in her condition.

Which of the following treatments, given intravenously, would be the most appropriate for this patient?

(Please select 1 option)

- Aminophylline
- Augmentin
- Hydrocortisone
- Magnesium
- Salbutamol

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

She is treated with high flow oxygen, nebulised bronchodilators and oral steroids but this is associated with little change in her condition.

Which of the following treatments, given intravenously, would be the most appropriate for this patient?

(Please select 1 option)

○	Aminophylline
○	Augmentin
○	Hydrocortisone
◉	Magnesium ✓ Correct
○	Salbutamol

This patient has acute severe asthma (PEFR 33-50% predicted/best, unable to complete sentences in one breath, respiratory rate >25 breaths/min, pulse rate >110 beats/minute).

She has not responded to initial treatment and the treatment of choice now is intravenous magnesium 1.2-2 g over 20 minutes.

Reference:
BTS guidelines on the Management of Asthma British Thoracic Society

OR

British Guideline on the Management of Asthma (Guideline 101) Scottish Intercollegiate Guidelines Network

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 3 hrs 31 mins 35 secs

Question: 59 of 100

A 40-year-old farmer presented to the Emergency Department with a 24 hour history of fever and increasing confusion.

On examination he was febrile 39.5°C. A generalised erythematous rash, covering most of his body, was observed. He also had a paronychial infection of his right index finger, with lymphangitis extending caudally, and with axillary lymphadenopathy.

His heart rate was measured at 120 beats per minute with a blood pressure of 80/60 mmHg.

What is the most likely diagnosis?

(Please select 1 option)

- Hantavirus infection
- Leptospirosis
- Orf
- Staphylococcal toxic shock syndrome
- Stevens-Johnson syndrome

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

http://my.onexamination.com/Assessment/Que
Questions Set : REF6296

◉	Orf ✕ Incorrect answer selected
○	Staphylococcal toxic shock syndrome ← This is the correct answer
○	Stevens-Johnson syndrome

The history is typical of staphylococcal toxic shock syndrome (TSS):

- shock
- fever
- confusion
- rash.

The primary source of infection in this case is the paronychia of his right index finger.

Hantavirus infections (viral zoonoses transmitted via rodents) typically have two distinct presentations:

1. either as a haemorrhagic fever with renal failure
2. or as an acute pulmonary syndrome.

The former manifestation is commonest in the Far East and eastern Europe, while the latter is the predominant form in the southwestern United States and South America.

Leptospirosis does not typically cause a rash and is often associated with jaundice; leptospirosis would not explain the lesion on his finger.

Orf, a zoonotic infection caused by a pox virus, presents with painless ulcerated lesions on the hands of farmers, but does not fully explain this clinical picture.

Stevens-Johnson syndrome typically starts with an erythema multiforme-type rash that spreads widely and involves the buccal mucosa and conjunctivae, often caused by antibiotic therapy; but does not fit the clinical picture presented here.

- Questions
- Scores
- Community
- Help
- Shop

A 24 year old law student attends with visual loss affecting the right eye. She reports a constant headache for the last three months, and absence of menses for six months.

On examination her visual acuity in the right eye is 6/24, with slight constriction of the temporal field in that eye but she has no other neurological deficit. She is afebrile and haemodynamically stable.

What is the diagnosis?

(Please select 1 option)

○	Glaucoma
○	Migraine
○	Multiple sclerosis
◉	Pituitary tumour ✓ Correct
○	Pregnancy

This patient has a pituitary lesion; the history of headache and amenorrhoea suggests a prolactinoma or non- functioning tumour. This has been complicated by involvement of the visual pathway which has precipitated her visual loss.

She needs urgent assessment of her pituitary function and imaging of the pituitary gland by MRI scanning. One of the most important investigations to perform would be a serum prolactin.

The amenorrhoea would argue against this being retrobulbar neuritis associated with multiple sclerosis (MS), and similarly the peripheral visual field constriction would be unusual as a central scotoma and fluctuating visual loss would be more typical.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Question: 6 of 100

A 52-year-old woman presents with left loin pain. Past history included hypertension and progressive cognitive decline.

On examination she was pyrexial, had livedo reticularis and a blood pressure of 180/100 mmHg. Examination of the abdomen revealed no masses but there was tenderness in the left flank.

Investigations revealed:

Haemoglobin	12.9 g/dl	(11.5-16.5)
White cell count	8.7 x 10^9/l	(4-11)
Platelet count	83 x 10^9/l	(150-400)
Serum creatinine	106 mol/l	(60-110)

Urine dipstick analysis:
Blood +++
Protein +

Which one of the following tests is most likely to be positive?

(Please select 1 option)

- Anti-cardiolipin antibody
- Anti-glomerular basement membrane antibody
- Anti-mitochondrial antibody
- Anti-neutrophil cytoplasmic antibody
- Anti-streptolysin O antibody

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd. All rights reserved. Terms and conditions. Privacy policy.

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 3 hrs 34 mins 46 secs

Question: 60 of 100

A 29-year-old female presents with acute right-sided weakness.

She has one child aged four years and had two spontaneous abortions in the past. After the birth of her child she developed a DVT and required three months' anticoagulation with warfarin.

Examination revealed a right hemiparesis. A CT head scan showed a left middle cerebral artery territory infarct.

What is the most likely finding on echocardiography?

(Please select 1 option)

- Atrial septal defect
- Bicuspid aortic valve
- Left atrial myxoma
- Normal appearances
- Ventricular septal defect

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Question: 60 of 100

A 29-year-old female presents with acute right-sided weakness.

She has one child aged four years and had two spontaneous abortions in the past. After the birth of her child she developed a DVT and required three months' anticoagulation with warfarin.

Examination revealed a right hemiparesis. A CT head scan showed a left middle cerebral artery territory infarct.

What is the most likely finding on echocardiography?

(Please select 1 option)

○	Atrial septal defect
○	Bicuspid aortic valve
○	Left atrial myxoma
◉	Normal appearances ✓ Correct
○	Ventricular septal defect

This patient has a prothrombotic tendency suggestive of the lupus anticoagulant with recurrent abortions, previous deep vein thrombosis (DVT) and now she has developed a left hemiparesis.

This has occurred off warfarin and it is highly unlikely to be due to any right to left transference of clot.

It is more likely to be due to spontaneous infarct related to the thrombophilia and her heart is likely to be normal.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Question: 61 of 100

A 42-year-old female is admitted following an overdose of diazepam and alcohol.

On examination she was unconscious with a core temperature of 34.5°C and a blood pressure of 110/80 mmHg.

Investigations reveal:

Creatinine	242 µmol/l	(60-100)
AST	500 U/l	(0-40)
Gamma GT	35 U/l	(<50)
Urine microscopy	No cells or organisms	
Urine dipstick analysis blood	+++	
Ultrasound abdomen	Normal	

Which one of the following is the most likely cause of these findings?

(Please select 1 option)

- Associated paracetamol poisoning
- Chronic renal failure
- Dehydration
- Hypothermia
- Rhabdomyolysis

Creatinine	242 µmol/l	(60-100)
AST	500 U/l	(0-40)
Gamma GT	35 U/l	(<50)
Urine microscopy	No cells or organisms	
Urine dipstick analysis blood	+++	
Ultrasound abdomen	Normal	

Which one of the following is the most likely cause of these findings?

(Please select 1 option)

- ○ Associated paracetamol poisoning
- ○ Chronic renal failure
- ○ Dehydration
- ○ Hypothermia
- ◉ Rhabdomyolysis ✓ Correct

This patient has taken an overdose of diazepam and has collapsed for an indeterminate period. She is now seen with renal impairment.

The features together with the elevated amino transferase (AST) (from muscle) suggest a diagnosis of rhabdomyolysis.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 3 hrs 37 mins 40 secs

Question: 62 of 100

A 40-year-old man suffers an intracerebral infarction.

Which of the following features in this patient would not be considered as a risk factor for his stroke?

(Please select 1 option)

- Blood pressure 156/72 mmHg
- Marijuana use
- Mitral valve prolapse
- Plasma cholesterol of 6.5 mmol/l
- Smoker of 5 cigarettes per day

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 3 hrs 38 mins 20 secs

Question: 62 of 100

A 40-year-old man suffers an intracerebral infarction.

Which of the following features in this patient would not be considered as a risk factor for his stroke?

(Please select 1 option)

○	Blood pressure 156/72 mmHg
◉	Marijuana use ✓ Correct
○	Mitral valve prolapse
○	Plasma cholesterol of 6.5 mmol/l
○	Smoker of 5 cigarettes per day

Like ischaemic heart disease/myocardial infarction (IHD/MI), epidemiological studies show an increased risk of stroke associated with hypercholesterolaemia. Other risk factors for stroke include isolated systolic hypertension in particular.

A previous history of deep vein thrombosis (DVT) may suggest a coagulation disorder.

Cocaine is associated with an increased risk of intracerebral infarction; marijuana is associated with increased susceptibility to schizophrenic episodes, particularly in the younger age group.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 3 hrs 38 mins 20 secs

Question: 63 of 100

A 35-year-old male with a long history of ulcerative colitis is treated for an acute exacerbation which settles following an alteration of his medication.

Six weeks after discharge he is re-admitted with sepsis and his results show:

Haemoglobin	10.5 g/dl	(13.0-18.0)
White cell count	2.0 x 10^9/l	(4-11)
Platelets	90 x 10^9/l	(150-400)

Which one of the following drugs is most likely to be the cause of his pancytopaenia?

(Please select 1 option)

- Azathioprine
- Mesalazine
- Metronidazole
- Pamidronate
- Prednisolone

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

A 35-year-old male with a long history of ulcerative colitis is treated for an acute exacerbation which settles following an alteration of his medication.

Six weeks after discharge he is re-admitted with sepsis and his results show:

Haemoglobin	10.5 g/dl	(13.0-18.0)
White cell count	2.0 x 10^9/l	(4-11)
Platelets	90 x 10^9/l	(150-400)

Which one of the following drugs is most likely to be the cause of his pancytopaenia?

(Please select 1 option)

- (●) Azathioprine ✓ Correct
- ( ) Mesalazine
- ( ) Metronidazole
- ( ) Pamidronate
- ( ) Prednisolone

The answer could be either azathioprine or mesalazine as both cause a pancytopaenia although azathioprine is the more common cause.

Hence it is a toss up but one would have to go for azathioprine.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 3 hrs 39 mins 38 secs

Question: 64 of 100

A 65-year-old male presents with acute severe headache, ataxia and vomiting. Six hours later he became drowsy.

On examination he had left horizontal nystagmus, a partial left sixth cranial nerve palsy and extensor plantar responses. His blood pressure was 188/110 mmHg.

What is the most likely cause for this deterioration?

(Please select 1 option)

- Brain stem herniation
- Cerebral oedema
- Dehydration
- Malignant hypertension
- Non-convulsive status epilepticus

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Question: 64 of 100

A 65-year-old male presents with acute severe headache, ataxia and vomiting. Six hours later he became drowsy.

On examination he had left horizontal nystagmus, a partial left sixth cranial nerve palsy and extensor plantar responses. His blood pressure was 188/110 mmHg.

What is the most likely cause for this deterioration?

(Please select 1 option)

○	Brain stem herniation ← This is the correct answer
◉	Cerebral oedema ✕ Incorrect answer selected
○	Dehydration
○	Malignant hypertension
○	Non-convulsive status epilepticus

The most likely explanation of the sudden deterioration will be brain stem herniation.

The acute onset of symptoms with headache and vomiting indicating an acute intracranial haemorrhage.

Mass effect created the brain stem herniation.

Intravenous mannitol, intubation/ventilation, urgent computerised tomography (CT) brain scan and neurosurgical referral are indicated.

Next question | Remove Tag | Remove question

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 3 hrs 41 mins 14 secs

Question: 65 of 100

A 78-year-old female with diabetes presented with a two day history of melaena and dizziness. She had taken an unknown analgesic four days previously.

On examination she was pale with a pulse of 90 beats per minute, a blood pressure of 100/65 mmHg and a lower midline scar from an operation for intermittent claudication three months previously.

Investigations revealed:

Haemoglobin	8 g/dl	(13.0-18.0)
Faecal occult blood	Strongly positive	
Upper gastrointestinal tract endoscopy	Normal	

What is the most likely cause of her upper gastrointestinal (GI) haemorrhage?

(Please select 1 option)

- ○ Aorto-enteric fistula
- ○ Gastric erosions
- ○ Gastric ulcer (GU)
- ○ Mallory-Weiss syndrome
- ○ Oesophageal varices

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd. All rights reserved. Terms and conditions. Privacy policy.

Investigations revealed:

Haemoglobin	8 g/dl	(13.0-18.0)
Faecal occult blood	Strongly positive	
Upper gastrointestinal tract endoscopy	Normal	

What is the most likely cause of her upper gastrointestinal (GI) haemorrhage?

(Please select 1 option)

- Aorto-enteric fistula ← This is the correct answer
- (●) Gastric erosions ✗ Incorrect answer selected
- Gastric ulcer (GU)
- Mallory-Weiss syndrome
- Oesophageal varices

The upper GI endoscopy is normal, therefore GU, gastric erosions, varices and Mallory-Weiss syndrome are unlikely.

The strongly positive faecal occult blood (FOB) suggests significant GI haemorrhage.

Aorto-enteric fistulae (AEF) are now known to occur following endovascular repair of abdominal aortic aneurysms (AAA), and secondary to aortic grafting of any kind, presumably because of mechanical forces of dislodged or migrating devices.

This patient may well have had an aorto-bifemoral graft, as treatment for peripheral vascular disease.

Further reading:
http://www.medscape.com/viewarticle/558939 (Requires log in)

Work Smart Session - MRCP Part 1

Time taken: 4 hrs 6 mins 41 secs

Question: 66 of 100

An 18-year-old woman presents three days after allegedly taking 50 paracetamol tablets (25 g).

Which of the following tests measured at this time point would be most helpful in determining the outcome?

(Please select 1 option)

- ALT concentration
- Bilirubin concentration
- Creatinine concentration
- Paracetamol concentration
- Prothrombin time

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

○	Bilirubin concentration
○	Creatinine concentration
○	Paracetamol concentration
◉	Prothrombin time ✓ Correct

The patient has ingested a seriously toxic dose of paracetamol.

The best determinant of this risk at 72 hours would be a prolonged prothrombin time.

Paracetamol concentrations would be rather meaningless at this point in time, and irrespective, she should be treated with N-acetylcysteine.

There are four phases of paracetamol overdose:

Phase 1 (0-24 hours)

- Asymptomatic
- Anorexia
- Nausea or vomiting
- Malaise
- Subclinical rise in serum aspartate transaminase (AST) - 12 hours post ingestion.

Phase 2 (18-72 hours)

- Right upper quadrant abdominal pain, anorexia, nausea, vomiting
- Continued rise in serum transaminases levels (note this is the time slot for our patient with the alanine transaminase [ALT] rises).

Phase 3 (72-96 hours)

- Anorexia
- Nausea or vomiting
- Malaise
- Subclinical rise in serum aspartate transaminase (AST) - 12 hours post ingestion.

Phase 2 (18-72 hours)

- Right upper quadrant abdominal pain, anorexia, nausea, vomiting
- Continued rise in serum transaminases levels (note this is the time slot for our patient with the alanine transaminase [ALT] rises).

Phase 3 (72-96 hours)

- Centrilobular hepatic necrosis with continued abdominal pain
- Jaundice
- Coagulopathy
- Hepatic encephalopathy
- Nausea and vomiting
- Renal failure
- Fatality rising international normalised ratio/prothrombin time (INR/PT) from three days.

Phase 4 (Four days to three weeks)

- Complete resolution of symptoms
- Complete resolution of organ failure.

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 4 hrs 7 mins 39 secs

Question: 67 of 100

These are the blood gas results obtained from a 20-year-old female admitted to hospital.

Hydrogen ion concentration	35 nmol/l	(35-45)
pH	7.45	(7.36-7.44)
pCO_2	6.8 kPa	(4.7-6.0)
Bicarbonate	32 mmol/l	(20-28)

Which of the following is the most likely cause of this patient's acid-base derangement?

(Please select 1 option)

- Amitriptyline overdose
- Cushing's syndrome
- Hepatic failure
- Pregnancy
- Salicylate poisoning

Submit answer | Skip question | Tag Question | Remove question

Hydrogen ion concentration	35 nmol/l	(35-45)
pH	7.45	(7.36-7.44)
pCO_2	6.8 kPa	(4.7-6.0)
Bicarbonate	32 mmol/l	(20-28)

Which of the following is the most likely cause of this patient's acid-base derangement?

(Please select 1 option)

- ○ Amitriptyline overdose
- ○ Cushing's syndrome
- ○ Hepatic failure
- ◉ Pregnancy ✓ Correct
- ○ Salicylate poisoning

This patient has a mild metabolic alkalosis with what appears to be respiratory compensation as reflected by the elevated pCO_2.

Amitriptyline overdose is associated with acidosis as is salicylate poisoning.

Hepatic failure usually presents with acidosis.

This type of picture is associated with prolonged vomiting (as in pregnancy), diarrhoea, diuretic therapy and in Cushing's syndrome, or in those receiving high dose corticosteroids. With no other information provided for this case, common things being common, one should select pregnancy as the best answer for a 20-year-old female.

Next question | Tag Question | Remove question

Work Smart Session - MRCP Part 1

Time taken: 4 hrs 9 mins 56 secs

Question: 68 of 100

A 70-year-old male is admitted with haematemesis. He is currently being treated with warfarin for atrial fibrillation and his INR returns as 10 (<1.4).

Which of the following is the most appropriate immediate treatment of his INR?

(Please select 1 option)

- Cryoprecipitate
- Fresh frozen plasma
- Intravenous vitamin K
- Oral vitamin K
- Recombinant Factor VIII concentrate

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 4 hrs 11 mins 55 secs

Question: 68 of 100

A 70-year-old male is admitted with haematemesis. He is currently being treated with warfarin for atrial fibrillation and his INR returns as 10 (<1.4).

Which of the following is the most appropriate immediate treatment of his INR?

(Please select 1 option)

○	Cryoprecipitate
◉	Fresh frozen plasma ✓ Correct
○	Intravenous vitamin K
○	Oral vitamin K
○	Recombinant Factor VIII concentrate

This patient has had a bleed related to a grossly elevated international normalised ratio (INR). Consequently the INR needs correction as rapidly as is possible.

Vitamin K will correct the INR over a few days, whereas fresh frozen plasma will correct the bleeding time rapidly.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 4 hrs 11 mins 55 secs

Question: 69 of 100

You have been called to the ward by the senior nurse, to review a repeat calcium result. The repeat result is 3.9 mmol/l (2.2-2.6), the previous result four hours earlier was 3.2.

The patient has a disseminated malignancy with an unknown primary.

Which of the following statements is most correct when considering the hypercalcaemia of malignancy?

(Please select 1 option)

- A prolonged QT interval is associated with hypercalcaemia
- Bisphosphonates inhibit osteoblast function thereby lowering calcium
- Calcitonin is of greater benefit than bisphosphonates in the treatment of hypercalcaemia of malignancy
- NSAIDs are indicated for bone pain in this patient
- On neurological examination, hyporeflexia may be exhibited

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

The patient has a disseminated malignancy with an unknown primary.

Which of the following statements is most correct when considering the hypercalcaemia of malignancy?

(Please select 1 option)

◉	A prolonged QT interval is associated with hypercalcaemia ✕ Incorrect answer selected
○	Bisphosphonates inhibit osteoblast function thereby lowering calcium
○	Calcitonin is of greater benefit than bisphosphonates in the treatment of hypercalcaemia of malignancy
○	NSAIDs are indicated for bone pain in this patient
○	On neurological examination, hyporeflexia may be exhibited ← This is the correct answer

This is an oncological emergency.

Hyporeflexia is a common clinical sign in patients with hypercalcaemia.

Non-steroidal anti-inflammatory drugs (NSAIDs) should not be prescribed in patients with hypercalcaemia as they reduce renal blood flow thus inhibiting urinary calcium excretion.

Bisphosphonates inhibit bone resorption by osteoclasts, and are the first line pharmacological treatment of hypercalcaemia of malignancy; calcitonin use is limited by its association with anaphylaxis.

Electrocardiogram changes in hypercalcaemia include bradycardia, prolonged PR interval, short QT interval, widened T waves and arrhythmias.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

White cell count	8.7 x 10^9/l	(4-11)
Platelet count	83 x 10^9/l	(150-400)
Serum creatinine	106 mol/l	(60-110)

Urine dipstick analysis:
Blood +++
Protein +

Which one of the following tests is most likely to be positive?

(Please select 1 option)

- (●) Anti-cardiolipin antibody ✓ Correct
- ( ) Anti-glomerular basement membrane antibody
- ( ) Anti-mitochondrial antibody
- ( ) Anti-neutrophil cytoplasmic antibody
- ( ) Anti-streptolysin O antibody

This patient has features to suggest systemic lupus erythematosus (SLE) with antiphospholipid syndrome in this presentation, possibly due to renal vein thrombosis (flank pain with blood and protein in urine).

The diagnosis would be supported by the thrombocytopenia, history of hypertension and the livedo reticularis.

Wegener's with positive anti-neutrophil cytoplasmic antibody (ANCA) would be a less likely diagnosis.

Further reading:
Antiphospholipid syndrome Hughes Syndrome Foundation

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 33 mins 18 secs

Question: 7 of 100

A 35-year-old woman with known seafood allergy presented after developing an itchy rash at a restaurant. She had widespread urticaria which spared her neck and face.

On examination, her blood pressure is 130/70 mmHg, pulse 95 bpm, respiratory rate 24/min and O_2 saturation 99% on air.

Intravenous hydrocortisone and intramuscular antihistamine have been given.

What is the next most appropriate step in the management of this patient?

(Please select 1 option)

- Inhaled adrenaline
- Intramuscular adrenaline
- Intravenous adrenaline
- Observe
- Subcutaneous adrenaline

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 4 hrs 13 mins 55 secs

Question: 70 of 100

A 70-year-old female who has a history of chronic anxiety presents with a three day history of severe left temporal headache radiating from the eye to the scalp. She had also experienced discomfort during eating.

Which one of the following drugs should be given to this patient while awaiting the results of diagnostic tests?

(Please select 1 option)

- Acyclovir
- Carbamazepine
- Diclofenac
- Prednisolone
- Sumatriptan

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 4 hrs 14 mins 39 secs

Question: 70 of 100

A 70-year-old female who has a history of chronic anxiety presents with a three day history of severe left temporal headache radiating from the eye to the scalp. She had also experienced discomfort during eating.

Which one of the following drugs should be given to this patient while awaiting the results of diagnostic tests?

(Please select 1 option)

○	Acyclovir
○	Carbamazepine
○	Diclofenac
◉	Prednisolone ✓ Correct
○	Sumatriptan

The history suggests temporal arteritis irrespective of the history of anxiety and in view of the sight-threatening nature of the disease, the patient should be commenced on steroids.

Although the differential diagnosis is also trigeminal neuralgia, steroids should be used here whilst awaiting diagnostic investigations as temporal arteritis may be sight-threatening if left untreated.

Next question

Tag Question
Remove question

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 4 hrs 14 mins 39 secs

Question: 71 of 100

A 52-year-old male is admitted with haematemesis and melaena.

Examination reveals that he is icteric, confused with a flapping tremor, has signs of chronic liver disease, a pulse rate of 110 bpm and blood pressure of 100/70 mmHg. Abdominal examination reveals ascites.

An urgent endoscopy reveals small oesophageal varices, without evidence of bleeding, but an oozing portal hypertensive gastropathy.

Which of the following measures would be the most appropriate treatment for this patient?

(Please select 1 option)

○	Endoscopic banding
○	Endoscopic injection of adrenaline
○	Endoscopic injection of ethanolamine
○	Intravenous vitamin K
○	Oral propranolol

Submit answer | Skip question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

A 52-year-old male is admitted with haematemesis and melaena.

Examination reveals that he is icteric, confused with a flapping tremor, has signs of chronic liver disease, a pulse rate of 110 bpm and blood pressure of 100/70 mmHg. Abdominal examination reveals ascites.

An urgent endoscopy reveals small oesophageal varices, without evidence of bleeding, but an oozing portal hypertensive gastropathy.

Which of the following measures would be the most appropriate treatment for this patient?

(Please select 1 option)

○	Endoscopic banding
◉	Endoscopic injection of adrenaline ✓ Correct
○	Endoscopic injection of ethanolamine
○	Intravenous vitamin K
○	Oral propranolol

The endoscopy shows small varices with no evidence of bleeding but diffuse oozing of blood. Hence endoscopic measures like banding for small varices will not be useful.

There is probably no evidence that vitamin K is helpful, as the coagulation is already likely to be deranged.

Oral propranolol is useful as a later prophylaxis of variceal bleed.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 4 hrs 15 mins 39 secs

Question: 72 of 100

A 55-year-old male presented six hours after taking an overdose of lithium tablets which had been prescribed for a bipolar affective disorder.

On examination he was tremulous, had suffered a convulsion and had a Glasgow coma scale of 12/15. His serum lithium concentration was 5.0 mmol/L (0.5-1.0)

What is the most appropriate management of this patient?

(Please select 1 option)

○	Activated charcoal
○	Forced alkaline diuresis
○	Furosemide 100 mg intravenously twice daily
○	Haemodialysis
○	Measure lithium concentration in 2 hours

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

A 55-year-old male presented six hours after taking an overdose of lithium tablets which had been prescribed for a bipolar affective disorder.

On examination he was tremulous, had suffered a convulsion and had a Glasgow coma scale of 12/15. His serum lithium concentration was 5.0 mmol/L (0.5-1.0)

What is the most appropriate management of this patient?

(Please select 1 option)

○	Activated charcoal
○	Forced alkaline diuresis
○	Furosemide 100 mg intravenously twice daily
◉	Haemodialysis ✓ Correct
○	Measure lithium concentration in 2 hours

The patient has a severe lithium overdose as reflected by markedly elevated lithium concentrations and features of impaired consciousness, tremor and seizures.

This needs urgent management.

Activated charcoal does not bind lithium effectively and is therefore ineffective except where co-ingestion of other poisons is suspected.

Haemodialysis is the mainstay of treatment for acute lithium toxicity.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Question: 73 of 100

An 18-year-old woman sustains severe head injuries in a road traffic accident.

The following day her investigations show:

Sodium	160 mmol/l	(137-144)
Potassium	3.7 mmol/l	(3.5-4.9)
Chloride	120 mmol/l	(95-107)
Urea	3.0 mmol/l	(2.5-7.5)
Creatinine	90 µmol/l	(60- 110)

Which one of the following statements is correct?

(Please select 1 option)

- Rapid rehydration with 5% dextrose is indicated
- She has the syndrome of inappropriate antidiuretic hormone secretion (SIADH)
- She should be treated with sodium restriction
- She will have a hypercholraemic acidosis
- Urine osmolality will be low

Submit answer | Skip question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Question: 73 of 100

An 18-year-old woman sustains severe head injuries in a road traffic accident.

The following day her investigations show:

Sodium	160 mmol/l	(137-144)
Potassium	3.7 mmol/l	(3.5-4.9)
Chloride	120 mmol/l	(95-107)
Urea	3.0 mmol/l	(2.5-7.5)
Creatinine	90 µmol/l	(60- 110)

Which one of the following statements is correct?

(Please select 1 option)

- Rapid rehydration with 5% dextrose is indicated
- She has the syndrome of inappropriate antidiuretic hormone secretion (SIADH)
- She should be treated with sodium restriction

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 4 hrs 19 mins 23 secs

Question: 74 of 100

A 60-year-old woman presents with raised, erythematous lesions on the limbs and blistering in the mouth and eyes. She had been taking a number of drugs prescribed by her GP.

Which may be responsible for her presentation?

(Please select 1 option)

- Nifedipine
- Paracetamol
- Paroxetine
- Prednisolone
- Sulphasalazine

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

○	Prednisolone
◉	Sulphasalazine ✓ Correct

This is a typical case of Stevens-Johnson syndrome.

Stevens-Johnson syndrome (SJS) is an immune-complex-mediated hypersensitivity complex that is a severe expression of erythema multiforme. It is now known also as erythema multiforme major.

SJS typically involves the skin and the mucous membranes. While minor presentations may occur, significant involvement of:

- oral
- nasal
- eye
- vaginal
- urethral
- gastrointestinal (GI)
- lower respiratory tract mucous membranes

may develop in the course of the illness.

GI and respiratory involvement may progress to necrosis.

SJS is a serious systemic disorder with the potential for severe morbidity and even death.

The drugs most closely associated with causing Stevens-Johnson syndrome are:

- antibacterials
- sulfonamides
- anticonvulsants (oxicam)
- non-steroidal anti-inflammatory agents (piroxicam and tenoxicam)
- chlormezanone
- allopurinol.

Work Smart Session - MRCP Part 1

Question: 75 of 100

A 58-year-old man presents with a month history of breathlessness. He was a non-smoker.

On examination, his temperature was 36.7°C, with a respiratory rate of 20 breaths per minute and normal breath sounds to auscultation and a pulse of 92 bpm.

Arterial blood gases on air showed:

pH	7.51 (7.36 - 7.44)
pO_2	8.4 kPa (11.3 - 12.6)
pCO_2	4.0 kPa (4.7 - 6.0)

What is the most likely diagnosis?

(Please select 1 option)

- Atypical pneumonia
- Fibrosing alveolitis
- Hysterical hyperventilation
- Inhaled foreign body
- Pulmonary thromboembolism

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Arterial blood gases on air showed:

pH	7.51 (7.36 - 7.44)
pO_2	8.4 kPa (11.3 - 12.6)
pCO_2	4.0 kPa (4.7 - 6.0)

What is the most likely diagnosis?

(Please select 1 option)

- Atypical pneumonia
- Fibrosing alveolitis ✕ Incorrect answer selected
- Hysterical hyperventilation
- Inhaled foreign body
- Pulmonary thromboembolism ← This is the correct answer

This patient has a respiratory alkalosis with type 1 respiratory failure as evidenced by low pO_2 and low pCO_2.

Chronic venous thromboembolism would be the most likely explanation for this man's presentation.

Hyperventilation would be excluded by the type 1 respiratory failure, an inhaled foreign body would not produce such a picture and an atypical pneumonia would be associated with pyrexia and some clinical signs.

The differential diagnosis here is pulmonary fibrosis but basal crackles may be expected and the history is somewhat short.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 4 hrs 34 mins 37 secs

Question: 76 of 100

A 50-year-old male presented with acute respiratory failure during an episode of acute pancreatitis and was thought to have developed adult respiratory distress syndrome (ARDS).

Which of the following would support a diagnosis of ARDS?

(Please select 1 option)

- ○ High protein pulmonary oedema
- ○ High pulmonary capillary wedge pressure
- ○ Hypercapnia
- ○ Increased lung compliance
- ○ Normal chest x ray

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

developed adult respiratory distress syndrome (ARDS).

Which of the following would support a diagnosis of ARDS?

(Please select 1 option)

◉	High protein pulmonary oedema ✓ Correct
○	High pulmonary capillary wedge pressure
○	Hypercapnia
○	Increased lung compliance
○	Normal chest x ray

ARDS is characterised by:

- hypoxaemia
- reduced lung compliance
- pulmonary hypertension
- pulmonary infiltrates on the chest x ray.

There is damage to the capillary and endothelial cell linings resulting in oedema and leakage of proteins and cells into the interstitial and alveolar spaces at normal pulmonary capillary hydrostatic pressures.

Wedge pressure, unlike the high pressures seen with left ventricular failure (LVF) and pulmonary oedema, is often normal.

Hypercapnia, often a late feature of ARDS, does not distinguish from any other cause of type 2 respiratory failure.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 4 hrs 40 mins 37 secs

Question: 77 of 100

A 55-year-old nurse developed bronchospasm and urticaria twenty minutes into surgery under general anaesthesia.

The mast cell tryptase concentration confirmed an acute allergic reaction.

Later, it transpired that she had developed allergic reactions at her dentist and had developed frequent episodes of wheezing when assisting at sterile procedures.

What is the most likely diagnosis?

(Please select 1 option)

- Allergy to anaesthetic induction agents
- Allergy to local anaesthetic agents
- Latex allergy
- Pressure urticaria
- Systemic mastocytosis

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

What is the most likely diagnosis?

(Please select 1 option)

○	Allergy to anaesthetic induction agents
○	Allergy to local anaesthetic agents
◉	Latex allergy ✓ Correct
○	Pressure urticaria
○	Systemic mastocytosis

This patient developed anaphylaxis during a surgical procedure and it appears that she had problems with allergies during dental treatment and whilst assisting during sterile procedures.

This would suggest that she is allergic to latex rather than induction agents or local anaesthesia as latex would be present in all three of the above procedures.

Systemic mastocytosis is a disease which usually affects the elderly and is associated with:

- urticaria pigmentosa
- diarrhoea
- hypotension
- sclerotic bone changes and
- mast cell infiltration of organs such as spleen, liver and kidneys.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 4 hrs 42 mins 20 secs

Question: 78 of 100

A 42-year-old woman presents with an acute attack of asthma. She is able to speak in short sentences.

Her respiratory rate is 28 breaths per minute and the peak expiratory flow rate 120 L/min (predicted 480 L/min.

What is the most appropriate treatment for this patient?

(Please select 1 option)

○	Intravenous aminophylline
○	Intravenous salbutamol
○	Nebulised salbutamol
○	Oral salbutamol
○	Oral theophylline

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

A 42-year-old woman presents with an acute attack of asthma. She is able to speak in short sentences.

Her respiratory rate is 28 breaths per minute and the peak expiratory flow rate 120 L/min (predicted 480 L/min.

What is the most appropriate treatment for this patient?

(Please select 1 option)

○	Intravenous aminophylline
○	Intravenous salbutamol
◉	Nebulised salbutamol ✓ Correct
○	Oral salbutamol
○	Oral theophylline

This patient has features of acute severe asthma, and should be given oxygen, steroids and nebulised salbutamol as immediate treatment.

Although the PFR is less than 33% of predicted normal (feature of life-threatening attack), we do not know what her previous best is. It could be low, for example, 240 L/min.

If it had been a life-threatening attack, nebulised ipratropium and intravenous aminophylline, salbutamol or terbutaline should be given. The guidelines do not specify a preference.

This is another clue that the answer should be nebulised salbutamol.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 4 hrs 43 mins 42 secs

Question: 79 of 100

A 72-year-old man presents with an episode of collapse.

He has had two similar episodes recently, each lasting about one minute. Four years ago he suffered an anterior myocardial infarction.

On examination he was orientated and symptom-free with a regular pulse rate of 80 bpm, BP 140/80 mmHg and the apex beat was displaced to the left. There was an apical systolic murmur.

There were no signs of trauma. ECG showed sinus rhythm, Q waves and ST segment elevation anteriorly without reciprocal depression.

What is the diagnosis?

(Please select 1 option)

- Acute anterior myocardial infarction
- Cerebrovascular accident
- Epileptic seizure
- Pulmonary embolism
- Ventricular tachycardia

Submit answer | Skip question | Tag Question | Remove question

displaced to the left. There was an apical systolic murmur.

There were no signs of trauma. ECG showed sinus rhythm, Q waves and ST segment elevation anteriorly without reciprocal depression.

What is the diagnosis?

(Please select 1 option)

○	Acute anterior myocardial infarction
◉	Cerebrovascular accident ✗ Incorrect answer selected
○	Epileptic seizure
○	Pulmonary embolism
○	Ventricular tachycardia ← This is the correct answer

The electrocardiogram is suggestive of a left ventricular (LV) aneurysm, which has a tendency for both a malignant arrhythmogenic focus and also for left ventricular thrombus.

The brief episode of loss of consciousness with no residual neurology makes the diagnosis for cerebral embolism unlikely.

The story is more suggestive of a ventricular tachycardia (VT) and would suggest further investigations. Prolonged heart rhythm monitoring and an echo are recommended.

If VT is proven then he should be on amiodarone and the indication for an automated implantable cardioverter/defibrillator strongly considered if the overall LV function is reduced.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

On examination, her blood pressure is 130/70 mmHg, pulse 95 bpm, respiratory rate 24/min and O_2 saturation 99% on air.

Intravenous hydrocortisone and intramuscular antihistamine have been given.

What is the next most appropriate step in the management of this patient?

(Please select 1 option)

○	Inhaled adrenaline
○	Intramuscular adrenaline
○	Intravenous adrenaline
◉	Observe ✓ Correct
○	Subcutaneous adrenaline

Where there is a history of a typical allergic reaction as here current United Kingdom resuscitation guidelines suggest adrenaline if there is:

- stridor
- wheeze
- respiratory distress or
- clinical evidence of shock.

A literature review in the BMJ includes a copy of the algorithm and a discussion of the evidence for adrenaline. BMJ 2003;327:1332-1335

Next question | Tag Question | Remove question

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 34 mins 16 secs

Question: 8 of 100

A 23-year-old man with known peanut allergy presented to the Emergency Department with anaphylaxis. He has a swollen face and lips. His BP is 90/60 mmHg, pulse 110 bpm and he is wheezy.

Which of the following formulations of adrenaline should be given?

(Please select 1 option)

- 0.5 ml of 1:10000 adrenaline IM
- 0.5 ml of 1:1000 adrenaline IM
- 5 ml of 1:1000 adrenaline IM
- 10 ml of 1:10000 adrenaline IV
- Nebulised adrenaline

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 4 hrs 46 mins 7 secs

Question: 80 of 100

A 59-year-old man who was active all his life develops sudden severe anterior chest pain that radiates to his back. Within minutes, he is unconscious.

He has a history of hypertension, but a recent treadmill test had revealed no evidence for cardiac disease.

Which of the following is the most likely diagnosis?

(Please select 1 option)

- Acute myocardial infarction (MI)
- Group A streptococcal infection
- Pulmonary embolus
- Right middle cerebral artery embolus
- Tear in the aortic intima

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 4 hrs 47 mins 41 secs

Question: 80 of 100

A 59-year-old man who was active all his life develops sudden severe anterior chest pain that radiates to his back. Within minutes, he is unconscious.

He has a history of hypertension, but a recent treadmill test had revealed no evidence for cardiac disease.

Which of the following is the most likely diagnosis?

(Please select 1 option)

○	Acute myocardial infarction (MI)
○	Group A streptococcal infection
○	Pulmonary embolus
○	Right middle cerebral artery embolus
◉	Tear in the aortic intima ✓ Correct

The history is typical of aortic dissection.

All the others could cause sudden collapse but not with acute chest pain radiating to the back in the presence of a recent normal exercise test.

Acute MI is possible but not the most likely.

Next question

Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 4 hrs 52 mins 38 secs

Question: 82 of 100

A 30-year-old man presents with a history of transient loss of consciousness and palpitations. His ECG shows ventricular tachycardia (VT).

Which of the following treatments should be avoided?

(Please select 1 option)

- Adenosine
- Amiodarone
- DC cardioversion
- Flecainide
- Verapamil

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Which of the following treatments should be avoided?

(Please select 1 option)

○	Adenosine
○	Amiodarone
○	DC cardioversion
○	Flecainide
◉	Verapamil ✓ Correct

If there were 'killer' questions (questions that if a candidate got wrong they would certainly fail the exam) in the MRCP examination then this would be one of them.

Verapamil should be avoided in cases of VT because it can cause a catastrophic fall in blood pressure.

Adenosine is useful diagnostically when the diagnosis of regular wide complex tachycardia is in doubt.

Amiodarone is a useful antiarrhythmic agent though its use acutely is limited by its irritant nature on veins.

DC cardioversion is probably the treatment of choice in this case.

Flecainide is a good antiarrhythmic and would be indicated in patients without left ventricular (LV) failure (it is associated with an increased risk of death in such cases).

Flecainide is widely used for atrial fibrillation.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 4 hrs 53 mins 58 secs

Question: 83 of 100

A 30-year-old man presents to the Emergency Department with a history of drug overdose.

He is known to be repeatedly admitted with similar episodes of self-harm. On this occasion he is drowsy and has prominent hypersalivation.

Which of the following agents, found on his person, is the likely cause?

(Please select 1 option)

- Chlormethiazole
- Cocaine
- Dosulepin
- L-dopa
- Solvent cannister

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Shop

(Please select 1 option)

○	Chlormethiazole ← This is the correct answer
○	Cocaine
◉	Dosulepin ✕ Incorrect answer selected
○	L-dopa
○	Solvent cannister

Hypersalivation is seen with:

- parasympathomimetic agents
- insecticides
- arsenic
- strychnine
- chlormethiazole
- clozapine

and others.

Solvent abuse may cause an acneiform rash around the buccal cavity.

Cocaine abuse leads to hypertension and nasal septum perforation.

The other agents are anticholinergic and would cause dry mouth in overdose.

Next question

Remove Tag Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

In considering the management of convulsions select the correct statement from the list below.

(Please select 1 option)

◉	Hypoglycaemia should always be considered. ✓ Correct
○	If the fit lasts longer than five minutes, then PR diazepam should be given.
○	Paraldehyde is best given intramuscularly.
○	Phenobarbitone is a useful therapy in school age children.
○	When associated with fever, antibiotics should always be given to cover the possibility of meningitis.

Status epilepticus is defined as continuous convulsion lasting longer than 30 minutes, or the occurrence of serial convulsions between which there is no return of consciousness. It may be generalised (tonic clonic, absent) or partial (simple, complex, or with secondary generalisation). Generalised tonic clonic seizures predominate. There are 3 major sub-types:

- Prolonged febrile seizures.
- Idiopathic status epilepticus (no underlying central nervous system [CNS] lesion or insult).
- Symptomatic (long-standing neurological disorder or metabolic abnormality).

The most common cause in a child less than 3 years is a prolonged febrile seizure. Sleep deprivation and drug withdrawal can also precipitate it.

The relationship between neurological outcome and duration of status epilepticus is unknown in children and adults. In the animal model, 60 minutes of constant seizure activity is associated with pathological changes, even when metabolic homeostasis is maintained.

Cell death thus results in increased metabolic demands from continually discharging neurones. Vulnerable areas include the hippocampus, the mid to low cerebellum, middle cortical areas, and thalamus.

Approximately 20 minutes of status epilepticus produces regional oxygen sufficiency deficiency promoting cell damage and necrosis. This is, therefore, used as the threshold in children.

Initial management begins with ABC. Hypoglycaemia should be excluded (if present 5ml/kg of 10% dextrose is given by IV infusion), and blood obtained for full blood count, electrolytes including calcium and magnesium, glucose, creatinine, anticonvulsant levels. Blood and urine may be

Paraldehyde is best given intramuscularly.

Phenobarbitone is a useful therapy in school age children.

When associated with fever, antibiotics should always be given to cover the possibility of meningitis.

Status epilepticus is defined as continuous convulsion lasting longer than 30 minutes, or the occurrence of serial convulsions between which there is no return of consciousness. It may be generalised (tonic clonic, absent) or partial (simple, complex, or with secondary generalisation). Generalised tonic clonic seizures predominate. There are 3 major sub-types:

- Prolonged febrile seizures.
- Idiopathic status epilepticus (no underlying central nervous system [CNS] lesion or insult).
- Symptomatic (long-standing neurological disorder or metabolic abnormality).

The most common cause in a child less than 3 years is a prolonged febrile seizure. Sleep deprivation and drug withdrawal can also precipitate it.

The relationship between neurological outcome and duration of status epilepticus is unknown in children and adults. In the animal model, 60 minutes of constant seizure activity is associated with pathological changes, even when metabolic homeostasis is maintained.

Cell death thus results in increased metabolic demands from continually discharging neurones. Vulnerable areas include the hippocampus, the mid to low cerebellum, middle cortical areas, and thalamus.

Approximately 20 minutes of status epilepticus produces regional oxygen sufficiency deficiency promoting cell damage and necrosis. This is, therefore, used as the threshold in children.

Initial management begins with ABC. Hypoglycaemia should be excluded (if present 5ml/kg of 10% dextrose is given by IV infusion), and blood obtained for full blood count, electrolytes including calcium and magnesium, glucose, creatinine, anticonvulsant levels. Blood and urine may be obtained for toxicology. Arterial blood gases should be done, and consideration given to lumbar puncture.

First line anticonvulsant therapy would be Lorazepam/Diazepam given IV if possible. If seizures persist then phenytoin may be given as a loading dose followed by an infusion. Phenobarbitone may be used as first line in infants. Paraldehyde can be given as a dilute solution intravenously, or administered rectally or IM. The latter two routes can produce tissue damage and sloughing, so these should be reserved for exceptional circumstances.

Copyright © 2002 Dr Colin Melville

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 5 hrs 3 mins 4 secs

Question: 85 of 100

Which of the following concerning the use of intravenous bicarbonate in cardiorespiratory arrest is correct?

(Please select 1 option)

- Exacerbates intracellular acidosis
- Has a positive inotropic effect on ischaemic myocardium
- Improves oxygen release to the tissues
- Increases cerebral blood flow
- Reduces pre-existent hyperkalaemia

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 5 hrs 6 mins 1 secs

Question: 85 of 100

Which of the following concerning the use of intravenous bicarbonate in cardiorespiratory arrest is correct?

(Please select 1 option)

○	Exacerbates intracellular acidosis ← This is the correct answer
◉	Has a positive inotropic effect on ischaemic myocardium ✕ Incorrect answer selected
○	Improves oxygen release to the tissues
○	Increases cerebral blood flow
○	Reduces pre-existent hyperkalaemia

Bicarbonate therapy can increase extracellular pH only if the carbon dioxide (CO_2) produced can be removed by adequate ventilation.

Indeed, if hypercapnia occurs then as CO_2 crosses cell membranes easily, intracellular pH may decrease even further with further deterioration of cellular function.

Bicarbonate has a negative inotropic effect, reducing cerebral blood flow; it shifts the oxygen dissociation curve to the left, inhibiting oxygen release to tissues.

Next question

Tag Question

Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 5 hrs 6 mins 1 secs

Question: 86 of 100

Which of the following statements concerning the treatment of acute myocardial infarction (MI) is correct?

(Please select 1 option)

- A pansystolic murmur developing within the first 24 hours does not require further investigation
- Dipyridamole therapy reduces reinfarction within the first year
- Heparin is beneficial if given with streptokinase
- Prophylactic lidocaine given in the first 48 hours is effective in preventing ventricular fibrillation
- Treatment with a dihydropyridine calcium antagonist is associated with increased cardiovascular mortality

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 5 hrs 7 mins 35 secs

Question: 86 of 100

Which of the following statements concerning the treatment of acute myocardial infarction (MI) is correct?

(Please select 1 option)

○	A pansystolic murmur developing within the first 24 hours does not require further investigation
◉	Dipyridamole therapy reduces reinfarction within the first year ✕ Incorrect answer selected
○	Heparin is beneficial if given with streptokinase
○	Prophylactic lidocaine given in the first 48 hours is effective in preventing ventricular fibrillation
○	Treatment with a dihydropyridine calcium antagonist is associated with increased cardiovascular mortality ← This is the correct answer

GISSI II revealed no survival advantage of heparin plus streptokinase in acute MI compared with streptokinase alone.

ISIS II revealed that dihydropyridine calcium antagonists were associated with increased cardiovascular risk after MI.

Dipyridamole does not reduce risk.

A newly discovered pansystolic murmur may signify acquired mitral regurgitation (MR) or ventricular septal defect (VSD).

Next question

Remove Tag

Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 5 hrs 7 mins 35 secs

Question: 87 of 100

Which of the following features would be expected in acute tubular necrosis?

(Please select 1 option)

- Creatinine clearance would be expected to be normal one year after the initial insult
- Heavy proteinuria on urinalysis
- Red cell casts on urinalysis
- Urine plasma osmolality ratio is more than 1:1
- Urine sodium concentration greater than 30 mmol/l

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 5 hrs 9 mins 43 secs

Question: 87 of 100

Which of the following features would be expected in acute tubular necrosis?

(Please select 1 option)

○	Creatinine clearance would be expected to be normal one year after the initial insult
○	Heavy proteinuria on urinalysis
◉	Red cell casts on urinalysis ✕ Incorrect answer selected
○	Urine plasma osmolality ratio is more than 1:1
○	Urine sodium concentration greater than 30 mmol/l ← This is the correct answer

Red cell casts suggest nephritis and normalisation of the creatinine clearance occurs in only 40% of cases one year later.

Proteinuria, usually mild, is common with granular casts found on urinalysis.

The urine sodium concentration is typically above 30 mmol/l and osmolality ratio <1:1.

Further reading:
Acute Tubular Necrosis eMedicine

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 5 hrs 9 mins 43 secs

Question: 88 of 100

Which of the following would be expected features of a left posterior cerebral artery occlusion?

(Please select 1 option)

- A right homonymous hemianopia
- Decerebrate state
- Internuclear ophthalmoplegia
- Pure aphasia (i.e. without alexia)
- Wernicke's aphasia

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 5 hrs 17 mins 31 secs

Question: 88 of 100

Which of the following would be expected features of a left posterior cerebral artery occlusion?

(Please select 1 option)

◉	A right homonymous hemianopia ✓ Correct
○	Decerebrate state
○	Internuclear ophthalmoplegia
○	Pure aphasia (i.e. without alexia)
○	Wernicke's aphasia

Internuclear ophthalmoplegia is typical of multiple sclerosis.

Wernicke's aphasia and Pure aphasia (i.e. without alexia) are middle cerebral artery.

Decerebrate state is most likely a pontine lesion.

Other possible findings in posterior left cerebral artery occlusion are:

- cortical blindness
- visual hallucinations
- thalamic syndrome
- Claude's and Weber's syndromes.

Next question

Tag Question | Remove question

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 5 hrs 17 mins 31 secs

Question: 89 of 100

A 70-year-old man was admitted with pallor, light-headedness and loss of energy.

On the day prior to admission he had reported loose dark stools.

Examination revealed a pulse of 110 per minute and a blood pressure of 106/70 mmHg.

Investigations revealed:

Haemoglobin	7.2 g/dl	(14-18)
MCV	72 fl	(80-96)
White cell count	11.3 x 10^9/l	(4-11)
Platelet count	480 x 10^9/l	(150-400)

What is the most appropriate next step in his management?

(Please select 1 option)

- ○ Barium meal
- ○ Blood transfusion
- ○ Endoscopy
- ○ Parenteral iron infusion
- ○ Proton pump inhibitor therapy

Platelet count	480 x 10^9/l	(150-400)

What is the most appropriate next step in his management?

(Please select 1 option)

○	Barium meal
○	Blood transfusion ← This is the correct answer
◉	Endoscopy ✕ Incorrect answer selected
○	Parenteral iron infusion
○	Proton pump inhibitor therapy

There is only one answer here and that is blood transfusion.

He has clearly had a major gastrointestinal (GI) bleed since he presents with symptoms of shock with a high resting heart rate and lowish blood pressure the day after what sounds like melaena. What is more he has a significant microcytic anaemia.

He should be resuscitated with blood transfusion and then sent for upper GI endoscopy.

A barium meal will not help a bleeding vessel.

Parenteral iron is for chronic anaemia not acute bleeds and proton pump inhibitors, although widely used, have no supportive evidence and are nowhere near as important as giving blood to this man.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 35 mins 41 secs

Question: 8 of 100

A 23-year-old man with known peanut allergy presented to the Emergency Department with anaphylaxis. He has a swollen face and lips. His BP is 90/60 mmHg, pulse 110 bpm and he is wheezy.

Which of the following formulations of adrenaline should be given?

(Please select 1 option)

○	0.5 ml of 1:10000 adrenaline IM
◉	0.5 ml of 1:1000 adrenaline IM ✓ Correct
○	5 ml of 1:1000 adrenaline IM
○	10 ml of 1:10000 adrenaline IV
○	Nebulised adrenaline

"For adults, a dose of 0.5 mL adrenaline 1:1000 solution (500 micrograms) should be administered intramuscularly, and repeated after about five minutes in the absence of clinical improvement or if deterioration occurs after the initial treatment especially if consciousness becomes - or remains - impaired as a result of hypotension. In some cases several doses may be needed, particularly if improvement is transient."
Resuscitation Council UK.

Adult EpiPen which allergy sufferers can carry with them contains 0.3 mg adrenaline in a 1:1000 dilution for intramuscular (IM) injection.

Next question | Tag Question | Remove question

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 35 mins 41 secs

Question: 9 of 100

A 55-year-old man presented to the emergency department with sudden breathlessness.

He is sweaty and obviously short of breath. He is a smoker with a past history of hypertension. There are crackles on inspiration at both his lung bases and his CXR shows upper lobe venous diversion and peri-hilar shadowing.

His ECG shows sinus tachycardia only and his cardiac enzymes, when they return the next day, are normal. His symptoms resolved quickly with oxygen and furosemide.

Which of the following conditions is the most likely explanation of this presentation?

(Please select 1 option)

- ○ Hypertrophic obstructive cardiomyopathy
- ○ Myocardial infarction
- ○ Phaeochromocytoma
- ○ Pulmonary embolism
- ○ Renal artery stenosis

Submit answer | Skip question | Tag Question | Remove question

Work Smart Session - MRCP Part 1

Time taken: 5 hrs 21 mins 28 secs

Question: 90 of 100

A 16-year-old girl with obesity was referred with abdominal swelling and mild ankle oedema.

On examination the blood pressure was 140/90 mmHg.

Investigations revealed:

Haemoglobin	10.5 g/dl	(11.5-16.5)
Serum biochemistry	Normal	
Serum albumin	34 g/l	(37-49)
Urine dipstick	Proteinuria +	

Which is the most appropriate investigation that you would request next for this patient?

(Please select 1 option)

- 24 hour urinary protein estimation
- Abdominal ultrasound
- Plasma protein electrophoresis
- Urinary albumin: creatinine ratio
- Urinary B-human chorionic gonadotrophin test (B-HCG)

Submit answer | Skip question | Tag Question | Remove question

Haemoglobin	10.5 g/dl	(11.5-16.5)
Serum biochemistry	Normal	
Serum albumin	34 g/l	(37-49)
Urine dipstick	Proteinuria +	

Which is the most appropriate investigation that you would request next for this patient?

(Please select 1 option)

○	24 hour urinary protein estimation
◉	Abdominal ultrasound ✕ Incorrect answer selected
○	Plasma protein electrophoresis
○	Urinary albumin: creatinine ratio
○	Urinary B-human chorionic gonadotrophin test (B-HCG) ← This is the correct answer

This young girl has been 'gaining weight', has abdominal swelling and ankle oedema. She is hypertensive and has a mild anaemia with proteinuria.

These signs should 'ring a bell' suggesting a concealed pregnancy with pre-eclampsia.

The most relevant investigation would be a pregnancy test - urinary B-HCG.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 5 hrs 24 mins 31 secs

Question: 91 of 100

A 70-year-old female is admitted 12 hours after taking an overdose of aspirin.

Investigations revealed:

Serum sodium	138 mmol/l	(137-144)
Serum potassium	5.9 mmol/l	(3.5-4.9)
Serum bicarbonate	14 mmol/l	(20-28)
Serum urea	18.1 mmol/l	(2.5-7.5)
Serum creatinine	238 mol/l	(60-110)
Serum salicylate	1120 mg/l	(8)

What is the most appropriate treatment of this patient?

(Please select 1 option)

- Haemodialysis
- Haemofiltration
- Intravenous sodium bicarbonate
- Peritoneal dialysis
- Urine alkalinisation

Submit answer | Skip question | Tag Question | Remove question

Serum creatinine	238 mol/l	(60-110)
Serum salicylate	1120 mg/l	(8)

What is the most appropriate treatment of this patient?

(Please select 1 option)

- ◉ Haemodialysis ✓ Correct
- ○ Haemofiltration
- ○ Intravenous sodium bicarbonate
- ○ Peritoneal dialysis
- ○ Urine alkalinisation

This patient is at major risk of aspirin toxicity as reflected by the excessive aspirin concentration and appears to have developed acute renal failure - she is acidotic with an elevated potassium.

Bicarbonate is recommended as a supportive therapy but in this patient, haemodialysis is the treatment of choice. The latter is advised when the plasma-salicylate concentration is greater than 700 mg/litre (5.1 mmol/litre) or in the presence of severe metabolic acidosis as recommended within the BNF poisons section.

There is nothing wrong with haemofiltration it just removes the toxin more slowly.

Read more (very detailed) about haemofiltration vs. haemodialysis in poisoning (pdf).

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 5 hrs 27 mins 26 secs

Question: 92 of 100

A 24-year-old man presented twelve hours after an overdose of dihydrocodeine 1.2 g and paracetamol 30 g.

He had pinpoint pupils, a Glasgow coma scale (GCS) score of 14 and a blood pressure of 100/60 mmHg.

Which one of the following is the most appropriate management?

(Please select 1 option)

○	500ml of 10% glucose intravenously over four hours.
○	Intravenous flumazenil.
○	Intravenous N-acetylcysteine.
○	Intravenous naloxone.
○	Oral activated charcoal.

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Question: 92 of 100

A 24-year-old man presented twelve hours after an overdose of dihydrocodeine 1.2 g and paracetamol 30 g.

He had pinpoint pupils, a Glasgow coma scale (GCS) score of 14 and a blood pressure of 100/60 mmHg.

Which one of the following is the most appropriate management?

(Please select 1 option)

○	500ml of 10% glucose intravenously over four hours.
○	Intravenous flumazenil.
◉	Intravenous N-acetylcysteine. ✓ Correct
○	Intravenous naloxone.
○	Oral activated charcoal.

This patient's GCS is reasonable and the opiate-like effects seem minimal (no evidence of respiratory depression).

However, this patient has received a hefty dose of paracetamol conferring a high risk of hepatic toxicity. The 12 hour delay makes the absorptive effects of charcoal limited and although it would be useful as gastric emptying may be delayed it is not as important in this patient as the paracetamol antidote.

Even though the paracetamol level is not provided, he should be treated with N-acetylcysteine without delay.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 5 hrs 30 mins 32 secs

Question: 93 of 100

A 44-year-old male with Child's grade C cirrhosis presented with haematemesis.

Which one of the following drugs, administered intravenously, would be the most appropriate, immediate treatment?

(Please select 1 option)

○	Isosorbide dinitrate
○	Omeprazole
○	Propranolol
○	Somatostatin
○	Tranexamic acid

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

A 44-year-old male with Child's grade C cirrhosis presented with haematemesis.

Which one of the following drugs, administered intravenously, would be the most appropriate, immediate treatment?

(Please select 1 option)

○	Isosorbide dinitrate
○	Omeprazole
○	Propranolol
◉	Somatostatin ✓ Correct
○	Tranexamic acid

The suggestion is that this patient is at particularly high risk of oesophageal varices.

Child's classification of cirrhosis is a points scale, based upon ascites/bilirubin etcetera, reflecting prognosis. The grades depend on the points scored from A-C, with C reflecting greatest risk.

Somatostatin acts to reduce portal pressures and has been demonstrated to be as effective as endoscopy at controlling variceal bleeding in the acute setting.

Beta-blockers can be used as oral prophylaxis for oesophageal varices.

Intravenous omeprazole has also been shown to be effective in reducing mortality in gastrointestingal haemorrhage of any cause (NEJM 2002) but somatostatin may be expected to be superior for the above patient.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 5 hrs 31 mins 45 secs

Question: 94 of 100

A 22-year-old woman complains of haemoptysis, abdominal pains and pyrexia for a month.

She is admitted to hospital and found to be apyrexial and not distressed. There are numerous crusted, linear lesions on her forearms.

What is the most likely diagnosis?

(Please select 1 option)

○	Acute intermittent porphyria
○	Factitious disorder
○	Systemic lupus erythematosus
○	TB
○	Wegener's granulomatosis

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 5 hrs 34 mins 2 secs

Question: 94 of 100

A 22-year-old woman complains of haemoptysis, abdominal pains and pyrexia for a month.

She is admitted to hospital and found to be apyrexial and not distressed. There are numerous crusted, linear lesions on her forearms.

What is the most likely diagnosis?

(Please select 1 option)

○	Acute intermittent porphyria
◉	Factitious disorder ✓ Correct
○	Systemic lupus erythematosus
○	TB
○	Wegener's granulomatosis

The history is very vague and the patient has no clinical features other than a rash which sounds typical of dermatitis artifacta.

The crusted lesions on the forearms suggest artefacta as this is the most typical site for these lesions.

Porphyria may be expected to have vesicles on sun exposed regions, face, arms and legs.

Next question | Tag Question | Remove question

Work Smart Session - MRCP Part 1

Time taken: 5 hrs 34 mins 2 secs

Question: 95 of 100

Which of the following is correct in malignant hyperpyrexia?

(Please select 1 option)

- A mortality rate of 20% may be expected
- Elevation of serum creatine kinase and myoglobinuria is diagnostic
- Muscle biopsy may be histologically normal
- The only available specific treatment is sodium dantrolene, which has a neutral pH
- The predisposing gene is thought to be on chromosome 9

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 5 hrs 35 mins 8 secs

Question: 96 of 100

An 18-year-old woman is admitted after taking drugs at a night club.

Which of the following features suggest she had taken Ecstasy (MDMA)?

(Please select 1 option)

○	A pyrexia of 40°C
○	Hypernatraemia
○	Hypokalaemia
○	Metabolic acidosis
○	Respiratory depression

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 5 hrs 35 mins 40 secs

Question: 96 of 100

An 18-year-old woman is admitted after taking drugs at a night club.

Which of the following features suggest she had taken Ecstasy (MDMA)?

(Please select 1 option)

◉	A pyrexia of 40°C ✓ Correct
○	Hypernatraemia
○	Hypokalaemia
○	Metabolic acidosis
○	Respiratory depression

Features of the amphetamine MDMA abuse include:

- hyponatraemia
- tachycardia
- hyperventilation
- hyperthermia.

Next question

Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 5 hrs 35 mins 40 secs

Question: 97 of 100

Which of the following is currently recommended as the drug of choice in treating refractory ventricular fibrillation or pulseless ventricular tachycardia?

(Please select 1 option)

- Adenosine
- Amiodarone
- Bretylium
- Lidocaine
- Magnesium

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 5 hrs 36 mins 20 secs

Question: 97 of 100

Which of the following is currently recommended as the drug of choice in treating refractory ventricular fibrillation or pulseless ventricular tachycardia?

(Please select 1 option)

○	Adenosine
○	Amiodarone ← This is the correct answer
○	Bretylium
○	Lidocaine
◉	Magnesium ✕ Incorrect answer selected

300 mg of amiodarone made up to 20 ml with 5% dextrose given as an intravenous bolus is the drug of choice.

100 mg of lidocaine may be given intravenously when amiodarone is unavailable.

Historically 5 mg/Kg of bretylium was given, but it is no longer recommended.

Next question

Remove Tag

Remove question

© 2011 BMJ Publishing Group Ltd. All rights reserved. Terms and conditions Privacy policy

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 5 hrs 36 mins 20 secs

Question: 98 of 100

In adult basic life support the correct ratio of chest compressions to ventilations is:

(Please select 1 option)

○	5 to 1
○	8 to 1
○	10 to 1
○	15 to 2
○	30 to 2

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 5 hrs 36 mins 47 secs

Question: 98 of 100

In adult basic life support the correct ratio of chest compressions to ventilations is:

(Please select 1 option)

○	5 to 1
○	8 to 1
○	10 to 1
○	15 to 2
◉	30 to 2 ✓ Correct

15 compressions to two breaths was the recommended ratio regardless of the number of rescuers performing basic life support, but the recent guidelines now suggest 30:2.

Next question

Tag Question

Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 5 hrs 36 mins 47 secs

Question: 99 of 100

In most cardiac arrest situations 1mg of adrenaline (epinephrine) is given intravenously every three minutes.

What is the correct volume and concentration of the adrenaline?

(Please select 1 option)

○	0.1 ml of 1 in 100
○	1 ml of 1 in 1000
○	10 ml of 1 in 1000
○	1 ml of 1 in 10,000
○	10 ml of 1 in 10,000

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 5 hrs 37 mins 17 secs

Question: 99 of 100

In most cardiac arrest situations 1mg of adrenaline (epinephrine) is given intravenously every three minutes.

What is the correct volume and concentration of the adrenaline?

(Please select 1 option)

○	0.1 ml of 1 in 100
◉	1 ml of 1 in 1000 ✕ Incorrect answer selected
○	10 ml of 1 in 1000
○	1 ml of 1 in 10,000
○	10 ml of 1 in 10,000 ← This is the correct answer

A 1 mg dose of adrenaline (epinephrine) would be administered with 0.1 ml of 1 in 100, 1 ml of 1 in 1000 and 10 ml of 1 in 10,000.

However, 10 ml of 1 in 10,000 is the recommended dose and concentration and is considered the optimum volume of adrenaline during cardiac arrest, and is recommended by the UK Research Council.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Question: 9 of 100

A 55-year-old man presented to the emergency department with sudden breathlessness.

He is sweaty and obviously short of breath. He is a smoker with a past history of hypertension. There are crackles on inspiration at both his lung bases and his CXR shows upper lobe venous diversion and peri-hilar shadowing.

His ECG shows sinus tachycardia only and his cardiac enzymes, when they return the next day, are normal. His symptoms resolved quickly with oxygen and furosemide.

Which of the following conditions is the most likely explanation of this presentation?

(Please select 1 option)

○	Hypertrophic obstructive cardiomyopathy
○	Myocardial infarction
○	Phaeochromocytoma
◉	Pulmonary embolism ✕ Incorrect answer selected
○	Renal artery stenosis ← This is the correct answer

Flash pulmonary oedema in someone with a history of hypertension, especially those suspected of being arteriopaths such as smokers, should raise the possibility of renal artery stenosis.

Further reading:
Renal artery stenosis BMJ 2000;320:1124-1127

Next question | Tag Question | Remove question

Is continuous haemofiltration as good as haemodialysis in eliminating poisons?

Nick Bateman

NPIS Edinburgh
Royal infirmary of Edinburgh
Scotland

NPIS Edinburgh

Acknowledgements

Professor Albert Jaeger
Service de Réanimation Médicale et Urgences Médicales, Strasbourg

Dr Barbara Groszek
Department of Clinical Toxicology, Jagiellonian University, Kraków

Dr Jane Goddard
Consultant in Renal Medicine, Royal Infirmary of Edinburgh

http://www.show.scot.nhs.uk/spib
click on documents

NPIS Edinburgh

"A scientific paper is a mythical reconstruction of what happened."

Professor Ian Purchase

Fraud, Error and Gamesmanship in Clinical Toxicology
The British Toxicological Society
Paton Prize lecture, 2004

NPIS Edinburgh

Background

- The physicochemical basis for dialysis was first described by the Scottish chemist Thomas Graham in 1854.
- In his paper "On Osmotic Force" he described the movements of various solutes of differing concentrations through a membrane he had fashioned from an ox bladder.

NPIS Edinburgh

Background

- The first artificial kidney was created in 1913,
- First one to be successful developed 1943.
- This involved a rotating drum of spiral-shaped cellophane tubing which contained a patient's blood, immersed in a dialysate bath.
- A parallel plate dialyzer was developed in 1948, and the first hollow fiber kidney was created in 1965.

NPIS Edinburgh

THE NEW ENGLAND JOURNAL OF MEDICINE

Vol. 253 No. 6 THERAPY FOR SALICYLISM — SCHREINER ET AL.

SPECIFIC THERAPY FOR SALICYLISM*

GEORGE E. SCHREINER, M.D.,† LEONARD B. BERGAN, M.D.,‡ JOHN GRIFFIN, M.D.,§ AND JEAN PETZ, M.D.¶

- 1957
- 2 cases of salicylate poisoning treated by haemodialysis

NPIS Edinburgh

First use of haemodialysis in aspirin poisoning,1957

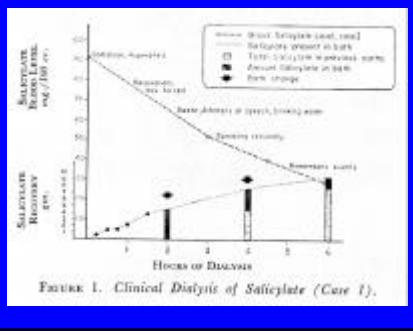


FIGURE 1. *Clinical Dialysis of Salicylate (Case 1).*

Twin-coil artificial kidney, 1960s

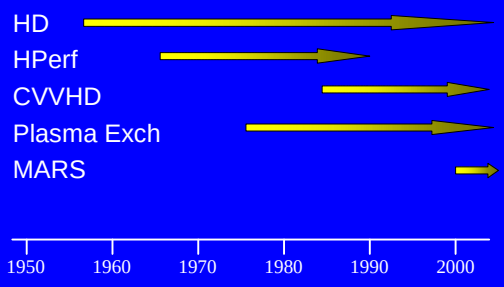
Extracorporeal elimination techniques

- Haemodialysis (HD)
- Haemofiltration (HF)
- Haemodiafiltration (HDF)

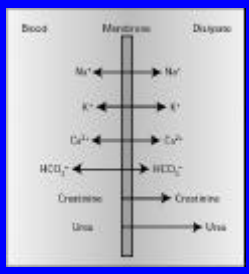
- *Haemoperfusion (HP)*
- *Plasma exchange (PE)*
- *Molecular adsorbent recirculating system (MARS)*

NPIS Edinburgh

Perfusion elimination techniques: History

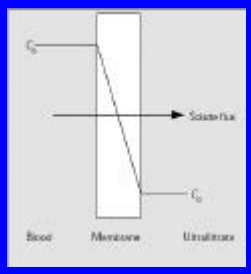


Dialysis



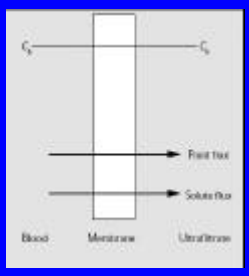
- dialysis is the process of separating elements in a solution by diffusion across a semi-permeable membrane, down a concentration gradient
- this is the principal process for removing small molecules and for repletion of the bicarbonate deficit of metabolic acidosis

Haemodialysis (HD)



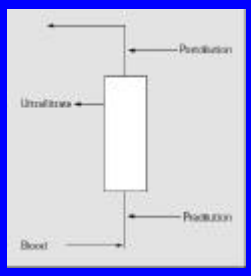
- molecules small enough to pass through the dialysis membrane diffuse down a concentration gradient, from a higher plasma concentration (C_b) to a lower dialysate concentration (C_d)

Haemofiltration (HF)



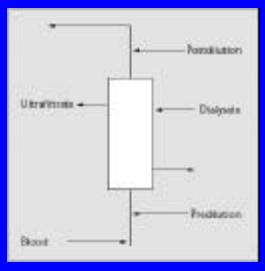
- haemofiltration achieves molecular clearance by convective transport (the solvent drag effect) through the membrane, with pore dimensions exceeding those in conventional dialysis treatment, by removing plasma water and toxin.

Fluid replacement in haemofiltration



- molecular clearance is achieved by removing large volumes of plasma water (contains dissolved solutes)
- the removed fluid must be replaced and is infused into the extracorporeal circuit after the blood leaves the filter (postdilution)

Haemodiafiltration (HDF)



- diffusive transport is added to haemofiltration to augment the clearance of solutes (usually small molecules)
- solute clearance is accomplished by circulating dialysate in the dialysate-ultrafiltrate compartment

Continuous renal replacement therapies

- CAVH, Continuous arterio- venous haemodialysis
- CVVH, Continuous veno- venous haemodialysis
- CVVHDF, Continuous veno- venous haemodialysis filtration

NPIS Edinburgh

Continuous renal replacement therapies: CAVH, CVVH, CVVHDF

- These methods allow continuous removal of smaller volume of fluid, and toxins, at low blood flow rates.
- Larger molecules up to 50 000 daltons may be removed in filtration.
- Techniques are better tolerated in haemodynamically unstable patients.
- In general flow, and thus extraction rates, lower than traditional techniques.

NPIS Edinburgh

High-performance haemodialysis

- High-efficiency dialysis – arbitrarily defined by urea clearance of >210 ml/min *(reflects capacity to remove urea)*
- High-flux dialysis – arbitrarily defined as a beta$_2$-microglobulin clearance of > 20 ml/min, is achieved using a high flux membrane *(reflects capacity to remove larger molecules)*

NPIS Edinburgh

High-efficiency and high-flux haemodialysis, continuous therapies

- These new modalities shorten the time of haemodialysis and have ability to remove "middle" molecules.
- The use of high-efficiency and high-flux membranes and continuous therapies steadily has increased over the past 10 years.
- Since reports of their effectiveness in renal replacement therapy, they have also been used for the treatment of poisoning.

NPIS
Edinburgh

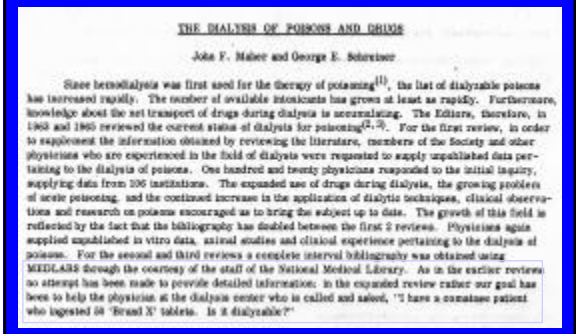
Haemodialysis or Haemofiltration?

Which agents?

Which techniques?

Which assessments?

NPIS
Edinburgh



THE DIALYSIS OF POISONS AND DRUGS

John F. Maher and George E. Schreiner

Since hemodialysis was first used for the therapy of poisoning[1], the list of dialyzable poisons has increased rapidly. The number of available intoxicants has grown at least as rapidly. Furthermore, knowledge about the net transport of drugs during dialysis is accumulating. The Editors, therefore, in 1963 and 1965 reviewed the current status of dialysis for poisoning[2, 3]. For the first review, in order to supplement the information obtained by reviewing the literature, members of the Society and other physicians who are experienced in the field of dialysis were requested to supply unpublished data pertaining to the dialysis of poisons. One hundred and twenty physicians responded to the initial inquiry, supplying data from 106 institutions. The expanded use of drugs during dialysis, the growing problem of acute poisoning, and the continued increase in the application of dialytic techniques, clinical observations and research on poisons encouraged us to bring the subject up to date. The growth of this field is reflected by the fact that the bibliography has doubled between the first 2 reviews. Physicians again supplied unpublished in vitro data, animal studies and clinical experience pertaining to the dialysis of poisons. For the second and third reviews a complete interval bibliography was obtained using MEDLARS through the courtesy of the staff of the National Medical Library. As in the earlier reviews no attempt has been made to provide detailed information; in the expanded review rather our goal has been to help the physician at the dialysis center who is called and asked, "I have a comatose patient who ingested 50 'Brand X' tablets. Is it dialyzable?"

Maher JF and Schreiner GE. Trans Amer Soc Artific Int Organs 1967;13:369-93.

Maher and Schreiner. The dialysis of poisons and drugs

TABLE 1

CURRENTLY KNOWN DIALYZABLE POISONS

Barbiturates*
Barbital
Phenobarbital
Amobarbital
Pentobarbital
Butabarbital
Secobarbital
Cyclobarbital

Other Sedatives and Tranquilizers
Glutethimide*
Diphenylhydantoin
Primidone
Meprobamate
Ethchlorvynol
Ethinamate
Methaqualone

Salicylates
Acetylsalicylic Acid*
Methylsalicylate*
Salicylamide*
Diisopropylfluorophosphate

Halides
Bromide*
Chloride*
Iodide
Fluoride

Metals
Bismuth*
Calcium*
Iron
Lead
Mercury
Arsenic
Sodium*
Potassium*
Magnesium*

Alcohols
Ethanol*
Methanol*
Ethylene Glycol*

Antibiotics
Streptomycin
Kanamycin
Neomycin
Penicillin
Ampicillin
Gallamycin
Cephalin
Cephalothin
Chloramphenicol
Tetracycline
Nitrofurantoin
Polymyxin
Isoniazid
Cycloserine

Endogenous Toxins
Ammonia
Uric Acid*
Toluol*
Ketones
Lactic Acid
Salicylates
Hexobarbital
Phenylketonuria
Porphyria
Cystine
Cystinosis

Miscellaneous Substances
Thiopental*
Atropine
Sodium Chloride
Potassium Chloride
Eucalyptus Oil
Boric Acid
Potassium Dichromate
Chromic Acid
Bromides
Dichloramphenicol
Sodium Citrate
Oxalate or Heparin
Arsenic Pentoxide
Cyclophosphamide
5-Fluorouracil
Methotrexate
Lithium Carbonate
Ergotamine
Cyclophosphamide
5-Fluorouracil
Methotrexate

* Kinetics of dialysis thoroughly studied and/or clinical experience extensive.

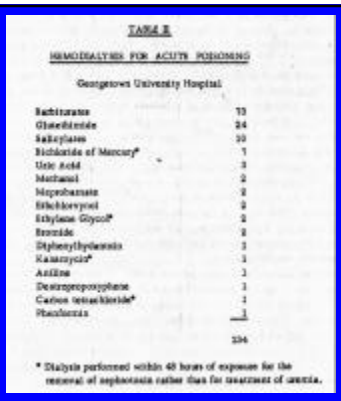


TABLE II

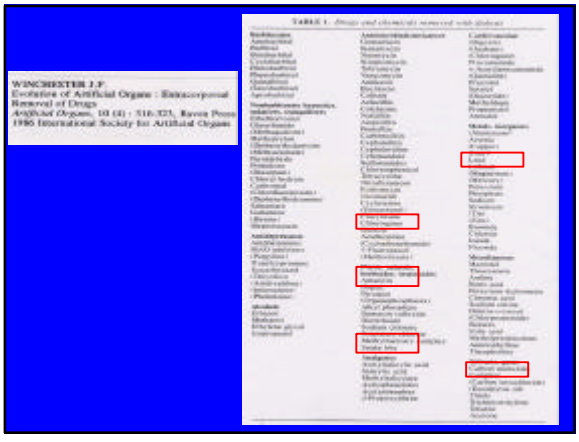
HEMODIALYSIS FOR ACUTE POISONING

Georgetown University Hospital

Barbiturates	73
Glutethimide	24
Salicylates	10
Bichloride of Mercury*	1
Uric Acid	1
Methanol	2
Meprobamate	2
Ethchlorvynol	2
Ethylene Glycol*	2
Bromide	2
Diphenylhydantoin	1
Kanamycin*	1
Aniline	1
Desipropyphene	1
Carbon tetrachloride*	1
Phenformin	1
	334

* Dialysis performed within 48 hours of exposure for the removal of nephrotoxin rather than for treatment of uremia.

Maher JF and Schreiner GE. Trans Amer Soc Artific Int Organs 1967;13:369-93.



WINCHESTER J.F.
Evolution of Artificial Organs : Extracorporeal Removal of Drugs
Artificial Organs, 10 (4) : 316-323, Raven Press
1986 International Society for Artificial Organs

Haemodialysis or Haemofiltration?

Which technique?

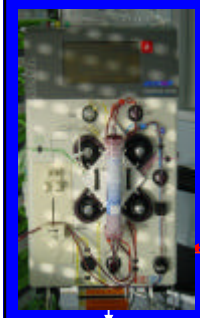
NPIS Edinburgh

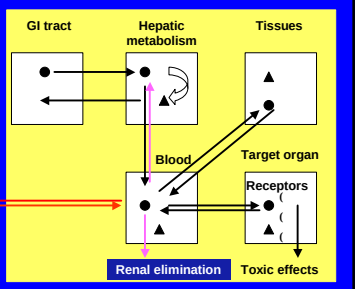
Evaluation of elimination techniques

- **Efficacy**
  - Does the technique increase the elimination of a given poison ?
- **Clinical Effectiveness**
  - Does the technique work in patients ?
- **Efficiency**
  - Does the technique compare favourably with other alternatives in terms of consequences (morbidity, mortality, adverse effects…) and costs ?

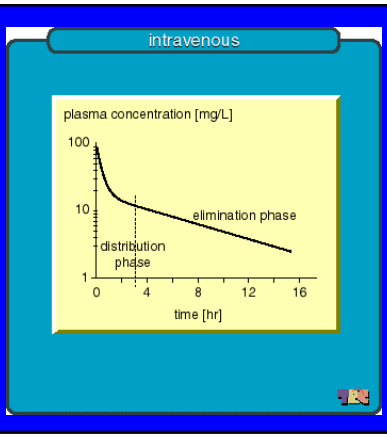
NPIS Edinburgh

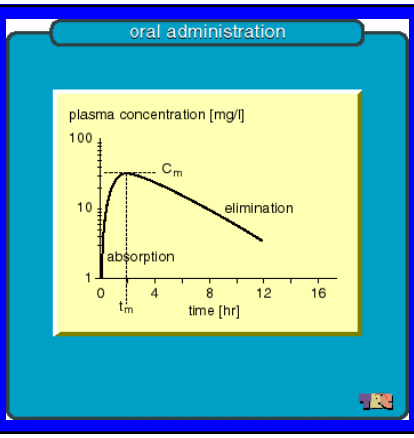
The kinetic approach





Elimination by the procedure



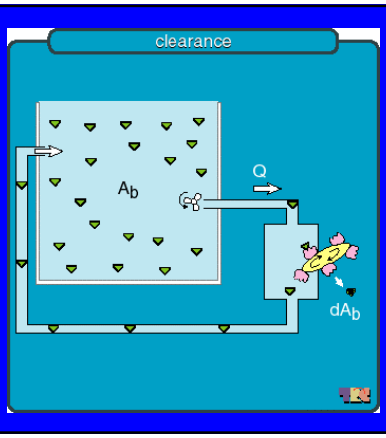


The kinetic approach: which parameters?

- **Plasma concentration** (units: mass/volume)
  = Amount bioavailable (mg)
  VD (l/kg) x weight (kg)

- **Plasma half-life** (units: time)
  = 0.693
  K el

- **Total clearance** (units: volume/time)
  = 0.693 x VD (ml) x weight(kg)
  T½ (min)



The kinetic approach: which parameters?

- Technique clearance (units: vol/time)

$$= \frac{(C_{in} - C_{out}) \times Q \text{ (ml/min)}}{C_{in}}$$

- Amount removed (units: mass)

$= C_{in}$ (mg/l) x Cl_{el} (ml/min) x time (min)

The kinetic approach

- The amount of drug removed depends on
  - plasma concentration
  - clearance achieved by the procedure
  - duration of the procedure

NPIS Edinburgh

The kinetic approach: criteria of efficacy ?

- T½ (during procedure) *vs* spontaneous T½
- Technique clearance *vs* *estimated* total clearance
- Amount recoverd *vs* *estimated* intrinsic elimination (renal, hepatic metabolism)

NPIS Edinburgh

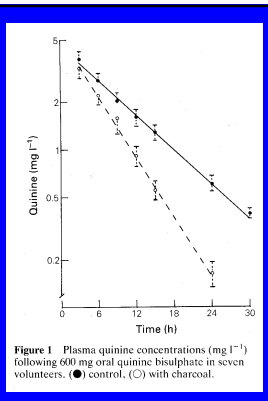


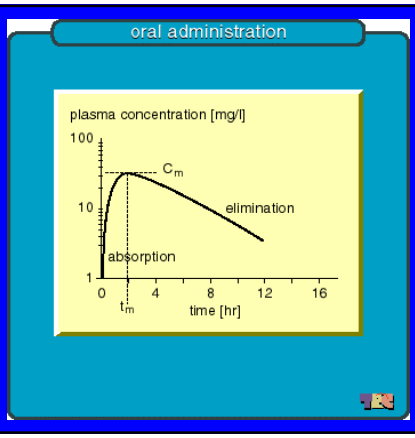
Figure 1 Plasma quinine concentrations (mg l^{-1}) following 600 mg oral quinine bisulphate in seven volunteers, (●) control, (○) with charcoal.

Lockey and Bateman, Br J Clin Pharmacol 1989;27:92-4.

The kinetic approach : pitfalls

- Dose estimate
- Role of continued absorption
- Decrease of plasma concentration may reflect clearance, absorption and distribution

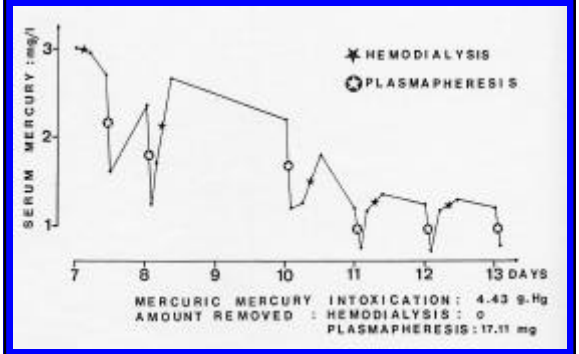
NPIS Edinburgh



The kinetic approach : pitfalls

- Over-estimation of procedure clearance
- Failure to assess procedure clearance *vs* Total clearance

NPIS Edinburgh



The kinetic approach

- Some drugs and poisons may be eliminated in a significant amount by elimination techniques

NPIS Edinburgh

Toxin removal by dialysis is determined by:

- Dialyzer conditions (blood flow rate, dialysate flow rate, dialyzer surface area, and pore structure of the chosen membrane)
- Toxicokinetic factors of the toxic substances
- Cardiovascular stability

NPIS Edinburgh

Hemodialysis: "ideal" toxin characteristics

low volume of distribution (<1 L/kg)
low endogenous clearance
a low molecular weight (<500 daltons)
high water solubility
? low protein binding

NPIS Edinburgh

Haemodialysis and poisoning

- To be clinically effective dialysis should improve the removal of a toxin in comparison to total body clearance

?? How much difference is needed

NPIS Edinburgh

Agents routinely dialyzed

lithium

methanol
ethylene glycol

salicylates

NPIS Edinburgh

Hemodialysis and poisoning

- early removal of toxic alcohols prevents toxicity from their toxic metabolites, which are also removed by hemodialysis
- the metabolic acidosis associated with methanol, ethylene glycol and salicylates is also corrected during hemodialysis

NPIS Edinburgh

The technical approach: conclusion

- Numerous drugs and poisons cross the dialysing membrane
- Clinical efficacy requires more than this

NPIS Edinburgh

Which criteria of efficacy ?

- clinical improvement
- decrease of the duration of poisoning
- decrease of severity, mortality, morbidity
- prevention of severe toxicity
  - ⇙ dependent on the kinetic-dynamic relationship

NPIS Edinburgh

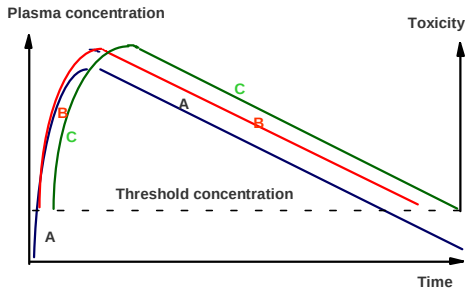
Enhanced elimination will only have a clinical benefit effect if :

- poisoning severity is related to the drug (or active metabolites) plasma concentration or body burden
- the prognosis depends on speed of elimination of the drug

NPIS Edinburgh

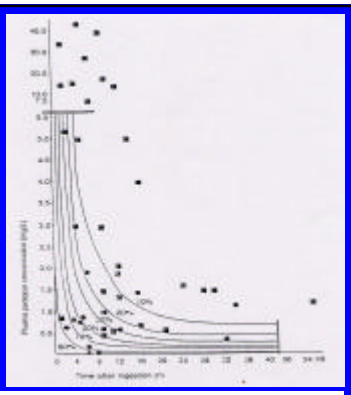
Kinetic-dynamic relationship : functional poison

(A = concentration ; B = toxicity ; C = delayed toxicity



Survivor (%) curves

- survivors
- non survivors



Hampson E. Failure of haemoperfusion and haemodialysis to prevent death in paraquat poisoning. A retrospective review of 42 patients. Med Toxicol, 1988; *3: 64-71*

The dynamic approach conclusion

- Clinical improvement
  =
  Efficacy of elimination technique
  - Clinical improvement without efficacy of the elimination technique
    - eg. : BZD, TCA…
  - Efficacy of the elimination technique without clinical improvement
    - eg. : paraquat, metals…

NPIS Edinburgh

Lithium

Renal excretion
Pumped by Na^+/K^+ pumps in distal tubule
Accumulates in renal impairment

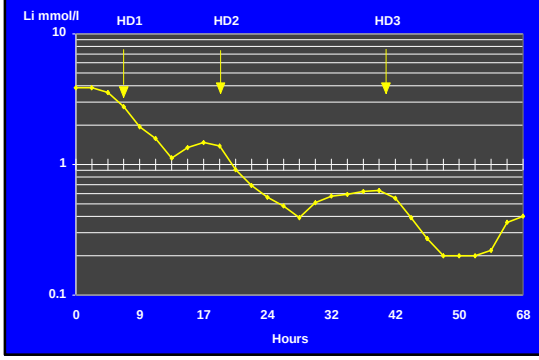
CAUSES: Renal, Thyroid and CNS toxicity

NPIS Edinburgh

Variations of lithium T1/2

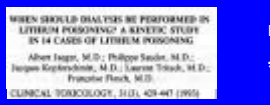
Authors	T ½ plasma (h)		
	acute	acute on chronic	chronic
Dyson et al 1987	11.8	20.9 +/- 1.3	32.2 +/- 3.3
Jaeger et al 1993	11.8 +/- 3.3	16.25 +/- 10.4	30.0 +/- 14.3
Ferron et al 1995		25.1 +/- 4.3	49.6 +/- 15.1

Lithium poisoning treated by HD



Lithium poisoning treated by HD

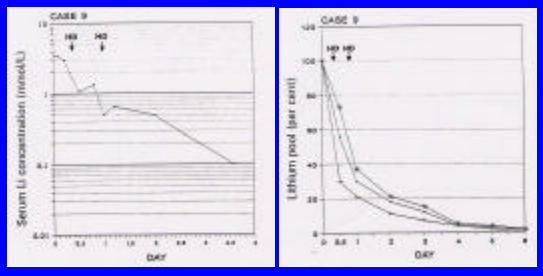
HD	Li (mmol/l)		T ½ (h)	Cl HD (ml/min)	Li eliminated (mmol)	
	Before	After			HD	Urine
1 H 7-13	2.76	1.12	4.75	85.9	56.0	1.11
2 H 15-25	1.38	0.39	5.75	84.8	36.2	0.37
3 H 38-46	0.55	<0.2	5.40	75.8	11.6	0.30


WHEN SHOULD DIALYSIS BE PERFORMED IN LITHIUM POISONING? A KINETIC STUDY IN 14 CASES OF LITHIUM POISONING

Albert Jaeger, M.D.; Philippe Sauder, M.D.; Jacques-Kopferschmitt, M.D.; Laurent Trinck, M.D.; Francoise Flesch, M.D.

CLINICAL TOXICOLOGY, 31(3), 429-447 (1993)

Lithium acute/chronic poisoning treated by haemodialysis:
* Total, + extracellular, ■ cellular

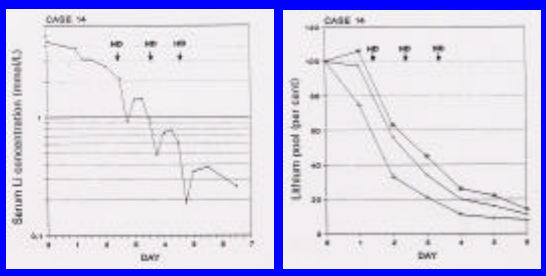


WHEN SHOULD DIALYSIS BE PERFORMED IN LITHIUM POISONING? A KINETIC STUDY IN 14 CASES OF LITHIUM POISONING

Albert Jaeger, M.D.; Philippe Sauder, M.D.; Jacques-Kopferschmitt, M.D.; Laurent Trinck, M.D.; Francoise Flesch, M.D.

CLINICAL TOXICOLOGY, 31(3), 429-447 (1993)

Lithium chronic poisoning treated by haemodialysis:
* Total, + extracellular, ■ cellular



Lithium and HD: criteria

- Clinical
  - * coma, convulsions, respiratory failure
  - * underlying disease favouring complications
  - * acute/chronic or chronic poisoning (severity increased)
- Kinetic
  - * decreased renal elimination
  - * increased Li concentration and half-life
  - * Li increasing with cellular diffusion

expected amount of Li removed by 6-H HD > amount eliminated in urine over 24 H

Jaeger et al. Clin Toxicol 1993;31:429-47.

NPIS Edinburgh

Lithium and CAVHF –CAVHD-CVVHDF

CAVHF - CVVHF

Gatell et al. 1989	1case
Hazouard et al. 1999	1 case
Van Bommel et al. 2000	1 case

CAVHDF - CVVHD

Bellomo et al. 1991	1 case
Desatnik-Pütz et al. 1995	2 cases
Leblanc et al. 1996	7 cases
Beckmann et al. 2001	1 case

NPIS Edinburgh

Lithium poisoning

- 49-old-year F , 21 g of lithium carbonate, acute/chronic
- serum Li = 5.3 mmol/L 6 hr HD; Li = 2.4 mmol/L
- CVVHDF (72 h) ; Total lithium removed by CVVHD = 6.5 g
- mean clearance = 23 ml/min !!
- *Conclusion: .."In lithium poisoning patients requiring dialysis, CVVHDF also appears to be efficacious and better tolerated by hemodynamically unstable patients"..*

Beckmann U et al..Efficacy of continuous venovenous hemodialysis in the treatment of severe lithium toxicity. J Toxicol Clin Toxicol 2001; 39(4):393-397.

Lithium and CAVHF –CAVHD-CVVHDF

	HD	HF	CAVHDF	CVVHD
Clearance ml/min	80-120	16.6 (1L) 33.3 (2 L)	20 (1 L) 36.1 (2 L) 42.8 (4 L)	48-62

Lithium poisoning

- 1). chronic lithium poisoning, Li = 5.4 mmol/L
- 2,5 h HD with high flux membrane; Li = 2.3 mmol/L
- 32 h CVVHDF Li = 0.91 mmol/L

- 2). acute/chronic poisoning, Li = 4.81 mmol/L
- 4 h HD with high flux membrane; Li = 1.34 mmol/L
- 22 h CVVHDF Li = 0.81 mmol/L
- *Conclusion: .."successful treatment...shows that HD followed by CVVHDF can be a safe and effective approach to management of severe lithium intoxication in children"*

Meyer RJ et al. Hemodialysis followed by continuous hemofiltration for treatment of lithium intoxication in children. Am J Kidney Dis 2001; 37(5): 1044-1047.

Methanol poisoning

- 44-year-old M – 125 ml – 2 hours before admission
- at admission – 3 pts GCS, respiratory failure; pH – 6.8, HCO_3 4.8 mmol/l, osmolal gap – 79 mosm/kg, anion gap – 37 mmol/L
- methanol serum level – 130 mg/dl
- Treatment: sodium bicarbonate, ethanol, folic acid; 2 h after admission HD (high-efficiency dialyzer)

Peces R, Alvarez R.: Effectiveness of hemodialysis with high-flux polysulfone membrane in the treatment of life-threatening methanol intoxication. Nephron 2002; 90(2):216-218.

Methanol poisoning

- Results: 1 h after HD - conscious, extubated; with no neurological and visual sequelae (CT scan normal); no acidosis

- Conclusion: ...*"modern HD using a bicarbonate dialysate and high-efficiency dialyzer (high-flux polysulfone) allow excellent removal of methanol and its metabolites and rapid correction of fluid, electrolyte and acid-base abnormalities"..*

Methanol poisoning

- 3 patients with methanol poisoning
- Haemodialysis vs CVVHDF
- Clearance increased 3 fold by CVVHDF
- Clearance by HD was 3 fold greater than CVVHDF
- Conclusion: CVVHDF an option in cardiovascular instability

Kan et al. Nephrol Dial Transplant 2003;18:2665.

Salicylate poisoning

- 18-year-old F, 600 tabl of 325-mg aspirin (=195 g)
- salicylate level (2 h post ingestion) = 674 mg/L
  - 1st HD – 455 mg/L, 7.5 hrs later = 828 mg/L
  - 2nd HD – 799 mg/L,
  - 3rd HD – 410 mg/L
- CVVHDF (21.5 hrs) – undetectable
- WBI
- Conclusion: *.."continued absorption of aspirin, necessitating intervention with WBI and CVVHD.."*

Chase PB et al. Whole bowel irrigation, hemodialysis, and continuous venovenous hemodiafiltration in the successful treatment of severe salicylate poisoning: case report. Dial Transplat 2002;31(6):387-391.

Kinetics of valproate

Half-life: 9-21 hrs (mean 15 hrs)

VD : 0.1-0.4 l/kg

NPIS Edinburgh

Valproate poisoning

- 25-year-old F – unknown amount
- VPA concentration: > 1,200 mg/L
  - HD high-flux 4 hr
- K_{el} = 0.25 (HD); post HD 0.029
- $T_{1/2}$ = 2.74 (HD); post HD 23.4
- *Conclusion: .. "toxic concentration of valproic acid can be effectively reduced with high-flux HD without the addition of charcoal haemoperfusion".. NO CLEARANCE ESTIMATE*

Kane SL et al. High-flux hemodialysis without hemoperfusion is effective in acute valproic acid overdose. Ann Pharmacother 2000; 34(10):1146-1151.

Valproate poisoning

- 24-year-old M, 30 g of valproic acid (coma, ventilatory failure, hypotension, hyperammonemia) VPA 670 mg/L
- 1st high-flux HD (4 hrs): VPA – 210 mg/L
- Cl = 121 ml/min, amount recovered = 5.9 g
- 2nd HD (flow 130 ml/min for 10 hrs):
- Cl = 56 ml/min, amount recovered = 3.3 g
- calculated total amount present in the body = 17.9 g;
- total removed 15.5 g (9.2 g during HD)
- *Conclusion: High-flux haemodialysis was more effective than endogenous elimination*

Kielstein JT et al. Efficacy of high-flux hemodialysis in the treatment of valproic acid intoxication. J Toxicol Clin Toxicol 2003; 41(6):873-876.

Valproate poisoning

- 48-year-old F - 48 g of sodium valproate
- VPA concentration: 332 – 1402 mg/L
  - CVVHDF with high-flux membrane (8 hr)
  - HD low flux 4 hr
- K_{el} = 0.036 – 0.062 (CVVHDF) – 0.31 (HD)
- $T_{1/2}$ = 28.5, 16.1 (CVVHDF), 2.2 (HD) hr
- HD: extraction ratio = 0.48 → 0.16
- clearance = 90 ml/min → 56 ml/min
- *Conclusion: .. "superior drug clearance and clinical response may be obtain with haemodialysis compared with CVVHDF"..*

Kay TD et al. Hemodialysis versus continous veno-venous hemodiafiltration in the management of severe valproate overdose. Clin Nephrol 2003; 59(1): 56-58.

Valproate poisoning

- 18-year-old girl, VPA concentration: 663 mg/L
  - HDF high-flux 4 hr
- K_{el} = 0.04/h preHDF, 0.31/h (HDF high-flux); post HDF 0.06/h
- $T_{1/2}$ = 15.9 h pre HDF; 2.23 (HDF high-flux); post HDF 21 h
- *Conclusion: .. " high-flux HDF is effective treatment modalities and should be offered to patients with valproic acid ingestion and neurological compromise.. "*

Dharnidharka VR et al. Extracorporeal removal of toxic valproic acid levels in children. Pediatr Nephrol 2002; 17: 312-315.

Carbamazepine

t1/2 30-40 hours single dose
8-15 hours repeat dosing

V.D. 0.8-2.0 l/kg

"Auto induction"
Active metabolite 10-11 Epoxide (half-life ~6 hours)

NPIS Edinburgh

Carbamazepine poisoning

- 18-month-old child
  peak concentration – 33 µg/ml
- High-efficiency HD (5 h) CBZ – 7.8 µg/ml
- $T_{1/2}$ before – 17.3 h
- $T_{1/2}$ during HEHD – 2.7 h
- $T_{1/2}$ after – 12.2 h
- *Conclusion: "..high-efficiency HD represents an alternative method for CBZ overdose*

BUT WHY DO IT??

Schuerer DJ et al. High-efficiency dialysis for carbamazepine overdose. J Toxicol Clin Toxicol 2000; 38(3):321-323.

Carbamazepine poisoning

- 31-year-old F – 4.5 g CBZ present in the body (calculated)
- CBZ concentration – 43 mg/L
- high-flux HD (3.5 h) CBZ – 33.8 mg/L
  - amount removed – 920 mg
- CHP (2h) – 20.9 ug/ml
  - amount removed – 950 mg
- *Conclusion: High-flux HD is as effective as CHP*

NO ASSESSMENT OF ENDOGENOUS CL

Kielstein JT et al. High-flux hemodialysis – an effective to hemoperfuison in the treatment of carbamazepine intoxication. Clin Nephrol 2002; 57(6):484-486.

Conclusions (1)

- High-performance HD seems to be more effective in the elimination of poisons - shorter time of procedure.
- HD delivers a more rapid elimination of toxin and a correction of associated acid-base and electrolyte disorders than continuous renal replacement therapy.

NPIS Edinburgh

Conclusions (2)

- Continuous techniques are more widely used in the intensive care unit, mainly due to better haemodynamic tolerance.
- Continuous techniques achieve clearances close to normal renal clearance.
- Continuous techniques should be considered in patients who are haemodymically unstable.

NPIS Edinburgh

The whole picture

- Dialysis efficacy depends on equipment clearance. High flow rates are therefore likely to be more effective.
- Patient cardiovascular stability is key to successful dialysis.
- Kinetic factors of the toxin are key to suitability of dialysis.
- Patient outcome is the key measure.

NPIS Edinburgh

Final Message

- Evaluate efficacy on kinetic and dynamic criteria
- Report inefficacy as well as success
- Evidence based medicine
  Role of the clinical toxicology societies position statements – guidelines

NPIS Edinburgh

Meningeal Signs: Kernig's Sign and Brudzinski's Sign

Series Editors and Contributing Authors:
Asif Saberi, MD
Saeed A. Syed, MD, MRCP

Meningitis, an inflammation of the meninges, is a life-threatening illness. If left untreated, meningitis has a high, almost absolute mortality and certain types of acute bacterial meningitis can be lethal within a matter of hours.[1] Therefore, early and accurate diagnosis and effective treatment are critical.

Several clinical signs facilitate the diagnosis of meningitis. Kernig's sign and Brudzinski's sign (**Sidebars**) are easy to elicit and can alert physicians to the precarious situation of a patient with meningitis. Both of these signs are thought to be caused by the irritation of motor nerve roots passing through inflamed meninges as the roots are brought under tension.

HISTORIC PERSPECTIVE

Meningitis has been recognized since antiquity.[2] As early as the 15th century BC, Hippocrates taught that "If during fever, the neck shalt have been suddenly twisted, the deglutition be rendered difficult without a tumor, it is a fatal sign."[3] Centuries later, King Henry II of France (1519–1559) is believed to have died from meningitis that he contracted after sustaining a scalp injury during sport.[4,5]

Meningitis was first described as a specific disease entity by British physician Thomas Willis (1621–1675) and Italian anatomist and pathologist Battista Morgagini (1682–1771).[6,7] The earliest recorded epidemic of meningitis on the American continent that might have been caused by bacterial meningitis was recorded at Medfield, MA, in 1806.[8] Autopsy data that showed pus between the patients' dura mater and pia mater substantiated bacterial meningitis as the causative factor.

MENINGEAL SIGNS

Kernig's Sign

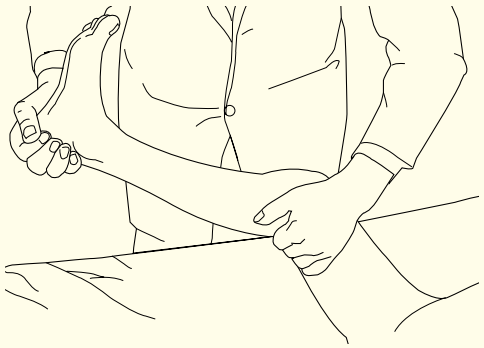
Russian physician Vladimir Kernig was born in Lepaia, Latvia, in 1840. Kernig received his medical degree in 1865 and joined the Obuhorsk Hospital in Saint Petersburgh, Russia, where he held a position until World War I.

Kernig first described the sign in the Saint Petersburgh Medizinische Wochenschrift in 1882.[9] During Kernig's examination, the patient was seated upright with hips and knees flexed. Kernig would then attempt to extend the patient's knee. He noted that, in patients with meningitis, he was unable to extend the knee beyond 135 degrees without causing pain.

Today, the maneuver is usually performed with the patient supine with hips and knees in flexion. Extension of the knees is attempted: the inability to extend the patient's knees beyond 135 degrees without causing pain constitutes a positive test for Kernig's sign.

KERNIG'S SIGN

Elicitation: Flexing the patient's hip 90 degrees then extending the patient's knee causes pain.



Drs. Saberi and Syed are Clinical Instructors, Department of Medicine, State University of New York at Buffalo, Buffalo, NY, and Staff Physicians, The Resource Center, Diagnostic and Treatment Outpatient Clinic, Dunkirk, NY.

BRUDZINSKI'S NECK SIGN

Elicitation: Flexing the patient's neck causes flexion of the patient's hips and knees.

Brudzinski's Sign

Jozef Brudzinski, a Polish physician in the early 20th century, became the dean of the University of Warsaw (Warsaw, Poland) and chief physician at the Hospital of Karl and Maria (Warsaw, Poland). By the beginning of the 20th century, Kernig's sign was well known and in widespread use in the medical community. However, Brudzinski's contribution to the understanding of meningeal signs is unique because Brudzinski used animal experiments to study the signs he elicited in patients with meningitis.[10,11]

Brudzinski's neck sign. Brudzinski actually described several different signs in patients with meningitis. Brudzinski's neck sign is most commonly recognized and is often simply referred to as *Brudzinski's sign*.

With the patient supine, the physician places one hand behind the patient's head and places the other hand on the patient's chest. The physician then raises the patient's head (with the hand behind the head) while the hand on the chest restrains the patient and prevents the patient from rising. Flexion of the patient's lower extremities (hips and knees) constitutes a positive sign. Brudzinski's neck sign has more sensitivity than Kernig's sign.[10]

Brudzinski's contralateral reflex sign. Brudzinski's contralateral reflex sign has two components: the identical and reciprocal contralateral reflux. The patient's hip and knee are passively flexed on one side; if the contralateral leg bends in reflex, identical contralateral reflex is demonstrated. Reciprocal contralateral reflex occurs when the leg that has flexed in response to the passive flexion of the contralateral hip and knee begins to extend passively.

SUMMARY

The importance of early recognition and treatment of meningitis cannot be overemphasized. With all the technological advances today, the medical community has yet to discover an economical, readily available screening test to supplant these easy-to-elicit physical signs. A positive result on these tests is an indication for the institution of antibiotic therapy, and treatment initiation need not be delayed until the performance of a lumbar puncture and receipt of the results. Overall mortality is still high, but with appropriate and timely treatment, most adult patients recover from meningitis and lead a normal life. Children recovering from meningitis occasionally experience sequelae such as hearing loss or cranial nerve deficit. These tests for meningitis are appropriately named to honor Kernig and Brudzinski, both of whom greatly contributed to medicine by facilitating the diagnosis of this life-threatening disease. **HP**

REFERENCES

1. Berkow R, ed: *The Merck Manual*, 16th ed. Rahway, NJ: Merck Research Laboratories, 1992:1466–1467.
2. Verghese A, Gallemore G: Kernig's and Brudzinski's signs revisited. *Rev Infect Dis* 1987;9:1187–1192.
3. Sigerist HE: *A History of Medicine*, vol 2. New York: Oxford University Press, 1961.
4. *Encyclopaedia Britannica*, vol 3, 15th ed. Chicago: Encyclopaedia Britannica, Inc, 1993:842.
5. Bendiner E: Andreas Vesalius: man of mystery in life and death. *Hosp Pract (Off Ed)* 1986;21:202–204.
6. Thomas Willis. *Encyclopaedia Britannica Online*. Available at:http://members.eb.com/bol/topic?eu=79154&sctn=1>. Accessed June 2, 1999.
7. *Encyclopaedia Britannica*, vol 3, 15th ed. Chicago: Encyclopaedia Britannica, Inc, 1993:31/8.
8. Danielson L, Mann E: The history of a singular and very mortal disease, which made its appearance in Medfield. *Medical and Agricultural Register* 1806;1:65–69.
9. Kernig VM: Ueber ein kankheits symptom der acuten meningitis. *St. Petersburgh Medizinische Woschenschrift* 1882;7:398.
10. Brudzinski J: Un sign nouveau sur les membres inferieurs dans les meningitis chez les infants (sign de la nuque). *Archives de la Medicine Enfant* 1910;12:745–752.
11. Brudzinski J: Ueber neue symptome von gehirnhautentizundung und reizung bei kindren, ins besondree bei tuberkulosen. *Berliner Klinische Wochenschrift* 1916;53:686–690.

Copyright 1999 by Turner White Communications Inc., Wayne, PA. All rights reserved.

SIGN
Scottish Intercollegiate Guidelines Network
Part of NHS Quality Improvement Scotland

NHS
Quality
Improvement
Scotland

101

British Guideline on the Management of Asthma

A national clinical guideline

May 2008
revised June 2009

NHS Quality Improvement Scotland (NHS QIS) is committed to equality and diversity. This guideline has been assessed for its likely impact on the six equality groups defined by age, disability, gender, race, religion/belief, and sexual orientation.

For the full equality and diversity impact assessment report please see the "published guidelines" section of the SIGN website at **www.sign.ac.uk/guidelines/published/numlist.html**. The full report in paper form and/or alternative format is available on request from the NHS QIS Equality and Diversity Officer.

This document is produced from elemental chlorine-free material and is sourced from sustainable forests

British Thoracic Society

Scottish Intercollegiate Guidelines Network

British Guideline on the Management of Asthma

A national clinical guideline

The College of
Emergency Medicine

May 2008

Revised June 2009

ISBN 978 1 905813 28 5

First published 2003
Revised edition published 2008
Revised edition published 2009

SIGN and the BTS consent to the photocopying of this guideline for the purpose of implementation in the NHS in England, Wales, Northern Ireland and Scotland.

Scottish Intercollegiate Guidelines Network
Elliott House, 8 -10 Hillside Crescent
Edinburgh EH7 5EA

www.sign.ac.uk

British Thoracic Society
17 Doughty Street,
London, WC1N 2PL

www.brit-thoracic.org.uk

Contents

1 Introduction 1

1.1 Statement of intent 1

2 Diagnosis 2

2.1 Diagnosis in children 2
2.2 Other investigations 8
2.3 Summary 9
2.4 Diagnosis in adults 11
2.5 Further investigations that may be useful in patients with an intermediate probability of asthma 16
2.6 Monitoring asthma 18

3 Non-pharmacological management 24

3.1 Primary prophylaxis 24
3.2 Secondary non-pharmacological prophylaxis 27
3.3 Other environmental factors 28
3.4 Dietary manipulation 29
3.5 Complementary and alternative medicine 31
3.6 Other complementary or alternative approaches 32

Revised 2009 **4 Pharmacological management 33**

4.1 Step 1: mild intermittent asthma 34
4.2 Step 2: introduction of regular preventer therapy 34
4.3 Step 3: initial add-on therapy 38
4.4 Step 4: poor control on moderate dose of inhaled steroid + add-on therapy: addition of fourth drug 40
4.5 Step 5: continuous or frequent use of oral steroids 41
4.6 Stepping down 46
4.7 Specific management issues 46

5 Inhaler devices 48

5.1 Technique and training 48
5.2 β_2 agonist delivery 48
5.3 Inhaled steroids for stable asthma 49
5.4 Cfc propellant pmdi vs hfa propellant pmdi 49
5.5 Prescribing devices 50
5.6 Use and care of spacers 50

Revised 2009 **6 Management of acute asthma 51**

6.1 Lessons from studies of asthma deaths and near-fatal asthma 51
6.2 Acute asthma in adults 53
6.3 Treatment of acute asthma in adults 56
6.4 Further investigation and monitoring 60
6.5 Asthma management protocols and proformas 60
6.6 Hospital discharge and follow up 60
6.7 Acute asthma in children aged over 2 years 61
6.8 Initial treatment of acute asthma in children aged over 2 years 63
6.9 Second line treatment of acute asthma in children aged over 2 years 66
6.10 Assessment of acute asthma in children aged less than 2 years 67
6.11 Treatment of acute asthma in children aged less than 2 years 68

7 Special situations 69

7.1 Difficult asthma 69
7.2 Factors contributing to difficult asthma 69
Revised 2009 7.3 Asthma in pregnancy 71
7.4 Management of acute asthma in pregnancy 72
7.5 Drug therapy in pregnancy 73
7.6 Management during labour 75
7.7 Drug therapy in breastfeeding mothers 76
7.8 Occupational asthma 77
7.9 Management of occupational asthma 79

8 Organisation and delivery of care, and audit 80

8.1 Routine primary care 80
8.2 Acute exacerbations 82
8.3 Audit 83

9 Patient education and self management 85

9.1 Self-management education and personalised asthma action plans 85
9.2 Compliance and concordance 86
9.3 Implementation in practice 88
9.4 Practical advice 88

10 Development of the guideline 90

10.1 Introduction 90
10.2 Executive and steering groups 90
10.3 Evidence review groups 91
10.4 Dissemination group 94
10.5 Systematic literature review 94
10.6 Consultation and peer review 95

Abbreviations 96
Annexes 97
References 109

KEY TO EVIDENCE STATEMENTS AND GRADES OF RECOMMENDATIONS

LEVELS OF EVIDENCE

1^{++}	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1^{+}	Well conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1 -	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2^{++}	High quality systematic reviews of case control or cohort studies High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2^{+}	Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, eg case reports, case series
4	Expert opinion

GRADES OF RECOMMENDATION

Note: The grade of recommendation relates to the strength of the evidence on which the recommendation is based. It does not reflect the clinical importance of the recommendation.

A	At least one meta-analysis, systematic review, or RCT rated as 1^{++}, and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1^{+}, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2^{++}, directly applicable to the target population, and demonstrating overall consistency of results; *or* Extrapolated evidence from studies rated as 1^{++} or 1^{+}
C	A body of evidence including studies rated as 2^{+}, directly applicable to the target population and demonstrating overall consistency of results; *or* Extrapolated evidence from studies rated as 2^{++}
D	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2^{+}

GOOD PRACTICE POINTS

☑	Recommended best practice based on the clinical experience of the guideline development group.
❖	Audit point

1 Introduction

In 1999 the British Thoracic Society (BTS) and the Scottish Intercollegiate Guidelines Network (SIGN) agreed to jointly produce a comprehensive new asthma guideline, both having previously published guidance on asthma. The original BTS guideline dated back to 1990 and the SIGN guidelines to 1996. Both organisations recognised the need to develop the new guideline using explicitly evidence based methodology. The joint process was further strengthened by collaboration with Asthma UK, the Royal College of Physicians of London, the Royal College of Paediatrics and Child Health, the General Practice Airways Group, and the British Association of Accident and Emergency Medicine (now the College of Emergency Medicine). The outcome of these efforts was the British Guideline on the Management of Asthma published in 2003.[1]

The 2003 guideline was developed using SIGN methodology,[2] adapted for UK-wide use. Electronic literature searches extended to 1995, although some sections required searches back as far as 1966. The pharmacological management section utilised the North of England Asthma guideline to address some of the key questions on adult management.[3] The North of England guideline literature search covered a period from 1984 to December 1997, and SIGN augmented this with a search from 1997 onwards.

Since 2003 sections within the guideline have been updated annually and posted on both the BTS (www.brit-thoracic.org.uk) and SIGN (www.sign.ac.uk) websites. In 2004 the sections on pharmacological management, acute asthma and patient self management and compliance were revised. In 2005 sections on pharmacological management, inhaler devices, outcomes and audit and asthma in pregnancy were updated, and occupational asthma was rewritten with help from the British Occupational Health Research Foundation.

In 2006 the pharmacological management section was again updated. While the web-based alterations appeared successful, it was felt an appropriate time to consider producing a new paper-based version in which to consolidate the various yearly updates. In addition, since 2006, the guideline has had input from colleagues from Australia and New Zealand.

The 2008 guideline considered literature published up to March 2007. It contains a completely rewritten section on diagnosis for both adults and children; a section on special situations which includes occupational asthma, asthma in pregnancy and the new topic of difficult asthma; updated sections on pharmacological and non-pharmacological management; and amalgamated sections on patient education and compliance, and on organisation of care and audit. The 2009 revisions include updates to pharmacological management, the management of acute asthma and asthma in pregnancy. Update searches were conducted on inhaler devices but there was insufficient new evidence to change the existing recommendations. The annexes have also been amended to reflect current evidence. The timescale of the literature search for each section is given in Annex 1. It is hoped that this asthma guideline continues to serve as a basis for high quality management of both acute and chronic asthma and a stimulus for research into areas of management for which there is little evidence. Sections of the guideline will continue to be updated on the BTS and SIGN websites on an annual basis.

2009

1.1 STATEMENT OF INTENT

This guideline is not intended to be construed or to serve as a standard of care. Standards of care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge and technology advance and patterns of care evolve. Adherence to guideline recommendations will not ensure a successful outcome in every case, nor should they be construed as including all proper methods of care or excluding other acceptable methods of care aimed at the same results. The ultimate judgement must be made by the appropriate healthcare professional(s) responsible for clinical decisions regarding a particular clinical procedure or treatment plan. This judgement should only be arrived at following discussion of the options with the patient, covering the diagnostic and treatment choices available. It is advised, however, that significant departures from the national guideline or any local guidelines derived from it should be fully documented in the patient's case notes at the time the relevant decision is taken.

2 Diagnosis

The diagnosis of asthma is a clinical one; there is no standardised definition of the type, severity or frequency of symptoms, nor of the findings on investigation. The absence of a gold standard definition means that it is not possible to make clear evidence based recommendations on how to make a diagnosis of asthma.

Central to all definitions is the presence of symptoms (more than one of wheeze, breathlessness, chest tightness, cough) and of variable airflow obstruction. More recent descriptions of asthma in children and in adults have included airway hyper-responsiveness and airway inflammation as components of the disease. How these features relate to each other, how they are best measured and how they contribute to the clinical manifestations of asthma, remains unclear.

Although there are many shared features in the diagnosis of asthma in children and in adults there are also important differences. The differential diagnosis, the natural history of wheezing illnesses, the ability to perform certain investigations and their diagnostic value, are all influenced by age.

2.1 DIAGNOSIS IN CHILDREN

Asthma in children causes recurrent respiratory symptoms of:

- wheezing
- cough
- difficulty breathing
- chest tightness.

Wheezing is one of a number of respiratory noises that occur in children. Parents often use "wheezing" as a non-specific label to describe any abnormal respiratory noise. It is important to distinguish wheezing – a continuous, high-pitched musical sound coming from the chest – from other respiratory noises, such as stridor or rattly breathing.[4]

There are many different causes of wheeze in childhood and different clinical patterns of wheezing can be recognised in children. In general, these patterns ("phenotypes") have been assigned retrospectively. They cannot reliably be distinguished when an individual child first presents with wheezing. In an individual child the pattern of symptoms may change as they grow older.

The commonest clinical pattern, especially in pre-school children and infants, is episodes of wheezing, cough and difficulty breathing associated with viral upper respiratory infections (colds), with no persisting symptoms. Most of these children will stop having recurrent chest symptoms by school age.

A minority of those who wheeze with viral infections in early life will go on to develop wheezing with other triggers so that they develop symptoms between acute episodes (interval symptoms) similar to older children with classical atopic asthma.[5-9] 2++

Children who have persisting or interval symptoms are most likely to benefit from therapeutic interventions.

2.1.1 MAKING A DIAGNOSIS IN CHILDREN

Initial clinical assessment

The diagnosis of asthma in children is based on recognising a characteristic pattern of episodic respiratory symptoms and signs *(see Table 1)* in the absence of an alternative explanation for them *(see Tables 2 and 3)*.

Table 1: Clinical features that increase the probability of asthma

More than one of the following symptoms: wheeze, cough, difficulty breathing, chest tightness, particularly if these symptoms:

- ◊ are frequent and recurrent[10-13]
- ◊ are worse at night and in the early morning[11,12,14]
- ◊ occur in response to, or are worse after, exercise or other triggers, such as exposure to pets, cold or damp air, or with emotions or laughter
- ◊ occur apart from colds[10]

- Personal history of atopic disorder[10,13,15]
- Family history of atopic disorder and/or asthma[10,16]
- Widespread wheeze heard on auscultation
- History of improvement in symptoms or lung function in response to adequate therapy

Table 2: Clinical features that lower the probability of asthma

- Symptoms with colds only, with no interval symptoms[10]
- Isolated cough in the absence of wheeze or difficulty breathing[17]
- History of moist cough[18]
- Prominent dizziness, light-headedness, peripheral tingling
- Repeatedly normal physical examination of chest when symptomatic
- Normal peak expiratory flow (PEF) or spirometry when symptomatic
- No response to a trial of asthma therapy[19]
- Clinical features pointing to alternative diagnosis *(see Table 3)*

Several factors are associated with a high (or low) risk of developing persisting wheezing or asthma through childhood.[15,20] The presence of these factors increases the probability that a child with respiratory symptoms will have asthma.

These factors include:

Age at presentation

The natural history of wheeze is dependent on age at first presentation. In general, the earlier the onset of wheeze, the better the prognosis. Cohort studies show a "break point" at around two years; most children who present before this age become asymptomatic by mid-childhood.[6,8,9,21] Co-existent atopy is a risk factor for persistence of wheeze independent of age of presentation. | 2^{++}

Sex

Male sex is a risk factor for asthma in pre-pubertal children. Female sex is a risk factor for the persistence of asthma in the transition from childhood to adulthood.[22,23] Boys with asthma are more likely to "grow out" of their asthma during adolescence than girls.[10,21,22,24-37]

Severity and frequency of previous wheezing episodes

Frequent or severe episodes of wheezing in childhood are associated with recurrent wheeze that persists into adolescence.[5,8,13,16,21,26,38,39] | 2^{++}

Coexistence of atopic disease

A history of other atopic conditions such as eczema and rhinitis increases the probability of asthma. Positive tests for atopy in a wheezing child also increase the likelihood of asthma. A raised specific IgE to wheat, egg white, or inhalant allergens such as house dust mite and cat dander, predicts later childhood asthma.[40,41] 2++

Other markers of allergic disease at presentation, such as positive skin prick tests and a raised blood eosinophil count, are related to the severity of current asthma and persistence through childhood.

Family history of atopy

A family history of atopy is the most clearly defined risk factor for atopy and asthma in children. The strongest association is with maternal atopy, which is an important risk factor for the childhood onset of asthma and for recurrent wheezing that persists throughout childhood.[6,34,37,42,43] 2++

Abnormal lung function

Persistent reductions in baseline airway function and increased airway responsiveness during childhood are associated with having asthma in adult life.[23] 3

Table 3: Clinical clues to alternative diagnoses in wheezy children (features not commonly found in children with asthma)

Perinatal and family history	**Possible diagnosis**
Symptoms present from birth or perinatal lung problem	Cystic fibrosis; chronic lung disease of prematurity; ciliary dyskinesia; developmental anomaly
Family history of unusual chest disease	Cystic fibrosis; neuromuscular disorder
Severe upper respiratory tract disease	Defect of host defence; ciliary dyskinesia
Symptoms and signs	
Persistent moist cough[18]	Cystic fibrosis; bronchiectasis; protracted bronchitis; recurrent aspiration; host defence disorder; ciliary dyskinesia
Excessive vomiting	Gastro-oesophageal reflux (± aspiration)
Dysphagia	Swallowing problems (± aspiration)
Breathlessness with light-headedness and peripheral tingling	Hyperventilation/panic attacks
Inspiratory stridor	Tracheal or laryngeal disorder
Abnormal voice or cry	Laryngeal problem
Focal signs in chest	Developmental anomaly; post-infective syndrome; bronchiectasis; tuberculosis
Finger clubbing	Cystic fibrosis; bronchiectasis
Failure to thrive	Cystic fibrosis; host defence disorder; gastro-oesophageal reflux
Investigations	
Focal or persistent radiological changes	Developmental anomaly; cystic fibrosis; post-infective disorder; recurrent aspiration; inhaled foreign body; bronchiectasis; tuberculosis

Case detection studies have used symptom questionnaires to screen for asthma in school-age children. A small number of questions - about current symptoms, their relation to exercise and their occurrence at night has been sufficient to detect asthma relatively efficiently.[11,12,14,44] The addition of spirometry[11,44] or bronchial hyper-responsiveness testing[45] to these questionnaires adds little to making a diagnosis of asthma in children. 2+

B **Focus the initial assessment in children suspected of having asthma on:**
- **presence of key features in the history and examination**
- **careful consideration of alternative diagnoses.**

☑ Record the basis on which a diagnosis of asthma is suspected.

2.1.2 ASSESSING THE PROBABLITY OF A DIAGNOSIS OF ASTHMA

Based on the initial clinical assessment it should be possible to determine the probability of a diagnosis of asthma.

With a thorough history and examination, an individual child can usually be classed into one of three groups *(see Figure 1)*:

- **high probability** – diagnosis of asthma likely
- **low probability** – diagnosis other than asthma likely
- **intermediate probability** – diagnosis uncertain.

2.1.3 HIGH PROBABILITY OF ASTHMA

In children with a high probability of asthma based on the initial assessment, move straight to a diagnostic trial of treatment. The initial choice of treatment will be based on an assessment of the degree of asthma severity *(see section 4)*.

The clinical response to treatment should be reassessed within 2-3 months. In this group, reserve more detailed investigations for those whose response to treatment is poor or those with severe disease.[19]

☑ In children with a high probability of asthma:
- start a trial of treatment
- review and assess response
- reserve further testing for those with a poor response.

2.1.4 LOW PROBABILITY OF ASTHMA

Where symptoms, signs or initial investigations suggest that a diagnosis of asthma is unlikely, *(see Table 2)*, or they point to an alternative diagnosis *(see Table 3)*, consider further investigations. This may require referral for specialist assessment *(see Table 4)*.

Reconsider a diagnosis of asthma in those who do not respond to specific treatments.

☑ In children with a low probability of asthma, consider more detailed investigation and specialist referral.

2.1.5 INTERMEDIATE PROBABILITY OF ASTHMA

In some children, and particularly those below the age of four to five, there is insufficient evidence at the first consultation to make a firm diagnosis of asthma, but no features to suggest an alternative diagnosis. There are several possible approaches to reaching a diagnosis in this group. Which approach is taken will be influenced by the frequency and severity of the symptoms.

These approaches include:

Watchful waiting with review

In children with mild, intermittent wheeze and other respiratory symptoms which occur only with viral upper respiratory infections (colds), it is often reasonable to give no specific treatment and to plan a review of the child after an interval agreed with the parents/carers.

Trial of treatment with review

The choice of treatment (for example, inhaled bronchodilators or corticosteroids) depends on the severity and frequency of symptoms. Although a trial of therapy with inhaled or oral corticosteroids is widely used to help make a diagnosis of asthma, there is little objective evidence to support this approach in children with recurrent wheeze.

It can be difficult to assess the response to treatment as an improvement in symptoms or lung function may be due to spontaneous remission. If it is unclear whether a child has improved, careful observation during a trial of withdrawing the treatment may clarify whether a response to asthma therapy has occurred.

Spirometry and reversibility testing

In children, as in adults, tests of airflow obstruction, airway responsiveness and airway inflammation may provide support for a diagnosis of asthma.[12,44] However, normal results on testing, especially if performed when the child is asymptomatic, do not exclude a diagnosis of asthma.[46] Abnormal results may be seen in children with other respiratory diseases. Measuring lung function in young children is difficult and requires techniques which are not widely available. 2+

Above five years of age, conventional lung function testing is possible in most children in most settings. This includes measures of airway obstruction (spirometry and peak flow), reversibility with bronchodilators, and airway hyper-responsiveness.

The relationship between asthma symptoms and lung function tests including bronchodilator reversibility is complex. Asthma severity classified by symptoms and use of medicines correlates poorly with single measurements of forced expiratory volume in one second (FEV_1) and other spirometric indices: FEV_1 is often normal in children with persistent asthma.[46,47] Serial measures of peak flow variability and FEV_1 show poor concordance with disease activity and do not reliably rule the diagnosis of asthma in or out.[47] Measures of gas trapping (residual volume and the ratio of residual volume to total lung capacity, RV/TLC) may be superior to measurements of expiratory flow at detecting airways obstruction especially in asymptomatic children.[46,48] 2+

A significant increase in FEV_1 (>12% from baseline)[49] or PEF after bronchodilator indicates reversible airflow obstruction and supports the diagnosis of asthma. It is also predictive of a good response to inhaled corticosteroids.[50] However, an absent response to bronchodilators does not exclude asthma.[51] 2+ 3

Between 2-5 years of age, many children can perform several newer lung function tests that do not rely on their cooperation or the ability to perform a forced expiratory manoeuvre. In general, these tests have not been evaluated as diagnostic tests for asthma. There is often substantial overlap between the values in children with and without asthma.[52] Of the tests available, specific airways resistance (sRaw), impulse oscillometry (IOS), and measurements of residual volume (RV) appear the most promising.[53] While some of these tests have been useful in research, their role in clinical practice is uncertain.[48,53,54] Most have only been used in specialist centres and are not widely available elsewhere. It is often not practical to measure variable airway obstruction in children below the age of five. 2+

2.1.6 CHILDREN WITH AN INTERMEDIATE PROBABILITY OF ASTHMA AND EVIDENCE OF AIRWAY OBSTRUCTION

Asthma is the by far the commonest cause of airways obstruction on spirometry in children. Obstruction due to other disorders, or due to multiple causes, is much less common in children than in adults. Spirometry and other lung function tests, including tests of PEF variability,[47] lung volumes and airway responsiveness,[45] are poor at discriminating between children with asthma and those with obstruction due to other conditions.

☑ In children with an intermediate probability of asthma who can perform spirometry and have evidence of airways obstruction, assess the change in FEV_1 or PEF in response to an inhaled bronchodilator (reversibility) and/or the response to a trial of treatment for a specified period:

- if there is significant reversibility, or if a treatment trial is beneficial, a diagnosis of asthma is probable. Continue to treat as asthma, but aim to find the minimum effective dose of therapy. At a later point, consider a trial of reduction or withdrawal of treatment.
- if there is no significant reversibility, and a treatment trial is not beneficial, consider tests for alternative conditions *(see Table 3)*.

2.1.7 CHILDREN WITH AN INTERMEDIATE PROBABILITY OF ASTHMA WITHOUT EVIDENCE OF AIRWAY OBSTRUCTION

In this group, further investigations, including assessment of atopic status and bronchodilator responsiveness and if possible tests of airway responsiveness, should be considered *(see section 2.2.1)*. This is particularly so if there has been a poor response to a trial of treatment or if symptoms are severe. In these circumstances, referral for specialist assessment is indicated.

C **In children with an intermediate probability of asthma who can perform spirometry and have no evidence of airways obstruction:**

- **consider testing for atopic status, bronchodilator reversibility and, if possible, bronchial hyper-responsiveness using methacholine, exercise or mannitol.**
- **consider specialist referral.**

2.1.8 CHILDREN WITH AN INTERMEDIATE PROBABILITY OF ASTHMA WHO CANNOT PERFORM SPIROMETRY

Most children under five years and some older children cannot perform spirometry. In these children, offer a trial of treatment for a specific period. If there is clear evidence of clinical improvement, the treatment should be continued and they should be regarded as having asthma (it may be appropriate to consider a trial of withdrawal of treatment at a later stage). If the treatment trial is not beneficial, then consider tests for alternative conditions and referral for specialist assessment.

☑ In children with an intermediate probability of asthma who cannot perform spirometry, offer a trial of treatment for a specified period:

- if treatment is beneficial, treat as asthma and arrange a review
- if treatment is not beneficial, stop asthma treatment and consider tests for alternative conditions and specialist referral.

2.2 OTHER INVESTIGATIONS

2.2.1 TESTS OF AIRWAY HYPER-RESPONSIVENESS

The role of tests of airway responsiveness (airway hyper-reactivity) in the diagnosis of childhood asthma is unclear.[45,55] For example, a methacholine challenge test has a much lower sensitivity than symptoms in diagnosing asthma in children and only marginally increases the diagnostic accuracy after the symptom history is taken into account.[45] However, a negative methacholine test in children, which has a high negative predictive value, makes a diagnosis of asthma improbable.[55] Similarly, a negative response to an exercise challenge test is helpful in excluding asthma in children with exercise related breathlessness.[56] 3

2.2.2 TEST OF EOSINOPHILIC AIRWAY INFLAMMATION

Eosinophilic inflammation in children can be assessed non-invasively using induced sputum differential eosinophil count or exhaled nitric oxide concentrations (FE_{NO}).

Sputum induction is feasible in school age children.[57,58] Higher sputum eosinophil counts are associated with more marked airways obstruction and reversibility, greater asthma severity and atopy.[59] In children with newly diagnosed mild asthma, sputum eosinophilia is present and declines with inhaled steroid treatment.[58] Sputum induction is possible in approximately 75% of children tested, but it is technically demanding and time consuming and at present remains a research tool. 2^{++}

It is feasible to measure FE_{NO} in unsedated children from the age of 3-4 years.[60] A raised FE_{NO} is neither a sensitive nor a specific marker of asthma with overlap with children who do not have asthma.[61] FE_{NO} is closely linked with atopic status, age and height.[62,63] In some studies, FE_{NO} correlated better with atopic dermatitis and allergic rhinitis than with asthma. It is not closely linked with underlying lung function. FE_{NO} could not differentiate between groups once atopy was taken into account.[64] Home measurements of FE_{NO} have a highly variable relationship with other measures of disease activity and vary widely from day to day.[65] 2^{+}

At present, there is insufficient evidence to support a role for markers of eosinophilic inflammation in the diagnosis of asthma in children. They may have a role in assessing severity of disease or response to treatment.

2.2.3 TESTS OF ATOPY

Positive skin tests,[66] blood eosinophilia $\geq 4\%$[10], or a raised specific IgE to cat, dog or mite,[67,68] increase the probability of asthma in a child with wheeze, particularly in children over five years of age.[66] It is important to recognise that non-atopic wheezing is as frequent as atopic wheezing in school-age children.[69] 2^{++}

2.2.4 CHEST X-RAY

A study in primary care in children age 0-6 years concluded that a chest X-ray (CXR), in the absence of a clinical indication, need not be part of the initial diagnostic work up.[70]

☑ Reserve chest X-rays for children with severe disease or clinical clues suggesting other conditions.

2.3 SUMMARY

Focus the initial assessment of children suspected of having asthma on:

- presence of key features in the history and clinical examination
- careful consideration of alternative diagnoses.

Record the basis on which the diagnosis of asthma is suspected.

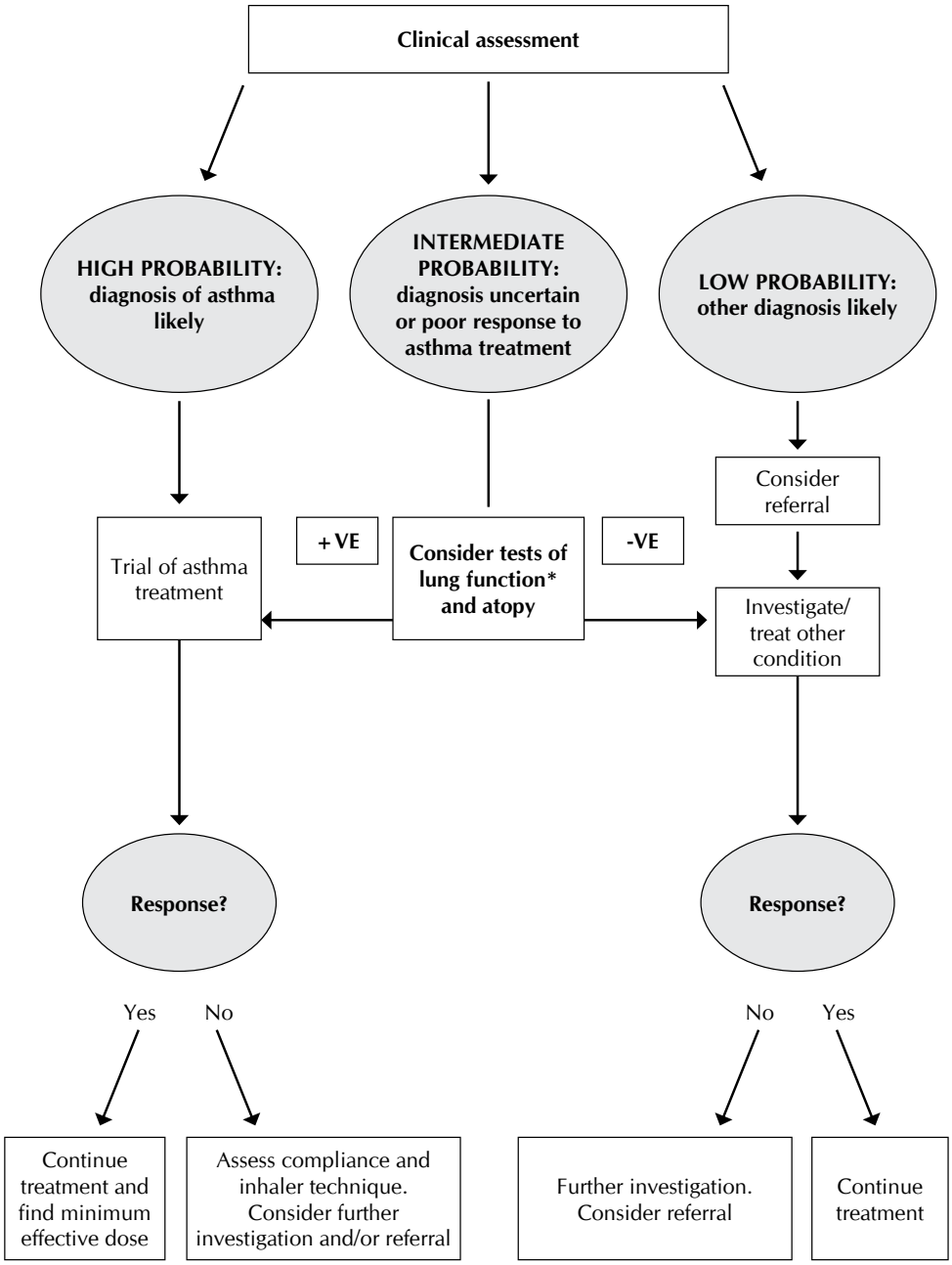
Using a structured questionnaire may produce a more standardised approach to the recording of presenting clinical features and the basis for a diagnosis of asthma.

1. **In children with a high probability of asthma:**
   - move straight to a trial of treatment
   - reserve further testing for those with a poor response.
2. **In children with a low probability of asthma:**
   - consider more detailed investigation and specialist referral.
3. **In children with an intermediate probability of asthma who can perform spirometry and have evidence of airways obstruction, offer a reversibility test and/or a trial of treatment for a specified period:**
   - if there is reversibility, or if treatment is beneficial, treat as asthma
   - if there is insignificant reversibility, and/or treatment trial is not beneficial, consider tests for alternative conditions.
4. **In children with an intermediate probability of asthma who can perform spirometry, and have no evidence of airways obstruction, consider testing for atopic status, bronchodilator reversibility and, if possible, bronchial hyper-responsiveness using methacholine or exercise.**
5. **In children with an intermediate probability of asthma, who cannot perform spirometry, consider testing for atopic status and offering a trial of treatment for a specified period:**
   - if treatment is beneficial, treat as asthma
   - if treatment is not beneficial, stop asthma treatment, and consider tests for alternative conditions and specialist referral.

Table 4: Indications for specialist referral in children

▪ Diagnosis unclear or in doubt
▪ Symptoms present from birth or perinatal lung problem
▪ Excessive vomiting or posseting
▪ Severe upper respiratory tract infection
▪ Persistent wet or productive cough
▪ Family history of unusual chest disease
▪ Failure to thrive
▪ Nasal polyps
▪ Unexpected clinical findings eg focal signs, abnormal voice or cry, dysphagia, inspiratory stridor
▪ Failure to respond to conventional treatment (particularly inhaled corticosteroids above 400 mcg/day or frequent use of steroid tablets)
▪ Parental anxiety or need for reassurance

Figure 1: Presentation with suspected asthma in children



* *Lung function tests include spirometry before and after bronchodilator (test of airway reversibility) and possible exercise or methacholine challenge (tests of airway responsiveness).*
Most children over the age of 5 years can perform lung function tests.

2.4 DIAGNOSIS IN ADULTS

The diagnosis of asthma is based on the recognition of a characteristic pattern of symptoms and signs and the absence of an alternative explanation for them *(see Table 5*). The key is to take a careful clinical history. In many cases this will allow a reasonably certain diagnosis of asthma, or an alternative diagnosis, to be made. If asthma does appear likely, the history should also explore possible causes, particularly occupational.

In view of the potential requirement for treatment over many years, it is important even in relatively clear cut cases, to try to obtain objective support for the diagnosis. Whether or not this should happen before starting treatment depends on the certainty of the initial diagnosis and the severity of presenting symptoms. Repeated assessment and measurement may be necessary before confirmatory evidence is acquired.

Confirmation hinges on demonstration of airflow obstruction varying over short periods of time. Spirometry, which is now becoming more widely available, is preferable to measurement of peak expiratory flow because it allows clearer identification of airflow obstruction, and the results are less dependent on effort. It should be the preferred test where available (although some training is required to obtain reliable recordings and to interpret the results). Of note, a normal spirogram (or PEF) obtained when the patient is not symptomatic does not exclude the diagnosis of asthma.

Results from spirometry are also useful where the initial history and examination leave genuine uncertainty about the diagnosis. In such cases, the differential diagnosis and approach to investigation is different in patients with and without airflow obstruction *(see Figure 2 and Table 6)*. In patients with a normal or near-normal spirogram when symptomatic, potential differential diagnoses are mainly non-pulmonary; [71,72] these conditions do not respond to inhaled corticosteroids and bronchodilators. In contrast, in patients with an obstructive spirogram the question is less whether they will need inhaled treatment but rather exactly what form and how intensive this should be.

Other tests of airflow obstruction, airway responsiveness and airway inflammation can also provide support for the diagnosis of asthma, but to what extent the results of the tests alter the probability of a diagnosis of asthma has not been clearly established, nor is it clear when these tests are best performed.

Table 5: Clinical features in adults that influence the probability that episodic respiratory symptoms are due to asthma

Features that increase the probability of asthma
▪ More than one of the following symptoms: wheeze, breathlessness, chest tightness and cough, particularly if: ◊ symptoms worse at night and in the early morning ◊ symptoms in response to exercise, allergen exposure and cold air ◊ symptoms after taking aspirin or beta blockers ▪ History of atopic disorder ▪ Family history of asthma and/or atopic disorder ▪ Widespread wheeze heard on auscultation of the chest ▪ Otherwise unexplained low FEV_1 or PEF (historical or serial readings) ▪ Otherwise unexplained peripheral blood eosinophilia
Features that lower the probability of asthma
▪ Prominent dizziness, light-headedness, peripheral tingling ▪ Chronic productive cough in the absence of wheeze or breathlessness ▪ Repeatedly normal physical examination of chest when symptomatic ▪ Voice disturbance ▪ Symptoms with colds only ▪ Significant smoking history (ie >20 pack-years) ▪ Cardiac disease ▪ Normal PEF or spirometry when symptomatic* * A normal spirogram/spirometry when not symptomatic does not exclude the diagnosis of asthma. Repeated measurements of lung function are often more informative than a single assessment.

☑ Base initial diagnosis on a careful assessment of symptoms and a measure of airflow obstruction:

- in patients with a high probability of asthma move straight to a trial of treatment. Reserve further testing for those whose response to a trial of treatment is poor.
- in patients with a low probability of asthma, whose symptoms are thought to be due to an alternative diagnosis, investigate and manage accordingly. Reconsider the diagnosis of asthma in those who do not respond.
- the preferred approach in patients with an intermediate probability of having asthma is to carry out further investigations, including an explicit trial of treatments for a specified period, before confirming a diagnosis and establishing maintenance treatment.

D **Spirometry is the preferred initial test to assess the presence and severity of airflow obstruction.**

2.4.1 FURTHER INVESTIGATION OF PATIENTS WITH AN INTERMEDIATE PROBABILITY OF ASTHMA

Patients with airways obstruction

Tests of peak expiratory flow variability, lung volumes, gas transfer, airway hyper-responsiveness and airway inflammation are of limited value in discriminating patients with established airflow obstruction due to asthma from those whose airflow obstruction is due to other conditions.[73-76] Patients may have more than one cause of airflow obstruction, which complicates the interpretation of any test. In particular, asthma and chronic obstructive pulmonary disease (COPD) commonly coexist.

☑ Offer patients with airways obstruction and intermediate probability of asthma a reversibility test and/or a trial of treatment for a specified period:

- if there is significant reversibility, or if a treatment trial is clearly beneficial treat as asthma
- if there is insignificant reversibility and a treatment trial is not beneficial, consider tests for alternative conditions.*

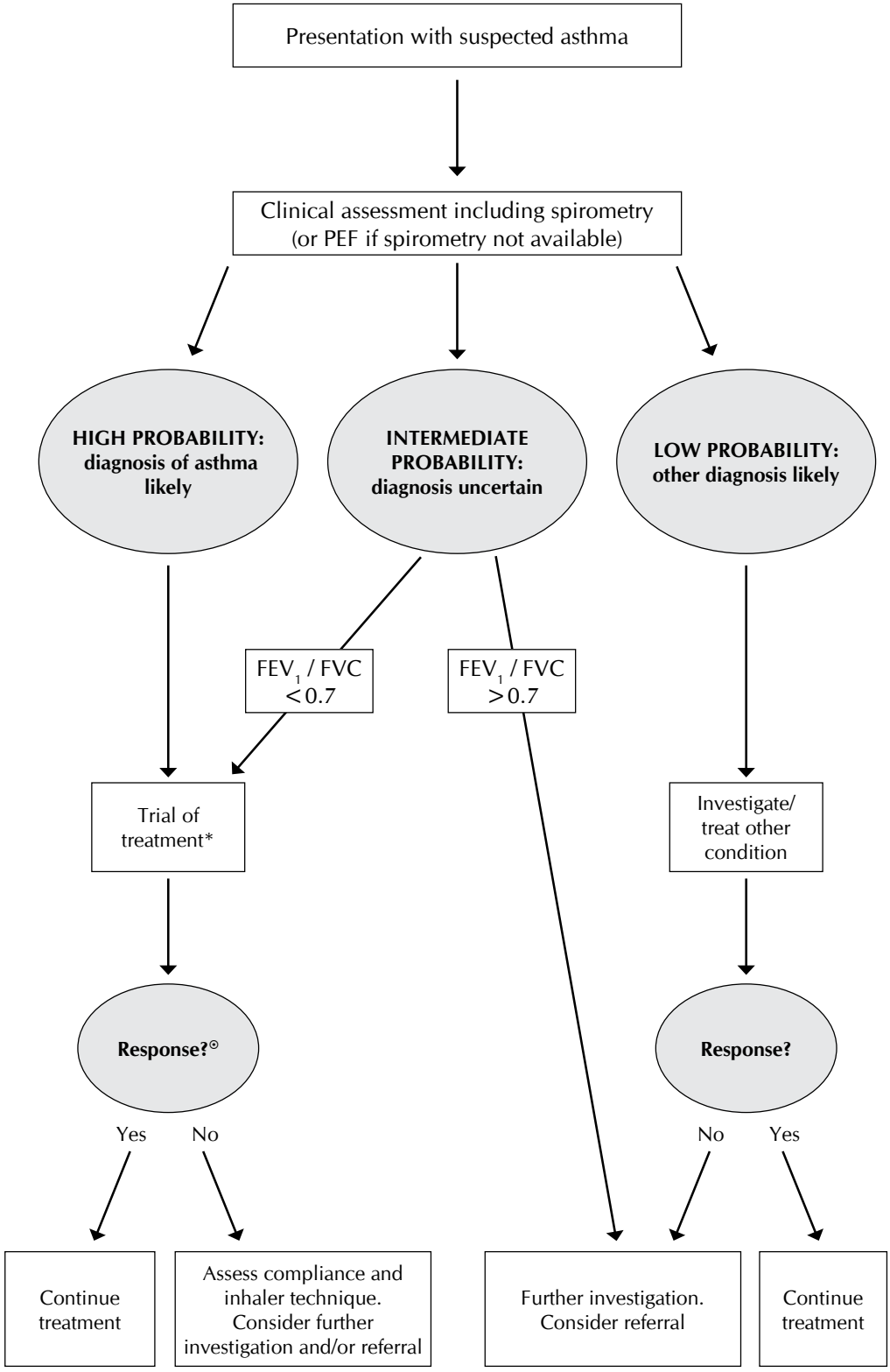
Patients without airways obstruction

In patients with a normal or near-normal spirogram it is more useful to look for evidence of airway hyper-responsiveness and/or airway inflammation [71,77-79] These tests are sensitive so normal results provide the strongest evidence against a diagnosis of asthma.

☑ In patients without evidence of airways obstruction and with an intermediate probability of asthma, arrange further investigations* before commencing treatment.

** see section 2.5 for more detailed information on further tests*

Figure 2: Presentation with suspected asthma in adults



*** See section 2.5.1**
⊙ See Table 6

Table 6: Differential diagnosis of asthma in adults, according to the presence or absence of airflow obstruction ($FEV_1/FVC < 0.7$).

Without airflow obstruction
▪ Chronic cough syndromes ▪ Hyperventilation syndrome ▪ Vocal cord dysfunction ▪ Rhinitis ▪ Gastro-oesophageal reflux ▪ Heart failure ▪ Pulmonary fibrosis
With airflow obstruction
▪ COPD ▪ Bronchiectasis* ▪ Inhaled foreign body* ▪ Obliterative bronchiolitis ▪ Large airway stenosis ▪ Lung cancer* ▪ Sarcoidosis* *may also be associated with non-obstructive spirometry

☑ Consider performing chest X-ray in any patient presenting atypically or with additional symptoms or signs. Additional investigations such as full lung function tests, blood eosinophil count, serum IgE and allergen skin prick tests may be of value in selected patients.

Criteria for referral to a specialist are outlined in box 1.

Box 1: Criteria for specialist referral in adults

- Diagnosis unclear
- Unexpected clinical findings (ie crackles, clubbing, cyanosis, cardiac disease)
- Unexplained restrictive spirometry
- Suspected occupational asthma
- Persistent non-variable breathlessness
- Monophonic wheeze or stridor
- Prominent systemic features (myalgia, fever, weight loss)
- Chronic sputum production
- CXR shadowing
- Marked blood eosinophilia ($>1 \times 10^9$/l)
- Poor response to asthma treatment
- Severe asthma exacerbation

2.5 FURTHER INVESTIGATIONS THAT MAY BE USEFUL IN PATIENTS WITH AN INTERMEDIATE PROBABILITY OF ASTHMA

Three studies have looked at tests to discriminate patients with asthma from those with conditions that are commonly confused with asthma.[71,77,79] These studies provide a basis for evaluating the diagnostic value of different tests. Table 7 summarises the sensitivity and specificity of different findings on investigation. As not all studies included patients with untreated asthma, these values may underestimate the value of the investigations in clinical practice, where many patients will be investigated before treatment is started. The diagnostic value of testing may also be greater when more than one test is done or if there are previous lung function results available in the patient's notes. The choice of test will depend on a number of factors including severity of symptoms and local availability of tests.

An alternative and promising approach to the classification of airways disease is to use tests which best identify patients who are going to respond to corticosteroid therapy.[78,80] A raised sputum eosinophil count and an increased exhaled nitric oxide concentration (FE_{NO}) are more closely related to corticosteroid response than other tests in a variety of clinical settings.[78,81-83] There is also evidence that markers of eosinophilic airway inflammation are of value in monitoring the response to corticosteroid treatment.[84-86] More experience with these techniques and more information on the long term response to corticosteroid in patients who do not have a raised sputum eosinophil count or FE_{NO} is needed before this approach can be recommended.

Table 7: Estimates of sensitivity and specificity of test results in adults with suspected asthma and normal or near-normal spirometric values.[71,77,79]

Test	Normal range	Validity	
		sensitivity	specificity
Methacholine PC_{20}	> 8 mg/ml	High	Medium
Indirect challenges*	varies	Medium#	High
FE_{NO}	< 25ppb	High#	Medium
Sputum eosinophil count	< 2%	High#	Medium
PEF A%H	< 8** < 20%***	Low	Medium

PC_{20} = the provocative concentration of methacholine required to cause a 20% fall in FEV_1. FE_{NO} = exhaled nitric oxide concentration. PEF A%H = peak expiratory flow amplitude percent highest.

**ie exercise challenge, inhaled mannitol # in untreated patients, **with twice daily readings ***with four or more readings*

2.5.1 TREATMENT TRIALS AND REVERSIBILITY TESTING

Treatment trials with bronchodilators or inhaled corticosteroids in patients with diagnostic uncertainty should use one or more objective methods of assessment. Using spirometric values or PEF as the prime outcome of interest is of limited value in patients with normal or near-normal pre-treatment lung function since there is little room for measurable improvement. One study has shown that the sensitivity of a positive response to inhaled corticosteroid, defined as a > 15% improvement in PEF, is 24%.[79] A variety of tools to assess asthma control is available to assess the response to a trial of treatment *(see Table 8).* | 2^+

Using FEV_1 or PEF as the primary method to assess reversibility or the response to treatment trials may be more helpful in patients with established airflow obstruction.

In adults, most clinicians would try a 6-8 week treatment trial of 200 mcg inhaled beclometasone (or equivalent) twice daily. In patients with significant airflow obstruction there may be a degree of inhaled corticosteroid resistance [87] and a treatment trial with oral prednisolone 30 mg daily for two weeks is preferred. | 2^+

A >400 ml improvement in FEV_1 to either β_2 agonists or corticosteroid treatment trials strongly suggests underlying asthma. Smaller improvements in FEV_1 are less discriminatory[71] and a decision on continuation of treatment should be based on objective assessment of symptoms using validated tools *(see Table 8)*. Trials of treatment withdrawal may be helpful where there is doubt. 2+

C **Assess FEV_1 (or PEF) and/or symptoms:**

- **before and after 400 mcg inhaled salbutamol in patients with diagnostic uncertainty and airflow obstruction present at the time of assessment**
- **in other patients, or if there is an incomplete response to inhaled salbutamol, after either inhaled corticosteroids** *(200 mcg twice daily beclometasone equivalent for 6-8 weeks)* **or oral prednisolone** *(30 mg once daily for 14 days).*

2.5.2 PEAK EXPIRATORY FLOW MONITORING

PEF should be recorded as the best of three forced expiratory blows from total lung capacity with a maximum pause of two seconds before blowing.[88] The patient can be standing or sitting. Further blows should be done if the largest two PEF are not within 40 l/min.[88]

PEF is best used to provide an estimate of variability of airflow from multiple measurements made over at least two weeks. Increased variability may be evident from twice daily readings. More frequent readings will result in a better estimate [89] but the improved precision is likely to be achieved at the expense of reduced patient compliance.[90]

PEF variability is best calculated as the difference between the highest and lowest PEF expressed as a percentage of either the mean or highest PEF.[91-93]

The upper limit of the normal range for the amplitude % highest is around 20% using four or more PEF readings per day [91,93,94] but may be lower using twice daily readings.[95] Epidemiological studies have shown sensitivities of between 19 and 33% for identifying physician-diagnosed asthma. [92,96]

PEF variability can be increased in patients with conditions commonly confused with asthma [71,73] so the specificity of abnormal PEF variability is likely to be less in clinical practice than it is in population studies.

PEF records from frequent readings taken at work and away from work are useful when considering a diagnosis of occupational asthma *(see section 7.8)*. A computer generated analysis of occupational records which provides an index of the work effect is available.[97]

☑ Peak flow records should be interpreted with caution and with regard to the clinical context. They are more useful in the monitoring of patients with established asthma than in making the initial diagnosis.

2.5.3 ASSESSMENT OF AIRWAY RESPONSIVENESS

Tests of airway responsiveness have been useful in research but are not yet widely available in everyday clinical practice. The most widely used method of measuring airway responsiveness relies on measuring response in terms of change in FEV_1 a set time after inhalation of increasing concentrations of histamine or methacholine. The agent can be delivered by breath-activated dosimeter, via a nebuliser using tidal breathing, or via a hand held atomiser.[98] The response is usually quantified as the concentration (or dose) required to cause a 20% fall in FEV_1 (PC_{20} or PD_{20}) calculated by linear interpolation of the log concentration or dose-response curve.

Community studies in adults have consistently shown that airway responsiveness has a unimodal distribution with between 90 and 95% of the normal population having a histamine or methacholine PC_{20} of >8 mg/ml (equivalent to a PD_{20} of >4 micromoles).[92,99,100] This value has a sensitivity of between 60-100% in detecting physician-diagnosed asthma.[92,96,99,100]

In patients with normal or near-normal spirometric values, assessment of airway responsiveness is significantly better than other tests in discriminating patients with asthma from patients with conditions commonly confused with asthma *(see Table 6)*.[71,77] In contrast, tests of airway responsiveness are of little value in patients with established airflow obstruction as the specificity is low.[73,76]

Other potentially helpful constrictor challenges include indirect challenges such as inhaled mannitol and exercise.[101] A positive response to these indirect stimuli (ie a >15% fall in FEV_1) is a specific indicator of asthma but the tests are less sensitive than tests using methacholine and histamine, particularly in patients tested while on treatment.[101,102]

2.5.4 TESTS OF EOSINOPHILIC AIRWAY INFLAMMATION

Eosinophilic airway inflammation can be assessed non-invasively using the induced sputum differential eosinophil count or the exhaled nitric oxide concentration (FE_{NO}).[103,104] A raised sputum eosinophil count (>2%) or FE_{NO} (>25 ppb at 50 ml/sec) is seen in 70-80% of patients with untreated asthma.[74,103] Neither finding is specific to asthma: 30-40% of patients with chronic cough [82,105,106] and a similar proportion of patients with COPD[81] have abnormal results. There is growing evidence that measures of eosinophilic airway inflammation are more closely linked to a positive response to corticosteroids than other measures even in patients with diagnoses other than asthma. [81,83,105]

Experience with induced sputum and FE_{NO} is limited to a few centres and more research needs to be done before any recommendations can be made.

C **In patients in whom there is diagnostic uncertainty and no evidence of airflow obstruction on initial assessment, test airway responsiveness wherever possible.**

2.6 MONITORING ASTHMA

In the majority of patients with asthma symptom-based monitoring is adequate. Patients achieving control of symptoms with treatment have a low risk for exacerbations.[107]

Table 8 summarises the methodology, measurement characteristics and interpretation of some of the validated tools used to assess symptoms and other aspects of asthma. Some measures provide information about future risk (ie sputum eosinophil count, airway responsiveness and FE_{NO}) rather than immediate clinical control. Risk reduction, eg minimising future adverse outcomes such as exacerbations and accelerated decline in lung function, is also a goal of asthma management.

A management strategy that controls eosinophilic airway inflammation [84-86] or airway hyper-responsiveness[108] results in better control of exacerbations than one which controls immediate clinical manifestations. The benefits of this more intensive approach are greater in patients with severe asthma, when exacerbations can occur frequently and unpredictably. More research is needed to assess the relative roles of the different measures and to address the feasibility and cost of incorporating them into monitoring protocols before they can be recommended more widely.

2.6.1 MONITORING IN PRIMARY CARE

Asthma is best monitored in primary care by routine clinical review on at least an annual basis *(see section 8.1.2)*.

The factors that should be monitored and recorded include:

- symptomatic asthma control: best assessed using directive questions such as the RCP '3 questions',[109] or the Asthma Control Questionnaire or Asthma Control Test *(see Table 8)*, since broad non-specific questions may underestimate symptoms
- lung function, assessed by spirometry or by PEF. Reduced lung function compared to previously recorded values may indicate current bronchoconstriction or a long term decline in lung function and should prompt detailed assessment
- exacerbations, oral corticosteroid use and time off work or school since last assessment
- inhaler technique *(see section 5)*
- compliance *(see section 9.2)* which can be assessed by reviewing prescription refill frequency
- bronchodilator reliance which can be assessed by reviewing prescription refill frequency
- possession of and use of self management plan/personal action plan *(see section 9.1)*.

Table 8: Summary of tools that can be used to assess asthma.

Measurement	Methodology	Measurement characteristics	Comments
Spirometry[110, 111]	Widely available. Enables clear demonstration of airflow obstruction. FEV_1 largely independent of effort and highly repeatable. Less applicable in acute severe asthma. Only assesses one aspect of the disease state.	Normal ranges widely available and robust. Short term (20 minute) 95% range for repeat measure of FEV_1 < 160 ml; FVC < 330 ml, independent of baseline value.	Good for short and longer term reversibility testing in subjects with pre-existing airflow obstruction. > 400 ml increase in FEV_1 highly suggestive of asthma. Less helpful in subjects with normal pre-treatment values because of ceiling effect.
Peak expiratory flow (PEF)[88, 91, 92, 112]	Widely available and simple. Applicable in a wide variety of circumstances including acute severe asthma. PEF variability can be determined from home readings in most subjects. PEF effort dependent and not as repeatable as FEV_1. Only assesses one aspect of the disease state.	Normal ranges of PEF are wide, and currently available normative tables are outdated and do not encompass ethnic diversity. Change in PEF more meaningful than absolute value. > 60 l/min increase in PEF suggested as best criteria for defining reversibility. Normal range of PEF variability defined as amplitude % highest < 8% or < 20% depending on number of readings and degree of patient coaching.	Useful for short and longer term reversibility testing in subjects with pre-existing airflow obstruction. Less helpful in subjects with normal pre-treatment values because of ceiling effect. Little information on the use of PEF variability as an index of treatment response.

Measurement	Methodology	Measurement characteristics	Comments
Royal College of Physicians (RCP) 3 Questions[109]	Yes/no or graded response to the following three questions: In the last week (or month) 1. Have you had difficulty sleeping because of your asthma symptoms (including cough)? 2. Have you had your usual asthma symptoms during the day (cough, wheeze, chest tightness or breathlessness)? 3. Has your asthma interfered with your usual activities (eg housework, work/ school etc)?	No to all questions consistent with controlled asthma.	Not well validated. Simplicity is attractive for use in day to day clinical practice.
Asthma Control Questionnaire[113-115]	Response to 7 questions, 5 relating to symptoms, 1 rescue treatment use and 1 FEV_1. Response usually assessed over the preceding week. Shortened, five question symptom only questionnaire is just as valid.	Well controlled ≤ 0.75, inadequately controlled ≥ 1.5. 95% range for repeat measure +/- 0.36. Minimal important difference 0.5.	Well validated composite scoring system with a strong bias to symptoms. Could be used to assess response to longer term treatment trials. Shortened five-point questionnaire is probably best for those with normal or near normal FEV_1.
Asthma Control Test (ACT)[116, 117]	Response to 5 questions, 3 related to symptoms, 1 medication use and 1 overall control. 5 point response score	Well controlled >19. Within subject intraclass correlation coefficient 0.77. 95% range for repeat measure and minimally clinically important difference not defined.	Could be used to assess response to longer term treatment trials, particularly in those with normal or near-normal spirometric values. 95% range for repeat measure and minimally clinically important difference need to be defined.

Measurement	Methodology	Measurement characteristics	Comments
Mini Asthma Quality of Life Questionnaire (AQLQ)[114, 118]	Response to 15 questions in 4 domains (symptoms, activity limitations, emotional function and environmental stimuli). Response usually assessed over the preceding week. Closely related to larger 32-item asthma quality of life questionnaire.	95% range for repeat measure +/- 0.36. Minimal important difference 0.5.	Well validated quality of life questionnaire. Could be used to assess response to longer term treatment trials.
Airway responsiveness[98, 108]	Only available in selected secondary care facilities. Responsive to change (particularly indirect challenges such as inhaled mannitol). Less of a ceiling effect. Not applicable in severe asthma or in acute severe asthma	Normal methacholine PC_{20} > 8 mg/ml. 95% range for repeat measure +/- 1.5-2 doubling doses.	Has not been widely used to monitor disease and assess treatment responses. Some evidence that using airway responsiveness as an additional measure for monitoring asthma results in a reduction in asthma exacerbations and improved airway pathology.

Measurement	Methodology	Measurement characteristics	Comments
Exhaled nitric oxide (FE_{NO})[78, 85, 103, 119, 120]	Not widely available. Monitors still expensive, although expect the technology to become cheaper and more widespread. Measurements can be obtained in almost all adults and children over 5 years. Immediate results are available. Reasonably close relationship between FE_{NO} and eosinophilic airway inflammation, which is independent of gender, age, atopy and inhaled corticosteroid use. Relationship is lost in smokers. Not closely related to other measures of asthma morbidity.	Normal range < 25 ppb at exhaled flow of 50 ml/sec. 95% range for repeat measure 4 ppb. > 50 ppb highly predictive of eosinophilic airway inflammation. < 25 ppb highly predictive of its absence.	Raised FE_{NO} (> 50 ppb) very predictive of a positive response to corticosteroids. Use of FE_{NO} to guide corticosteroid treatment has been shown to result in a non-significant 25% reduction in exacerbations with 40% less corticosteroid. Low FE_{NO} (< 25 ppb) may be of particular value in identifying patients who can step down corticosteroid treatment safely. Protocols for diagnosis and monitoring have not been well defined and experience with the technique is limited.
Sputum eosinophil differential count[83, 84, 121, 122]	Only available in specialist centres although technology is widely available and inexpensive. Information available in 80-90% of patients although immediate results are not available. Sputum eosinophil count not closely related to other measures of asthma morbidity	Normal range < 2%; 95% range for repeat measure +/- 2-3 fold.	Close relationship between raised sputum eosinophil count and corticosteroid responsiveness. Use of sputum eosinophil count to guide corticosteroid therapy has been consistently shown to result in better outcome for the same exposure to corticosteroids. Benefits are greater in patients with more severe disease.

3 Non-pharmacological management

There is a common perception amongst patients and carers that there are numerous environmental, dietary and other triggers of asthma and that avoiding these triggers will improve asthma and reduce the requirement for pharmacotherapy. Failure to address a patient, parent or carer's concern about environmental triggers may compromise concordance with recommended pharmacotherapy. Evidence that non-pharmacological management is effective can be difficult to obtain and more well controlled intervention studies are required.

This section distinguishes:

1. primary prophylaxis - interventions introduced before the onset of disease and designed to reduce its incidence.
2. secondary prophylaxis - interventions introduced after the onset of disease to reduce its impact.

3.1 PRIMARY PROPHYLAXIS

The evidence for primary interventional strategies is based predominantly on observational studies, though some have been tested using experimental methods. Many are multifaceted and it can be difficult to disentangle the effects of one exposure or intervention from another.

3.1.1 AEROALLERGEN AVOIDANCE

Exposure to high levels of house dust mite allergen in early life is associated with an increased likelihood of sensitisation to house dust mite by three to seven years of age.[123] Sensitisation to house dust mite is an important risk factor for the development of asthma[124,125] and a few studies have suggested that high early house dust mite exposure increases the risks of subsequent asthma.[126,127] A UK study showed that low levels of house dust mite and cat allergen exposures in early life increased the risk of IgE sensitisation and asthma at five years, with some attenuation at high levels of exposure, but there were significant interactions with heredity and birth order.[128]

Outcomes from intervention studies attempting to reduce exposure to house dust mites are inconsistent. A multifaceted Canadian intervention study showed a reduced prevalence of doctor-diagnosed asthma but no impact on other allergic diseases, positive skin prick tests or bronchial hyper-responsiveness;[129] others have shown no effect on either allergic sensitisation or symptoms of allergic diseases.[130] In one UK study, early results from environmental manipulation commenced in early pregnancy and focused mainly on house dust mite avoidance, showed reductions in some respiratory symptoms in the first year of life.[131] Subsequent results showed a paradoxical effect with increased allergy but better lung function in the intervention group.[132] 1+

The considerable variation in the methodology used in these studies precludes the merging of data or generation of meta-analyses.

Intensive house dust mite avoidance may reduce exposure to a range of other factors including endotoxin. Epidemiological studies suggest that close contact with a cat or a dog in early life may reduce the subsequent prevalence of allergy and asthma.[133,134] This has raised the question of whether high pet allergen exposure causes high-dose immune tolerance or increases exposure to endotoxin and other microbial products as a component of the "hygiene hypothesis".

In the absence of consistent evidence of benefit from domestic aeroallergen avoidance it is not possible to recommend it as a strategy for preventing childhood asthma.

3.1.2 FOOD ALLERGEN AVOIDANCE

Sensitisation to foods, particularly eggs, frequently precedes the development of aeroallergy and subsequent asthma.[135] Food allergen avoidance in pregnancy and postnatally has not been shown to prevent the later development of asthma.[136] Allergen avoidance during pregnancy may adversely affect maternal, and perhaps fetal, nutrition.[137] High-dose food allergen exposure during pregnancy may reduce subsequent sensitisation rates by inducing tolerance.[138] 1+

B **In the absence of any evidence of benefit and given the potential for adverse effects, maternal food allergen avoidance during pregnancy and lactation is not recommended as a strategy for preventing childhood asthma.**

3.1.3 BREAST FEEDING

A systematic review of observational studies on the allergy preventive effects of breast feeding indicates that it is effective for all infants irrespective of allergic heredity. The preventive effect is more pronounced in high-risk infants provided they are breast fed for at least four months.[139] However, not all studies have demonstrated benefit and in a large birth cohort there was no protective effect against atopy and asthma and maybe even an increase in risk.[140] 2+

Observational studies have the potential to be confounded by, for example, higher rates of breast feeding in atopic families, and taking this into account, the weight of evidence is in favour of breast feeding as a preventive strategy.

C **Breast feeding should be encouraged for its many benefits, and as it may also have a potential protective effect in relation to early asthma.**

3.1.4 MODIFIED INFANT MILK FORMULAE

Trials of modified milk formulae have not included sufficiently long follow up to establish whether there is any impact on asthma. A Cochrane review identified inconsistencies in findings and methodological concerns amongst studies, which mean that hydrolysed formulae cannot currently be recommended as part of an asthma prevention strategy.[141] A review of the use of soy formulae found no significant effect on asthma or any other allergic disease.[142] 1+

In the absence of any evidence of benefit from the use of modified infant milk formulae it is not possible to recommend it as a strategy for preventing childhood asthma.

3.1.5 WEANING

There are conflicting data on the association between early introduction of allergenic foods into the infant diet and the subsequent development of allergy and atopic eczema. No evidence was identified in relation to asthma.[143] In one study late introduction of egg was associated with a non-significant increase in pre-school wheezing.[144]

In the absence of evidence on outcomes in relation to asthma no recommendations on modified weaning can be made.

3.1.6 NUTRITIONAL SUPPLEMENTATION - FISH OILS

Fish oils have a high level of omega-3 polyunsaturated fatty acids (n-3PUFAs). Western diets have a low intake of n-3 PUFAs with a corresponding increase in intake of n-6 PUFAs. This change has been associated with increasing rates of allergic disease and asthma.[143] Two randomised controlled studies have investigated early life fish oil dietary supplementation in relation to asthma outcomes in children at high risk of atopic disease (at least one parent or sibling had atopy with or without asthma). In a study, powered only to detect differences in cord blood, maternal dietary fish oil supplementation during pregnancy was associated with reduced cytokine release from allergen stimulated cord blood mononuclear cells. However, effects on clinical outcomes at one year, in relation to atopic eczema, wheeze and cough, were marginal.[145] In a second study, fish oil supplementation commencing in early infancy with or without additional house dust mite avoidance, was associated with a significant reduction in wheeze at 18 months of age. By five years of age fish oil supplementation was not associated with effects on asthma or other atopic diseases.[146] 1+

In the absence of any evidence of benefit from the use of fish oil supplementation in pregnancy it is not possible to recommend it as a strategy for preventing childhood asthma.

3.1.7 OTHER NUTRIENTS

A number of observational studies have suggested an increased risk of subsequent asthma following reduced (maternal) intakes of selenium (based on umbilical cord levels),[147]or vitamin E based on maternal pregnancy intake.[148] No intervention studies in relation to selenium or vitamin E have yet been conducted and overall there is insufficient evidence to make any recommendations on maternal dietary supplementation as an asthma prevention strategy.[143] Observational studies suggest that intervention trials are warranted.

3.1.8 MICROBIAL EXPOSURE

The "hygiene hypothesis" suggested that early exposure to microbial products would switch off allergic responses thereby preventing allergic diseases such as asthma. The hypothesis is supported by some epidemiological studies comparing large populations who have or have not had such exposure.[149,150]

The concept is sometimes described as "the microbial exposure hypothesis". A double blind placebo controlled trial of the probiotic lactobacillus GG given to mothers resulted in a reduced incidence of atopic eczema in their children but had no effect on IgE antibody or allergic skin test responses. The small sample size and short follow up in this study limit its interpretation.[151] Other trials of a range of probiotics and prebiotics are now in progress. There remains insufficient understanding of the ecology of gut flora in infancy in relation to outcomes. Bifido-bacteria may be more important than lactobacilli in reducing susceptibility to allergic disease.[152]

There is insufficient evidence to indicate that the use of dietary probiotics in pregnancy reduces the incidence of childhood asthma.

This is a key area for further work with longer follow up to establish outcomes in relation to asthma.

3.1.9 AVOIDANCE OF TOBACCO SMOKE AND OTHER AIR POLLUTANTS

No evidence has been found to support a link between exposure to environmental tobacco smoke (ETS) or other air pollutants and the induction of allergy.

There is an increased risk of infant wheezing associated with maternal smoking during pregnancy which adversely affects infant lung function.[153-156] Evidence suggests that early life ETS exposure is associated with later persistent asthma[157,158] with a strong interaction with genetic polymorphisms which affect antioxidant activity.[159] 2+

B **Parents and parents-to-be should be advised of the many adverse effects which smoking has on their children including increased wheezing in infancy and increased risk of persistent asthma.**

The limited data on antenatal or early life exposure to other pollutants suggest similar effects to those for ETS, namely increased infant wheezing, enhanced by additional ETS exposure and antioxidant gene variations.[160-162] There is one small study suggesting that vitamin C supplementation will modify the combined effects of genetic polymorphisms and pollution on lung function in children with asthma.[163] Further research is required before recommendations for practice can be made. 3 4

3.1.10 IMMUNOTHERAPY

Three observational studies with contemporaneous untreated controls in over 8,000 patients have shown that allergen immunotherapy in individuals with a single allergy reduces the numbers subsequently developing new allergic sensitisation over a three to four year follow up.[164-166] One trial compared pollen allergen immunotherapy in children with allergic rhinitis with contemporaneous untreated controls and showed a lower rate of onset of asthma during three years of treatment.[167] This effect was sustained for two years after stopping the therapy.[168] More studies are required to establish whether immunotherapy might have a role in primary prophylaxis.

3.1.11 IMMUNISATION

In keeping with the "microbial exposure hypothesis" some studies have suggested an association between tuberculin responsiveness and subsequent reduced prevalence of allergy, implying a protective effect of BCG. At present, it is not possible to disentangle whether poor tuberculin responsiveness represents an underlying defect which increases the risk of allergy and asthma or whether the immunisation itself has a protective effect.[169] 2^+

Investigation of the effects of any other childhood immunisation suggests that at worst there is no influence on subsequent allergic disease and maybe some protective effect against the development of asthma.[170]

C **All childhood immunisations should proceed normally as there is no evidence of an adverse effect on the incidence of asthma.**

3.2 SECONDARY NON-PHARMACOLOGICAL PROPHYLAXIS

3.2.1 HOUSE DUST MITE AVOIDANCE

Increased allergen exposure in sensitised individuals is associated with an increase in asthma symptoms, bronchial hyper-responsiveness and deterioration in lung function.[127,171,172] However, evidence that reducing allergen exposure can reduce morbidity and/or mortality in asthma is tenuous. In uncontrolled studies, children and adults have derived benefit from removal to a low allergen environment such as occurs at high altitude, although the benefits seen are not necessarily attributable to allergen avoidance alone.[173]

Cochrane reviews on house dust mite control measures in a normal domestic environment have concluded that chemical and physical methods aimed at reducing exposure to house dust mite allergens cannot be recommended.[174] Subsequent studies involving large numbers of patients tend to support this conclusion.[175,176] Heterogeneity between studies with regard to the intervention and monitoring of outcomes makes interpretation of the systematic review difficult. 1^{++}

Studies of mattress barrier systems have suggested that benefits in relation to treatment requirements for asthma and lung function can occur.[177,178] Larger and more carefully conducted controlled studies employing combinations of house dust mite reduction strategies are required. At present house dust mite control measures do not appear to be a cost-effective method of achieving benefit, although it is recognised that many families are very committed to attempts to reduce exposure to triggers. 2^+

Measures to decrease house dust mites have been shown to reduce numbers of house dust mites, but have not been shown to have an effect on asthma severity.

☑ Families with evidence of house dust mite allergy and who wish to try mite avoidance might consider the following:

- complete barrier bed-covering systems
- removal of carpets
- removal of soft toys from bed
- high temperature washing of bed linen
- acaricides to soft furnishings
- good ventilation with or without dehumidification.

3.2.2 OTHER ALLERGENS

Animal allergens, particularly from cat and dog, are potent provokers of asthma symptoms. The reported effects of removal of pets from homes are paradoxical, with either no benefit for asthma[179,180] or a potential for continued high exposure to induce a degree of tolerance.[181] In homes where there is no cat but still detectable cat allergen, there may be a benefit from introducing additional avoidance measures such as air filters and high efficiency vacuum cleaners for cat allergic patients.[182,183]

Although fungal exposure has been strongly associated with hospitalisation and increased mortality in asthma, no controlled trials have addressed the efficacy of reduction of fungal exposure in relation to control of asthma. Cockroach allergy is not a common problem in the UK and studies of attempts to avoid this allergen elsewhere have produced conflicting results.[184]

Studies of individual aeroallergen avoidance strategies show that single interventions have limited or no benefit. A multi faceted approach is more likely to be effective if it addresses all the indoor asthma triggers. Such approaches may even be cost effective.[185] A strategy with a potential impact on mites, mould allergens and indoor pollutants is the use of a mechanical ventilation system to reduce humidity and increase indoor air exchange. The only trial that has assessed this in a controlled fashion failed to demonstrate any significant effects, but the numbers involved were small.[120] A systematic review of this topic concluded that more research is required.[186]

3.3 OTHER ENVIRONMENTAL FACTORS

3.3.1 SMOKING

Direct or passive exposure to cigarette smoke adversely affects quality of life, lung function, need for rescue medications for acute episodes of asthma and long term control with inhaled steroids.[187-190]

There are very few trials which have assessed smoking cessation in relation to asthma control. Two studies have demonstrated decreases in childhood asthma severity when parents were able to stop smoking.[191,192] One study in adults with asthma suggested that smoking cessation improved asthma-specific quality of life, symptoms and drug requirements.[193] Intervention to reduce smoking has had disappointing outcomes.[194,195] It is likely that more intensive intervention will be required to achieve meaningful outcomes.[196] 2+

Uptake of smoking in teenagers increases the risks of persisting asthma. One study showed a doubling of risk for the development of asthma over six years in 14 year old children who started to smoke[197] *(see section 4.2.4 for effect of smoking on treatment).* 3

C **Parents with asthma should be advised about the dangers of smoking to themselves and their children with asthma and offered appropriate support to stop smoking.**

3.3.2 AIR POLLUTION

Challenge studies demonstrate that various pollutants can enhance the response of patients with asthma to allergen inhalation.[198,199] Time-series studies suggest that air pollution may provoke acute asthma attacks or aggravate existing chronic asthma although the effects are very much less than those with infection or allergen exposure.[200,201] While it might seem likely that moving from a highly polluted environment might help, in the UK, asthma is more prevalent in 12-14 year olds in non-metropolitan rather than metropolitan areas.[202] Much less attention has been focused on indoor pollutants in relation to asthma and more work is required.[203,204]

3.3.3 IMMUNOTHERAPY

Subcutaneous immunotherapy

Trials of allergen specific immunotherapy by subcutaneous injection of increasing doses of allergen extracts have consistently demonstrated beneficial effects compared with placebo in the management of allergic asthma. Allergens included house dust mite, grass pollen, tree pollen, cat and dog allergen and moulds. Cochrane reviews have concluded that immunotherapy reduces asthma symptoms, the use of asthma medications and improves bronchial hyper-reactivity. The most recent review included 36 trials with house dust mite, 20 with pollen, 10 with animal allergens, two with cladosporium mould, one with latex and six with multiple allergens.[205] 1++

Evidence comparing the roles of immunotherapy and pharmacotherapy in the management of asthma is lacking. One study directly compared allergen immunotherapy with inhaled steroids and found that symptoms and lung function improved more rapidly in the group on inhaled steroids.[206] Further comparative studies are required. 2+

Immunotherapy for allergic rhinitis has been shown to have a carry over effect after therapy has stopped.[207] 3

B **Immunotherapy can be considered in patients with asthma where a clinically significant allergen cannot be avoided. The potential for severe allergic reactions to the therapy must be fully discussed with patients.**

Sublingual immunotherapy

There has been increasing interest in the use of sublingual immunotherapy, which is associated with far fewer adverse reactions than subcutaneous immunotherapy. A systematic review suggested there were some benefits for asthma control but the magnitude of the effect was small.[208] Further randomised controlled trials are required. 1++

B **Sublingual immunotherapy cannot currently be recommended for the treatment of asthma in routine practice.**

3.4 DIETARY MANIPULATION

3.4.1 ELECTROLYTES

Increasing dietary sodium has been implicated in the geographical variations in asthma mortality[209] and high sodium intake is associated with increased bronchial hyper-responsiveness.[210,211] A systematic review of intervention studies reducing salt intake identified only minimal effects and concluded that dietary salt reduction could not be recommended in the management of asthma.[212] Low magnesium intakes have been associated with a higher prevalence of asthma with increasing intake resulting in reduced bronchial hyper-responsiveness and higher lung function.[213] Magnesium plays a beneficial role in the treatment of asthma through bronchial smooth muscle relaxation, leading to the use of intravenous or inhaled preparations of magnesium sulphate for acute exacerbations of asthma.[214] Studies of oral supplementation are limited and more trials are required.[215-217]

3.4.2 FISH OILS/LIPIDS

In vitro studies suggest that supplementing the diet with omega n-3 fatty acids, which are most commonly found in fish oils, might reduce the inflammation associated with asthma.[218,219] Results from observational studies are inconsistent and a Cochrane review of nine randomised controlled trials concluded that there was insufficient evidence to recommend fish oil supplementation for the treatment of asthma.[220]

3.4.3 ANTIOXIDANTS

Observational studies have reported that low vitamin C, vitamin E and selenium intakes are associated with a higher prevalence of asthma.[143] Intervention studies suggest that neither supplementation with vitamin C, vitamin E or selenium is associated with clinical benefits in people with asthma.[221-223] Observational studies in both adults and children have also consistently shown that a high intake of fresh fruit and vegetable is associated with less asthma and better pulmonary function.[224-230] No intervention studies evaluating the intake of fruit or vegetables and their effects on asthma have been reported.

3.4.4 WEIGHT REDUCTION IN OBESE PATIENTS WITH ASTHMA

Several studies have reported an association between increasing body mass index and symptoms of asthma.[231-234] One randomised parallel group study has shown improved asthma control following weight reduction in obese patients with asthma.[235] 3 1+

C **Weight reduction is recommended in obese patients with asthma to promote general health and to improve asthma control.**

3.4.5 PROBIOTICS

Studies have suggested that an imbalance in gut flora is associated with a higher risk of development of allergy.[236] Trials have investigated the use of probiotics in the treatment of established allergic disease with variable results.[237,238] Only one study focused on asthma, finding a decrease in eosinophilia but no effect on clinical parameters.[239] 1+ 2+

In the absence of evidence of benefit, it is not possible to recommend the use of probiotics in the management of asthma.

3.4.6 IMMUNISATIONS

A number of large studies have concluded that high vaccination coverage has no significant impact on any allergic outcome or asthma. There is a suggestion that the higher the vaccine coverage the greater the possibility that there is a degree of protection against the development of allergy in the first years of life.[240-243]

There is some discussion about whether BCG immunisation may confer protection against allergy and asthma. Research has focused on primary prophylaxis, though there are some studies investigating the use of BCG, with or without allergen, as a means to switch off allergic immune responses. There are some observations suggesting that benefit might occur, [244] but results of trials have been disappointing.[245,246] This is an area that requires further investigation.

There has been concern that influenza vaccination might aggravate respiratory symptoms, though any such effect would be outweighed by the benefits of the vaccination.[247] Studies in children have suggested that immunisation with the vaccine does not exacerbate asthma[248] but has a small beneficial effect on quality of life in children with asthma.[249] The immune response to the immunisation may be adversely affected by high-dose inhaled corticosteroid therapy and this requires further investigation.[250] A Cochrane review of pneumococcal vaccine found very limited evidence to support its use specifically in individuals with asthma.[251] 1++

B **Immunisations should be administered independent of any considerations related to asthma. Responses to vaccines may be attenuated by high-dose inhaled steroids.**

3.5 COMPLEMENTARY AND ALTERNATIVE MEDICINE

Successive reviews have concluded that the evidence to support any recommendations on complementary or alternative medicine is lacking.[252] It is recognised that a lack of evidence does not necessarily mean that treatment is ineffective and high quality research, conducted in the same rigorous and objective fashion as that for conventional therapy, is required.

3.5.1 ACUPUNCTURE

A Cochrane review of 21 trials highlighted many methodological problems with the studies reviewed. Only seven of the trials in 174 patients employed randomisation to active (recognised in traditional Chinese medicine to be of benefit in asthma) or sham acupuncture points (with no recognised activity) for the treatment of persistent or chronic asthma. Blinding was a major problem in the assessment of the results and there were considerable inconsistencies in methodology. The review concluded that there was no evidence for a clinically valuable benefit for acupuncture and no significant benefits in relation to lung function.[253] A later systematic review and meta-analysis of 11 randomised controlled trials found no evidence of an effect in reducing asthma severity but a suggestion that where broncho-constriction was induced to establish efficacy of acupuncture there was a beneficial effect. Concern was expressed about potential preferential publication in favour of positive outcome studies.[254] Two other trials of acupuncture in relation to induced asthma were also negative.[255,256] 1+

3.5.2 AIR IONISERS

Ionisers have been widely promoted as being of benefit for patients with asthma. A Cochrane review of five studies using negative ion generators and one with a positive ion generator found no evidence of benefit in reducing symptoms in patients with asthma.[257] One study demonstrated an increase in night-time cough to a level which approached statistical significance.[258] 1++ 1+

A **Air ionisers are not recommended for the treatment of asthma.**

3.5.3 BREATHING EXERCISES INCLUDING YOGA AND THE BUTEYKO BREATHING TECHNIQUE

The principle of yoga and Buteyko breathing technique is to control hyperventilation by lowering respiratory frequency. A Cochrane review of breathing exercises found no change in routine measures of lung function.[259] One study showed a small reduction in airway responsiveness to histamine utilising pranayama, a form of yoga breathing exercise.[260] 1++ 1+

The Buteyko breathing technique specifically focuses on control of hyperventilation and any ensuing hypocapnia. Four clinical trials suggest benefits in terms of reduced symptoms and bronchodilator usage but no effect on lung function.[261-264] 1+

B **Buteyko breathing technique may be considered to help patients to control the symptoms of asthma.**

3.5.4 HERBAL AND TRADITIONAL CHINESE MEDICINE

A Cochrane review identified 17 trials, nine of which reported some improvement in lung function but it was not clear that the results would be generalisable.[265] A more recent double blind placebo controlled trial of a Chinese herb decoction (Ding Chuan Tang) showed improvement in airway hyper-responsiveness in children with stable asthma.[266] It is difficult to disentangle the effects of multiple ingredients; Ding Chuan Tang for example contains nine components. In a second study,100 children with asthma found that a five-herb mixture gave some benefits in relation to lung function and symptoms compared with placebo.[267] 1+

The conclusions of these trials of Chinese herbal therapy are not generalisable due to variations in the herbal mixtures and study designs. There are likely to be pharmacologically active ingredients in the mixtures and further investigations are warranted. There is a need for large appropriately powered placebo controlled studies.

3.5.5 HOMEOPATHY

A Cochrane review identified only three methodologically sound randomised controlled trials, two of which reported some positive effects. A criticism of the studies was that they did not employ individualised homeopathy, which is the essence of this approach to treatment.[268] A more recent trial of individualised homeopathy in childhood asthma, which was placebo controlled and appropriately powered, failed to show any evidence of benefit over conventional treatment in primary care.[269]

1++
1+

3.5.6 HYPNOSIS AND RELAXATION THERAPIES

A systematic review of relaxation therapies, including hypnotherapy, identified five controlled trials, two of which showed some benefits. Overall the methodology of the studies was poor and the review concluded that there was a lack of evidence of efficacy but that muscle relaxation could conceivably benefit lung function in patients with asthma.[270]

1++

3.6 OTHER COMPLEMENTARY OR ALTERNATIVE APPROACHES

3.6.1 MANUAL THERAPY INCLUDING MASSAGE AND SPINAL MANIPULATION

A Cochrane review identified four relevant RCTs.[271] The two trials of chiropractic suggest that there is no place for this modality of treatment in the management of asthma. No conclusions can be drawn on massage therapy.

3.6.2 PHYSICAL EXERCISE TRAINING

A Cochrane review [259] has shown no effect of physical training on PEF, FEV_1, FVC or VEmax. However, oxygen consumption, maximum heart rate, and work capacity all increased significantly. Most studies discussed the potential problems of exercise induced asthma, but none made any observations on this phenomenon. As physical training improves indices of cardiopulmonary efficiency, it should be seen as part of a general approach to improving lifestyle and rehabilitation in asthma, with appropriate precautions advised about exercise induced asthma *(see section 4.7.2)*.

3.6.3 FAMILY THERAPY

A Cochrane review identified two trials, in 55 children, showing that family therapy may be a useful adjunct to medication in children with asthma.[272] Small study size limits the recommendations.

☑ In difficult childhood asthma, there may be a role for family therapy as an adjunct to pharmacotherapy.

Revised 2009

4 Pharmacological management

The aim of asthma management is control of the disease. Control of asthma is defined as:

- no daytime symptoms
- no night-time awakening due to asthma
- no need for rescue medication
- no exacerbations
- no limitations on activity including exercise
- normal lung function (in practical terms FEV_1 and/or PEF > 80% predicted or best) with minimal side effects.

In clinical practice patients may have different goals and may wish to balance the aims of asthma management against the potential side effects or inconvenience of taking medication necessary to achieve perfect control.

☑ Lung function measurements cannot be reliably used to guide asthma management in children under five years of age.

A stepwise approach aims to abolish symptoms as soon as possible and to optimise peak flow by starting treatment at the level most likely to achieve this. Patients should start treatment at the step most appropriate to the initial severity of their asthma. The aim is to achieve early control and to maintain by stepping up treatment as necessary and stepping down when control is good *(see figures 4, 5 and 6 for summaries of stepwise management in adults and children)*.

☑ Before initiating a new drug therapy practitioners should check compliance with existing therapies *(see section 9.2)*, inhaler technique *(see section 5)* and eliminate trigger factors *(see section 3)*.

2009 Until May 2009 all doses of inhaled steroids in this section have been referenced against beclometasone (BDP) given via CFC-MDIs (metered dose inhaler). As BDP CFC is phased out, the reference inhaled steroid will be the BDP-HFA equivalent, which can be used at the same dosage. Adjustments to doses will have to be made for other devices and other corticosteroid molecules *(see section 4.2)*.

In this and the following section, each recommendation has been graded and the supporting evidence assessed for adults (>12 years old), children 5-12 years, and children under 5 years. The evidence is less clear in children under two and the threshold for seeking an expert opinion should be lowest in these children.

1 2 3 **1 Adults**
2 Children aged 5-12 years
3 Children under 5 years

■ **Recommendation does not apply to this age group.**

4.1 STEP 1: MILD INTERMITTENT ASTHMA

>12 years	5-12 years	<5 years
1++	1+	4
1+	1++	
1++		
1++		

The following medicines act as short-acting bronchodilators:

inhaled short-acting β_2 agonists[273]

inhaled ipratropium bromide[274]

β_2 agonist tablets or syrup[273]

theophyllines.[273]

Short-acting inhaled β_2 agonists work more quickly and/or with fewer side effects than the alternatives.[273]

A B C **Prescribe an inhaled short-acting β_2 agonist as short term reliever therapy for all patients with symptomatic asthma.**

4.1.1 FREQUENCY OF DOSING OF INHALED SHORT-ACTING β_2 AGONISTS

>12 years	5-12 years	<5 years
1++	1++	1++

Using short-acting β_2 agonists as required is at least as good as regular (four times daily) administration.[275,276] Unless individual patients are shown to benefit from regular use of inhaled short-acting β_2 agonists then as required use is recommended.

Good asthma control is associated with little or no need for short-acting β_2 agonist. Using two or more canisters of β_2 agonists per month or >10-12 puffs per day is a marker of poorly controlled asthma that puts patients at risk of fatal or near-fatal asthma.

☑ Patients with a high usage of inhaled short-acting β_2 agonists should have their asthma management reviewed.

4.2 STEP 2: INTRODUCTION OF REGULAR PREVENTER THERAPY

For steps 2, 3, and 4, treatments have been judged on their ability to improve symptoms, improve lung function, and prevent exacerbations, with an acceptable safety profile. Improvement of quality of life, while important, is the subject of too few studies to be used to make recommendations at present.

4.2.1 COMPARISON OF INHALED STEROIDS

Many studies comparing different inhaled steroids are of inadequate design and have been omitted from further assessment. In view of the clear differences between normal volunteers and asthma patients in the absorption of inhaled steroids, data from normal volunteers have not been taken into account. Only studies in which more than one dose of at least one of the inhaled steroids or both safety and efficacy had been studied together in the same trial were evaluated. Non-blinded studies also had to be considered because of the problems of obtaining competitors' delivery devices. A series of Cochrane reviews comparing different inhaled steroids using a different methodology have come to the same conclusion.

BDP and budesonide are approximately equivalent in clinical practice, although there may be variations with different delivery devices. There is limited evidence from two open studies of less than ideal design that budesonide via the turbohaler is more clinically effective.[295] However, at present a 1:1 ratio should be assumed when changing between BDP and budesonide.

Fluticasone provides equal clinical activity to BDP and budesonide at half the dosage. The evidence that it causes fewer side effects at doses with equal clinical effect is limited.

Mometasone appears to provide equal clinical activity to BDP and budesonide at half the dosage.[296] The relative safety of mometasone is not fully established.

2009

Table 8b: Equivalent doses of inhaled steroids relative to BDP and current licensed age indications

These dosage equivalents are approximate and will depend on other factors such as inhaler technique.

		UK licence covers		
Steroid	**Equivalent dose**	**>12 years**	**5 – 12 years**	**<5 years**
Beclometasone dipropionate CFC	400 mcg	**No longer available**		
Beclometasone				
Clenil modulite	400 mcg	✓	✓	✓
Clickhaler		✓	Over age 6	×
Aerobec Autohaler		✓	×	×
Asmabec Clickhaler		✓	Over age 6	×
Dry powder (Becodisks)		✓	✓	✓
Easyhaler		✓	×	×
Pulvinal		✓	Over age 6	×
Filair		✓	✓	✓
Qvar	200 to 300 mcg	✓	×	×
Fostair	200 mcg	Over age 18	×	×
Budesonide				
Turbohaler	400 mcg	✓	✓	×
Metered dose inhaler		✓	✓	Over age 2
Easyhaler		✓	Over age 6	×
Novolizer		✓	Over age 6	×
Symbicort		✓	Over age 6	×
Symbicort (regular and as required dosing)		Over age 18	×	×
Fluticasone				
Metered dose inhaler (HFA)	200 mcg	✓	✓	Over age 4
Accuhaler		✓	✓	Over age 4
Seretide HFA		✓	✓	Over age 4
Seretide (Accuhaler)		✓	✓	Over age 4
Mometasone	200 mcg	✓	×	×
Ciclesonide	200 to 300 mcg	✓	×	×

Ciclesonide is a new inhaled steroid. Evidence from clinical trials suggests that it has less systemic activity and fewer local oropharyngeal side effects than conventional inhaled steroids.[297-301] The clinical benefit of this is not clear as the exact efficacy to safety ratio compared to other inhaled steroids has not been fully established.

Non-CFC beclometasone is available in more than one preparation, and the potency relative to CFC beclometasone is not consistent between these *(see section 5.4)*.

4.2.2 INHALED STEROIDS

Inhaled steroids are the most effective preventer drug for adults and older children for achieving overall treatment goals.[278-282] There is an increasing body of evidence demonstrating that, at recommended doses, they are also safe and effective in children under five years with asthma.[283-286]

>12 years	5-12 years	<5 years
1++	1++	1++

Many non-atopic children with recurrent episodes of viral-induced wheezing in children under five years do not go on to have chronic atopic asthma. The majority do not require treatment with regular inhaled steroids *(see section 2.1)*.

A	A	A	**Inhaled steroids are the recommended preventer drug for adults and children for achieving overall treatment goals.**

Inhaled steroids should be considered for adults, children aged 5-12 and children under the age of five with any of the following features: using inhaled β_2 agonists three times a week or more; symptomatic three times a week or more; or waking one night a week. In addition, inhaled steroids should be considered in adults and children aged 5-12 who have had an exacerbation of asthma requiring oral corticosteroids in the last two years.[287,288 767-769]

>12 years	5-12 years	<5 years
1+	1+	1+

Inhaled steroids should be considered for patients with any of the following asthma-related features:

B	C	■	**exacerbations of asthma in the last two years**
B	B	B	**using inhaled β_2 agonists three times a week or more**
B	B	B	**symptomatic three times a week or more**
B	C	☑	**waking one night a week.**

Starting dose of inhaled steroids

In mild to moderate asthma, starting at very high doses of inhaled steroids and stepping down confers no benefit.[289]

>12 years	5-12 years	<5 years
1+	1+	

☑ Start patients at a dose of inhaled steroids appropriate to the severity of disease.

☑ In adults, a reasonable starting dose will usually be 400 mcg BDP per day and in children 200 mcg BDP per day. In children under five years, higher doses may be required if there are problems in obtaining consistent drug delivery.

☑ Titrate the dose of inhaled steroid to the lowest dose at which effective control of asthma is maintained.

Frequency of dosing of inhaled steroids

Most current inhaled steroids are slightly more effective when taken twice rather than once daily, but may be used once daily in some patients with milder disease.[273,279,290,767,770]

>12 years	5-12 years	<5 years
1+	1+	1+

There is little evidence of benefit for dosage frequency more than twice daily.[279]

A	D	D	**Give inhaled steroids initially twice daily, except ciclesonide which is given once daily.**
A	D	D	**Once a day inhaled steroids at the same total daily dose can be considered if good control is established.**

4.2.3 SAFETY OF INHALED STEROIDS

The safety of inhaled steroids is of crucial importance and a balance between benefits and risks for each individual needs to be assessed. Account should be taken of other topical steroid therapy when assessing systemic risk. It has been suggested that steroid warning cards should be issued to patients on higher dose inhaled steroids, but the benefits and possible disadvantages, particularly with regard to compliance, of such a policy remain to be defined.

Adults

There is little evidence that doses below 800 mcg BDP per day cause any short term detrimental effects apart from the local side effects of dysphonia and oral candidiasis. However, the possibility of long term effects on bone has been raised. One systematic review reported no effect on bone density at doses up to 1,000 mcg BDP per day.[291] The significance of small biochemical changes in adrenocortical function is unknown.

☑ Titrate the dose of inhaled steroid to the lowest dose at which effective control of asthma is maintained.

Children

Administration of inhaled steroids at or above 400 mcg BDP a day or equivalent may be associated with systemic side effects.[292] These may include growth failure and adrenal suppression. Isolated growth failure is not a reliable indicator of adrenal suppression and monitoring growth cannot be used as a screening test of adrenal function.[290,293]

Clinical adrenal insufficiency has been identified in a small number of children who have become acutely unwell at the time of intercurrent illness. Most of these children had been treated with high doses of inhaled corticosteroids. The dose or duration of inhaled steroid treatment required to place a child at risk of clinical adrenal insufficiency is unknown but is likely to occur at ≥800 mcg BDP per day or equivalent. The low-dose ACTH test is considered to provide a physiological stimulation of adrenal responsiveness but it is not known how useful such a sensitive test is at predicting clinically relevant adrenal insufficiency.[59,294] In addition, it is unknown how frequently tests of adrenal function would need to be repeated if a child remained on high-dose inhaled corticosteroid. At higher doses, add-on agents, for example, long-acting β_2 agonists, should be actively considered.

2009 While the use of inhaled corticosteroids may be associated with adverse effects (including the potential to reduced bone mineral density) with careful inhaled steroid dose adjustment this risk is likely to be outweighed by their ability to reduce the need for multiple bursts of oral corticosteroids.[771]

☑ Monitor height of children on high doses of inhaled steroids on a regular basis.

☑ The lowest dose of inhaled steroids compatible with maintaining disease control should be used.

For children treated with ≥800 mcg BDP per day or equivalent:

☑ Specific written advice about steroid replacement (eg Steroid Alert Card) in the event of a severe intercurrent illness or surgery should be part of the management plan.

☑ The child should be under the care of a specialist paediatrician for the duration of the treatment.

Consider the possibility of adrenal insufficiency in any child maintained on inhaled steroids presenting with shock or a decreased level of consciousness; serum biochemistry and blood glucose levels should be checked urgently. Consider whether intramuscular (IM) hydrocortisone is required.

4.2.4 SMOKING

Current and previous smoking reduces the effect of inhaled steroids; which may be overcome with increased doses.[187,302]

Patients should be advised that smoking reduces the effectiveness of therapy.

B **Clinicians should be aware that higher doses of inhaled steroids may be needed in patients who are smokers or ex-smokers.**

4.2.5 OTHER PREVENTER THERAPIES

Inhaled steroids are the first choice preventer drug. Long-acting inhaled β_2 agonists should not be used without inhaled corticosteroids.[303] Alternative, less effective preventer therapies in patients taking short-acting β_2 agonists alone are:

	>12 years	5-12 years	<5 years
▪ Chromones			
- Sodium cromoglicate is of some benefit in adults[273, 304] and is effective in children aged 5-12[305]	1^+	1^+	
- Nedocromil sodium is also of benefit in adults and children >5[306,307]	1^{++}	1^+	
- There is no clear evidence of benefit with sodium cromoglicate in children aged <5[308]			
▪ Leukotriene receptor antagonists have some beneficial clinical effect[279,309,310]	1^{++}	1^{++}	1^{++}
▪ Theophyllines have some beneficial effect[273,278]	1^+	1^+	1^+
▪ Antihistamines and ketotifen are ineffective[311]	1^{++}	1^{++}	1^{++}

☑ In children under five years who are unable to take inhaled corticosteroids, leukotriene receptor antagonists are an effective first line preventor.

4.3 STEP 3: INITIAL ADD-ON THERAPY

A proportion of patients with asthma may not be adequately controlled at step 2. Before initiating a new drug therapy practitioners should recheck compliance, inhaler technique and eliminate trigger factors. The duration of a trial of add-on therapy will depend on the desired outcome. For instance, preventing nocturnal awakening may require a relatively short trial of treatment (days or weeks), whereas preventing exacerbations of asthma or decreasing steroid tablet use may require a longer trial of therapy (weeks or months). If there is no response to treatment the drug should be discontinued.

4.3.1 CRITERIA FOR INTRODUCTION OF ADD-ON THERAPY

	>12 years	5-12 years	<5 years
No exact dose of inhaled steroid can be deemed the correct dose at which to add another therapy. The addition of other treatment options to inhaled steroids has been investigated at doses from 200-1,000 mcg BDP in adults and up to 400 mcg BDP in children.[312-315] Many patients will benefit more from add-on therapy than from increasing inhaled steroids above doses as low as 200 mcg BDP/day. At doses of inhaled steroid above 800 mcg BDP/day side effects become more frequent. An absolute threshold for introduction of add-on therapy in all patients cannot be defined.	1^+	1^+	

4.3.2 ADD-ON THERAPY

	>12 years	5-12 years	<5 years
Options for add-on therapy are summarised in Figure 3.			
In adult patients taking inhaled steroids at doses of 200-800 mcg BDP/day and in children taking inhaled steroids at a dose of 400 mcg/day the following interventions are of value:			
▪ first choice would be the addition of an inhaled long-acting β_2 agonist (LABA), which improves lung function and symptoms, and decreases exacerbations.[312,316,317]	1^{++}	1^{++}	

A B

The first choice as add-on therapy to inhaled steroids in adults and children *(5-12 years)* **is an inhaled long-acting β_2 agonist, which should be considered before going above a dose of 400 mcg BDP or equivalent per day and certainly before going above 800 mcg BDP.**

B

The first choice as add-on therapy to inhaled steroids in children under five years old is leukotriene receptor antagonists.

If, as occasionally happens, there is no response to inhaled long-acting β_2 agonist, stop the LABA and increase the dose of inhaled steroid to 800 mcg BDP/day *(adults)* or 400 mcg BDP/day *(children)* if not already on this dose. If there is a response to LABA, but control remains suboptimal, continue with the LABA and increase the dose of inhaled steroid to 800 mcg/day (adults) or 400 mcg/day (children 5-12 years).[318]

>12 years	5-12 years	<5 years
4	4	

D D

If asthma control remains suboptimal after the addition of an inhaled long-acting β_2 agonist then the dose of inhaled steroids should be increased to 800 mcg/day in adults or 400 mcg/day in children *(5-12 years)***, if not already on these doses.**

>12 years	5-12 years	<5 years
1^{++}	1^{++}	1^{+}
1^{+}	1^{-}	
1^{++}		

- **Leukotriene receptor antagonists** may provide improvement in lung function, a decrease in exacerbations, and an improvement in symptoms.[310,319,320]
- **Theophyllines** may improve lung function and symptoms, but side effects occur more commonly.[313]
- **Slow-release β_2 agonist tablets** may also improve lung function and symptoms, but side effects occur more commonly.[312]

☑ If control remains inadequate after stopping a LABA and increasing the dose of inhaled steroid, consider sequential trials of add-on therapy, ie leukotriene receptor antagonists, theophyllines, slow-release β_2 agonist tablets *(this in adults only)*.

Addition of short-acting anticholinergics is generally of no value.[314,321] Addition of nedocromil is of marginal benefit.[304,315]

>12 years	5-12 years	<5 years
1^{+}		

2009

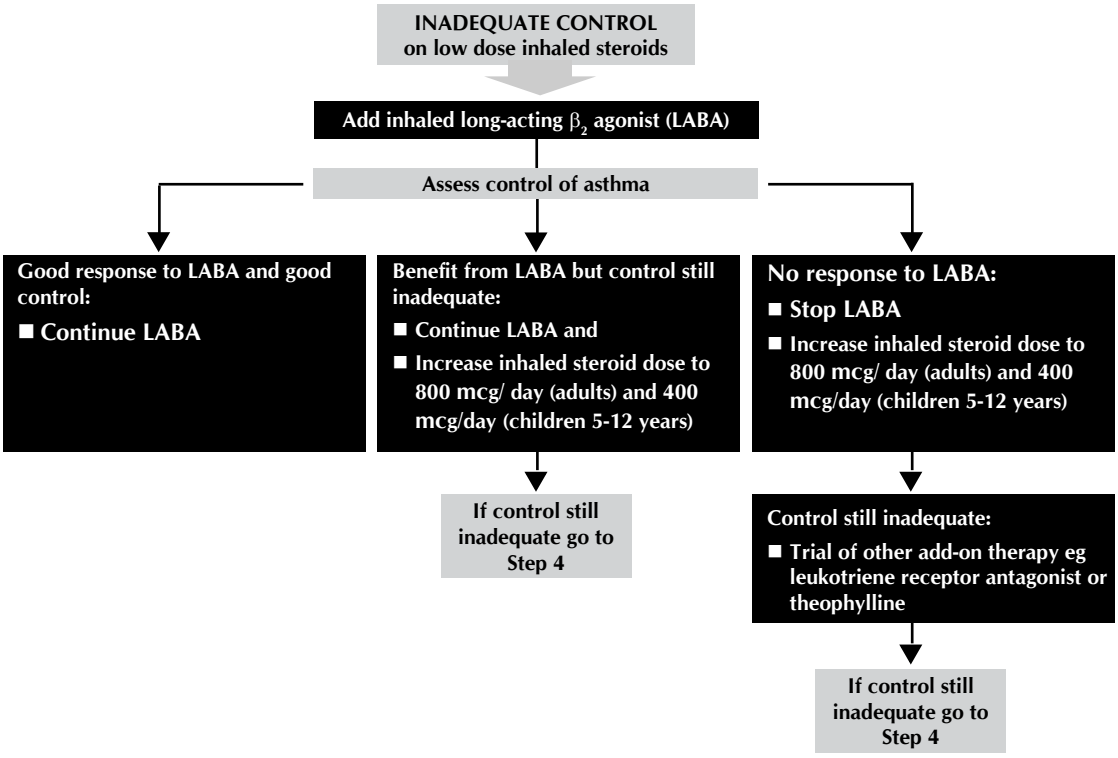
In selected adult patients at step 3 who are poorly controlled or in selected adult patients at step 2 (above BDP 400 mcg/day who are poorly controlled), the use of budesonide/formoterol in a single inhaler as rescue medication instead of a short-acting β_2 agonist, in addition to its regular use as controller therapy has been shown to be an effective treatment regimen.[323-327] When this management option is introduced the total regular dose of daily inhaled corticosteroids should not be decreased. The regular maintenance dose of inhaled steroids may be budesonide 200 mcg twice daily or budesonide 400 mcg twice daily. Patients taking rescue budesonide/formoterol once a day or more should have their treatment reviewed. Careful education of patients about the specific issues around this management strategy is required.

In patients on inhaled steroids whose asthma is stable, no intervention has been consistently shown to decrease inhaled steroid requirement in a clinically significant manner compared to placebo.

The Medicines and Healthcare products Regulatory Agency (MHRA) has completed a full review of the balance of risks and benefits associated with long-acting β_2 agonists in the management of asthma and chronic obstructive pulmonary disease.[322] They have concluded that long-acting β_2 agonists can continue to be used in the management of asthma provided they are used with inhaled corticosteroids. This issue has been reviewed by the guideline development group, which came to the same conclusion.

☑ Long-acting inhaled β_2 agonists should only be started in patients who are already on inhaled corticosteroids.

Figure 3: Summary of step 3: Add-on therapy



4.3.3 COMBINATION INHALERS

>12 years	5-12 years	<5 years
1++	1++	

There is no difference in efficacy in giving inhaled steroid and long-acting β_2 agonist in combination or in separate inhalers.[318]

Once a patient is on stable therapy, combination inhalers have the advantage of guaranteeing that the long-acting β_2 agonist is not taken without inhaled steroid.

4.4 STEP 4: POOR CONTROL ON MODERATE DOSE OF INHALED STEROID + ADD-ON THERAPY: ADDITION OF FOURTH DRUG

In a small proportion of patients asthma is not adequately controlled on a combination of short-acting β_2 agonist as required, inhaled steroid (800 mcg BDP daily), and an additional drug, usually a long-acting β_2 agonist. There are very few clinical trials in this specific patient group to guide management. The following recommendations are largely based on extrapolation from trials of add-on therapy to inhaled steroids alone.

D D

If control remains inadequate on 800 mcg BDP daily *(adults)* **and 400 mcg daily** *(children)* **of an inhaled steroid plus a long-acting β_2 agonist, consider the following interventions:**

- **increasing inhaled steroids to 2000 mcg BDP/day** *(adults)* **or 800 mcg BDP/day** *(children 5-12 years)* *****
- **leukotriene receptor antagonists**
- **theophyllines**
- **slow release β_2 agonist tablets, though caution needs to be used in patients already on long-acting β_2 agonists.**

* at high doses of inhaled steroid via MDI, a spacer should be used.

There are no controlled trials indicating which of these is the best option, although the potential for side effects is greater with theophyllines and β_2 agonist tablets.

☑ If a trial of an add-on treatment is ineffective, stop the drug (or in the case of increased dose of inhaled steroid, reduce to the original dose).

☑ Before proceeding to step 5, refer patients with inadequately controlled asthma, especially children, to specialist care.

4.5 STEP 5: CONTINUOUS OR FREQUENT USE OF ORAL STEROIDS

☑ For the small number of patients not controlled at step 4, use daily steroid tablets in the lowest dose providing adequate control.

4.5.1 PREVENTION AND TREATMENT OF STEROID TABLET-INDUCED SIDE EFFECTS

Patients on long term steroid tablets (eg longer than three months) or requiring frequent courses of steroid tablets (eg three to four per year) will be at risk of systemic side effects.[59]

- blood pressure should be monitored
- urine or blood sugar and cholesterol should be checked. Diabetes mellitus and hyperlipidaemia may occur
- bone mineral density should be monitored. When a significant reduction occurs, treatment with a long-acting bisphosphonate should be offered (see British Osteoporosis Society guidelines, www.nos.org.uk)[328]
- growth (height and weight) should be monitored in children
- cataracts may be screened for in children through community optometric services.

4.5.2 STEROID TABLET-SPARING MEDICATION

The aim of treatment is to control the asthma using the lowest possible dose or, if possible, to stop long term steroid tablets completely.

Inhaled steroids are the most effective drug for decreasing requirement for long term steroid tablets.[280,281]

>12 years	5-12 years	<5 years
1++	4	

There is limited evidence for the ability of long-acting β_2 agonists, theophyllines, or leukotriene receptor antagonists to decrease requirement for steroid tablets, but they may improve symptoms and pulmonary function.[329]

A D

In adults, the recommended method of eliminating or reducing the dose of steroid tablets is inhaled steroids, at doses of up to 2,000 mcg/day, if required.

In children aged 5-12, consider very carefully before going above an inhaled steroid dose of 800 mcg/day.

D D D

There is a role for a trial of treatment with long acting β_2 agonists, leukotriene receptor antagonists, and theophyllines for about six weeks. They should be stopped if no improvement in steroid dose, symptoms or lung function is detected.

Immunosuppressants (methotrexate, ciclosporin and oral gold) decrease long term steroid tablet requirements, but all have significant side effects. There is no evidence of persisting beneficial effect after stopping them; and there is marked variability in response.[330]

>12 years	5-12 years	<5 years
1++	3	

☑ Immunosuppressants (methotrexate, ciclosporin and oral gold) may be given as a three month trial, once other drug treatments have proved unsuccessful. Their risks and benefits should be discussed with the patient and their treatment effects carefully monitored. Treatment should be in a centre with experience of using these medicines.

	>12 years	5-12 years	<5 years
Colchicine and intravenous immunoglobulin have not been shown to have any beneficial effect in adults.[330]	1+		
Continuous subcutaneous terbutaline infusion has been reported to be beneficial in severe asthma but efficacy and safety have not been assessed in RCTs.[331,332,772,773]	4	3	3
Anti-TNF alpha therapy has been investigated in severe asthma [333,334] but these studies are too small and too short term to allow recommendation of anti-TNF therapy outside the context of a controlled clinical trial.			

4.5.3 ANTI-IGE MONOCLONAL ANTIBODY

Omalizumab is a humanised monoclonal antibody which binds to circulating IgE, markedly reducing levels of free serum IgE.[774,775] In adults and children over 12, it is licensed in the UK with the following indication; patients on high-dose inhaled steroids and long-acting β_2 agonists who have impaired lung function are symptomatic with frequent exacerbations, and have allergy as an important cause of their asthma. Omalizumab is given as a subcutaneous injection every two to four weeks depending on dose. The total IgE must be less than 700 iu/litre for it to be effective.

In the single study in the licensed group, there was a 19% reduction in exacerbations of asthma requiring oral steroids which was non-significant. When corrected for imbalance in the exacerbation history at baseline, there was a 26% reduction in severe exacerbations (0.91 on placebo vs 0.68 on omalizumab over a 28 week period, $p = 0.042$). This was associated with a 2.8% increase in FEV_1, a non-significant 0.5 puffs/day decrease in β_2 agonist use and 13% more patients having a significant improvement in health related quality of life. At IgE levels below 76 iu/l the beneficial effect is reduced.[776]	1-

Local skin reactions may occur. Anaphylaxis, presenting as bronchospasm, hypotension, syncope, urticaria, and/or angioedema of the throat or tongue has been reported to occur after administration of omalizumab. Anaphylaxis has occurred as early as the first dose, but has also occurred after one year. Due to risk of anaphylaxis, omalizumab should only be administered to patients in a healthcare setting under direct medical supervision.

☑ Omalizumab treatment should only be initiated in specialist centres with experience of evaluation and management of patients with severe and difficult asthma.

4.5.4 STEROID FORMULATIONS

Prednisolone is the most widely used steroid tablet for maintenance therapy in chronic asthma. There is no evidence that other formulations offer any advantage.

4.5.5 FREQUENCY OF DOSING OF STEROID TABLETS

Although popular in paediatric practice, there are no studies to show whether alternate day steroids produce fewer side effects than daily steroids.

Figure 4: Summary of stepwise management in adults

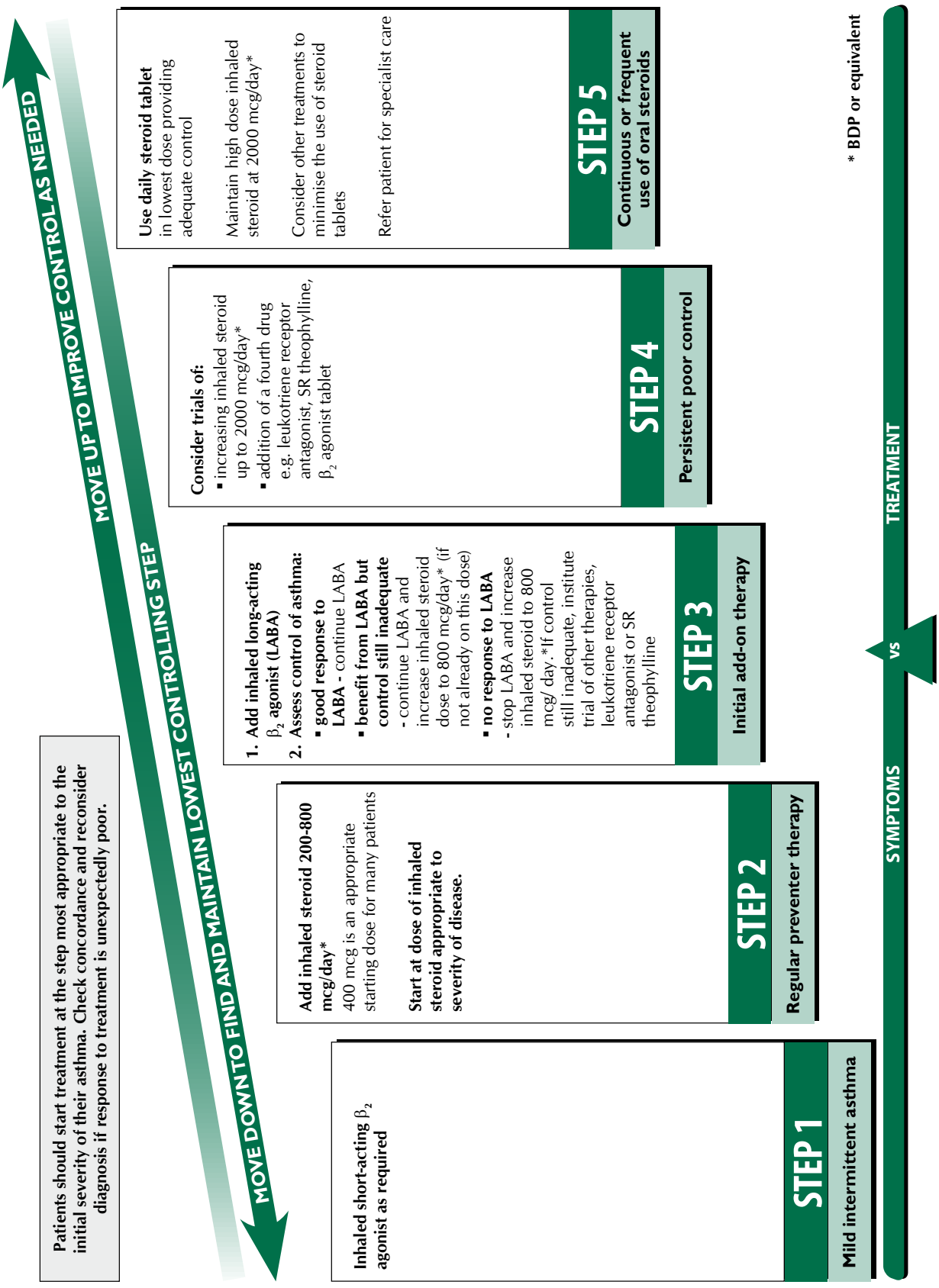


Figure 5: Summary of stepwise management in children aged 5-12 years

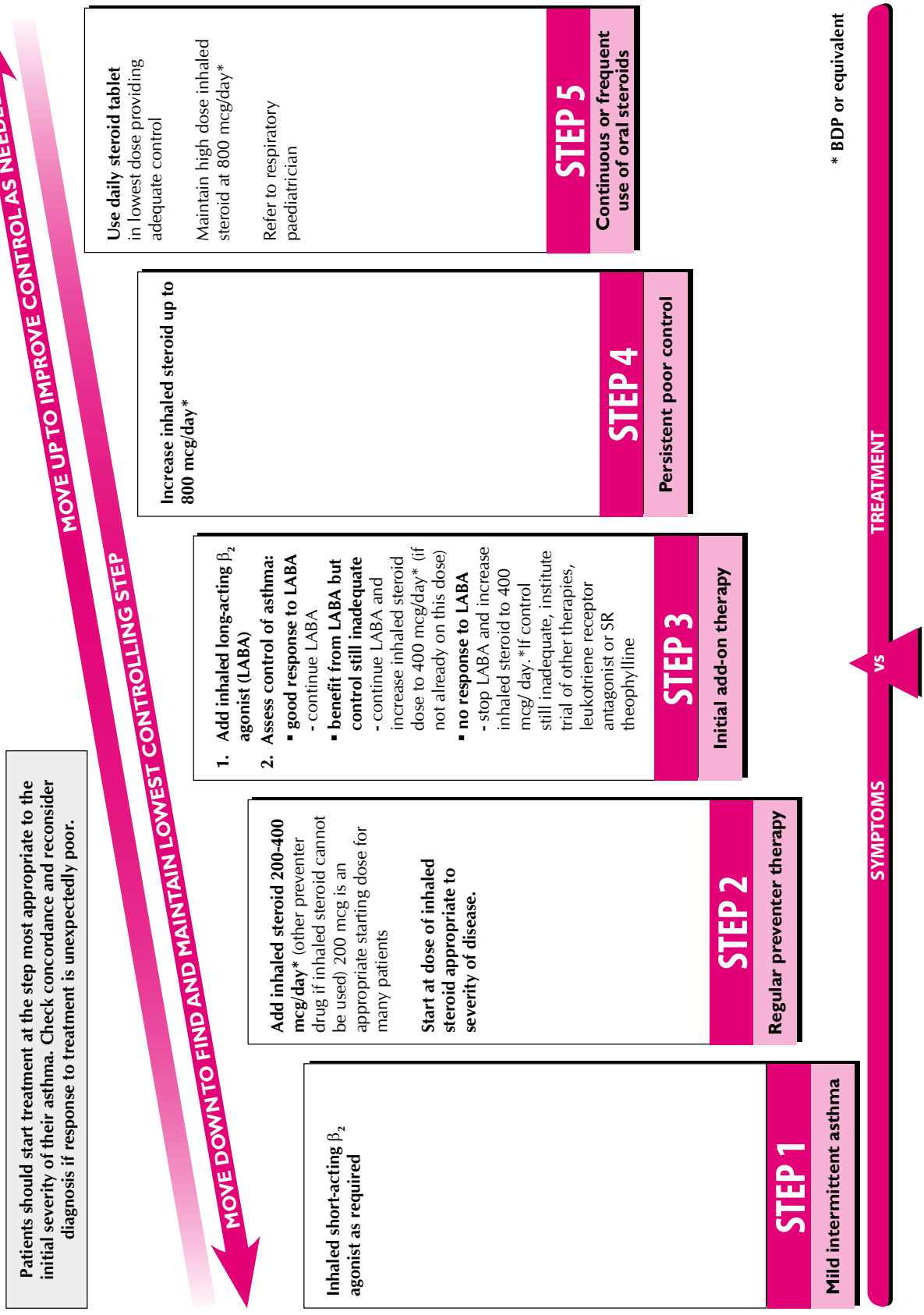
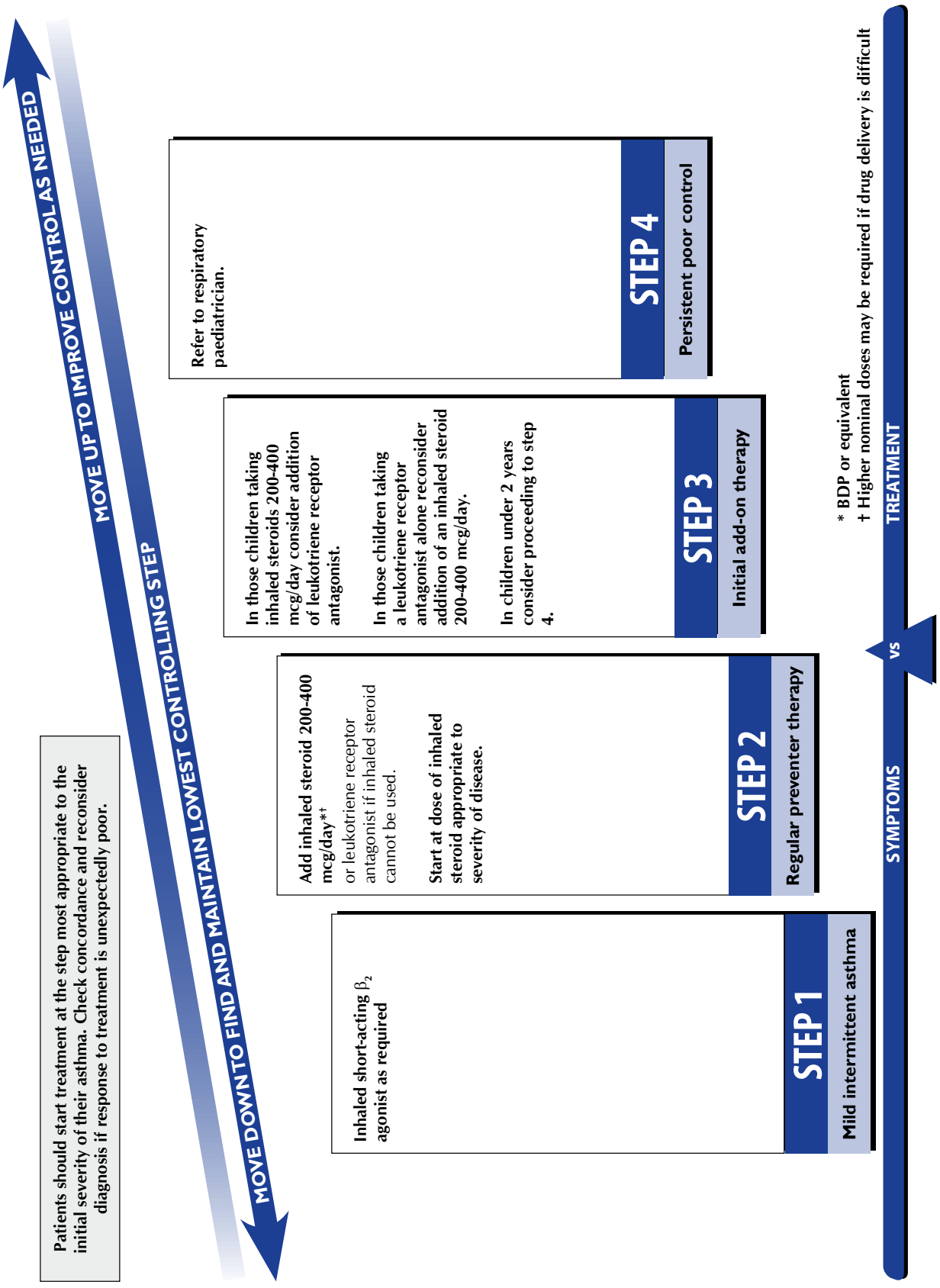


Figure 6: Summary of stepwise management in children less than 5 years



4.6 STEPPING DOWN

Stepping down therapy once asthma is controlled is recommended, but often not implemented leaving some patients over-treated. There are few studies that have investigated the most appropriate way to step down treatment. A study in adults on at least 900 mcg per day of inhaled steroids has shown that for patients who are stable it is reasonable to attempt to halve the dose of inhaled steroids every three months.[334]

2009 Some children with milder asthma and a clear seasonal pattern to their symptoms may have a more rapid dose reduction during their 'good' season.

☑ Regular review of patients as treatment is stepped down is important. When deciding which drug to step down first and at what rate, the severity of asthma, the side effects of the treatment, time on current dose, the beneficial effect achieved, and the patient's preference should all be taken into account.

☑ Patients should be maintained at the lowest possible dose of inhaled steroid. Reduction in inhaled steroid dose should be slow as patients deteriorate at different rates. Reductions should be considered every three months, decreasing the dose by approximately 25-50% each time.

4.7 SPECIFIC MANAGEMENT ISSUES

4.7.1 EXACERBATIONS OF ASTHMA

Although recommended for both adults and children in previous guidelines and as part of asthma action plans, doubling the dose at the time of an exacerbation is of unproven value.[335] In adult patients on a low dose (200 mcg BDP) of inhaled steroids, a fivefold increase in dose at the time of exacerbation leads to a decrease in the severity of exacerbations.[335,336] This study should not be extrapolated to patients already taking higher doses of inhaled steroids and further evidence in this area is required.

	>12 years	5-12 years	<5 years
2009 There is some limited evidence that leukotriene antagonists may be used intermittently in children with episodic asthma. Treatment is started at the onset of either asthma symptoms or of coryzal symptoms and continued for seven days.[777]		1^{++}	1^{++}

The benefits of parent-initiated oral steroids at the start of an exacerbation has not been proven.[778]

4.7.2 EXERCISE INDUCED ASTHMA

When given chronically the following medicines give protection against exercise induced asthma:	>12 years	5-12 years	<5 years
▪ inhaled steroids[280, 281,337]	1^{++}	1^{++}	
▪ short-acting β_2 agonists[273]	1^{++}	1^{++}	
▪ long-acting β_2 agonists[338]	1^{++}	1^{++}	
▪ theophyllines[329,339]	1^{-}	2^{+}	
▪ leukotriene receptor antagonists[340]	1^{++}	2^{+}	
▪ chromones[341]	1^{++}	2^{+}	
▪ β_2 agonist tablets.[342]	1^{++}	1^{+}	
The following medicines do not give protection against exercise induced asthma at normal doses:			
▪ anticholinergics[343]	1^{+}	1^{+}	
▪ ketotifen[344]	1^{+}	1^{+}	
▪ antihistamine.[345]	1^{++}	1^{++}	

Long-acting β_2 agonists and leukotriene antagonists provide more prolonged protection than short-acting β_2 agonists, but a degree of tolerance develops with LABA particularly with respect to duration of action. No tolerance has been demonstrated with leukotriene receptor antagonists.[338,340,779]	>12 years	5-12 years	<5 years
	1^{++}	1^{++}	

☑ For most patients, exercise induced asthma is an expression of poorly controlled asthma and regular treatment including inhaled steroids should be reviewed.

If exercise is a specific problem in patients taking inhaled steroids who are otherwise well controlled, consider the following therapies:

A C ▪ **leukotriene receptor antagonists**

A A ▪ **long-acting β_2 agonists**

C C ▪ **chromones**

A A ▪ **oral β_2 agonists**

C C ▪ **theophyllines.**

Immediately prior to exercise, inhaled short-acting β_2 agonists are the drug of choice.[273]

A A **Immediately prior to exercise, inhaled short-acting β_2 agonists are the drug of choice.**

4.7.3 RHINITIS

Patients with asthma often have rhinitis. The most effective therapy is intranasal steroids.[346] Treatment of allergic rhinitis with intranasal steroids has not been shown in double blind placebo-controlled trials to improve asthma control.

>12 years	5-12 years	<5 years
1+		

4.7.4 ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS

In adult patients with allergic bronchopulmonary aspergillosis (ABPA), itraconazole may decrease steroid tablet dose and improve asthma control.[347,348]

>12 years	5-12 years	<5 years
1+ 2+		

C **In adult patients with ABPA, a four month trial of itraconazole should be considered.**

☑ Careful monitoring for side effects, particularly hepatic, is recommended.

4.7.5 ASPIRIN-INTOLERANT ASTHMA

There are theoretical reasons to suggest that leukotriene receptor antagonists might be of particular value in the treatment of aspirin-intolerant asthma. However, there is little evidence to justify managing patients with aspirin-intolerant asthma in a different manner to other patients with asthma, apart from the rigorous avoidance of non-steroidal anti-inflammatory medications.[349]

4.7.6 GASTRO-OESOPHOGEAL REFLUX

A Cochrane review of twelve double blind controlled trials found that treatment of gastro-oesophageal reflux had no benefit on asthma symptoms or lung function when both conditions were present. Reduction in dry cough was observed although this was probably not due to improved asthma control.[350,351]

4.7.7 β-BLOCKERS

β-blockers, including eye drops, are contraindicated in patients with asthma.

5 Inhaler devices

Although studies of inhaler devices are more suitable for an evidence based approach than many other aspects of asthma management, a number of methodological issues complicate evidence review in this area. In young (0-5 years) children, little or no evidence is available on which to base recommendations.

5.1 TECHNIQUE AND TRAINING

Studies of technique and the effects of training have used arbitrary non-standardised scores making comparison difficult. Although technique will have some bearing, it does not necessarily relate to clinical effectiveness.

The proportion of patients making no mistakes with an inhaler in one well conducted study was 23-43% for pMDI, 53-59% for dry powder inhaler (DPI) and 55-57% for pMDI + spacer. When technique was assessed as number of steps correct out of the total number of steps, pMDI + spacer was slightly better than DPI.[352]

Teaching technique improved the correct usage score from a mean of 60% to 79%. Figures for no mistakes post-teaching were 63% for pMDI, 65% for DPI, and 75% for breath-actuated MDI (the latter figure based on one study of 2,467 patients).[352]

>12 years	5-12 years	<5 years
1++		

B ☑ ☑ **Prescribe inhalers only after patients have received training in the use of the device and have demonstrated satisfactory technique.**

5.2 β_2 AGONIST DELIVERY

5.2.1 ACUTE ASTHMA

pMDI + spacer is at least as good as a nebuliser at treating mild and moderate exacerbations of asthma in children and adults.[353-356]

>12 years	5-12 years	<5 years
1++	1++	

A A B **Children and adults with mild and moderate exacerbations of asthma should be treated by pMDI + spacer with doses titrated according to clinical response.**

There are no data to make recommendations in severe (life threatening) asthma.

5.2.2 STABLE ASTHMA

For children aged 0-5, there is no evidence comparing nebuliser and other inhalers and the data are insufficiently extensive or robust to draw conclusions for pMDI vs. DPI.

In children aged 5-12 there is no significant difference between pMDI and DPI. In adults there is no significant difference between pMDI + spacer and DPI. The lower pulse rate with pMDI v Turbohaler is the only difference with regard to side effects. Patients have been shown to prefer Turbohaler to pMDI.[352,357,358]

>12 years	5-12 years	<5 years
	1++	

A **In children aged 5-12, pMDI + spacer is as effective as any other hand held inhaler.**

A **In adults, pMDI ± spacer is as effective as any other hand held inhaler, but patients may prefer some types of DPI.**

There are no data to make recommendations in children under five.

☑ Choice of reliever inhaler for stable asthma should be based on patient preference and assessment of correct use. Many patients will not be prepared to carry a spacer.

5.3 INHALED STEROIDS FOR STABLE ASTHMA

There are no comparative data on inhaled steroids for stable asthma in children under five years. A single study included 4-5 year olds, but the data were not extractable.

For the delivery of inhaled steroids in stable asthma in children aged 5-12 years, pMDI is as effective as Clickhaler,[359,360] and Pulvinal is as effective as Diskhaler.[361] No significant clinical difference was found between pMDI and Turbohaler at half the dose for the same drug (budesonide).[352,362] This comparison cannot necessarily be made against other inhaled steroid /device combinations.

>12 years	5-12 years	<5 years

In adults, there is no clinical difference in effectiveness of pMDI ± spacer v DPI. Breath-actuated MDI is as effective as pMDI. More recent DPIs are as effective as older DPIs.[305] Nebulisers have not been shown to be superior to pMDI + spacer for delivery of inhaled steroids in chronic asthma. A specialised specific nebuliser may provide improved lung function and reduced rescue therapy use, but at high prescribed doses. Higher doses (>2 mg) are generally only licensed for use from a nebuliser.[352,362]

>12 years	5-12 years	<5 years
1++	1++	

[ ] [A] [ ] **In children aged 5-12 years, pMDI + spacer is as effective as any DPI.**

[A] [ ] [ ] **In adults, a pMDI ± spacer is as effective as any DPI.**

No recommendation can be given for nebulised therapy in children aged 5-12 years and there is no evidence relating to children aged <5 years.

5.4 CFC PROPELLANT PMDI VS HFA PROPELLANT PMDI

HFA pMDI salbutamol is as effective as CFC pMDI salbutamol at standard therapeutic doses.[359,363-368]

>12 years	5-12 years	<5 years
1++		

It is important to differentiate Qvar from other HFA beclametasone products. Many studies now show Qvar equivalence at half the dose of CFC BDP pMDI, whereas non-Qvar HFA BDP pMDI studies show equivalence at 1:1 dosing. [360,369-375]

HFA fluticasone is as effective as CFC fluticasone across the standard clinical dose range.[376-380]

>12 years	5-12 years	<5 years
1++		

[A] [ ] [ ] **Salbutamol HFA can be substituted for salbutamol CFC at 1:1 dosing.**

[A] [ ] [ ] **HFA BDP pMDI (Qvar) may be substituted for CFC BDP pMDI at 1:2 dosing. This ratio does not apply to reformulated HFA BDP pMDIs.**

[A] [ ] [ ] **Fluticasone HFA can be substituted for fluticasone CFC at 1:1 dosing.**

5.5 PRESCRIBING DEVICES

There is no evidence to dictate an order in which devices should be tested for those patients who cannot use pMDI. In the absence of evidence, the most important points to consider are patient preference and local cost.

☑
- The choice of device may be determined by the choice of drug.
- If the patient is unable to use a device satisfactorily an alternative should be found.
- The patient should have their ability to use an inhaler device assessed by a competent healthcare professional *(see section 5.1)*.
- The medication needs to be titrated against clinical response to ensure optimum efficacy.
- Reassess inhaler technique as part of structured clinical review *(see section 8.1.2)*.

☑ In children aged 0-5 years, pMDI and spacer are the preferred method of delivery of β_2 agonists or inhaled steroids. A face mask is required until the child can breathe reproducibly using the spacer mouthpiece. Where this is ineffective a nebuliser may be required.

5.6 USE AND CARE OF SPACERS

☑
- The spacer should be compatible with the pMDI being used.
- The drug should be administered by repeated single actuations of the metered dose inhaler into the spacer, each followed by inhalation.
- There should be minimal delay between pMDI actuation and inhalation.
- Tidal breathing is as effective as single breaths.
- Spacers should be cleaned monthly rather than weekly as per manufacturer's recommendations or performance is adversely affected. They should be washed in detergent and allowed to dry in air. The mouthpiece should be wiped clean of detergent before use.
- Drug delivery may vary significantly due to static charge. Metal and other antistatic spacers are not affected in this way.
- Plastic spacers should be replaced at least every 12 months but some may need changing at six months.

Revised 2009

6 Management of acute asthma

6.1 LESSONS FROM STUDIES OF ASTHMA DEATHS AND NEAR-FATAL ASTHMA

Confidential enquires into over 200 asthma deaths in the UK conclude there are factors associated with the disease, the medical management and the patient's behaviour or psychosocial status which contribute to death. Most deaths occurred before admission to hospital.[381-385]

6.1.1 DISEASE FACTORS

Most patients who died of asthma had chronically severe asthma. In a minority the fatal attack occurred suddenly in a patient with mild or moderately severe background disease.[381-386] 2++

6.1.2 MEDICAL MANAGEMENT

Many of the deaths occurred in patients who had received inadequate treatment with inhaled steroid or steroid tablets and/or inadequate objective monitoring of their asthma. Follow up was inadequate in some and others should have been referred earlier for specialist advice. Asthma deaths are associated with fewer general practice contacts and more home visits.[780] There was widespread under-use of written management plans. Heavy or increasing use of β_2 agonist therapy was associated with asthma death.[381-385,387,388] 2++

2009 Deaths continue to be reported following inappropriate prescription of β-blockers and NSAIDs; all asthma patients should be asked about past reactions to these agents *(see section 4.7.7)*.

2009 Patients with acute asthma should not be sedated unless this is to allow anaesthetic or intensive care procedures (*see section 6.3.12*).[781]

6.1.3 ADVERSE PSYCHOSOCIAL AND BEHAVIOURAL FACTORS

Behavioural and adverse psychosocial factors were recorded in the majority of patients who died of asthma.[381-385] The most important are shown in Table 9.

Table 9: Patients at risk of developing near-fatal or fatal asthma

A COMBINATION OF SEVERE ASTHMA recognised by one or more of:
▪ previous near-fatal asthma, eg previous ventilation or respiratory acidosis ▪ previous admission for asthma especially if in the last year ▪ requiring three or more classes of asthma medication ▪ heavy use of β_2 agonist ▪ repeated attendances at ED for asthma care especially if in the last year ▪ "brittle" asthma.
AND ADVERSE BEHAVIOURAL OR PSYCHOSOCIAL FEATURES recognised by one or more of:
▪ non-compliance with treatment or monitoring ▪ failure to attend appointments ▪ fewer GP contacts ▪ frequent home visits ▪ self discharge from hospital ▪ psychosis, depression, other psychiatric illness or deliberate self harm ▪ current or recent major tranquilliser use ▪ denial ▪ alcohol or drug abuse ▪ obesity ▪ learning difficulties ▪ employment problems ▪ income problems ▪ social isolation ▪ childhood abuse ▪ severe domestic, marital or legal stress.

2009

Case control studies support most of these observations.[389,390] Compared with control patients admitted to hospital with asthma, those who died were significantly more likely to have learning difficulties; psychosis or prescribed antipsychotic drugs; financial or employment problems; repeatedly failed to attend appointments or discharged themselves from hospital; drug or alcohol abuse; obesity; or a previous near-fatal attack. 2++

Compared with control patients with asthma in the community, patients who died had more severe disease; more likelihood of a hospital admission or visit to the ED for their asthma in the previous year; more likelihood of a previous near-fatal attack; poor medical management; failure to measure pulmonary function; and non-compliance.

B **Healthcare professionals must be aware that patients with severe asthma and one or more adverse psychosocial factors are at risk of death.**

Studies comparing near-fatal asthma with deaths from asthma have concluded that patients with near-fatal asthma have identical adverse factors to those described in table 9, and that these contribute to the near-fatal asthma attack.[391-393] Compared with patients who die, those with near-fatal asthma are significantly younger, are significantly more likely to have had a previous near-fatal asthma attack, are less likely to have concurrent medical conditions, are less likely to experience delay in receiving medical care, and more likely to have ready access to acute medical care. 2+

With near-fatal asthma it is advisable to involve a close relative when discussing future management.

Patients with brittle or difficult asthma should also be identified *(see sections 6.2.3 and 7.1.1 and Table 10)*.

☑ Keep patients who have had near-fatal asthma or brittle asthma under specialist supervision indefinitely.

6.1.4 SEASONAL FACTORS

In the UK there is a peak of asthma deaths in people aged up to 44 years in July and August and in December and January in older people.[391,394] | 2++

6.1.5 PREDICTION AND PREVENTION OF A SEVERE ASTHMA ATTACK

Most attacks of asthma severe enough to require hospital admission develop relatively slowly over a period of six hours or more. In one study, over 80% developed over more than 48 hours.[395-400] There is, therefore, time for effective action to reduce the number of attacks requiring hospitalisation. There are many similarities between patients who die from asthma, patients with near-fatal asthma and control patients with asthma who are admitted to hospital. | 2++

☑ A respiratory specialist should follow up patients admitted with severe asthma for at least one year after the admission.

6.2 ACUTE ASTHMA IN ADULTS

Annexes 2-4 contain algorithms summarising the recommended treatment for patients presenting with acute or uncontrolled asthma in primary care *(Annex 2)*, ED *(Annex 3)*, and hospital *(Annex 4)*.

6.2.1 RECOGNITION OF ACUTE ASTHMA

Definitions of increasing levels of severity of acute asthma exacerbations are provided in table 10.[322,401-405] Predicted PEF values[406] should be used only if the recent best PEF (within two years) is unknown. | 2+ 4

6.2.2 SELF TREATMENT BY PATIENTS DEVELOPING ACUTE OR UNCONTROLLED ASTHMA

Patients with asthma, and all patients with severe asthma, should have an agreed written action plan and their own peak flow meter, with regular checks of inhaler technique and compliance. They should know when and how to increase their medication and when to seek medical assistance. Asthma action plans can decrease hospitalisation for[407] and deaths from[408] asthma *(see section 9.1)*.

6.2.3 INITIAL ASSESSMENT

All possible initial contact personnel, eg practice receptionists, ambulance call takers, NHS Direct (England and Wales), NHS24 (Scotland), should be aware that asthma patients complaining of respiratory symptoms may be at risk and should have immediate access to a doctor or trained asthma nurse. The assessments required to determine whether the patient is suffering from an acute attack of asthma, the severity of the attack and the nature of treatment required are detailed in tables 10 and 11. It may be helpful to use a systematic recording process. Proformas have proved useful in the ED setting.[409]

Table 10: Levels of severity of acute asthma exacerbations

Near-fatal asthma	Raised $PaCO_2$ and/or requiring mechanical ventilation with raised inflation pressures[391-393]	
Life threatening asthma	Any one of the following in a patient with severe asthma:	
	Clinical signs	Measurements
	Altered conscious level	PEF < 33% best or predicted
	Exhaustion	SpO_2 < 92%
	Arrhythmia	PaO_2 < 8 kPa
	Hypotension	"normal" $PaCO_2$ (4.6–6.0 kPa)
	Cyanosis	
	Silent chest	
	Poor respiratory effort	
Acute severe asthma	Any one of: - PEF 33-50% best or predicted - respiratory rate ≥ 25/min - heart rate ≥ 110/min - inability to complete sentences in one breath	
Moderate asthma exacerbation	- Increasing symptoms - PEF > 50-75% best or predicted - no features of acute severe asthma	
Brittle asthma	- Type 1: wide PEF variability (> 40% diurnal variation for > 50% of the time over a period > 150 days) despite intense therapy - Type 2: sudden severe attacks on a background of apparently well controlled asthma	

6.2.4 PREVENTION OF ACUTE DETERIORATION

A register of patients at risk may help primary care health professionals to identify patients who are more likely to die from their asthma. A system should be in place to ensure that these patients are contacted if they fail to attend for follow up.

6.2.5 CRITERIA FOR REFERRAL

D **Refer to hospital any patients with features of acute severe or life threatening asthma.**

Other factors, such as failure to respond to treatment, social circumstances or concomitant disease, may warrant hospital referral.

Table 11: Initial assessment - the role of symptoms, signs and measurements

	Clinical features	Clinical features can identify some patients with severe asthma, eg severe breathlessness (including too breathless to complete sentences in one breath), tachypnea, tachycardia, silent chest, cyanosis, accessory muscle use, altered consciousness or collapse.[322, 401-405,782]	2+
2009		None of these singly or together is specific. Their absence does not exclude a severe attack.	
	PEF or FEV_1	Measurements of airway calibre improve recognition of the degree of severity, the appropriateness or intensity of therapy, and decisions about management in hospital or at home.[410, 411]	
2009		PEF or FEV_1 are useful and valid measures of airway calibre. PEF is more convenient in the acute situation.	2+
		PEF expressed as a percentage of the patient's previous best value is most useful clinically. PEF as a percentage of predicted gives a rough guide in the absence of a known previous best value. Different peak flow meters give different readings. Where possible the same or similar type of peak flow meter should be used.	
	Pulse oximetry	Measure oxygen saturation (SpO_2) with a pulse oximeter to determine the adequacy of oxygen therapy and the need for arterial blood gas (ABG) measurement. The aim of oxygen therapy is to maintain SpO_2 94-98%.[783]	
2009			
	Blood gases (ABG)	Patients with $SpO_2 < 92\%$ (irrespective of whether the patient is on air or oxygen) or other features of life threatening asthma require ABG measurement.[322, 401-403, 405,413] $SpO_2 < 92\%$ is associated with a risk of hypercapnea. Hypercapnea is not detected by pulse oximetry.[784] In contrast the risk of hypercapnea with $SpO_2 > 92\%$ is much less.[783]	2+ 4
2009			
	Chest X-ray	Chest X-ray is not routinely recommended in patients in the absence of: – suspected pneumomediastinum or pneumothorax – suspected consolidation – life threatening asthma – failure to respond to treatment satisfactorily – requirement for ventilation.	4
	Systolic paradox	Systolic paradox (*pulsus paradoxus*) is an inadequate indicator of the severity of an attack and should not be used.[322, 401-405,414]	2+

6.2.6 CRITERIA FOR ADMISSION

B **Admit patients with any feature of a life threatening or near-fatal attack.**[381-385, 391,393]

B **Admit patients with any feature of a severe attack persisting after initial treatment.**[381-385, 391,393]

C **Patients whose peak flow is greater than 75% best or predicted one hour after initial treatment may be discharged from ED unless they meet any of the following criteria, when admission may be appropriate:**

- **still have significant symptoms**
- **concerns about compliance**
- **living alone/socially isolated**
- **psychological problems**
- **physical disability or learning difficulties**
- **previous near-fatal or brittle asthma**
- **exacerbation despite adequate dose steroid tablets pre-presentation**
- **presentation at night**
- **pregnancy.**

Criteria for admission in adults are summarised in annexes 2 and 3.

6.3 TREATMENT OF ACUTE ASTHMA IN ADULTS

6.3.1 OXYGEN

2009 Many patients with acute severe asthma are hypoxaemic.[415-418] Supplementary oxygen should be given urgently to hypoxaemic patients, using a face mask, Venturi mask or nasal cannulae with flow rates adjusted as necessary to maintain SpO_2 of 94-98%.[783] | 2^+ 4

2009 Hypercapnea indicates the development of near-fatal asthma and the need for emergency specialist/anaesthetic intervention.

2009 C **Give supplementary oxygen to all hypoxaemic patients with acute severe asthma to maintain an SpO_2 level of 94-98%. Lack of pulse oximetry should not prevent the use of oxygen.**

2009 Oxygen-driven nebulisers are preferred for nebulising β_2 agonist bronchodilators because of the risk of oxygen desaturation while using air-driven compressors.[322,353,419] | 1^{++}

2009 Emergency oxygen should be available in hospitals, ambulances and primary care. A flow rate of 6 l/min is required to drive most nebulisers. Where oxygen cylinders are used, a high flow regulator must be fitted.[783] | 4

2009 The absence of supplemental oxygen should not prevent nebulised therapy from being administered when appropriate.[420] | 4

2009 A **In hospital, ambulance and primary care, nebulised β_2 agonist bronchodilators should preferably be driven by oxygen.**

6.3.2 β_2 AGONIST BRONCHODILATORS

2009 In most cases inhaled β_2 agonists given in high doses act quickly to relieve bronchospasm with few side effects.[421-423] There is no evidence for any difference in efficacy between salbutamol and terbutaline. Nebulised adrenaline (epinephrine), a non-selective β_2 agonist, does not have significant benefit over salbutamol or terbutaline.[785] | 1^+ 1++

In acute asthma without life threatening features, β_2 agonists can be administered by repeated activations of a pMDI via an appropriate large volume spacer or by wet nebulisation driven by oxygen, if available.[786] Inhaled β_2 agonists are as efficacious and preferable to intravenous β_2 agonists (meta-analysis has excluded subcutaneous trials) in adult acute asthma in the majority of cases.[424] 1++

Metered dose inhalers with spacers can be used for patients with exacerbations of asthma other than life threatening.[786] 1++

A **Use high-dose inhaled β_2 agonists as first line agents in acute asthma and administer as early as possible. Reserve intravenous β_2 agonists for those patients in whom inhaled therapy cannot be used reliably.**

☑ In acute asthma with life threatening features the nebulised route (oxygen-driven) is recommended.

Parenteral β_2 agonists, in addition to inhaled β_2 agonists, may have a role in ventilated patients or those in extremis; however there is limited evidence to support this.

Most cases of acute asthma will respond adequately to bolus nebulisation of β_2 agonists. Continuous nebulisation of β_2 agonists with an appropriate nebuliser may be more effective than bolus nebulisation in relieving acute asthma for patients with a poor response to initial therapy.[425-427] 1+

A **In severe asthma that is poorly responsive to an initial bolus dose of β_2 agonist, consider continuous nebulisation with an appropriate nebuliser.**

Repeat doses of β_2 agonists at 15-30 minute intervals or give continuous nebulisation of salbutamol at 5-10 mg/hour (requires appropriate nebuliser) if there is an inadequate response to initial treatment. Higher bolus doses, eg 10 mg of salbutamol, are unlikely to be more effective.

6.3.3 STEROID THERAPY

Steroids reduce mortality, relapses, subsequent hospital admission and requirement for β_2 agonist therapy. The earlier they are given in the acute attack the better the outcome.[428,429] 1++

A **Give steroids in adequate doses in all cases of acute asthma.**

Steroid tablets are as effective as injected steroids, provided they can be swallowed and retained.[428] Prednisolone 40-50 mg daily or parenteral hydrocortisone 400 mg daily (100 mg six-hourly) are as effective as higher doses.[430] For convenience, steroid tablets may be given as 2 x 25 mg tablets daily rather than 8-10 x 5 mg tablets. Where necessary soluble prednisolone (sodium phosphate) 5 mg tablets are available. In cases where oral treatment may be a problem consider intramuscular methylprednisolone 160 mg as an alternative to a course of oral prednisolone.[787] 1++

2009

☑ Continue prednisolone 40-50 mg daily for at least five days or until recovery.

Following recovery from the acute exacerbation steroids can be stopped abruptly. Doses do not need tapering provided the patient receives inhaled steroids[431,432] (apart from patients on maintenance steroid treatment or rare instances where steroids are required for three or more weeks). 1+

It is not known if inhaled steroids provide further benefit in addition to systemic steroids. Inhaled steroids should however be started, or continued as soon as possible to commence the chronic asthma management plan.[788,789] 1++

2009

6.3.4 IPRATROPIUM BROMIDE

Combining nebulised ipratropium bromide with a nebulised β_2 agonist produces significantly greater bronchodilation than a β_2 agonist alone, leading to a faster recovery and shorter duration of admission. Anticholinergic treatment is not necessary and may not be beneficial in milder exacerbations of asthma or after stabilisation.[434-436] 1++

B **Add nebulised ipratropium bromide** *(0.5 mg 4-6 hourly)* **to β_2 agonist treatment for patients with acute severe or life threatening asthma or those with a poor initial response to β_2 agonist therapy.**

6.3.5 MAGNESIUM SULPHATE

2009 There is some evidence that, in adults, magnesium sulphate has bronchodilator effects.[790] Experience suggests that magnesium is safe when given by the IV or nebulised route. Trials comparing these routes of administration are awaited. 1++

2009 Studies report the safe use of nebulised magnesium sulphate, in a dose of 135 mg-1152 mg, in combination with β_2 agonists, with a trend towards benefit in hospital admission.[791,792] A single dose of IV magnesium sulphate is safe and may improve lung function in patients with acute severe asthma.[437] 1++

The safety and efficacy of repeated IV doses have not been assessed. Repeated doses could cause hypermagnesaemia with muscle weakness and respiratory failure. 1++

B **Consider giving a single dose of IV magnesium sulphate for patients with:**

- **acute severe asthma who have not had a good initial response to inhaled bronchodilator therapy**
- **life threatening or near fatal asthma.**

☑ IV magnesium sulphate (1.2-2 g IV infusion over 20 minutes) should only be used following consultation with senior medical staff.

2009 More studies are needed to determine the optimal route, frequency and dose of magnesium sulphate therapy.

6.3.6 INTRAVENOUS AMINOPHYLLINE

In acute asthma, IV aminophylline is not likely to result in any additional bronchodilation compared to standard care with inhaled bronchodilators and steroids. Side effects such as arrhythmias and vomiting are increased if IV aminophylline is used.[438] 1++

☑ Use IV aminophylline only after consultation with senior medical staff.

Some patients with near-fatal asthma or life threatening asthma with a poor response to initial therapy may gain additional benefit from IV aminophylline (5 mg/kg loading dose over 20 minutes unless on maintenance oral therapy, then infusion of 0.5-0.7 mg/kg/hr). Such patients are probably rare and could not be identified in a meta-analysis of trials.[438] If IV aminophylline is given to patients on oral aminophylline or theophylline, blood levels should be checked on admission. Levels should be checked daily for all patients on aminophylline infusions.

6.3.7 LEUKOTRIENE RECEPTOR ANTAGONISTS

There is insufficient evidence at present to make a recommendation about the use of leukotriene receptor antagonists in the management of acute asthma.

6.3.8 ANTIBIOTICS

When an infection precipitates an exacerbation of asthma it is likely to be viral. The role of bacterial infection has been overestimated.[439] 1++

B **Routine prescription of antibiotics is not indicated for acute asthma.**

6.3.9 HELIOX

2009

The use of heliox, (helium/oxygen mixture in a ratio of 80:20 or 70:30), either as a driving gas for nebulisers, as a breathing gas, or for artificial ventilation in adults with acute asthma is not supported on the basis of present evidence.[440, 441] A systematic review of ten trials, including 544 patients with acute asthma, found no improvement in pulmonary function or other outcomes in adults treated with heliox, although the possibility of benefit in patients with more severe obstruction exists.[793, 794] Heliox requires the use of specifically designed or modified breathing circuits and ventilators. 1+ 1++

B **Heliox is not recommended for use in acute asthma outside a clinical trial setting.**

6.3.10 INTRAVENOUS FLUIDS

There are no controlled trials, observational or cohort studies of differing fluid regimes in acute asthma. Some patients with acute asthma require rehydration and correction of electrolyte imbalance. Hypokalaemia can be caused or exacerbated by β_2 agonist and/or steroid treatment and must be corrected.

6.3.11 NEBULISED FUROSEMIDE

2009

Although theoretically furosemide may produce bronchodilation, a review of three small trials failed to show any significant benefit of treatment with nebulised furosemide compared to β_2 agonists.[795] 1+

6.3.12 REFERRAL TO INTENSIVE CARE

Indications for admission to intensive care or high-dependency units include patients requiring ventilatory support and those with severe acute or life threatening asthma who are failing to respond to therapy, as evidenced by:

- deteriorating PEF
- persisting or worsening hypoxia
- hypercapnea
- arterial blood gas analysis showing fall in pH or rising H^+ concentration 2+
- exhaustion, feeble respiration
- drowsiness, confusion, altered conscious state
- respiratory arrest.[322,401]

Not all patients admitted to the Intensive Care Unit (ICU) need ventilation, but those with worsening hypoxia or hypercapnea, drowsiness or unconsciousness and those who have had a respiratory arrest require intermittent positive pressure ventilation. Intubation in such patients is very difficult and should ideally be performed by an anaesthetist or ICU consultant. [322,401]

C **All patients transferred to intensive care units should be accompanied by a doctor suitably equipped and skilled to intubate if necessary.**

6.3.13 NON-INVASIVE VENTILATION

Non-invasive ventilation (NIV) is well established in the management of ventilatory failure caused by extrapulmonary restrictive conditions and exacerbations of COPD. Hypercapneic respiratory failure developing during an acute asthmatic episode is an indication for urgent ICU admission. It is unlikely that NIV would replace intubation in these very unstable patients but it has been suggested that this treatment can be used safely and effectively.[442] 4

2009 A Cochrane review found only one trial, with 30 patients, on NIV which showed improvement in hospitalisation rates, discharge from emergency departments and lung function. Larger RCTs are needed to determine the role of NIV in treating patients with acute asthma.[796] 1++

2009 ☑ NIV should only be considered in an ICU or equivalent clinical setting.

6.4 FURTHER INVESTIGATION AND MONITORING

☑
- Measure and record PEF 15-30 minutes after starting treatment, and thereafter according to the response. Measure and record PEF before and after nebulised or inhaled β_2 agonist bronchodilator *(at least four times daily)* throughout the hospital stay and until controlled after discharge.
- Record oxygen saturation by oximetry and maintain arterial SpO_2 at 94-98%.
- Repeat measurements of blood gas tensions within one hour of starting treatment if:
  - the initial PaO_2 is <8 kPa unless SpO_2 is $>92\%$; or
  - the initial $PaCO_2$ is normal or raised; or
  - the patient's condition deteriorates.

2009

☑
- Measure them again if the patient's condition has not improved by 4-6 hours.
- Measure and record the heart rate.
- Measure serum potassium and blood glucose concentrations.
- Measure the serum theophylline concentration if aminophylline is continued for more than 24 hours *(aim at a concentration of 10-20mg/l or 55-110 mol/l)*.

6.5 ASTHMA MANAGEMENT PROTOCOLS AND PROFORMAS

The use of structured proformas facilitates improvements in the process of care in emergency departments and hospital wards and improves patient outcomes. The use of this type of documentation can assist data collection aimed at determining quality of care and outcomes.[409,443,445] 2++

6.6 HOSPITAL DISCHARGE AND FOLLOW UP *(see annex 4)*

6.6.1 TIMING OF DISCHARGE

No single physiological parameter defines absolutely the timing of discharge from an admission with acute asthma. Patients should have clinical signs compatible with home management, be on reducing amounts of β_2 agonist (preferably no more than four hourly) and be on medical therapy they can continue safely at home.

Although diurnal variability of PEF is not always present during an exacerbation, evidence suggests that patients discharged with PEF $<75\%$ best or predicted and with diurnal variability $>25\%$ are at greater risk of early relapse and readmission.[446,447] 2+

6.6.2 PATIENT EDUCATION

Following discharge from hospital or emergency departments, a proportion of patients re-attend with more than 15% re-attending within two weeks. Some repeat attenders need emergency care, but many delay seeking help, and are under-treated and/or under-monitored.[448] 2+

Prior to discharge, trained staff should give asthma education. This should include education on inhaler technique and PEF record keeping, with a written PEF and symptom-based action plan being provided allowing the patient to adjust their therapy within recommendations. These measures have been shown to reduce morbidity after the exacerbation and reduce relapse rates.[449] 1++

2009 There is some experience of a discrete population of patients who use emergency departments rather than primary care services for their asthma care.[90] Education has been shown to reduce subsequent hospital admission and improve attendance at scheduled appointments and self management techniques but does not improve re-attendance at emergency departments.[797] 1++

For the above groups there is a role for a trained asthma liaison nurse based in, or associated with, the emergency department.[797]

See also section 9

6.6.3 FOLLOW UP

A careful history should elicit the reasons for the exacerbation and explore possible actions the patient should take to prevent future emergency presentations.

Medication should be altered depending upon the assessment and the patient provided with an asthma action plan aimed at preventing relapse, optimising treatment and preventing delay in seeking assistance in the future.

Follow up should be arranged prior to discharge with the patient's general practitioner or asthma nurse within two working days; and with a hospital specialist asthma nurse or respiratory physician at about one month after admission.

2009 In a small RCT follow-up care by a nurse specialist was as effective and safe as that given by a respiratory doctor.[798] 1+

2009 Assisting patients in making appointments while being treated for acute asthma in emergency departments may improve subsequent attendance at primary care centres.[799] 1+

☑ It is essential that the patient's primary care practice is informed within 24 hours of discharge from the emergency department or hospital following an asthma exacerbation. Ideally this communication should be directly with a named individual responsible for asthma care within the practice, by means of fax or email.

6.7 ACUTE ASTHMA IN CHILDREN AGED OVER 2 YEARS

6.7.1 CLINICAL ASSESSMENT

Table 12 details criteria for assessment of severity of acute asthma attacks in children. *See also annexes 5-7.*

2009 *Table 12: Clinical features for assessment of severity*[800]

Life threatening asthma	Any one of the following in a child with severe asthma:	
	Clinical signs	Measurements
	Silent chest	SpO_2 < 92%
	Cyanosis	PEF < 33% best or predicted
	Poor respiratory effort	
	Hypotension	
	Exhaustion	
	Confusion	
Acute severe asthma	Can't complete sentences in one breath or too breathless to talk or feed SpO_2 < 92% PEF 33-50% best or predicted Pulse > 140 in children aged 2-5 years > 125 in children aged > 5 years Respiration > 40 breaths/min aged 2-5 years > 30 breaths/min aged 7-5 years	
Moderate asthma exacerbation	Able to talk in sentences SpO_2 ≥ 92% PEF ≥ 50% best or predicted Heart rate ≤140/min in children aged 2-5 years ≤125/min in children > 5 years Respiratory rate ≤ 40/min in children aged 2-5 years ≤ 30/min in children > 5 years	

Before children can receive appropriate treatment for acute asthma in any setting, it is essential to assess accurately the severity of their symptoms. The following clinical signs should be recorded:

- Pulserate
  (increasing tachycardia generally denotes worsening asthma; a fall in heart rate in life threatening asthma is a pre-terminal event)
- Respiratory rate and degree of breathlessness
  (ie too breathless to complete sentences in one breath or to feed)
- Use of accessory muscles of respiration
  (best noted by palpation of neck muscles)
- Amount of wheezing
  (which might become biphasic or less apparent with increasing airways obstruction)
- Degree of agitation and conscious level
  (always give calm reassurance).

Clinical signs correlate poorly with the severity of airways obstruction.[450-453] Some children with acute severe asthma do not appear distressed. | 2++

☑ Decisions about admission should be made by trained clinicians after repeated assessment of the response to bronchodilator treatment.

6.7.2 PULSE OXIMETRY

2009 Accurate measurements of oxygen saturation are essential in the assessment of all children with acute wheezing. Oxygen saturation monitors should be available for use by all health professionals assessing acute asthma in both primary and secondary care settings.

Low oxygen saturations after initial bronchodilator treatment selects a more severe group of patients.[450,453] 2++

B **Consider intensive inpatient treatment for children with SpO_2 < 92% in air after initial bronchodilator treatment.**

6.7.3 PEF

2009 PEF measurements can be of benefit in assessing children who are familiar with the use of such devices. The best of three PEF measurements, ideally expressed as a percentage of personal best, can be useful in assessing the response to treatment.

A measurement of < 50% predicted PEF or FEV_1 with poor improvement after initial bronchodilator treatment is predictive of a more prolonged asthma attack.

6.7.4 CHEST X-RAY

Chest X-rays rarely provide additional useful information and are not routinely indicated.[454,455]

2009 ☑ A chest X-ray should be performed if there is subcutaneous emphysema, persisting unilateral signs suggesting pneumothorax, lobar collapse or consolidation and/or life threatening asthma not responding to treatment.

6.7.5 BLOOD GASES

2009 Blood gas measurements should be considered if there are life threatening features not responding to treatment. Arteriolised ear lobe blood gases can be used to obtain an accurate measure of pH and pCO_2.[783] If ear lobe sampling is not practicable a finger prick sample can be an alternative. Normal or raised pCO_2 levels are indicative of worsening asthma. A more easily obtained free flowing venous blood pCO_2 measurement of < 6kPA (45mm Hg) excludes hypercapnia.[783] 4

6.8 INITIAL TREATMENT OF ACUTE ASTHMA IN CHILDREN AGED OVER 2 YEARS

2009 There is good evidence supporting recommendations for the initial treatment of acute asthma presenting to primary and secondary healthcare resources. There is less evidence to guide the use of second line therapies to treat the small number of severe cases poorly responsive to first line measures. Despite this, the risks of death and other adverse outcomes after admission to hospital are extremely small irrespective of the treatment options chosen.

2009 ☑ β_2 agonists should be given as first line treatment. Increase β_2 agonist dose by two puffs every two minutes according to response up to ten puffs.

2009 ☑ Children with acute asthma at home and symptoms not controlled by up to 10 puffs of salbutamol via pMDI and spacer, or 2.5-5 mg of nebulised salbutamol, should seek urgent medical attention. Additional doses of bronchodilator should be given as needed whilst awaiting medical attention if symptoms are severe.

2009 ☑ Paramedics attending to children with acute asthma should administer nebulised salbutamol driven by oxygen if symptoms are severe whilst transferring the child to the emergency department.

2009 ☑ Children with severe or life threatening asthma should be transferred to hospital urgently.

Emergency units attending to children with acute asthma should have a registered sick children's nurse available on duty at all times and staff familiar with the specific needs of children. Using a proforma can increase the accuracy of severity assessment.

2009 The use of an assessment-driven algorithm and an integrated care pathway has been shown to reduce hospital stay without substantial increases in treatment costs.[801]

D **The use of structured care protocols detailing bronchodilator usage, clinical assessment, and specific criteria for safe discharge is recommended.**

6.8.1 OXYGEN

☑ Children with life threatening asthma or SpO_2 <94% should receive high flow oxygen via a tight fitting face mask or nasal cannula at sufficient flow rates to achieve normal saturations.

6.8.2 INHALED β_2 AGONISTS (SALBUTAMOL/TERBUTALINE)

A **Inhaled β_2 agonists are the first line treatment for acute asthma.[457-460]**

Assessment of response should be based on accurately recorded clinical observations and repeat measurements of oxygenation (SpO_2). Children receiving β_2 agonists via pMDI + spacer are less likely to have tachycardia and hypoxia than when the same drug is given via a nebuliser.[353] 1+

A **pMDI + spacer is the preferred option in mild to moderate asthma.**

Children aged <3 years are likely to require a face mask connected to the mouthpiece of a spacer for successful drug delivery. Inhalers should be actuated into the spacer in individual puffs and inhaled immediately by tidal breathing (for five breaths).

Frequent doses of β_2 agonists are safe for the treatment of acute asthma,[457-459] although children with mild symptoms benefit from lower doses.[460] 1+

B **Individualise drug dosing according to severity and adjust according to the patient's response.**

2009 Two to four puffs of a salbutamol 100 mcg repeated every 10-20 minutes according to clinical response might be sufficient for mild attacks although up to 10 puffs might be needed for more severe asthma. Single puffs should be given one at a time and inhaled separately with five tidal breaths. If hourly doses of bronchodilators are needed for more than 4-6 hours, the patient should be switched to nebulised bronchodilators.

2009 Children with severe or life threatening asthma (SpO_2 <92%) should receive frequent doses of nebulised bronchodilators driven by oxygen (2.5-5 mg salbutamol or 5-10 mg terbutaline).

2009 Doses can be repeated every 20-30 minutes. Continuous nebulised β_2 agonists are of no greater benefit than the use of frequent intermittent doses in the same total hourly dosage.[463,464] If there is poor response to the initial dose of β_2 agonists, subsequent doses should be given in combination with nebulised ipratropium bromide.

2009 ☑ Discontinue long-acting β_2 agonists when short-acting β_2 agonists are required more often than four-hourly.

6.8.3 IPRATROPIUM BROMIDE

2009 There is good evidence for the safety and efficacy of frequent doses of ipratropium bromide (every 20-30 minutes) used in addition to β_2 agonists for the first two hours of a severe asthma attack. Benefits are more apparent in the most severe patients.[471] 1+

A **If symptoms are refractory to initial β_2 agonist treatment, add ipratropium bromide** *(250 mcg/dose mixed with the nebulised β_2 agonist solution).*

2009 Frequent doses up to every 20-30 minutes (250 mcg/dose mixed with 5 mg of salbutamol solution in the same nebuliser) should be used for the first few hours of admission. Salbutamol dose should be weaned to one-to two-hourly thereafter according to clinical response. The ipratropium dose should be weaned to four-to-six-hourly or discontinued. Once improving on two- to four-hourly salbutamol, patients should be switched to pMDI and spacer treatment as tolerated.

☑ Repeated doses of ipratropium bromide should be given early to treat children who are poorly responsive to β_2 agonists.

6.8.4 STEROID THERAPY

Steroid tablets

2009 The early use of steroids in emergency departments and assessment units can reduce the need for hospital admission and prevent a relapse in symptoms after initial presentation.[428, 429] Benefits can be apparent within three to four hours.

A **Give prednisolone early in the treatment of acute asthma attacks.**

A soluble preparation dissolved in a spoonful of water is preferable in those unable to swallow tablets. Use a dose of 20 mg for children 2-5 years old and 30-40 mg for children >5 years.

Oral and intravenous steroids are of similar efficacy.[430,465,466] Intravenous hydrocortisone (4 mg/kg repeated four-hourly) should be reserved for severely affected children who are unable to retain oral medication. 1+

Larger doses do not appear to offer a therapeutic advantage for the majority of children.[467] There is no need to taper the dose of steroid tablets at the end of treatment. 2+

☑ Use a dose of 20 mg prednisolone for children aged 2-5 years and a dose of 30-40 mg for children >5 years. Those already receiving maintenance steroid tablets should receive 2 mg/kg prednisolone up to a maximum dose of 60 mg.

- Repeat the dose of prednisolone in children who vomit and consider intravenous steroids in those who are unable to retain orally ingested medication.
- Treatment for up to three days is usually sufficient, but the length of course should be tailored to the number of days necessary to bring about recovery. Weaning is unnecessary unless the course of steroids exceeds 14 days.[431,432]

Inhaled steroids

There is insufficient evidence to support the use of inhaled steroids as alternative or additional treatment to steroid tablets for acute asthma.[433,468-470]

☑ Do not initiate inhaled steroids in preference to steroid tablets to treat children with acute asthma.

Children with chronic asthma not receiving regular preventative treatment will benefit from initiating inhaled steroids as part of their long term management. There is no evidence that increasing the dose of inhaled steroids is effective in treating acute symptoms, but it is good practice for children already receiving inhaled steroids to continue with their usual maintenance doses.

6.8.5 LEUKOTRIENE RECEPTOR ANTAGONISTS

2009 Initiating oral montelukast in primary care settings, early after the onset of acute asthma symptoms, can result in decreased asthma symptoms and the need for subsequent healthcare attendances in those with mild exacerbations.[777, 802] There is no clear evidence to support the use of leukotriene receptor antagonists for moderate to severe acute asthma.[803] 1+

6.9 SECOND LINE TREATMENT OF ACUTE ASTHMA IN CHILDREN AGED OVER 2 YEARS

2009 Children with continuing severe asthma despite frequent nebulised β_2 agonists and ipratropium bromide plus oral steroids, and those with life threatening features, need urgent review by a specialist with a view to transfer to a high dependency unit or paediatric intensive care unit (PICU) to receive second line intravenous therapies. There are three options to consider; salbutamol, aminophylline and magnesium sulphate.

6.9.1 IV SALBUTAMOL

The role of intravenous β_2 agonists in addition to nebulised treatment remains unclear.[424] One study has shown that an IV bolus of salbutamol given in addition to near-maximal doses of nebulised salbutamol results in clinically significant benefits for those with moderate to severe asthma.[424] 1+

B **Consider early addition of a single bolus dose of intravenous salbutamol** *(15 mcg/kg over 10 minutes)* ***in*** **severe cases where the patient has not responded to initial inhaled therapy.**

2009 A continuous intravenous infusion of salbutamol should be considered when there is uncertainty about reliable inhalation or for severe refractory asthma. This should be given in a high dependency unit with continuous ECG monitoring and twice daily electrolyte monitoring. Doses above 1-2 mcg/kg/min (200 mcg/ml solution) should be given in a PICU setting (up to 5 mcg/kg/min). Nebulised bronchodilators should be continued while the patient is receiving intravenous bronchodilators. Once the patient is improving the intravenous infusion should be reduced before reducing the frequency of nebulised bronchodilators.

2009 ☑ When inserting an IV cannula take a blood sample to measure serum electrolytes. Serum potassium levels are often low after multiple doses of β_2 agonists and should be replaced.

6.9.2 IV AMINOPHYLLINE

2009 There is no evidence that aminophylline is of benefit for mild to moderate asthma and side effects are common and troublesome.[438, 472] One well conducted study has shown evidence of benefit in severe acute asthma unresponsive to multiple doses of β_2 agonists and steroids, although the loading dose used was double that currently recommended in the UK and a third of patients were withdrawn from active medication because of vomiting.[473] Two studies have compared intravenous β_2 agonists with intravenous theophylline/aminophylline. One demonstrated equivalence.[804] The other resulted in a shorter period of inpatient treatment among the children receiving an aminophylline bolus followed by infusion but in the salbutamol arm of the study an infusion was not given after the bolus dose.[805] 1+ 2+

A **Aminophylline is not recommended in children with mild to moderate acute asthma.**

2009 C **Consider aminophylline in a HDU or PICU setting for children with severe or life threatening bronchospasm unresponsive to maximal doses of bronchodilators plus steroids.**

A 5 mg/kg loading dose should be given over 20 minutes with ECG monitoring (omit in those receiving maintenance oral theophyllines) followed by a continuous infusion at 1 mg/kg/hour. Measure serum theophylline levels in patients already receiving oral treatment and in those receiving prolonged treatment.

6.9.3 IV MAGNESIUM SULPHATE

Intravenous magnesium sulphate is a safe treatment for acute asthma although its place in management is not yet established.[437,475] Doses of up to 40 mg/kg/day (maximum 2 g) by slow infusion have been used. Studies of efficacy for severe childhood asthma unresponsive to more conventional therapies have been inconsistent in providing evidence of benefit. 1+

6.9.4 OTHER THERAPIES

There is no evidence to support the use of heliox, DNase or mucolytics for the treatment of acute asthma in childhood. Nebulised magnesium sulphate is being evaluated as a treatment for acute asthma but is not yet recommended.

There is insufficient evidence to support or refute the role of antibiotics in acute asthma,[305] but the majority of acute asthma attacks are triggered by viral infection.

☑ Do not give antibiotics routinely in the management of children with acute asthma.

6.9.5 DISCHARGE PLANNING

Children can be discharged when stable on 3-4 hourly inhaled bronchodilators that can be continued at home.[476] PEF and/or FEV_1 should be >75% of best or predicted and SpO_2 >94%.

Adult studies show that "optimal care" comprising self monitoring, regular review and a written asthma action plan can improve outcomes.[407] Acute asthma attacks should be considered a failure of preventive therapy and thought should be given about how to help families avoid further severe episodes.

Discharge plans should address the following:

- check inhaler technique
- consider the need for preventer treatment
- 2009 provide a written asthma action plan for subsequent asthma exacerbations with clear instructions about the use of bronchodilators and the need to seek urgent medical attention in the event of worsening symptoms not controlled by up to 10 puffs of salbutamol 4 hourly
- arrange follow up by primary care services within 48 hours
- arrange follow up in a paediatric asthma clinic within one to two months
- 2009 arrange referral to a paediatric respiratory specialist if there have been life threatening features.

6.10 ASSESSMENT OF ACUTE ASTHMA IN CHILDREN AGED LESS THAN 2 YEARS

The assessment of acute asthma in early childhood can be difficult *(see Annex 8)*. Intermittent wheezing attacks are usually due to viral infection and the response to asthma medication is inconsistent. Prematurity and low birth weight are risk factors for recurrent wheezing. The differential diagnosis of symptoms includes aspiration pneumonitis, pneumonia, bronchiolitis, tracheomalacia, and complications of underlying conditions such as congenital anomalies and cystic fibrosis. These guidelines are intended for those who are thought to have asthma causing acute wheeze. They should not be used as a guide for treating acute bronchiolitis (see SIGN 91: Bronchiolitis in children).[806]

6.11 TREATMENT OF ACUTE ASTHMA IN CHILDREN AGED LESS THAN 2 YEARS

6.11.1 β_2 AGONIST BRONCHODILATORS

A trial of bronchodilator therapy should be considered when symptoms are of concern. If inhalers have been successfully administered but there is no response, review the diagnosis and consider the use of other treatment options.

Inhaled β_2 agonists are the initial treatment of choice for acute asthma. Close fitting face masks are essential for optimal drug delivery. The dose received is increased if the child is breathing appropriately and not taking large gasps because of distress and screaming.

There is good evidence that pMDI + spacer is as effective as, if not better than, nebulisers for treating mild to moderate asthma in children aged ≤ 2 years.[355,478,479] | 1^+

A **For mild to moderate acute asthma, a pMDI + spacer is the optimal drug delivery device.**

Whilst β_2 agonists offer marginal benefits to children aged < 2 years with acute wheeze, there is little evidence for an impact on the need for hospital admission or length of hospital stay.[480-482] | 1^+

Oral β_2 agonists have not been shown to affect symptom score or length of hospital stay for acute asthma in infancy when compared to placebo.[477] | 1^+

B **Oral β_2 agonists are not recommended for acute asthma in infants.**

6.11.2 STEROID THERAPY

Steroid tablets in conjunction with β_2 agonists have been shown to reduce hospital admission rates when used in the emergency department.[483] Steroid tablets have also been shown to reduce the length of hospital stay.[477,480,483] | 1^+

B **Consider steroid tablets in infants early in the management of severe episodes of acute asthma in the hospital setting.**

One study has shown similar benefits when comparing oral and nebulised steroids for acute asthma.[480]

☑ Steroid tablet therapy *(10 mg of soluble prednisolone for up to three days)* is the preferred steroid preparation for use in this age group.

6.11.3 IPRATROPIUM BROMIDE

The addition of ipratropium bromide to β_2 agonists for acute severe asthma may lead to some improvement in clinical symptoms and reduce the need for more intensive treatment. It does not reduce the length of hospital stay either in combination with β_2 agonists or in comparison with placebo.[484] | 1^+

B **Consider inhaled ipratropium bromide in combination with an inhaled β_2 agonist for more severe symptoms.**

6.11.4 FURTHER INVESTIGATION AND MONITORING

Many children with recurrent episodes of viral-induced wheezing in infancy do not go on to have chronic atopic asthma. The majority do not require treatment with regular inhaled steroids. Parents should be advised about the relationship between cigarette smoke exposure and wheezy illnesses *(see sections 3.1.9 and 3.3.1)*. Referral to suitable agencies should be offered to those who wish to give up smoking.

Parents of wheezy infants should receive appropriate discharge plans along similar lines to those given for older children *(see section 6.9.5)*.

7 Special situations

7.1 DIFFICULT ASTHMA

7.1.1 DEFINING AND ASSESSING DIFFICULT ASTHMA

The term difficult asthma generally refers to a clinical situation where a prior diagnosis of asthma exists, and asthma-like symptoms and exacerbations persist, despite prescription of high-dose asthma therapy. There is no universally agreed definition of difficult asthma in children or adults, and specifically at what level of treatment prescription or exacerbation frequency, the term difficult asthma should apply. Consequently there are no precise data on the prevalence of this clinical problem. Previous consensus studies have suggested failure to achieve symptom control despite prescribed high-dose inhaled steroid as a minimum requirement, whilst more recent consensus work has stipulated a treatment level equivalent to at least step 4 *(see section 4.4 and Figures 4, 5 and 6)*, before labelling as "difficult".[485,486]

In this guideline difficult asthma is defined as persistent symptoms and/or frequent exacerbations despite treatment at step 4 or step 5.

Observational uncontrolled studies in subjects with difficult asthma, using multidisciplinary assessment models have identified high rates of alternative or coexistent diagnoses and psychological comorbidity.[29,487-489] These uncontrolled studies, using systematic multidisciplinary assessment and management, have suggested improved outcomes in adults and children, but controlled clinical trials are required. Within this broadly defined group of subjects with difficult asthma, a proportion will have refractory disease, which is relatively resistant to currently available therapies. This group can only be identified after detailed evaluation, including exclusion of alternative causes of persistent symptoms, management of other comorbidities and confirmation of adherence with therapy. 3

D **Patients with difficult asthma should be systematically evaluated, including:**

- **confirmation of the diagnosis of asthma and**
- **identification of the mechanism of persisting symptoms and assessment of adherence with therapy.**

D **This assessment should be facilitated through a dedicated multidisciplinary difficult asthma service, by a team experienced in the assessment and management of difficult asthma.**

7.2 FACTORS CONTRIBUTING TO DIFFICULT ASTHMA

7.2.1 POOR ADHERENCE

Poor adherence with asthma medication is associated with poor asthma outcome in adults and children *(see section 9.2)*. Few studies have addressed this issue in subjects defined as having difficult asthma. In a case control series, poor adherence based on prescription records was identified in 22% of children with difficult to control asthma, though adherence was not reported in the stable controls.[490] In a descriptive study of 100 adult subjects, with a physician diagnosis of 'severe asthma' 28 patients were on >15 mg prednisolone and of these nine (32%) were found to be non-adherent with prednisolone.[488] There is no published evidence that poor adherence, if identified, can be successfully addressed in this population. 2+ 3

C **Poor adherence with maintenance therapy should be considered as a possible mechanism in difficult asthma.**

7.2.2 PSYCHOSOCIAL FACTORS

Fatal and near-fatal asthma have been associated with psychosocial dysfunction *(see section 6.1.3)*. Most observational studies[29, 488, 491-494] and a case control study[495] in subjects with difficult asthma have also suggested a high level of psychological morbidity, though this observation has not been universal.[496,497] 3 2+

A meta-analysis of behavioural adjustment in children suggested increasing 'asthma severity', defined on the basis of treatment requirements was associated with greater behavioural difficulties.[498] The core issue of 'cause and effect' remains unclear; specifically the extent to which persistent asthma symptoms despite aggressive treatment results in psychological morbidity or whether pre-existing psychological morbidity makes asthma difficult to control. 2++

There is a lack of evidence that interventions specifically targeting psychological morbidity in difficult asthma are of benefit. A small proof of concept study targeting depression demonstrated a reduction in oral steroid use[499] and an observational study in 'high-risk' children with asthma suggested potential benefit from joint consultation with a child psychiatrist with an improvement in symptom scores and adherence with therapy.[500] However, a non-blinded randomised intervention study in adults with difficult asthma showed no benefit from a six month nurse-delivered psychoeducational programme.[501] A meta-analysis of psychoeducational interventions in difficult asthma concluded that many of the studies were of poor quality, though there was some evidence of positive effect of psychosocial educational interventions on hospital admissions in adults and children and on symptoms in children. There was not enough evidence to warrant significant changes in clinical practice and little information available on cost effectiveness.[502] 1+ 3

C **Healthcare professionals should be aware that difficult asthma is commonly associated with coexistent psychological morbidity.**

D **Assessment of coexistent psychological morbidity should be performed as part of a difficult asthma assessment. In children this may include a psychosocial assessment of the family.**

7.2.3 DYSFUNCTIONAL BREATHING

Observational uncontrolled studies in subjects with difficult asthma have identified high rates of dysfunctional breathing as an alternative or concomitant diagnosis to asthma causing symptoms.[29,488] It remains unclear what is the best mechanism of identifying and managing this problem. 3

D **Dysfunctional breathing should be considered as part of a difficult asthma assessment.**

7.2.4 ALLERGY

Acute asthma has been associated with IgE dependent sensitisation to indoor allergens.[503] In case control studies, mould sensitisation has been associated with recurrent admission to hospital and oral steroid use[504, 505] and with intensive care unit admissions and respiratory arrest.[506,507] There is no published evidence of any intervention study in this group. Research in this area is required. 2++ 3

C **In patients with difficult asthma and recurrent hospital admission, allergen testing to moulds should be performed.**

7.2.5 MONITORING AIRWAY RESPONSE

Two randomised blinded controlled trials and one open randomised study have supported the use of titrating steroid treatment against sputum eosinophilia in adults with moderate to severe asthma, with greatest benefit seen in patients receiving higher doses of inhaled steroid therapy.[84,86,508] In the study with the largest numbers of patients receiving high dose inhaled steroid treatment, patients who were considered to be poorly adherent with treatment, or had inadequately controlled aggravating factors, such as rhinitis or gastro-oesophageal reflux were specifically excluded.[84] Case series have suggested that sputum induction is safe in patients with difficult to control asthma.[57,509-512] 1+ 1- 3

Controlled studies using FE_{NO} to target treatment have not specifically targeted adults or children with difficult asthma.[85,513,514] 1+

B **In patients with difficult asthma, consider monitoring induced sputum eosinophil counts to guide steroid treatment.**

Revised 2009

7.3 ASTHMA IN PREGNANCY

7.3.1 NATURAL HISTORY AND MANAGEMENT OF STABLE ASTHMA

The majority of women with asthma have normal pregnancies and the risk of complications is small in those with well controlled asthma. Several physiological changes occur during pregnancy that could worsen or improve asthma, but it is not clear which, if any, are important in determining the course of asthma during pregnancy. Pregnancy can affect the course of asthma and asthma and its treatment can affect pregnancy outcomes.

Course of asthma in pregnancy

The natural history of asthma during pregnancy is extremely variable. In a prospective cohort study of 366 pregnancies in 330 women with asthma, the asthma worsened during pregnancy in 35%.[515] 2009 A more recent prospective cohort study of 1,739 pregnant women showed an overall improvement in 23% and deterioration in 30.3%.[807] The conclusions of a meta-analysis of 14 studies is in agreement with the commonly quoted generalisation that during pregnancy about one third of asthma patients experience an improvement in their asthma, one third experience a worsening of symptoms, and one third remain the same.[518] 2009 There is also some evidence that the course of asthma is similar in successive pregnancies.[515,808] A systematic review showed no effect of pregnancy or stage of pregnancy on FEV_1.[809] 1+ 2+

Studies suggest that 11-18% of pregnant women with asthma will have at least one emergency department visit for acute asthma and of these 62% will require hospitalisation.[516,517] Severe asthma is more likely to worsen during pregnancy than mild asthma,[515] but some patients with very severe asthma may experience improvement, whilst symptoms may deteriorate in some patients with mild asthma. 2009 In a large US study, the rates of asthma exacerbation were 13%, 26% and 52% in those with mild, moderate and severe asthma respectively.[807] The corresponding rates of hospitalisation were 2%, 7% and 27%. 2- 2+

2009 A systematic review concluded that, if symptoms do worsen, this is most likely in the second and third trimesters, with the peak in the sixth month.[808] In a large cohort study, the most severe symptoms were experienced by patients between the 24th and 36th week of pregnancy. Thereafter symptoms decreased significantly in the last four weeks and 90% had no asthma symptoms during labour or delivery. Of those who did, only two patients required anything more than inhaled bronchodilators.[515] A further study has confirmed the observation that the last month of pregnancy is the one in which patients are least likely to have an asthma exacerbation.[519] 2+

Effect of asthma on pregnancy

A systematic review has shown that baseline asthma severity does determine what happens to the course of asthma in pregnancy and asthma may affect the risk of adverse outcomes.[521] A cohort study comparing 198 pregnant women with asthma to 198 women without asthma reported that non-atopic patients with asthma tend to have more severe asthma. Pre-eclampsia was also more common in this group. However with adequate surveillance and treatment, pregnancy and delivery complications can be avoided.[520] 2++ 2+

Uncontrolled asthma is associated with many maternal and fetal complications, including hyperemesis, hypertension, pre-eclampsia, vaginal haemorrhage, complicated labour, fetal growth restriction, pre-term birth, increased perinatal mortality, and neonatal hypoxia.[522-525, 807] A large Swedish population based study using record linkage data demonstrated increased risks for pre-term birth, low birth weight, perinatal mortality and pre-eclampsia in women with asthma. The risks for pre-term delivery and low birth weight were higher in women with more severe asthma necessitating admission.[526] 2+

2009 A large prospective cohort study comparing women with moderate and severe asthma with women without asthma found the only significant difference was an increased Caesarean section rate (OR 1.4, 95% CI, 1.1 to 1.8).[807] Logistic regression analysis of the severe group showed an increased risk of gestational diabetes (AOR 3 (95% CI, 1.2 to 7.8)) and pre-term delivery < 37 weeks (AOR 2.2 95% CI, 1.2 to 4.2) but this could have been an effect of corticosteroids. In the Yale asthma study no effect of asthma symptoms or severity was seen on pre-term delivery but oral steroids increased the rate of pre-term delivery and reduced gestation by 2.2 weeks (AOR 1.05 95% CI, 1.01 to1.09).[810] Daily asthma symptoms were associated with an increased risk of fetal growth restriction (AOR 2.25 95% CI, 1.25 to 4.06) and there was a 24% increase with each increased symptom step. This is supported by a systematic review of four studies that concluded asthma exacerbation in pregnancy increases the risk of low birth weight.[811] The RR was 2.54 (95% CI, 1.52 to 4.25) compared to women without asthma. In a large cohort study of 2,123 women with asthma, there was an association of both mean FEV_1 and mean FEV_1 < 80% predicted with gestational hypertension, pre-term delivery < 37 weeks, < 32 weeks and low birth weight.[812] 2+ 2++

In contrast, if asthma is well controlled throughout pregnancy there is little or no increased risk of adverse maternal or fetal complications.[515,516] Pregnancy should therefore be an indication to optimise therapy and maximise lung function in order to reduce the risk of acute exacerbation. 2+

2009 **C** **Monitor pregnant women with moderate/severe asthma closely to keep their asthma well controlled.**

2009 **B** **Women should be advised of the importance of maintaining good control of their asthma during pregnancy to avoid problems for both mother and baby.**

☑ Advise women who smoke about the dangers for themselves and their babies and give appropriate support to stop smoking.

7.4 MANAGEMENT OF ACUTE ASTHMA IN PREGNANCY

The management of acute asthma in pregnancy may be affected by concerns about harmful effects of medication on the fetus. In a prospective controlled study of 51 pregnant women and 500 non-pregnant women presenting with acute asthma to an emergency department in Boston, USA, pregnant patients with asthma were less likely to receive appropriate treatment with steroids and, as a result, were more likely to experience ongoing exacerbation at two weeks.[527] Available studies give little cause for concern regarding treatment side effects *(see section 7.3)* and the maternal and fetal risks of uncontrolled asthma are much greater than the risks from using conventional asthma medications for management of acute asthma. In the last four confidential enquiries into maternal deaths in the UK (covering 1994-2005) there were seventeen deaths from asthma.[528,529 813,814] 2+

2009 Oxygen should be delivered to maintain saturation 94-98% in order to prevent maternal and fetal hypoxia.[783] When interpreting arterial blood gases in pregnancy it should be remembered that the progesterone-driven increase in minute ventilation may lead to relative hypocapnia and a respiratory alkalosis, and higher PaO_2 [815, 816] but oxygen saturations are unaltered.[817] Acidosis is poorly tolerated by the fetus. 4

2009 Drug therapy should be given as for a non-pregnant patient with acute asthma, including nebulised β_2 agonists and early administration of steroid tablets.[515, 517, 519, 522, 523] In severe cases, intravenous β_2 agonists, aminophylline, or intravenous bolus magnesium sulphate can be used as indicated.[818] 2^+

2009 Continuous fetal monitoring should be performed when asthma is uncontrolled or severe, or when fetal assessment on admission is not reassuring. Consideration should be given to early referral to critical care services as impaired ventilatory mechanics in late pregnancy can lower functional residual capacity and may result in earlier oxygen desaturation.[819] Pregnant women may be more difficult to intubate due to anatomical changes especially if they have pre-eclampsia.[820]

2009 C **Give drug therapy for acute asthma as for the non-pregnant patient including systemic steroids and magnesium sulphate.**

2009 D **Deliver high flow oxygen immediately to maintain saturation 94-98%.**

D **Acute severe asthma in pregnancy is an emergency and should be treated vigorously in hospital.**

☑ Continuous fetal monitoring is recommended for severe acute asthma.

2009 ☑ For women with poorly controlled asthma during pregnancy there should be close liaison between the respiratory physician and obstetrician, with early referral to critical care physicians for women with acute severe asthma.

7.5 DRUG THERAPY IN PREGNANCY

2009 In general, the medicines used to treat asthma are safe in pregnancy.[530, 821] A large UK population based case control study found no increased risk of major congenital malformations in children of women receiving asthma treatment in the year before or during pregnancy.[822] The risk of harm to the fetus from severe or chronically under-treated asthma outweighs any small risk from the medications used to control asthma. 2^+

2009 B **Counsel women with asthma regarding the importance and safety of continuing their asthma medications during pregnancy to ensure good asthma control.**

7.5.1 β_2 AGONISTS

2009 No significant association has been demonstrated between major congenital malformations or adverse perinatal outcome and exposure to short-acting β_2 agonists.[530, 531,821-823] A prospective study of 259 pregnant patients with asthma who were using bronchodilators compared with 101 pregnant patients with asthma who were not, and 295 control subjects, found no differences in perinatal mortality, congenital abnormalities, prematurity, mean birth weight, apgar scores or labour/delivery complications.[532] A case control study including 2,460 infants exposed to short-acting β_2 agonists found no increased risk of congenital malformations in exposed infants.[807] 2^+ 3

2009 With regard to long-acting β_2 agonists (LABAs), evidence from prescription event monitoring suggests that salmeterol is safe in pregnancy[533] and although there are some data on formoterol, numbers are small.[824] Systematic review of studies including 190 exposures to LABA demonstrated no increased risk of congenital malformations, pre-term delivery or pre-eclampsia.[825] A case control study including 156 infants exposed to LABA found no increased risk of major congenital malformations.[822] As in other settings, LABAs should be used with an inhaled corticosteroid, ideally as a combination product.[826] 2^+

2009 Data on the use of combination products in pregnancy are scarce although there are no theoretical reasons why these would be more harmful than the same agents given separately. There are some safety data for seretide (salmeterol/fluticasone) but with small numbers.[827]

2009 **B** **Use short acting β_2 agonists as normal during pregnancy.**

2009 **C** **Use long acting β_2 agonists (LABA) as normal during pregnancy.**

7.5.2 INHALED STEROIDS

2009 No significant association has been demonstrated between major congenital malformations or adverse perinatal outcome and exposure to inhaled steroids.[530,534-537, 822, 825, 828] A meta-analysis of four studies of inhaled corticosteroid use in pregnancy showed no increase in the rate of major malformations, pre-term delivery, low birth weight or pregnancy-induced hypertension.[829] The UK case control study included 1,429 infants exposed to inhaled steroids and found no increased risk of major congenital malformations.[822] 2- 2+ 2++

2009 Inhaled anti-inflammatory treatment has been shown to decrease the risk of an acute attack of asthma in pregnancy[519] and the risk of readmission following asthma exacerbation.[517] A randomised placebo controlled trial of inhaled beclometasone versus oral theophylline in moderate asthma in pregnancy showed no difference in the primary outcome of one or more asthma exacerbations resulting in medical intervention, but inhaled beclometasone was better tolerated.[807] 2+

B **Use inhaled steroids as normal during pregnancy.**

7.5.3 THEOPHYLLINES

No significant association has been demonstrated between major congenital malformations or adverse perinatal outcome and exposure to methylxanthines.[530,538] 2+

For women requiring theophylline to maintain asthma control, measurement of theophylline levels is recommended. Since protein binding decreases in pregnancy, resulting in increased free drug levels, a lower therapeutic range is probably appropriate.[539] 4

C **Use oral and intravenous theophyllines as normal during pregnancy.**

D **Check blood levels of theophylline in acute severe asthma and in those critically dependent on therapeutic theophylline levels.**

7.5.4 STEROID TABLETS

2009 There is much published literature showing that steroid tablets are not teratogenic[522, 530, 540] but a slight concern that they may be associated with oral clefts. Data from several studies have failed to demonstrate this association with first trimester exposure to steroid tablets[540, 830] but one case control study found a significant association, although this increase is not significant if only paired controls are considered.[542] Although one meta-analysis reported an increased risk,[541] a prospective study by the same group found no difference in the rate of major birth defects in prednisolone-exposed and control babies.[541] A more recent population based case control study revealed a crude odds ratio of corticosteroid exposure from four weeks before through to 12 weeks after conception of 1.7 (95% CI, 1.1-2.6) for cleft lip.[831] Another case control study[822] including 262 exposed infants found no such association, although this was not limited to first trimester exposure. 2+ 2-

The association is therefore not definite and even if it is real, the benefit to the mother and the fetus of steroids for treating a life threatening disease justify the use of steroids in pregnancy.[524, 815] Moreover, the various studies of steroid exposure include many patients with conditions other than asthma, and the pattern of steroid use was generally as a regular daily dose rather than as short courses, which is how asthma patients would typically receive oral steroids. 2+

Prednisolone is extensively metabolized by placental enzymes so only 10% reaches the fetus, making this the oral steroid of choice to treat maternal asthma in pregnancy. Pregnant women with acute asthma exacerbation are less likely to be treated with steroid tablets than non-pregnant women.[527] Failure to administer steroid tablets when indicated increases the risk of ongoing exacerbation and therefore the risk to the mother and her fetus. 2+

2009 Some studies have found an association between steroid tablet use and pregnancy-induced hypertension or pre-eclampsia, pre-term labour[520] and fetal growth but severe asthma may be a confounding variable.[832] 2+

2009 C **Use steroid tablets as normal when indicated during pregnancy for severe asthma. Steroid tablets should never be withheld because of pregnancy. Women should be advised that the benefits of treatment with oral steroids outweigh the risks.**

7.5.5 LEUKOTRIENE RECEPTOR ANTAGONISTS

2009 Data regarding the safety of leukotriene antagonists (LTRA) in pregnancy are limited. Animal studies and post-marketing surveillance for zafirlukast with 28 pregnancies with 20 exposed in the first trimester and montelukast are reassuring.[833] There are animal data of concern for zileuton.[543] A case control study with 96 cases exposed to LTRAs found no increased risk of major malformations between women with asthma exposed to LTRA and women with asthma taking only beta agonists.[832] A systematic review found no increased risk of malformations or pre-term delivery in nine exposed women.[810, 825] 2- 4 2+ 2++

2009 D **Leukotriene antagonists may be continued in women who have demonstrated significant improvement in asthma control with these agents prior to pregnancy not achievable with other medications.**

7.5.6 CHROMONES

No significant association has been demonstrated between major congenital malformations or adverse perinatal outcome and exposure to chromones.[529, 530,825, 832] 2+

C **Use chromones as normal during pregnancy.**

7.5.7 IMMUNOMODULATION THERAPY

2009 There are as yet no clinical data on the use of omalizumab for moderate-severe allergic asthma in pregnancy. There are some reassuring animal studies re teratogenicity (classed as FDA category B). A registry of pregnancy exposures is being undertaken.

7.6 MANAGEMENT DURING LABOUR

Acute attacks of asthma are very rare in labour, perhaps due to endogenous steroid production. In women receiving steroid tablets there is a theoretical risk of maternal hypothalamic-pituitary-adrenal axis suppression. Women with asthma may safely use all forms of usual labour analgesia.

2009 In some studies there is an association between asthma and an increased Caesarean section rate,[520,544,545] but this may be due to planned Caesarean sections[519] or inductions of labour rather than due to any direct effect of asthma on intrapartum indications. A large prospective cohort study comparing women with moderate and severe asthma with women without asthma found the only significant difference was an increased Caesarean section rate (OR 1.4, 95% CI 1.1-1.8).[807] 2+

Data suggest that the risk of postpartum exacerbation of asthma is increased in women having Caesarean sections.[544] This may relate to the severity of their asthma rather than to the Caesarean section, or to factors such as postoperative pain with diaphragmatic splinting, hypoventilation and atelectasis. Prostaglandin E2 may safely be used for labour inductions.[539] Prostaglandin F2α (carboprost/hemobate®) used to treat postpartum haemorrhage due to uterine atony may cause bronchospasm.[539] Although ergometrine may cause bronchospasm particularly in association with general anaesthesia,[539] this is not a problem encountered when syntometrine (syntocinon/ergometrine) is used for postpartum haemorrhage prophylaxis. 2- 3

Although suppression of the fetal hypothalamic-pituitary-adrenal axis is a theoretical possibility with maternal systemic steroid therapy, there is no evidence from clinical practice or the literature to support this.[546]

☑ Advise women that acute asthma is rare in labour.

☑ Advise women to continue their usual asthma medications in labour.

☑ In the absence of acute severe asthma, reserve Caesarean section for the usual obstetric indications.

C **If anaesthesia is required, regional blockade is preferable to general anaesthesia in women with asthma.**

☑ Women receiving steroid tablets at a dose exceeding prednisolone 7.5 mg per day for more than two weeks prior to delivery should receive parenteral hydrocortisone 100 mg 6-8 hourly during labour.

D **Use prostaglandin F2α with extreme caution in women with asthma because of the risk of inducing bronchoconstriction.**

7.7 DRUG THERAPY IN BREASTFEEDING MOTHERS

The medicines used to treat asthma, including steroid tablets, have been shown in early studies to be safe to use in nursing mothers.[547] There is less experience with newer agents. Less than 1% of the maternal dose of theophylline is excreted into breast milk.[547] 2+

Prednisolone is secreted in breast milk, but milk concentrations of prednisolone are only 5-25% of those in serum.[351] The proportion of an oral or intravenous dose of prednisolone recovered in breast milk is less than 0.1%.[548-550] For maternal doses of at least 20 mg once or twice daily the nursing infant is exposed to minimal amounts of steroid with no clinically significant risk.[548-550] 2+ 3

C **Encourage women with asthma to breastfeed.**

C **Use asthma medications as normal during lactation, in line with manufacturers' recommendations.**

7.8 OCCUPATIONAL ASTHMA

7.8.1 INCIDENCE

The true frequency of occupational asthma is not known, but under-reporting is likely. Published reports, which come from surveillance schemes, compensation registries or epidemiological studies, estimate that occupational asthma may account for about 9-15% of adult onset asthma.[551-553] It is now the commonest industrial lung disease in the developed world with over 400 reported causes.[554-556] 2++

The diagnosis should be suspected in all adults with symptoms of airflow limitation, and positively searched for in those with high-risk occupations or exposures. Patients with pre-existing asthma aggravated non-specifically by dust and fumes at work (work-aggravated asthma) should be distinguished from those with pre-existing asthma who become additionally sensitised to an occupational agent.

B **In patients with adult onset, or reappearance of childhood asthma, clinicians should be suspicious that there may be an occupational cause.**

7.8.2 AT-RISK POPULATIONS

Several hundred agents have been reported to cause occupational asthma and new causes are reported regularly in the medical literature.

The most frequently reported causative agents include isocyanates, flour and grain dust, colophony and fluxes, latex, animals, aldehydes and wood dust.[557-565]

The workers most commonly reported to occupational asthma surveillance schemes include paint sprayers, bakers and pastry makers, nurses, chemical workers, animal handlers, welders, food processing workers and timber workers. [557,558,560,562-568] 2++

Workers reported to be at increased risk of developing asthma include bakers, food processors, forestry workers, chemical workers, plastics and rubber workers, metal workers, welders, textile workers, electrical and electronic production workers, storage workers, farm workers, waiters, cleaners, painters, dental workers and laboratory technicians.[569-572] 2+

7.8.3 DIAGNOSIS

Occupational asthma should be considered in all workers with symptoms of airflow limitation. The best screening question to ask is whether symptoms improve on days away from work. This is more sensitive than asking whether symptoms are worse at work, as many symptoms deteriorate in the hours after work or during sleep.

☑ Adults with airflow obstruction should be asked:

- Are you better on days away from work?
- Are you better on holiday?

Those with positive answers should be investigated for occupational asthma.

These questions are not specific for occupational asthma and also identify those with asthma due to agents at home (who may improve on holidays), and those who do much less physical exertion away from work.[573]

Occupational asthma can be present when tests of lung function are normal, limiting their use as a screening tool. Asthmatic symptoms improving away from work can produce false negative diagnoses, so further validation is needed.

Serial measurement of peak respiratory flow is the most readily available initial investigation, and the sensitivity and specificity of serial peak flow measurement in the diagnosis of occupational asthma are high.[574-580] 3

Although skin prick tests or blood tests for specific IgE are available, there are few standardized allergens commercially available which limits their use. A positive test denotes sensitisation, which can occur with or without disease. The diagnosis of occupational asthma can usually be made without specific bronchial provocation testing, considered to be the gold standard diagnostic test. The availability of centres with expertise and facilities for specific provocation testing is very limited in the UK and the test itself is time consuming.

As a general observation, the history is more useful in excluding occupational asthma than in confirming it. A significant proportion of workers with symptoms that improve on days away from work or on holiday have been shown by objective tests not to have occupational asthma.[581] Expert histories have poor specificity compared with specific challenge testing. Free histories taken by experts have high sensitivity but their specificity is lower.[582-587] 3

D **In suspected work-related asthma, the diagnosis of asthma should be confirmed using standard objective criteria.**

7.8.4 SENSISTIVITY AND SPECIFICITY OF SERIAL PEAK FLOW MEASUREMENTS

Direct and blinded comparisons of serial peak flow measurement with either specific bronchial provocation testing, or an expert diagnosis based on a combination of other types of evidence, reported consistently high sensitivities and specificities, averaging 80% and 90% respectively.[575-578,580,588,589] 3

Just one computed method of analysis has been reported, with a sensitivity of 75% and a specificity of 94%.[97,590] 2^+

Computed analysis of peak flow records has good diagnostic performance, but statistical analysis of serial peak flow measurements appears to be of limited diagnostic value compared to expert interpretation.[578,588,589]

Serial measurements of peak expiratory flow

Measurements should be made every two hours from waking to sleeping for four weeks, keeping treatment constant and documenting times at work.

Minimum standards for diagnostic sensitivity >70% and specificity >85% are:

- At least three days in each consecutive work period
- At least three series of consecutive days at work with three periods away from work (usually about three weeks)
- At least four evenly spaced readings per day.[580]

The analysis is best done with the aid of a criterion-based expert system. Suitable record forms and support are available from www.occupationalasthma.com

D **Objective diagnosis of occupational asthma should be made using serial peak flow measurements, with at least four readings per day.**

7.8.5 NON-SPECIFIC REACTIVITY

Studies of non-specific reactivity are confounded by different methods used, different cut-offs for normality and the interval between last occupational exposure and the performance of the test (increasing time may allow recovery of initial hyper-reactors). Such studies show that non-specific bronchial hyper-reactivity may be normal in 5-40% of specific challenge positive workers. Testing with higher concentrations of methacholine or histamine, at which some people without asthma would react, reduces the number of non-reacting people with occupational asthma, but still leaves some non-reactors. One study showed no additional benefit of non-specific bronchial reactivity measurement over and above a history and specific IgE to inhaled antigens. A normal test of non-specific reactivity is not sufficiently specific to exclude occupational asthma in clinical practice. [576,581,583,586,587,589,591-602] 2^{++}

Changes in non-specific reactivity at and away from work alone have been found to have only moderate sensitivity and specificity for diagnosis. Three studies were identified where at and away from work exposure measurements were attempted. One did not investigate workers further when at work reactivity was normal, limiting its interpretation. Using a 3.2 fold change in reactivity, one study found a sensitivity of 48% and a specificity of 64%. Reducing the required change to twofold increased the sensitivity to 67%, reducing specificity to 54%. A smaller study with 14 workers with occupational asthma showed a sensitivity of 62% and specificity of 78%. [577,589,601] 2-

7.8.6 SPECIFIC BRONCHIAL PROVOCATION TESTING

Specific provocation challenges are usually used as the gold standard for occupational asthma diagnosis making assessments of their diagnostic validity difficult. In addition, there are no standardised methods for many occupational agents. There is also evidence that the threshold exposure increases with time since last exposure, making the tests less sensitive after prolonged absence from work. There are reports of people having non-specific reactions to specific challenges at concentrations likely to be found in the workplace or of negative reactions to specific challenges in workers with otherwise good evidence of occupational asthma when challenge concentrations are confined to levels below occupational exposure standards. [594,597,600,603,604] 4

D **A negative specific bronchial challenge in a worker with otherwise good evidence of occupational asthma is not sufficient to exclude the diagnosis.**

7.9 MANAGEMENT OF OCCUPATIONAL ASTHMA

The aim of management is to identify the cause, remove the worker from exposure, and for the worker to have worthwhile employment.

Complete avoidance of exposure may or may not improve symptoms and bronchial hyperresponsiveness. Both the duration of continued exposure following the onset of symptoms and the severity of asthma at diagnosis may be important determinants of outcome. Early diagnosis and early avoidance of further exposure, either by relocation of the worker or substitution of the hazard offer the best chance of complete recovery. Workers who remain in the same job and continue to be exposed to the same causative agent after diagnosis are unlikely to improve and symptoms may worsen. The likelihood of improvement or resolution of symptoms or of preventing deterioration is greater in workers who have no further exposure to the causative agent. [576,605-613] 2++

Several studies have shown that the prognosis for workers with occupational asthma is worse for those who remain exposed for more than one year after symptoms develop, compared with those removed earlier.[614-616]

D **Relocation away from exposure should occur as soon as diagnosis is confirmed, and ideally within 12 months of the first work-related symptoms of asthma.**

There is consistent evidence from clinical and workforce case series that about one third of workers with occupational asthma are unemployed after diagnosis. It is unclear whether this risk is higher than that for other adults with asthma. [582,617,618] The risk of unemployment may fall with increasing time after diagnosis.[619] There is consistent evidence that loss of employment following a diagnosis of occupational asthma is associated with loss of income. Adults with occupational asthma may find employment more difficult than adults with non-occupational asthma.[617,618] Approximately one third of workers with occupational asthma have been shown to be unemployed up to six years after diagnosis.[582,617-624] 2-

8 Organisation and delivery of care, and audit

8.1 ROUTINE PRIMARY CARE

8.1.1 ACCESS TO ROUTINE PRIMARY CARE

Primary care services delivered by doctors and nurses trained in asthma management improves diagnosis, prescribing, education, monitoring, and continuity of care [625,626] Successful training programmes typically include outreach educational visits to practices or practitioners using interactive educational methods focused around clinical guidelines, occasionally including audit and feedback of care.[625,627,628] 1+

A **All people with asthma should have access to primary care services delivered by doctors and nurses with appropriate training in asthma management.**

❖ *Audit the percentage of clinicians who have taken part in a suitable asthma educational update within last two years.*

8.1.2 STRUCTURED REVIEW

Proactive clinical review of people with asthma improves clinical outcomes. Evidence for benefit is strongest when reviews include discussion and use of a written action plan.[407] Benefits include reduced school or work absence, reduced exacerbation rate, improved symptom control and reduced attendance at the emergency department.[629,630] Proactive structured review, as opposed to opportunistic or unscheduled review, is associated with reduced exacerbation rate and days lost from normal activity.[626,631,632] It is difficult to be prescriptive about the frequency of review as need will vary with the severity of the disease. Outcome is probably similar whether a practice nurse (PN), or a general practitioner (GP) conducts the review. Clinicians trained in asthma management achieve better outcomes for their patients.[626,633,634] 2+ 3 4 1+

A **In primary care, people with asthma should be reviewed regularly by a nurse or doctor with appropriate training in asthma management. Review should incorporate a written action plan.**

❖ *Audit the percentage of patients reviewed annually. Consider focusing on particular groups such as those overusing bronchodilators, patients on higher treatment steps, those with exacerbations or from groups with more complex needs.*

❖ *Audit the percentage of patients receiving action plans. Consider focusing on subgroups listed above.*

READ coding of patients who are newly diagnosed or register at a practice will ensure a meaningful database for audit and review purposes. Specifically identifying patients with high risk asthma (eg those with frequent admissions) in an effort to target more detailed input is logical but supported by limited evidence.[635] Not all patients want regular review, or are willing to attend a pre-arranged appointment. Reviews carried out by telephone may be as effective as those using face-to-face consultations,[636] but face-to-face review will be appropriate for some patients, such as those with poor asthma control or inhaler-related problems. 2++

B **Consider carrying out routine reviews by telephone for people with asthma.**

Asthma clinics in primary care may be a convenient way of delivering care, but there is limited evidence that they themselves improve outcome.[291] Most practices will provide asthma reviews as part of routine appointment sessions. It is what happens during the review consultation that matters.[637-640] Audit that feeds back guidelines recommendations on the management of individual patients may improve outcomes.[641,642]

C **General practices should maintain a register of people with asthma.**

C **Clinical review should be structured and utilise a standard recording system.**

B **Feedback of audit data to clinicians should link guidelines recommendations to management of individual patients.**

The ideal content of an asthma review consultation is uncertain. Discussion and provision of a written action plan leads to improved outcomes.[643] Other activities likely to be important are reviewing understanding of medication role and use, checking inhaler technique, recording lung function. Structured review systems such as the Royal College of Physicians 'Three Key Questions',[109] the Tayside Asthma Stamp,[644] and the modified Jones Morbidity Index[645] improve the recording of relevant data and may prompt a search for causes of suboptimal asthma control, such as under-treatment, poor adherence or poor inhaler technique. However, such tools can lead to a more physician-centred or template-directed consultation. Reviewing patients using a patient-centred style of consultation can lead to improved outcomes.[625]

8.1.3 SHARED CARE

Shared care schemes have been shown to be effective in some healthcare environments. There are no UK studies directly comparing primary and secondary care management, but international work suggests there may be little difference: what is done would appear to be more important than who by or where. [646] 1+ 2+

Integrated care schemes such as Grampian Asthma Study in Integrated Care (GRASSIC) suggest that place of care is not directly linked to clinical outcome.[647-650] Shared care had a similar outcome to outpatient care. Outreach support for primary care by asthma specialist nurses may reduce unscheduled asthma care but only if targeted around follow-up of patients recently attending secondary care with exacerbations. 1+ 2+

Community pharmacists trained in asthma care and teaching self management skills may improve asthma control,[651,652] although evidence is sparse and inconsistent.[653] 1-

8.1.4 PATIENT SUBGROUPS

Ethnic subgroups have adverse clinical outcomes, including higher hospital admission and exacerbation rates.[654,655] In some countries ethnic minority groups have higher death rates due to asthma than do their contemporaries.[656,657] Minority groups describe poorer access to primary care and acute medical care,[658] and compared with majority groups, have a higher use of emergency facilities for routine care.[659] Educating primary care clinicians improves diagnosis, prescribing, education, and continuity of care for minority group children.[659] There is an established link between poor socioeconomic status and adverse asthma outcome.[660-664] 2+ 3 4 1+

Adolescents and the elderly are particularly vulnerable to the adverse effects of asthma. Adolescents and young adults make more frequent use of emergency asthma healthcare services, make less use of structured clinical review services than other age groups, and have high reliance on bronchodilators.[665,666] Asthma in the elderly is a neglected area of research, despite high mortality and morbidity.[391,667,668] 3

D **Healthcare professionals who provide asthma care should have heightened awareness of the complex needs of ethnic minorities, socially disadvantaged groups, adolescents, the elderly and those with communication difficulties.**

❖ *Audit asthma outcomes in relevant subgroups of the population.*

8.2 ACUTE EXACERBATIONS

People with asthma who experience deterioration in symptom control leading to an acute exacerbation can access a wide variety of sources of care. Few studies have looked at the relative merits of one type of service compared to another. Exceptions include a UK study showing a better outcome for patients managed by a specialist respiratory ward compared to a general medical ward, and a US study showing more favourable outcome in patients managed by specialist allergists compared to generalists.[669,670] 2+ 3

C **Manage hospital inpatients with asthma in specialist rather than general units.**

☑ All services involved in the care of acute asthma should be staffed by appropriately trained personnel and have access to all the equipment needed to manage acute asthma.

❖ *Audit the percentage of inpatients receiving care from specialist asthma nurse or chest physician.*

Models of care addressing access such as NHS Direct/NHS 24 produce similar outcomes to routine general practice, but have high referral rates and are unlikely to promote the continuity of care required for longer term management.[671] 3

A structured clinical assessment and a standardised recording system are associated with favourable outcome in acute exacerbations.[672] Audit of the management of patients with acute asthma attacks is associated with improved concordance with recommended guidelines and in turn improved clinical outcome and reduced exacerbation rate.[673-675] 2+ 2- 3

There is no evidence that the publication of guidelines per se improves care: clinicians need to link best practice to the management of individual patients. This effect is apparent in hospital and general practice care.[447] Certain actions, for example early prescription of oral corticosteroids for acute exacerbations of asthma, reduce hospitalisation and relapse rates. Clinicians should refer to relevant chapters in this guideline for advice.

B **Clinicians in primary and secondary care should treat asthma according to recommended guidelines.**

❖ *Audit the percentage of patients treated according to key guideline recommendations.*

Using acute asthma management protocols and clinical pathways can be beneficial and cost effective. Sub-optimal control of asthma leading to exacerbation is more expensive to manage than well controlled asthma.[630] Early discharge schemes from hospital and emergency departments may be cost effective.[445,676] 2+ 3

The safety of telephone help lines has not been established. 'Direct dial' emergency admission schemes may be of benefit to a small group of patients with severe or 'brittle' asthma but there is insufficient evidence to justify their widespread introduction.[677] Admission criteria are discussed elsewhere *(see section 6.2.6)*. 4

Criteria for and timing of discharge from hospital and emergency departments has been studied. The key event in recovery appears to be improved symptoms and peak flow rather than a complete return to normality. Discharge when improvement is apparent may be as safe as discharge when full stability is achieved. Asthma specialist nurse education of adults and school-age (but not pre-school) children at or shortly after hospital attendance improves symptom control, self management and re-attendance rates.[678-683] 1+ 2++ 2+ 2-

Making an appointment for review in primary care prior to discharge improves follow-up rates (but not outcomes).[684] Review within 30 days after hospital attendance with acute asthma is associated with reduced risk of further acute episodes.[685] There is most evidence of benefit when follow up is provided by specialist nurses. Various types of follow up after an acute exacerbation have been evaluated including GP care, hospital outpatient, and telephone follow up.[680,686] There would appear to be little difference in outcome depending on place or personnel involved in follow up *(see section 6.6)*.[676] 3 1+

A **Discharge from hospital or the emergency department should be a planned, supervised event which includes self management planning. It may safely take place as soon as clinical improvement is apparent.**

A **All people attending hospital with acute exacerbations of asthma should be reviewed by a clinician with particular expertise in asthma management, preferably within 30 days.**

❖ *Audit the percentage of people receiving specialist nurse advice including self management planning before discharge.*

❖ *Audit the percentage of people reviewed within 30 days after hospital attendance with acute exacerbation of asthma.*

8.3 AUDIT

Audit is a moderately effective way to improve the process and probably outcome of care.[687] Its impact is increased if combined with other strategies to change clinician behaviour, for example outreach education programmes. Whilst trials of audit in asthma care are few, those showing benefits have tended to incorporate feedback data to clinicians on the process of care such as frequency of review, checking of inhaler technique or lung function measurement. Passive feedback of aggregated data, for instance on prescribing patterns, does not change practice.[688]

8.3.1 TYPES OF AUDIT IN ASTHMA CARE

National or regional audits of asthma deaths have focused attention on delivery of care for severe asthma. Some primary care trusts have PCT-wide programmes of audit which extract practice data electronically and feedback comparative data on process of care, promoting a benchmarking approach to quality improvement.[689] The GMS Quality and Outcomes Framework (QOF) links audit of asthma care to financial incentives. Critical event audit focuses on an adverse event such as an asthma death, or failure of delivery care. How effective these activities are in improving outcomes of asthma care is uncertain.

Common sense suggests that auditing activities shown to improve patient outcomes is worthwhile. This chapter links suggestions for audit to guideline recommendations. Audit datasets are available at www.brit-thoracic.org.uk.

8.3.2 SUMMARY OF RECOMMENDED AUDITS

Diagnosis

Audit the percentage of adults with an Asthma Control Questionnaire score recorded and an Asthma Control Questionnaire of >0.75.

Non-pharmacological management

Audit the percentage of patients and parents-to be with smoking status recorded and the percentage who have received smoking cessation advice.

Pharmacological management

Audit:

- *the percentage of patients with potential adverse effects of treatment, for example, the percentage of children prescribed or using >800 micrograms/day of inhaled beclametasone who are not under the care of a specialist respiratory physician*
- *the percentage of patients in whom there has been documented consideration of downward dose titration for inhaled corticosteroid*
- *the percentage of patients using >800 micrograms/day of inhaled beclametasone without documented consideration of add-on therapy*
- *the percentage of patients in whom there has been documented consideration of downward dose titration for inhaled corticosteroid.*

Inhaler devices

Audit the percentage of patients in whom there is a record of satisfactory inhaler technique.

Audit the percentage of patients using a spacer device for mild to moderately severe exacerbations.

Management of acute asthma

Audit the percentage of patients in whom key steps in the management of acute asthma have been followed, for example, the percentage with a PEF measurement, the percentage with a justified X-ray on admission to hospital, or the percentage receiving corticosteroid tablets in adequate dosage and duration.

Asthma in pregnancy

Audit:

- *the percentage of pregnant women with documented discussion of the need to continue β_2 agonists and inhaled corticosteroid medication in pregnancy*
- *the percentage of pregnant women and partners who smoke with documented advice on smoking cessation.*

Occupational asthma

Audit the number of adults with adult-onset asthma for whom an occupational cause has been considered.

Organisation and delivery of care

Audit:

- *the percentage of clinicians who have taken part in suitable asthma educational update within last two years*
- *the percentage of patients reviewed annually. Consider focusing on particular groups such as those overusing bronchodilators, patients on higher treatment steps, those with exacerbations or from groups with more complex needs*
- *asthma outcomes in relevant subgroups of the population*
- *the percentage of inpatients receiving care from specialist asthma nurse or chest physician*
- *the percentage of patients treated according to key guideline recommendations*
- *the percentage of people receiving specialist nurse advice including self management planning before discharge*
- *the percentage of people reviewed within 30 days after hospital attendance with acute exacerbation of asthma.*

Patient education and self management

Audit the percentage of patients receiving written action plans.

Concordance and compliance

Audit prescription requests to determine compliance.

9 Patient education and self management

9.1 SELF-MANAGEMENT EDUCATION AND PERSONALISED ASTHMA ACTION PLANS

Written personalised action plans as part of self management education have been shown to improve health outcomes for people with asthma.[407,678,679,682,690-710] The evidence is particularly good for those in secondary care with moderate to severe disease, and those who have had recent exacerbations where successful interventions have reduced hospitalisations and emergency department attendances in people with severe asthma.[682,705,711,712] A consistent finding in many studies has been improvement in patient outcomes such as self-efficacy, knowledge and confidence.[690,701-703,709,713-727] 1+

A **Patients with asthma should be offered self-management education that focuses on individual needs, and be reinforced by a written personalised action plan.**

A **Prior to discharge, in-patients should receive written personalised action plans, given by clinicians with expertise in asthma management.**

9.1.1 COMPONENTS OF A SELF MANAGEMENT PROGRAMME

Self management education is a multi-faceted intervention with wide variation in the construction of programmes.[728,729] One systematic review has identified key components associated with beneficial outcome *(see Table 13)*.[730] While self management programmes are effective, individual components are not effective in isolation reinforcing the need to support the provision of personalised action plans with patient education.[728,731] 1+

Successful programmes vary considerably, but encompass:

- Structured education, reinforced with written personal action plans, though the duration, intensity and format for delivery may vary.[690,729]
- Specific advice about recognising loss of asthma control, though this may be assessed by symptoms or peak flows or both.[678,679,690,692,696-698,728,730,732-735]
- Actions, summarised as two or three action points, to take if asthma deteriorates, including seeking emergency help, commencing oral steroids (which may include provision of an emergency course of steroid tablets) recommencing or temporarily increasing inhaled steroids, as appropriate to clinical severity.[730]

Some published studies report long, intensive programmes.[709,736-738] However, there is evidence that short programmes are as effective,[679,739] and that usual care can be raised to a standard that incorporates many of the core elements of the successful extensive programmes.[740,741] 1+

A **Introduce personalised action plans as part of a structured educational discussion.**

Checklist 1. Suggested content for an educational programme/discussion

This checklist is intended as an example, which health professionals should adapt to meet the needs of individual patients and/or carers. The purpose of education is to empower patients and/or carers to undertake self management more appropriately and effectively. Information given should be tailored to individual patient's social, emotional and disease status, and age. Different approaches are needed for different ages.

- Nature of the disease
- Nature of the treatment
- Identify areas where patient most wants treatment to have effect
- How to use the treatment
- Development of self monitoring/self assessment skills
- Negotiation of the personalised action plan in light of identified patient goals
- Recognition and management of acute exacerbations
- Appropriate allergen or trigger avoidance.

9.1.2 SELF MANAGEMENT PROGRAMMES IN SPECIFIC PATIENT GROUPS

A range of different patient populations are included in the trials. It cannot be assumed that a successful intervention in one setting will be feasible or appropriate in another. The greatest benefits are shown in those managed in secondary care.[682,711,712] Primary care studies have also shown benefit,[698,700,702,741] though effects are weaker, perhaps because clinical benefit is harder to demonstrate in people with mild asthma. Innovative approaches to self management education in teenagers (web-based, peer delivered within schools) appear to have more success than more traditional programmes.[699-701,706,709,742-744] A different approach may be needed for pre-school children, many of whom have viral induced wheeze.[683,745,746] There are no studies which specifically address the provision of self-management education to the elderly. Sub group analyses from UK trials have suggested that existing self-management programmes may be of less benefit in ethnic minority groups, but there is a lack of studies evaluating more appropriate interventions.[698,705]

Self management programmes will only achieve better health outcomes if the prescribed asthma treatment is appropriate and within guideline recommendations.[713,717] There is some evidence that ownership of a self management plan may attract better treatment (ie increased steroid provision from attending physicians).[682,698,701]

9.2 COMPLIANCE AND CONCORDANCE

The term compliance embodies a traditional model of prescriptive care which refers to the objectively measured usage of prescribed medication, or frequency of monitoring. Non-compliance may be intentional or unintentional. The term 'concordance' signifies a negotiated agreement between the professional and the patient. Non-concordance describes an inability of both parties to come to an understanding, not merely a failure of the patient to follow the health professional's instructions.[747] Studies which assess whether or not the patient believes that their behaviour is appropriate find correlations between beliefs about illness and medicine and concordance.[748,749] Achieving concordance is likely to improve (though not guarantee) compliance.

9.2.1 COMPLIANCE WITH MONITORING AND TREATMENT

Compliance with regular monitoring with peak flow meters, even in clinical drug trials is poor, with recorded daily use as low as 6%.[750, 751] The lack of evidence supporting long term peak flow monitoring,[647,735,752,753] however, does not negate the use of home charting at critical times: for example, at diagnosis and initial assessment, when assessing response to changes in treatment, as part of a personalised action plan during exacerbations.[735] Comparison should be with the patients' best peak flow (not predicted).[730]

Patients are more likely to under-use than over-use treatment[754-756] and under-use should be considered when there is a failure to control asthma symptoms. Patient self reporting and health care professional assessment both overestimate regular use of prophylactic medication.[754,755,757] Computer repeat-prescribing systems, widely available in general practice, provide a good indication of adherence with prescribed asthma regimens. Electronic monitoring, whilst the most accurate method, is only practical in clinical drug trials.[754]

☑ Computer repeat-prescribing systems provide a useful index of compliance.

☑ Where the patient agrees with the health professional that the action is appropriate compliance is more likely.

9.2.2 INTERVENTIONS TO IMPROVE COMPLIANCE AND CONCORDANCE

Compliance can be improved by simple written instructions and reminders of when to use medication.[758] There is a suggestion in the literature that interventions designed to improve communication between patients and health professionals achieve better programme adherence.[625,737,759] Presenting important information first and repeating it can improve patient recall.[760] Computer,[761] and innovative web-based self management programmes may increase use of regular medication.[762] Within managed care programmes, nurse-led telephone-based self management education supported by written information can increase the use of inhaled steroids.[763,764]

☑ Provide simple, verbal and written instructions and information on drug treatment for patients and carers.

There is insufficient evidence to make clear recommendations on how the broader issues of concordance may be improved. Some practical tips for improving compliance are given in checklist 2.

Checklist 2: Practical tips for improving concordance

Open-ended questions like "If we could make one thing better for your asthma what would it be?" may help to elicit a more patient-centred agenda.

Make it clear you are listening and responding to the patient's concerns and goals.

Reinforce practical information and negotiated treatment plans with written instruction.

Consider reminder strategies.

Recall patients who miss appointments.

9.3 IMPLEMENTATION IN PRACTICE

Successful interventions have been delivered by trained asthma healthcare professionals, in the UK usually doctors and nurses, though a quality improvement programme which trained professionals in asthma self management showed no impact on clinical outcomes.[678,679,690,692,694,765]

Three primary care studies explicitly link the provision of self management education with the facilitation of regular, structured review, consistent with the concept of 'guided self management'. All three increased ownership of personalised action plans and one showed a reduction in episodes of 'speech limiting wheeze'.[631,741,766] 1+

B **Initiatives which encourage regular, structured review explicitly incorporating self management education should be used to increase ownership of personalised action plans.**

9.4 PRACTICAL ADVICE

9.4.1 AVAILABLE RESOURCES

A number of resources are available to support health professionals, including the 'Be in Control' materials produced by Asthma UK. Annex 11 reproduces the Asthma UK personalised action plan available from their website www.asthma.org.uk/control. Additional support and information for patients and carers is also available from the Asthma UK website (www.asthma.org.uk) and their Adviceline run by asthma specialist nurses: 08457 01 02 03 which includes an interpreting service covering 22 languages and Typetalk.

9.4.2 GOOD PRACTICE POINTS

Every asthma consultation is an opportunity to review, reinforce and extend both knowledge and skills. This is true whether the patient is seen in primary care, the accident and emergency department or the outpatient clinic. It is important to recognise that education is a process and not a single event.

☑
- A hospital admission represents a window of opportunity to review self management skills. No patient should leave hospital without a written personalised action plan and the benefit may be greatest at first admission.
- An acute consultation offers the opportunity to determine what action the patient has already taken to deal with the exacerbation. Their self management strategy may be reinforced or refined and the need for consolidation at a routine follow up considered.
- A consultation for an upper respiratory tract infection or other known trigger is an opportunity to rehearse with the patient their self management in the event of their asthma deteriorating.
- Brief simple education linked to patient goals is most likely to be acceptable to patients.

Table 13. Summary of the key components of a personalised action plan (adapted from Gibson et al)[730]

Component of an action plan	Result	Practical considerations
Format of action points: Symptom vs peak flow triggered Standard written instructions Traffic light configuration	 Similar effect Consistently beneficial Not clearly better than standard instructions	Asthma UK action plans include both symptom triggers and peak flow levels at which action should be taken.
Number of action points 2-3 action points 4 action points	 Consistently beneficial Not clearly better than 2-3 points	Usual action points are: PEF <80% best: increase inhaled steroids PEF <60% best: commence oral steroids PEF <40% best: seek urgent medical advice
Peak expiratory flow (PEF) levels Based on percentage personal best PEF Based on percentage predicted PEF	 Consistently beneficial Not consistently better than usual care	Personal best should be assessed once treatment has been optimised and peak flows are stable. Best peak flow should be updated every few years in adults, and more frequently in growing children.
Treatment instructions Individualised using inhaled and oral steroids Individualised using oral steroids only Individualised using inhaled steroids	 Consistently beneficial Insufficient data to evaluate Insufficient data to evaluate	Patients may safely hold an emergency supply of prednisolone tablets for use if their symptoms continue to deteriorate and/or if their peak flow falls to 60% of their best. Increasing inhaled steroids is ineffective if patients are already taking moderate or high doses (≥400 mcg daily) and these patients should be advised to move straight to the oral steroid step. Those on low doses (eg 200 mcg) of inhaled steroids may be advised to increase the dose substantially (eg to 1,200 mcg daily) at the onset of a deterioration.[631] Any patients who have stopped medication should be reminded to recommence their inhaled steroids.

10 Development of the guideline

10.1 INTRODUCTION

The guideline has been developed by multidisciplinary groups of practising clinicians using a standard methodology based on a systematic review of the evidence. Further details about SIGN and the guideline development methodology are contained in "SIGN 50: A Guideline Developer's Handbook", available at **www.sign.ac.uk**

Development involved the work of ten different multidisciplinary evidence review groups, a steering group and an executive group, chaired jointly by Dr Bernard Higgins on behalf of the BTS and Dr Graham Douglas on behalf of SIGN.

All members of the guideline development group made declarations of interest and further details of these are available on request from the SIGN Executive. Guideline development and literature review expertise, support and facilitation were provided by the SIGN Executive.

10.2 EXECUTIVE AND STEERING GROUPS

Dr Graham Douglas* (Co-chair)	*Consultant Respiratory Physician, Aberdeen Royal Infirmary*
Dr Bernard Higgins* (Co-chair)	*Consultant Respiratory Physician, Freeman Hospital, Newcastle upon Tyne*
Professor Neil Barnes	*Consultant Respiratory Physician, Barts and The London NHS Trust*
Dr Anne Boyter	*Senior Lecturer, Strathclyde Institute of Pharmacy and Biomedical Sciences, Glasgow*
Professor Sherwood Burge	*Consultant Respiratory Physician, Birmingham Heartlands Hospital*
Dr Chris Cates*	*Senior Research Fellow, St George's, University of London*
Dr Gary Connett	*Consultant Paediatrician, Southampton General Hospital*
Dr Jon Couriel*	*Consultant in Paediatric Respiratory Medicine, Alder Hey Children's Hospital, Liverpool*
Dr Paul Cullinan	*Consultant Physician/Reader, Imperial College, London*
Mrs Sheila Edwards*	*Chief Executive, British Thoracic Society, London*
Ms Erica Evans	*Asthma Care Development Manager, Asthma UK, London*
Ms Monica Fletcher	*Chief Executive, Education for Health, Warwick*
Professor Chris Griffiths	*Professor of Primary Care, Institute of Health Science Education, London*
Dr Liam Heaney	*Senior Lecturer in Respiratory Medicine, Queen's University, Belfast*
Ms Michele Hilton Boon*	*Information Officer, SIGN Executive*
Dr Steve Holmes	*General Practitioner and Chair, General Practice Airways Group, Somerset*
Mrs Ruth McArthur	*Practice Nurse/National Training Co-ordinator, Education for Health, East Kilbride*
Dr Cathy Nelson-Piercy	*Consultant Obstetric Physician, St Thomas' Hospital, London*
Professor Martyn Partridge*	*Professor of Respiratory Medicine, Imperial College, London and Chief Medical Adviser, Asthma UK*
Dr James Paton*	*Reader and Honorary Consultant Paediatrician, Royal Hospital for Sick Children, Glasgow*

Professor Ian Pavord*	*Consultant Physician/Honorary Professor of Medicine, Glenfield Hospital, Leicester*
Ms Elaine Carnegie	*Asthma Policy Officer, Asthma UK, Scotland*
Dr Hilary Pinnock	*General Practitioner, Whitstable Medical Practice, Kent*
Dr Safia Qureshi*	*Programme Director, SIGN*
Professor Colin Robertson	*Consultant in Emergency Medicine, Edinburgh Royal Infirmary*
Professor Mike Shields	*Professor of Child Health, Queen's University, Belfast*
Professor John Warner	*Professor of Paediatrics and Head of Department, Imperial College, London*
Dr John White	*Consultant Respiratory Physician, York District Hospital*

* Executive group

10.3 EVIDENCE REVIEW GROUPS

DIAGNOSIS

Dr Jon Couriel (Co-chair)	*Consultant in Paediatric Respiratory Medicine, Royal Liverpool Children's Hospital*
Dr James Paton (Co-chair)	*Reader and Honorary Consultant Paediatrician, Royal Hospital for Sick Children, Glasgow*
Professor Ian Pavord (Co-chair)	*Consultant Physician/Honorary Professor of Medicine, Glenfield Hospital, Leicester*
Professor Justin Beilby	*Head of the Department of General Practice, University of Adelaide, Australia*
Professor Anne Chang	*Head of Child Health Division, Menzies School of Health Research, Darwin and Royal Children's Hospital, Brisbane, Australia*
Dr Peter Gibson	*Adult Respiratory Physician, John Hunter Chest Institute, New South Wales, Australia*
Professor Peter Helms	*Professor of Child Health, University of Aberdeen*
Dr Bernard Higgins	*Consultant Respiratory Physician, Freeman Hospital, Newcastle upon Tyne*
Mrs Ruth McArthur	*Practice Nurse/National Training Co-ordinator, Education for Health, East Kilbride*
Dr Sarah Mayell	*Specialist Registrar, Alder Hey Hospital, Liverpool*
Dr Dominick Shaw	*Specialist Registrar, City Hospital Campus, Nottingham*
Dr Mike Thomas	*Asthma UK Senior Research Fellow, University of Aberdeen/ General Practitioner, Gloucestershire*

NON-PHARMACOLOGICAL MANAGEMENT

Dr Paul Cullinan (Co-chair)	*Reader in Occupational and Environmental Lung Disease, Royal Brompton Hospital, London*
Professor John Warner (Co-chair)	*Professor of Paediatrics and Head of Department, Imperial College, London*
Dr David Bellamy	*General Practitioner, Bournemouth and Pool Primary Care Trust*
Dr Graham Devereux	*Consultant in Thoracic Medicine, Aberdeen Royal Infirmary*

Dr David Reilly	*Lead Consultant Physician, Glasgow Homoeopathic Hospital*
Dr Janet Rimmer	*Respiratory Physician, Darlinghurst, New South Wales, Australia*
Dr Lyn Smurthwaite	*Research Development Manager, Asthma UK, London*
Mrs Deryn Thompson	*Nursing Tutor, Division of Health Sciences, University of South Australia*

PHARMACOLOGICAL MANAGEMENT

Professor Neil Barnes (Co-chair)	*Consultant Respiratory Physician, Barts and The London NHS Trust*
Professor Mike Shields (Co-chair)	*Professor of Child Health, Queen's University, Belfast*
Dr Anne Boyter	*Senior Lecturer, Strathclyde Institute of Pharmacy and Biomedical Sciences, Glasgow*
Dr Steve Cunningham	*Consultant Paediatrician, Royal Hospital for Sick Children, Edinburgh*
Dr Graeme Currie	*Consultant Physician, Aberdeen Royal Infirmary*
Ms Grainne d'Ancona	*Lead Pharmacist for Medicine, Guys and St Thomas' Hospital, London*
Dr Mike McKean	*Consultant in Respiratory Paediatrics, Royal Victoria Infirmary, Newcastle upon Tyne*
Ms Linda Pearce	*Respiratory Nurse Consultant, West Suffolk Hospital*
Dr Savitha Pushparajah	*General Practitioner, London*
Dr Mike Smith	*Consultant Paediatrician, Craigavon Area Group Hospital, Northern Ireland*
Dr David Spencer	*Consultant Respiratory Paediatrician, Freeman Hospital, Newcastle upon Tyne*
Dr Alison Whittaker	*Consultant Physician, Newport Chest Clinic, Gwent*

INHALER DEVICES

Dr John White (Chair)	*Consultant Respiratory Physician, York District Hospital*
Dr Chris Cates	*Senior Research Fellow, St George's, University of London*
Professor Henry Chrystyn	*Head of Pharmacy, University of Huddersfield*
Ms Monica Fletcher	*Chief Executive, Education for Health, Warwick*
Sr Karen Heslop	*Respiratory Nurse Specialist, Royal Victoria Infirmary, Newcastle upon Tyne*
Dr Alex Horsley	*Specialist Registrar, Western General Hospital, Edinburgh*

MANAGEMENT OF ACUTE ASTHMA

Dr Gary Connett (Co-chair)	*Consultant Paediatrician, Southampton General Hospital*
Professor Colin Robertson (Co-chair)	*Consultant in Emergency Medicine, Edinburgh Royal Infirmary*
Dr Richard Chavasse	*Consultant in Respiratory Paediatrics, St Helier Hospital, Surrey*
Dr Graham Douglas	*Consultant Respiratory Physician, Aberdeen Royal Infirmary*

Dr Mike Greenstone	*Consultant Physician, Castle Hill Hospital, East Yorkshire*
Dr Nick Innes	*Consultant in Respiratory and General Medicine, The Ipswich Hospital*
Dr Mark Levy	*General Practitioner, The Kenton Bridge Medical Centre, Middlesex*
Dr Rob Niven	*Senior Lecturer in Respiratory Medicine, Whythenshawe Hospital, Manchester*
Dr Ronan O'Driscoll	*Respiratory Physician, Hope Hospital, Salford*
Dr Ed Paterson	*Specialist Registrar in Respiratory Medicine, Aberdeen Royal Infirmary*
Dr Colin Powell	*Consultant Paediatrician, University Hospital of Wales, Cardiff*
Dr Lindsay Reid	*Specialist Registrar in Emergency Medicine, Edinburgh Royal Infirmary*
Dr Peter Weller	*Consultant Paediatrician (Respiratory Medicine), Birmingham Children's Hospital*

DELIVERY/ ORGANISATION OF CARE

Professor Chris Griffiths (Chair)	*Professor of Primary Care, Institute of Health Science Education, London*
Ms Monica Fletcher	*Chief Executive, Education for Health, Warwick*
Professor David Price	*GPIAG Professor of Primary Care Respiratory Medicine, Foresterhill Health Centre, Aberdeen*
Dr Richard Russell	*Consultant Physician, Heatherwood and Wexham Park Hospitals, Berkshire*

PATIENT EDUCATION, SELF MANAGEMENT AND COMPLIANCE

Dr Hilary Pinnock (Chair)	*General Practitioner, Whitstable Medical Practice, Kent*
Dr Graham Douglas	*Consultant Respiratory Physician, Aberdeen Royal Infirmary*
Mrs Erica Evans	*Care Development Manager, Asthma UK, London*
Dr Liesl Osman	*Senior Research Fellow, Aberdeen Royal Infimary*

SPECIAL SITUATIONS

Difficult asthma

Dr Liam Heaney (Chair)	*Senior Lecturer in Respiratory Medicine, Queens University, Belfast*
Dr Chris Brightling	*Senior Clinical Research Fellow, Glenfield Hospital, Leicester*
Dr Andrew Menzies-Gow	*Consultant Respiratory Physician, Royal Brompton Hospital, London*
Dr Brian Smith	*South Australian State President of the Thoracic Society of Australia*
Dr Nicola Wilson	*Honorary Consultant Paediatrician, Royal Brompton Hospital, London*

Asthma in pregnancy

Dr Cathy Nelson-Piercy (Chair)	*Consultant Obstetric Physician, St Thomas' Hospital, London*
Dr Bernard Higgins	*Consultant Respiratory Physician, Freeman Hospital, Newcastle upon Tyne*
Dr Laura Price	*Research Fellow, Imperial College, London*

Occupational asthma

Dr Sherwood Burge (Chair)	*Consultant Respiratory Physician, Birmingham Heartlands Hospital*
Professor Anthony Frew	*Professor of Allergy and Respiratory Medicine, Brighton General Hospital*

10.4 DISSEMINATION GROUP

Professor Martyn Partridge (Chair)	*Professor of Respiratory Medicine, Imperial College, London and Chief Medical Adviser, Asthma UK*
Mrs Sheila Edwards	*Chief Executive, British Thoracic Society, London*
Ms Monica Fletcher	*Chief Executive, Education for Health, Warwick*
Dr Bernard Higgins	*Consultant Respiratory Physician, Freeman Hospital, Newcastle upon Tyne*
Dr Steve Holmes	*General Practitioner and Chair, General Practice Airways Group, Somerset*
Dr James Paton	*Reader and Honorary Consultant Paediatrician, Royal Hospital for Sick Children, Glasgow*
Dr Hilary Pinnock	*General Practitioner, Whitstable Medical Practice, Kent*
Dr Safia Qureshi	*Programme Director, SIGN*
Mrs Sally Welham	*Deputy Chief Executive, British Thoracic Society, London*

10.5 SYSTEMATIC LITERATURE REVIEW

The evidence base for this guideline built on the reviews carried out for the original (2003) version of the guideline and subsequent updates.

All searches covered the Cochrane Library, Embase, and Medline. See Annex 1 for details of the time period covered for each topic. A copy of the search narrative, including listings of strategies, is available on the SIGN website as part of the supporting material for this guideline.

10.6 CONSULTATION AND PEER REVIEW

10.6.1 CONSULTATION

The most recent changes to this guideline were presented for discussion in draft form at the Winter Meeting of the British Thoracic Society in December 2008. The draft guideline was also available on the SIGN and BTS websites for a limited period at this stage to allow those unable to attend the meeting to contribute to the development of the guideline.

10.6.2 SPECIALIST REVIEWERS

The guideline was also reviewed in draft form by the following independent expert referees, who were asked to comment primarily on the comprehensiveness and accuracy of interpretation of the evidence base supporting the recommendations in the guideline. SIGN and the BTS are very grateful to all of these experts for their contribution to the guideline.

Ms Charlotte Allen	*Clinical Nurse Specialist - Asthma, Princess Margaret Hospital, Perth, Australia*
Dr Sandra Anderson	*Principal Hospital Scientist, Royal Prince Alfred Hospital, Sydney, Australia*
Professor Richard Beasley	*Professor of Medicine, Medical Research Institute of New Zealand, Wellington*
Dr David A R Boldy	*Consultant Respiratory Physician, Pilgrim Hospital, Boston, Lincolnshire*
Professor Chris Brightling	*Wellcome Senior Clinical Fellow and Honorary Consultant, Institute for Lung Health,* Leicester
Ms Karen Burnett	*Lay representative, Inverness*
Ms Suzanne Clark	*Lay representative, Glasgow*
Mr Michael Dennis	*Deputy Head of Prescribing, Great Yarmouth and Waveney (Teaching) PCT, Suffolk*
Dr Kevin Gruffydd-Jones	*Respiratory Lead, Royal College of General Practitioners, Joint Policy Lead, General Practice Airways Group and General Practitioner, Box Surgery, Wiltshire*
Dr John Haughney	*General Practitioner, Alison Lea Medical Centre, East Kilbride*
Miss Tracy Horner	*Medicines Management Technician, Bexhill Hospital, East Sussex*
Dr Norman Johnson	*Chairman of the BTS Standards of Care Committee, British Thoracic Society, London*
Dr Duncan Keeley	*General Practitioner, Thame Health Centre, Oxon*
Professor Helen Redell	*Clinical Associate Professor, University of Sydney, Australia*
Dr Robert Scott-Jupp	*Consultant Paediatrician, Salisbury District Hospital, Salisbury*
Professor Anne Tattersfield	*Head of Respiratory Medicine, University of Nottingham*
Professor Neil C Thomson	*Professor of Respiratory Medicine, Gartnavel General Hospital, Glasgow*
Dr Mark Woodhead	*Consultant in General and Respiratory Medicine, Central Manchester and Manchester Children's University Hospitals*

Abbreviations

ABG	arterial blood gas
ABPA	allergic bronchopulmonary aspergillosis
ACT	Asthma Control Test
ACTH	adrenocorticotropic hormone
AQLQ	Asthma Quality of Life Questionnaire
BDP	beclometasone
BTS	British Thoracic Society
COPD	chronic obstructive pulmonary disease
CXR	chest X-ray
DPI	dry powder inhaler
ED	emergency department
ETS	environmental tobacco smoke
FENO	exhaled nitric oxide concentration
FEV_1	forced expiratory volume in one second
FVC	forced vital capacity
GMS	General Medical Services
GP	general practitioner
GRASSIC	Grampian Asthma Study in Integrated Care
HDU	high dependency unit
ICU	intensive care unit
IM	intramuscular
IOS	impulse oscillometry
LABA	long-acting β_2 agonist
MDI	metered dose inhaler
MHRA	Medicines and Healthcare products Regulatory Agency
n-3PUFA	omega-3 polyunsaturated fatty acid
NIV	non-invasive ventilation
NSAIDS	Non-steroidal anti-inflammatory drugs
PaCO2	partial pressure of carbon dioxide in arterial blood
PaO2	partial pressure of oxygen in arterial blood
PC20	the provocative concentration of bronchoconstrictor (eg methacholine) required to cause a 20% fall in FEV_1
PD20	the provocative dose of bronchoconstrictor (eg methacholine) required to cause a 20% fall in FEV_1
PEF	peak expiratory flow
PEF A%H	peak expiratory flow amplitude percent highest
PICU	paediatric intensive care unit
PN	practice nurse
ppb	parts per billion
QOF	Quality and Outcomes Framework
RCP	Royal College of Physicians
RCT	randomised controlled trial
RV	residual volume
SIGN	Scottish Intercollegiate Guidelines Network
SpO2	saturation of peripheral oxygen
sRaw	specific airways resistance
VEmax	ventilation at maximal exercise capacity

Annex 1

Summary of search histories by section

Literature searches to support the various sections of this guideline are conducted on a rolling basis. This summary indicates the currency of the searches supporting each section. Searches in all databases began with the earliest year available at that time, which varied from database to database; for example, searches in Embase extended back to 1980 and in CINAHL to 1982. Specific date coverage is provided for Medline. Detailed search strategies are available on the SIGN website in the supplementary material section.

Section 2 Diagnosis

Diagnosis in children

The search was last updated in April 2007. Coverage in Medline extends from 2003-2006. This search supplemented the broader search on diagnosis conducted for the original 2003 diagnosis section.

Diagnosis in adults; monitoring

The search was last updated in February 2006. Coverage in Medline extends from 1966-2005.

Section 3 Non-pharmacological management

The search was last updated in February 2006. Coverage in Medline extends from 1966-2005.

Section 4 Pharmacological management

The search was last updated in June 2008. Coverage in Medline extends from 1966-May 2008.

Section 5 Inhaler devices

The search was last updated in June 2008. Coverage in Medline extends from 1998-January 2008.

Section 6 Management of acute asthma

The search was last updated in June 2008. Coverage in Medline extends from 1966-2008.

Section 7 Special situations

Difficult asthma

The search was conducted in July 2007 and covered 1996-June 2007.

Asthma in pregnancy

The search was last updated in June 2008. Coverage in Medline extends from 1966-January 2008.

Occupational asthma

The search was last updated by SIGN in March 2003. In 2005, a systematic review by the British Occupational Health Research Foundation was used as the basis for updating this section.

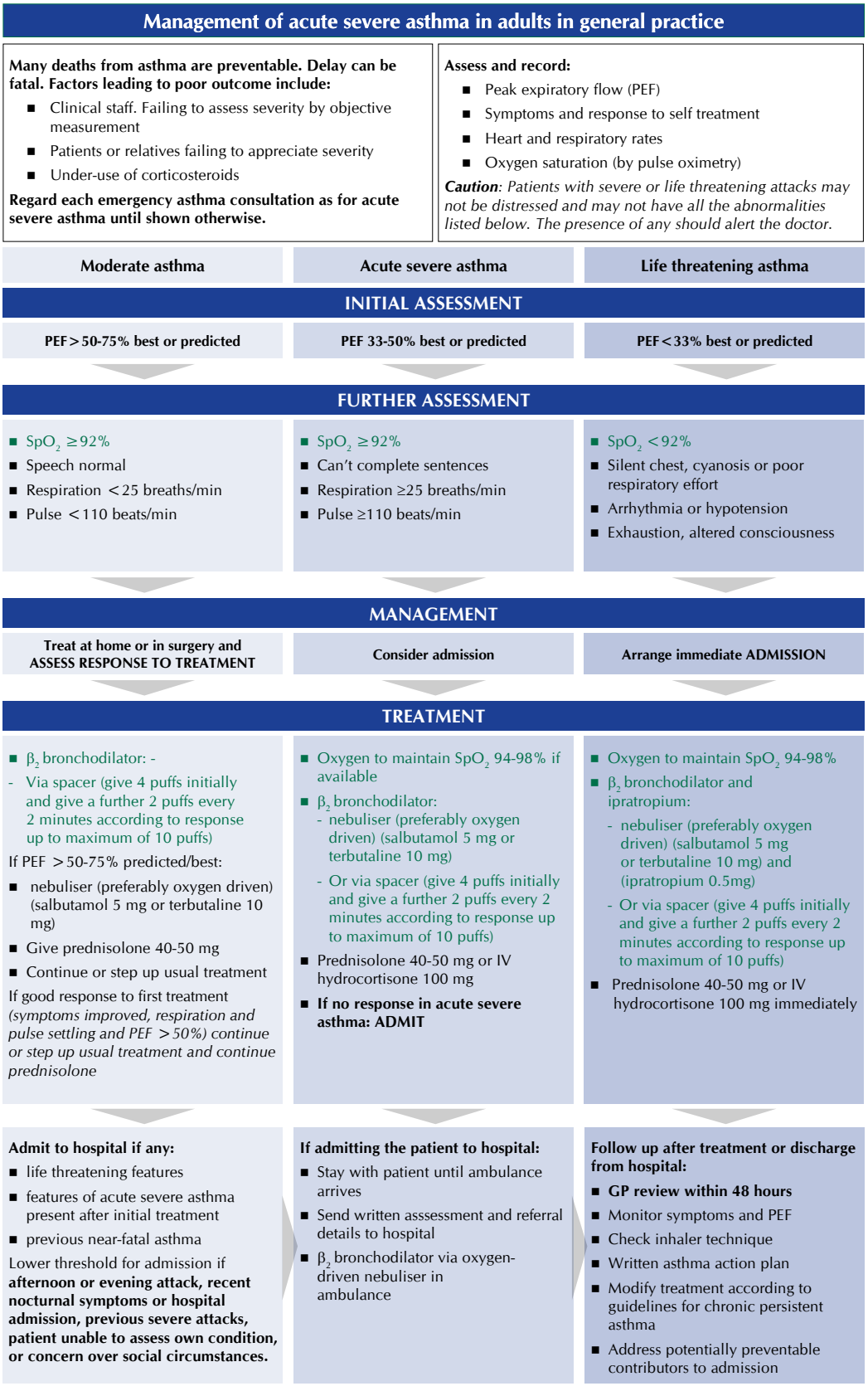
Section 8 Organisation and delivery of care, and audit

The search was last updated in March 2003. Coverage in Medline extends from 1966-2003.

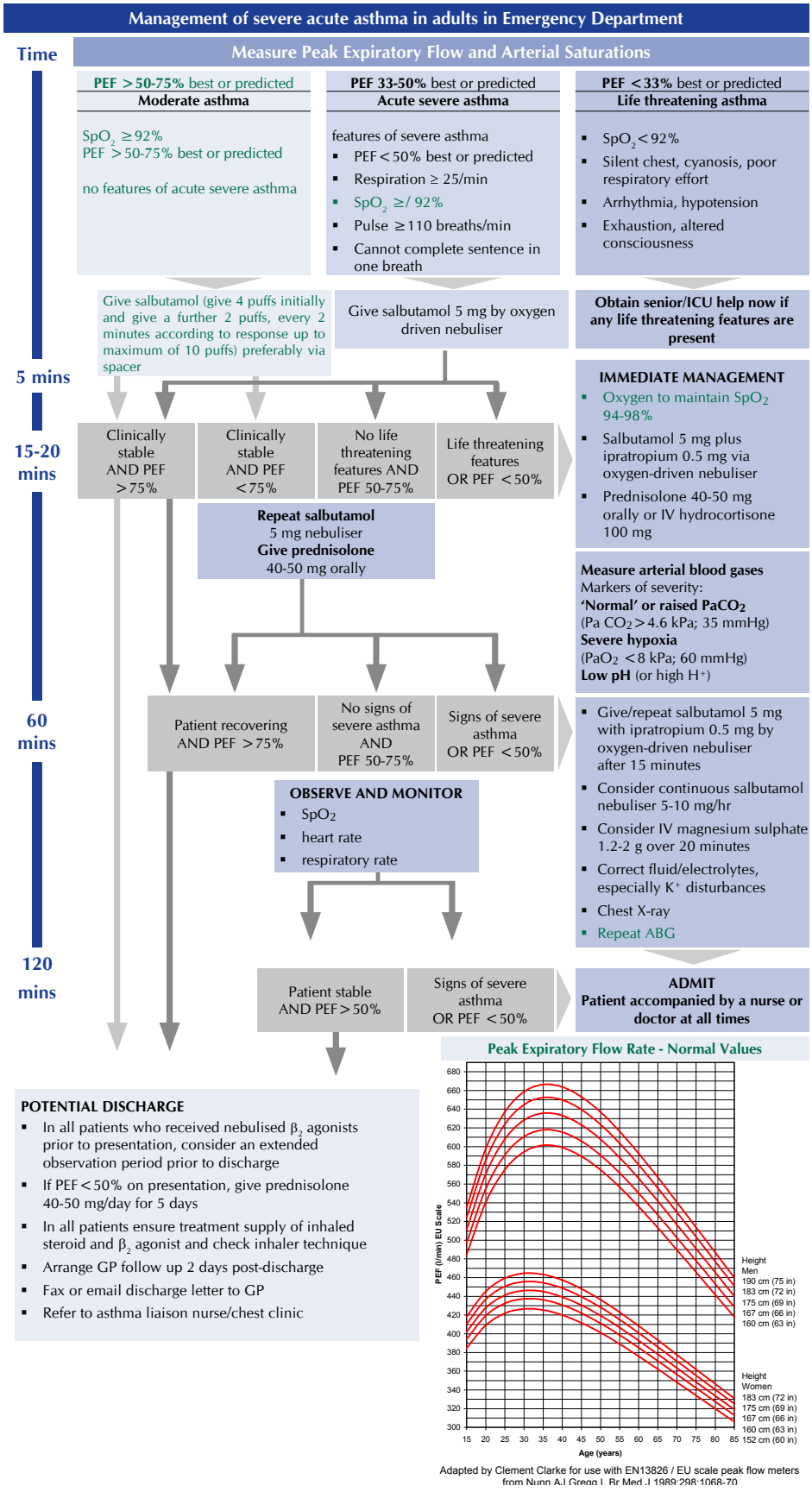
Section 9 Patient education and self management

The search was last updated in February 2006. Coverage in Medline extends from 1966-2005.

Annex 2


Management of acute severe asthma in adults in general practice
Many deaths from asthma are preventable. Delay can be fatal. Factors leading to poor outcome include:
Clinical staff. Failing to assess severity by objective measurement
Patients or relatives failing to appreciate severity
Under-use of corticosteroids
Regard each emergency asthma consultation as for acute severe asthma until shown otherwise.
Assess and record:
Peak expiratory flow (PEF)
Symptoms and response to self treatment
Heart and respiratory rates
Oxygen saturation (by pulse oximetry)
Caution: Patients with severe or life threatening attacks may not be distressed and may not have all the abnormalities listed below. The presence of any should alert the doctor.
Moderate asthma
Acute severe asthma
Life threatening asthma
INITIAL ASSESSMENT
PEF > 50-75% best or predicted
PEF 33-50% best or predicted
PEF < 33% best or predicted
FURTHER ASSESSMENT
SpO2 ≥ 92%
Speech normal
Respiration < 25 breaths/min
Pulse < 110 beats/min
SpO2 ≥ 92%
Can't complete sentences
Respiration ≥25 breaths/min
Pulse ≥110 beats/min
SpO2 < 92%
Silent chest, cyanosis or poor respiratory effort
Arrhythmia or hypotension
Exhaustion, altered consciousness
MANAGEMENT
Treat at home or in surgery and ASSESS RESPONSE TO TREATMENT
Consider admission
Arrange immediate ADMISSION
TREATMENT
β2 bronchodilator: -
- Via spacer (give 4 puffs initially and give a further 2 puffs every 2 minutes according to response up to maximum of 10 puffs)
If PEF > 50-75% predicted/best:
nebuliser (preferably oxygen driven) (salbutamol 5 mg or terbutaline 10 mg)
Give prednisolone 40-50 mg
Continue or step up usual treatment
If good response to first treatment (symptoms improved, respiration and pulse settling and PEF > 50%) continue or step up usual treatment and continue prednisolone
Oxygen to maintain SpO2 94-98% if available
β2 bronchodilator:
- nebuliser (preferably oxygen driven) (salbutamol 5 mg or terbutaline 10 mg)
- Or via spacer (give 4 puffs initially and give a further 2 puffs every 2 minutes according to response up to maximum of 10 puffs)
Prednisolone 40-50 mg or IV hydrocortisone 100 mg
If no response in acute severe asthma: ADMIT
Oxygen to maintain SpO2 94-98%
β2 bronchodilator and ipratropium:
- nebuliser (preferably oxygen driven) (salbutamol 5 mg or terbutaline 10 mg) and (ipratropium 0.5mg)
- Or via spacer (give 4 puffs initially and give a further 2 puffs every 2 minutes according to response up to maximum of 10 puffs)
Prednisolone 40-50 mg or IV hydrocortisone 100 mg immediately
Admit to hospital if any:
life threatening features
features of acute severe asthma present after initial treatment
previous near-fatal asthma
Lower threshold for admission if afternoon or evening attack, recent nocturnal symptoms or hospital admission, previous severe attacks, patient unable to assess own condition, or concern over social circumstances.
If admitting the patient to hospital:
Stay with patient until ambulance arrives
Send written asssessment and referral details to hospital
β2 bronchodilator via oxygen-driven nebuliser in ambulance
Follow up after treatment or discharge from hospital:
GP review within 48 hours
Monitor symptoms and PEF
Check inhaler technique
Written asthma action plan
Modify treatment according to guidelines for chronic persistent asthma
Address potentially preventable contributors to admission

Annex 3


Management of severe acute asthma in adults in Emergency Department
Time
Measure Peak Expiratory Flow and Arterial Saturations
PEF >50-75% best or predicted
Moderate asthma
SpO2 ≥92%
PEF >50-75% best or predicted
no features of acute severe asthma
PEF 33-50% best or predicted
Acute severe asthma
features of severe asthma
PEF <50% best or predicted
Respiration ≥ 25/min
SpO2 ≥/ 92%
Pulse ≥110 breaths/min
Cannot complete sentence in one breath
PEF <33% best or predicted
Life threatening asthma
SpO2 <92%
Silent chest, cyanosis, poor respiratory effort
Arrhythmia, hypotension
Exhaustion, altered consciousness
Give salbutamol (give 4 puffs initially and give a further 2 puffs, every 2 minutes according to response up to maximum of 10 puffs) preferably via spacer
Give salbutamol 5 mg by oxygen driven nebuliser
Obtain senior/ICU help now if any life threatening features are present
5 mins
15-20 mins
Clinically stable AND PEF >75%
Clinically stable AND PEF <75%
No life threatening features AND PEF 50-75%
Life threatening features OR PEF <50%
IMMEDIATE MANAGEMENT
Oxygen to maintain SpO2 94-98%
Salbutamol 5 mg plus ipratropium 0.5 mg via oxygen-driven nebuliser
Prednisolone 40-50 mg orally or IV hydrocortisone 100 mg
Repeat salbutamol 5 mg nebuliser
Give prednisolone 40-50 mg orally
Measure arterial blood gases
Markers of severity:
'Normal' or raised PaCO2
(Pa CO2 >4.6 kPa; 35 mmHg)
Severe hypoxia
(PaO2 <8 kPa; 60 mmHg)
Low pH (or high H+)
60 mins
Patient recovering AND PEF >75%
No signs of severe asthma AND PEF 50-75%
Signs of severe asthma OR PEF <50%
Give/repeat salbutamol 5 mg with ipratropium 0.5 mg by oxygen-driven nebuliser after 15 minutes
Consider continuous salbutamol nebuliser 5-10 mg/hr
Consider IV magnesium sulphate 1.2-2 g over 20 minutes
Correct fluid/electrolytes, especially K+ disturbances
Chest X-ray
Repeat ABG
OBSERVE AND MONITOR
SpO2
heart rate
respiratory rate
120 mins
Patient stable AND PEF >50%
Signs of severe asthma OR PEF <50%
ADMIT
Patient accompanied by a nurse or doctor at all times
POTENTIAL DISCHARGE
In all patients who received nebulised β2 agonists prior to presentation, consider an extended observation period prior to discharge
If PEF <50% on presentation, give prednisolone 40-50 mg/day for 5 days
In all patients ensure treatment supply of inhaled steroid and β2 agonist and check inhaler technique
Arrange GP follow up 2 days post-discharge
Fax or email discharge letter to GP
Refer to asthma liaison nurse/chest clinic
Peak Expiratory Flow Rate - Normal Values
PEF (l/min) EU Scale
680
660
640
620
600
580
560
540
520
500
480
460
440
420
400
380
360
340
320
300
15 20 25 30 35 40 45 50 55 60 65 70 75 80 85
Age (years)
Height Men
190 cm (75 in)
183 cm (72 in)
175 cm (69 in)
167 cm (66 in)
160 cm (63 in)
Height Women
183 cm (72 in)
175 cm (69 in)
167 cm (66 in)
160 cm (63 in)
152 cm (60 in)
Adapted by Clement Clarke for use with EN13826 / EU scale peak flow meters
from Nunn AJ Gregg I. Br Med J 1989;298:1068-70

Annex 4

Management of acute severe asthma in adults in hospital

Features of acute severe asthma

- Peak expiratory flow (PEF) 33-50% of best (use % predicted if recent best unknown)
- Can't complete sentences in one breath
- Respirations ≥25 breaths/min
- Pulse ≥110 beats/min

Life threatening features

- PEF <33% of best or predicted
- SpO_2 <92%
- Silent chest, cyanosis, or feeble respiratory effort
- Arrhythmia or hypotension
- Exhaustion, altered consciousness

If a patient has any life threatening feature, measure arterial blood gases. No other investigations are needed for immediate management.

Blood gas markers of a life threatening attack:

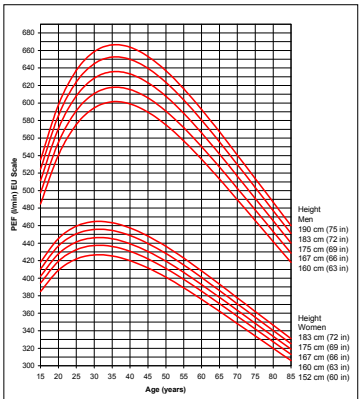
- 'Normal' (4.6-6 kPa, 35-45 mmHg) $PaCO_2$
- Severe hypoxia: PaO_2 <8 kPa (60mmHg) irrespective of treatment with oxygen
- A low pH (or high H^+)

Caution: Patients with severe or life threatening attacks may not be distressed and may not have all these abnormalities. The presence of any should alert the doctor.

Near fatal asthma

- Raised $PaCO_2$
- Requiring mechanical ventilation with raised inflation pressures

Peak Expiratory Flow Rate - Normal Values



Adapted by Clement Clarke for use with EN13826 / EU scale peak flow meters from Nunn AJ Gregg I, Br Med J 1989:298;1068-70

IMMEDIATE TREATMENT

- Oxygen to maintain SpO_2 94-98%
- Salbutamol 5 mg or terbutaline 10 mg via an oxygen-driven nebuliser
- Ipratropium bromide 0.5 mg via an oxygen-driven nebuliser
- Prednisolone tablets 40-50 mg or IV hydrocortisone 100 mg
- No sedatives of any kind
- Chest X ray if pneumothorax or consolidation are suspected or patient requires mechanical ventilation

IF LIFE THREATENING FEATURES ARE PRESENT:

- Discuss with senior clinician and ICU team
- Consider IV magnesium sulphate 1.2-2 g infusion over 20 minutes (unless already given)
- Give nebulised β_2 agonist more frequently e.g. salbutamol 5 mg up to every 15-30 minutes or 10 mg per hour via continuous nebulisation (requires special nebuliser)

SUBSEQUENT MANAGEMENT

IF PATIENT IS IMPROVING continue:

- Oxygen to maintain SpO_2 94-98%
- Prednisolone 40-50mg daily or IV hydrocortisone 100 mg 6 hourly
- Nebulised β_2 agonist and ipratropium 4-6 hourly

IF PATIENT NOT IMPROVING AFTER 15-30 MINUTES:

- Continue oxygen and steroids
- Use continuous nebulisation of salbutamol at 5-10 mg/hour if an appropriate nebuliser is available. Otherwise give nebulised salbutamol 5 mg every 15-30 minutes
- Continue ipratropium 0.5 mg 4-6 hourly until patient is improving

IF PATIENT IS STILL NOT IMPROVING:

- Discuss patient with senior clinician and ICU team
- Consider IV magnesium sulphate 1.2-2 g over 20 minutes (unless already given)
- Senior clinician may consider use of IV β_2 agonist or IV aminophylline or progression to mechanical ventilation

MONITORING

- Repeat measurement of PEF 15-30 minutes after starting treatment
- Oximetry: maintain SpO_2 >94-98%
- Repeat blood gas measurements within 1 hour of starting treatment if:
  - initial PaO_2 <8 kPa (60 mmHg) unless subsequent SpO_2 >92%
  - $PaCO_2$ normal or raised
  - patient deteriorates
- Chart PEF before and after giving β_2 agonists and at least 4 times daily throughout hospital stay

Transfer to ICU accompanied by a doctor prepared to intubate if:

- Deteriorating PEF, worsening or persisting hypoxia, or hypercapnea
- Exhaustion, altered consciousness
- Poor respiratory effort or respiratory arrest

DISCHARGE

When discharged from hospital, patients should have:

- Been on discharge medication for 12-24 hours and have had inhaler technique checked and recorded
- PEF >75% of best or predicted and PEF diurnal variability <25% unless discharge is agreed with respiratory physician
- Treatment with **oral and inhaled steroids** in addition to bronchodilators
- Own PEF meter and **written asthma action plan**
- GP follow up arranged within 2 working days
- Follow up appointment in respiratory clinic within 4 weeks

Patients with severe asthma (indicated by need for admission) **and adverse behavioural or psychosocial features are at risk of further severe or fatal attacks**

- Determine reason(s) for exacerbation and admission
- Send details of admission, discharge and potential best PEF to GP

Annex 5

Management of acute asthma in children in general practice

Age 2-5 years

ASSESS ASTHMA SEVERITY

Moderate asthma	Severe asthma	Life threatening asthma
■ SpO_2 ≥92% ■ Able to talk ■ Heart rate ≤140/min ■ Respiratory rate ≤40/min	■ SpO_2 <92% ■ Too breathless to talk ■ Heart rate >140/min ■ Respiratory rate >40/min ■ Use of accessory neck muscles	SpO_2 <92% plus any of: ■ Silent chest ■ Poor respiratory effort ■ Agitation ■ Altered consciousness ■ Cyanosis
■ β_2 agonist 2-10 puffs via spacer ± facemask ■ Consider soluble prednisolone 20 mg	■ Oxygen via face mask ■ 2-10 puffs of β_2 agonist [give 2 puffs, every 2 minutes according to response up to maximum of 10 puffs] or nebulised salbutamol 2.5 mg or terbutaline 5 mg ■ Soluble prednisolone 20 mg	■ Oxygen via face mask ■ Nebulise: - salbutamol 2.5 mg *or* terbutaline 5 mg + - ipratropium 0.25 mg ■ Soluble prednisolone 20 mg *or* IV hydrocortisone 50 mg
Increase β_2 agonist dose by 2 puffs every 2 minutes according to response up to 10 puffs	**Assess response to treatment 15 mins after β_2 agonist**	
IF POOR RESPONSE ARRANGE ADMISSION	**IF POOR RESPONSE REPEAT β_2 AGONIST AND ARRANGE ADMISSION**	**REPEAT β_2 AGONIST VIA OXYGEN-DRIVEN NEBULISER WHILST ARRANGING IMMEDIATE HOSPITAL ADMISSION**

GOOD RESPONSE
- Continue β_2 agonist via spacer or nebuliser, as needed but not exceeding 4-hourly
- **If symptoms are not controlled repeat β_2 agonist and refer to hospital**
- Continue prednisolone for up to 3 days
- Arrange follow-up clinic visit

POOR RESPONSE
- Stay with patient until ambulance arrives
- Send written assessment and referral details
- Repeat β_2 agonist via oxygen-driven nebuliser in ambulance

LOWER THRESHOLD FOR ADMISSION IF:
- Attack in late afternoon or at night
- Recent hospital admission or previous severe attack
- Concern over social circumstances or ability to cope at home

NB: If a patient has signs and symptoms across categories, always treat according to their most severe features

Age >5 years

ASSESS ASTHMA SEVERITY

Moderate asthma	Severe asthma	Life threatening asthma
■ SpO_2 ≥92% ■ PEF ≥50% best or predicted ■ Able to talk ■ Heart rate ≤125/min ■ Respiratory rate ≤30/min	■ SpO_2 <92% ■ PEF 33-50% best or predicted ■ Too breathless to talk ■ Heart rate >125/min ■ Respiratory rate >30/min ■ Use of accessory neck muscles	SpO_2 <92% plus any of: ■ PEF <33% best or predicted ■ Silent chest ■ Poor respiratory effort ■ Agitation ■ Altered consciousness ■ Cyanosis
■ β_2 agonist 2-10 puffs via spacer ■ Consider soluble prednisolone 30-40 mg	■ Oxygen via face mask ■ 2-10 puffs of β_2 agonist [give 2 puffs, every 2 minutes according to response up to maximum of 10 puffs] or nebulised salbutamol 2.5-5 mg or terbutaline 5-10 mg ■ Soluble prednisolone 30-40 mg	■ Oxygen via face mask ■ Nebulise: - salbutamol 5 mg *or* terbutaline 10 mg + - ipratropium 0.25 mg ■ Soluble prednisolone 30-40 mg *or* IV hydrocortisone 100 mg
Increase β_2 agonist dose by 2 puffs every 2 minutes according to response up to 10 puffs	**Assess response to treatment 15 mins after β_2 agonist**	
IF POOR RESPONSE ARRANGE ADMISSION	**IF POOR RESPONSE REPEAT β_2 AGONIST AND ARRANGE ADMISSION**	**REPEAT β_2 AGONIST VIA OXYGEN-DRIVEN NEBULISER WHILST ARRANGING IMMEDIATE HOSPITAL ADMISSION**

GOOD RESPONSE
- Continue β_2 agonist via spacer or nebuliser, as needed but not exceeding 4-hourly
- **If symptoms are not controlled repeat β_2 agonist and refer to hospital**
- Continue prednisolone for up to 3 days
- Arrange follow-up clinic visit

POOR RESPONSE
- Stay with patient until ambulance arrives
- Send written assessment and referral details
- Repeat β_2 agonist via oxygen-driven nebuliser in ambulance

LOWER THRESHOLD FOR ADMISSION IF:
- Attack in late afternoon or at night
- Recent hospital admission or previous severe attack
- Concern over social circumstances or ability to cope at home

NB: If a patient has signs and symptoms across categories, always treat according to their most severe features

Annex 6

Management of acute asthma in children in Emergency Department

Age 2-5 years

ASSESS ASTHMA SEVERITY

Moderate asthma
- SpO_2 ≥92%
- No clinical features of severe asthma

NB: If a patient has signs and symptoms across categories, always treat according to their most severe features

- β_2 agonist 2-10 puffs via spacer ± facemask [given one at a time single puffs, tidal breathing and inhaled separately]
- Increase β_2 agonist dose by 2 puffs every 2 minutes up to 10 puffs according to response
- Consider soluble oral prednisolone 20 mg

Reassess within 1 hour

DISCHARGE PLAN
- Continue β_2 agonist 4 hourly prn
- Consider prednisolone 20 mg daily for up to 3 days
- Advise to contact GP if not controlled on above treatment
- Provide a written asthma action plan
- Review regular treatment
- Check inhaler technique
- Arrange GP follow up

Severe asthma
- SpO_2 <92%
- Too breathless to talk or eat
- Heart rate >140/min
- Respiratory rate >40/min
- Use of accessory neck muscles

Oxygen via face mask/nasal prongs to achieve SpO_2 94-98%

- β_2 agonist 10 puffs via spacer ± facemask or nebulised salbutamol 2.5 mg or terbutaline 5 mg
- Soluble prednisolone 20 mg or IV hydrocortisone 4 mg/kg
- Repeat β_2 agonist up to every 20-30 minutes according to response
- **If poor response** add 0.25 mg nebulised ipratropium bromide

Life threatening asthma

SpO_2 <92% plus any of:
- Silent chest
- Poor respiratory effort
- Agitation
- Altered consciousness
- Cyanosis

- Nebulised β_2 agonist: salbutamol 2.5 mg or terbutaline 5 mg **plus** ipratropium bromide 0.25 mg nebulised
- Oral prednisolone 20mg or IV Hydrocortisone 4mg/kg if vomiting

Discuss with senior clinician, PICU team or paediatrician

- Repeat bronchodilators every 20-30 minutes

Arrange immediate transfer to PICU/HDU if poor response to treatment

Admit all cases if features of severe exacerbation persist after initial treatment

Age >5 years

ASSESS ASTHMA SEVERITY

Moderate asthma
- SpO_2 ≥92%
- PEF ≥50% best or predicted
- No clinical features of severe asthma

NB: If a patient has signs and symptoms across categories, always treat according to their most severe features

- β_2 agonist 2-10 puffs via spacer
- Increase β_2 agonist dose by 2 puffs every 2 minutes up to 10 puffs according to response
- Oral prednisolone 30-40 mg

Reassess within 1 hour

DISCHARGE PLAN
- Continue β_2 agonist 4 hourly as necessary
- Consider prednisolone 30-40 mg daily for up to 3 days
- Advise to contact GP if not controlled on above treatment
- Provide a written asthma action plan
- Review regular treatment
- Check inhaler technique
- Arrange GP follow up

Severe asthma
- SpO_2 <92%
- PEF 33-50% best or predicted
- Heart rate >125/min
- Respiratory rate >30/min
- Use of accessory neck muscles

Oxygen via face mask/nasal prongs to achieve SpO_2 94-98%

- β_2 agonist 10 puffs via spacer or nebulised salbutamol 2.5-5 mg or terbutaline 5-10 mg
- Oral prednisolone 30-40 mg or IV hydrocortisone 4 mg/kg if vomiting
- **If poor response** nebulised ipratropium bromide 0.25 mg
- Repeat β2 agonist and ipratropium up to every 20-30 minutes according to response

Life threatening asthma

SpO_2 <92% plus any of:
- PEF <33% best or predicted
- Silent chest
- Poor respiratory effort
- Altered consciousness
- Cyanosis

- Nebulised β_2 agonist: salbutamol 5 mg or terbutaline 10 mg **plus** ipratropium bromide 0.25 mg nebulised
- Oral prednisolone 30-40mg or IV Hydrocortisone 4mg/kg if vomiting

Discuss with senior clinician, PICU team or paediatrician

- Repeat bronchodilators every 20-30 minutes

Arrange immediate transfer to PICU/HDU if poor response to treatment

Admit all cases if features of severe exacerbation persist after initial treatment

Annex 7

Management of acute asthma in children in hospital

Age 2-5 years

ASSESS ASTHMA SEVERITY

Moderate asthma
- SpO_2 ≥92%
- No clinical features of severe asthma

NB: If a patient has signs and symptoms across categories, always treat according to their most severe features

- β_2 agonist 2-10 puffs via spacer ± facemask [given one at a time single puffs, tidal breathing and inhaled separately]
- Increase β_2 agonist dose by 2 puffs every 2 minutes up to 10 puffs according to response
- Consider soluble oral prednisolone 20 mg

Reassess within 1 hour

Severe asthma
- SpO_2 <92%
- Too breathless to talk or eat
- Heart rate >140/min
- Respiratory rate >40/min
- Use of accessory neck muscles

Life threatening asthma

SpO_2 <92% plus any of:
- Silent chest
- Poor respiratory effort
- Agitation
- Altered consciousness
- Cyanosis

Oxygen via face mask/nasal prongs to achieve SpO_2 94-98%

- β_2 agonist 10 puffs via spacer ± facemask or nebulised salbutamol 2.5 mg or terbutaline 5 mg
- Soluble prednisolone 20 mg or IV hydrocortisone 4 mg/kg
- Repeat β_2 agonist up to every 20-30 minutes according to response
- **If poor response** add 0.25 mg nebulised ipratropium bromide

- Nebulised β_2 agonist: salbutamol 2.5 mg or terbutaline 5 mg **plus** ipratropium bromide 0.25 mg nebulised
- Oral prednisolone 20mg or IV hydrocortisone 4mg/kg if vomiting

Discuss with senior clinician, PICU team or paediatrician

- Repeat bronchodilators every 20-30 minutes

ASSESS RESPONSE TO TREATMENT
Record respiratory rate, heart rate and oxygen saturation every 1-4 hours

RESPONDING
- Continue bronchodilators 1-4 hours prn
- Discharge when stable on 4 hourly treatment
- Continue oral prednisolone for up to 3 days

At discharge
- Ensure stable on 4 hourly inhaled treatment
- Review the need for regular treatment and the use of inhaled steroids
- Review inhaler technique
- Provide a written asthma action plan for treating future attacks
- Arrange follow up according to local policy

NOT RESPONDING
- **Arrange HDU/PICU transfer**

Consider:
- **Chest X-ray and blood gases**
- **IV salbutamol** 15 mcg/kg bolus over 10 minutes **followed** by continuous infusion 1-5 mcg/kg/min (dilute to 200 mcg/ml)
- **IV aminophylline** 5 mg/kg loading dose over 20 minutes (omit in those receiving oral theophyllines) **followed by** continuous infusion 1 mg/kg/hour

Age >5 years

ASSESS ASTHMA SEVERITY

Moderate asthma
- SpO_2 ≥92%
- PEF >50% best or predicted
- No clinical features of severe asthma

NB: If a patient has signs and symptoms across categories, always treat according to their most severe features

- β_2 agonist 2-10 puffs via spacer
- Increase β_2 agonist dose by 2 puffs every 2 minutes up to 10 puffs according to response
- Oral prednisolone 30-40 mg

Reassess within 1 hour

Severe asthma
- SpO_2 <92%
- PEF 33-50% best or predicted
- Heart rate >125/min
- Respiratory rate >30/min
- Use of accessory neck muscles

Oxygen via face mask/nasal prongs to achieve SpO_2 94-98%

- β_2 agonist 10 puffs via spacer or nebulised salbutamol 2.5-5 mg or terbutaline 5-10 mg
- Oral prednisolone 30-40 mg or IV hydrocortisone 4 mg/kg if vomiting
- **If poor response** nebulised ipratropium bromide 0.25 mg
- Repeat β2 agonist and ipratropium up to every 20-30 minutes according to response

Life threatening asthma

SpO_2 <92% plus any of:
- PEF <33% best or predicted
- Silent chest
- Poor respiratory effort
- Altered consciousness
- Cyanosis

- Nebulised β_2 agonist: salbutamol 5 mg or terbutaline 10 mg **plus** ipratropium bromide 0.25 mg nebulised
- Oral prednisolone 30-40mg or IV hydrocortisone 4mg/kg if vomiting

Discuss with senior clinician, PICU team or paediatrician

- Repeat bronchodilators every 20-30 minutes

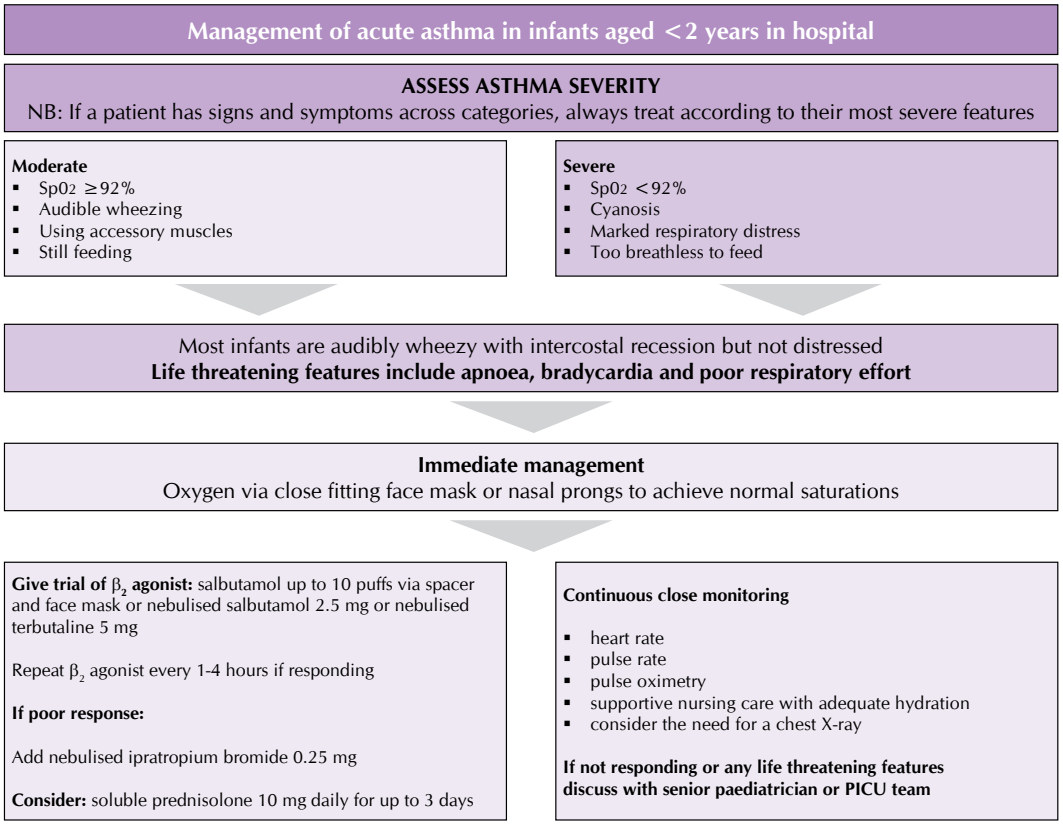
ASSESS RESPONSE TO TREATMENT
Record respiratory rate, heart rate, oxygen saturation and PEF/FEV every 1-4 hours

RESPONDING
- Continue bronchodilators 1-4 hours prn
- Discharge when stable on 4 hourly treatment
- Continue oral prednisolone 30-40 mg for up to 3 days

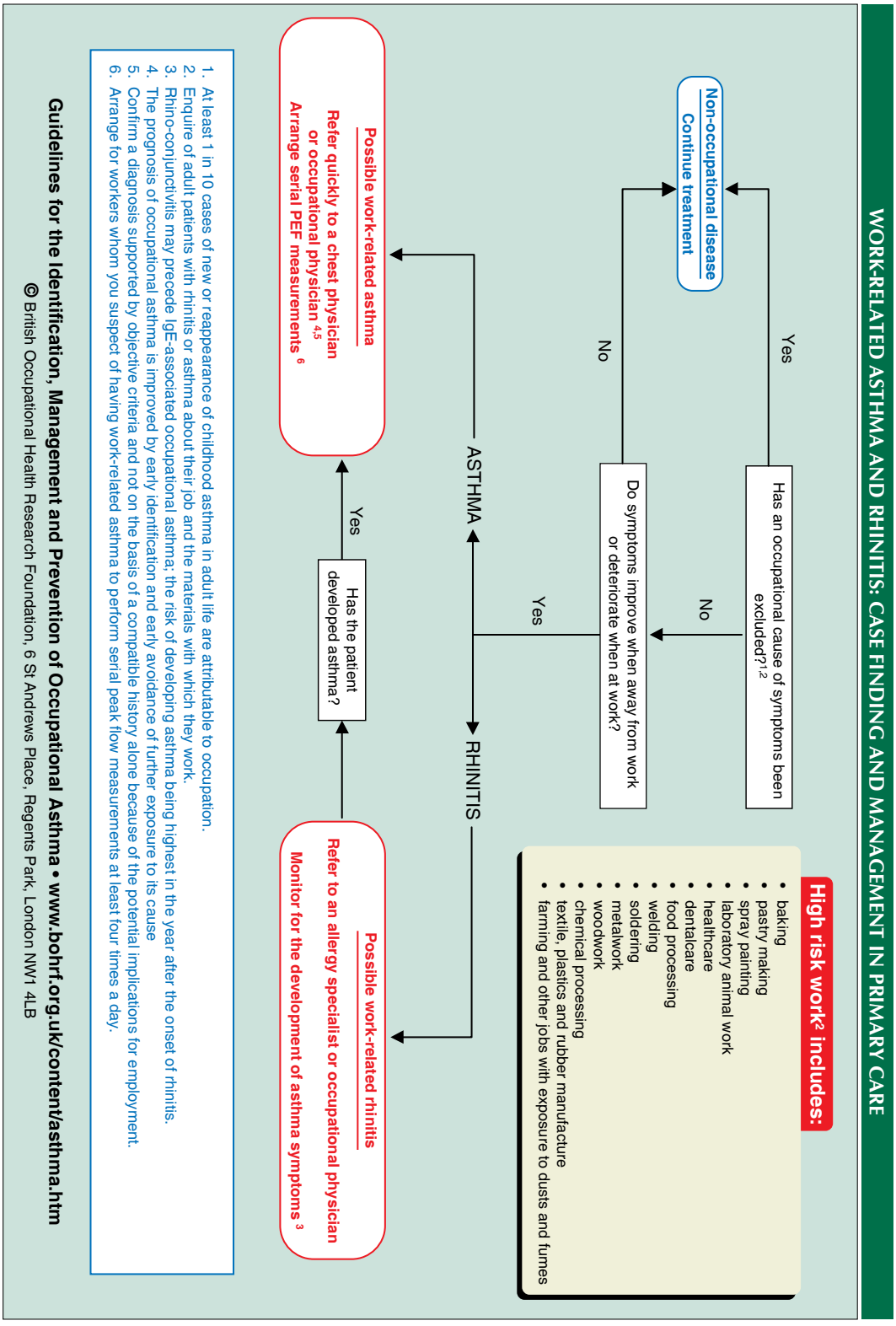
At discharge
- Ensure stable on 4 hourly inhaled treatment
- Review the need for regular treatment and the use of inhaled steroids
- Review inhaler technique
- Provide a written asthma action plan for treating future attacks
- Arrange follow up according to local policy

NOT RESPONDING
- **Continue 20-30 minute nebulisers and arrange HDU/PICU transfer**
- Consider: **Chest X-ray and blood gases**
- **Consider risks and benefits of:**
- **Bolus IV salbutamol** 15 mcg/kg if not already given
- Continuous **IV salbutamol infusion** 1-5 mcg/kg/min (200 mcg/ml solution)
- **IV aminophylline** 5 mg/kg loading dose over 20 minutes (omit in those receiving oral theophyllines) **followed by** continuous infusion 1mg/kg/hour
- **Bolus IV infusion of magnesium sulphate** 40 mg/kg (max 2 g) over 20 minutes

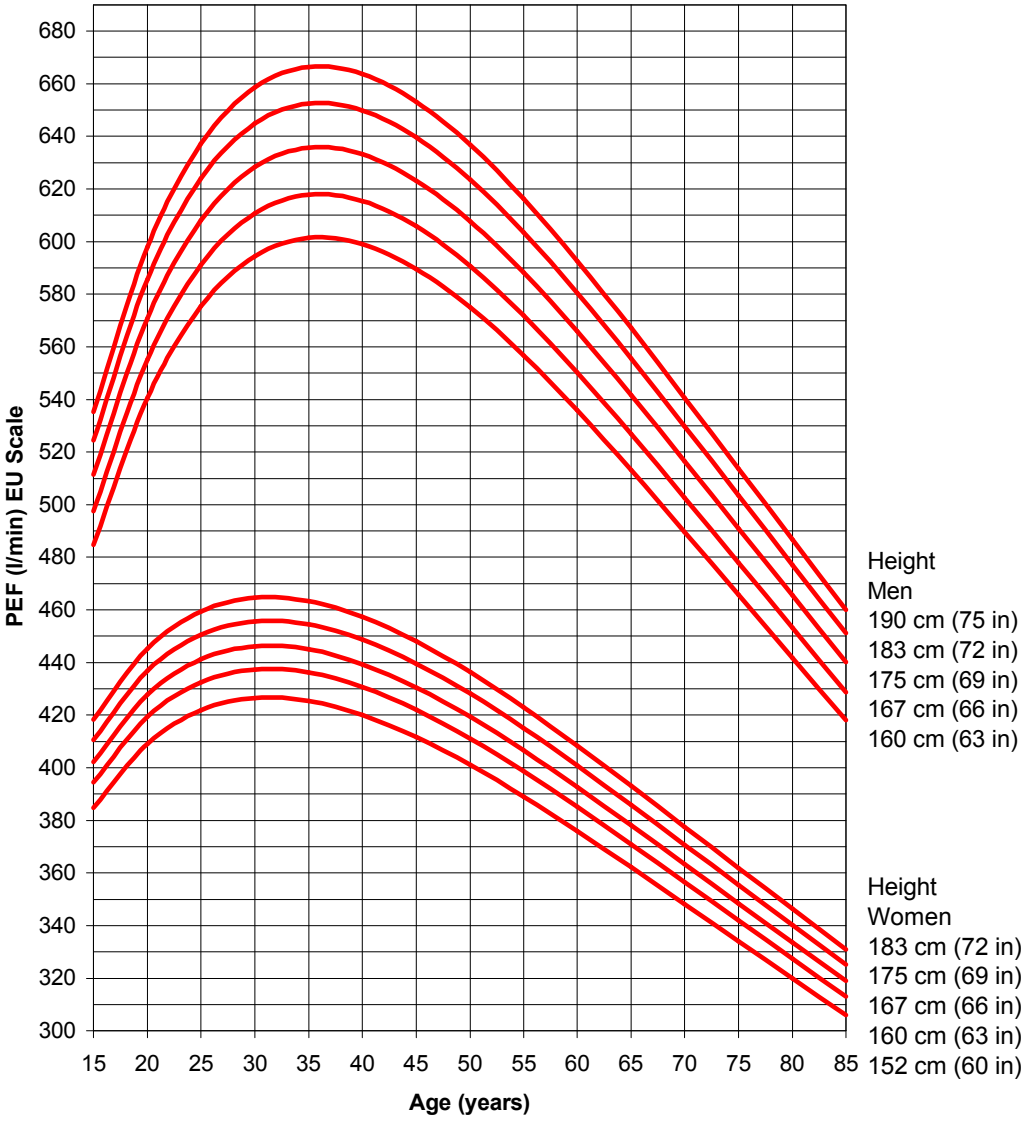
Annex 8


Management of acute asthma in infants aged < 2 years in hospital
ASSESS ASTHMA SEVERITY
NB: If a patient has signs and symptoms across categories, always treat according to their most severe features
Moderate
Sp02 ≥92%
Audible wheezing
Using accessory muscles
Still feeding
Severe
Sp02 <92%
Cyanosis
Marked respiratory distress
Too breathless to feed
Most infants are audibly wheezy with intercostal recession but not distressed
Life threatening features include apnoea, bradycardia and poor respiratory effort
Immediate management
Oxygen via close fitting face mask or nasal prongs to achieve normal saturations
Give trial of β2 agonist: salbutamol up to 10 puffs via spacer and face mask or nebulised salbutamol 2.5 mg or nebulised terbutaline 5 mg
Repeat β2 agonist every 1-4 hours if responding
If poor response:
Add nebulised ipratropium bromide 0.25 mg
Consider: soluble prednisolone 10 mg daily for up to 3 days
Continuous close monitoring
heart rate
pulse rate
pulse oximetry
supportive nursing care with adequate hydration
consider the need for a chest X-ray
If not responding or any life threatening features discuss with senior paediatrician or PICU team

Annex 9


WORK-RELATED ASTHMA AND RHINITIS: CASE FINDING AND MANAGEMENT IN PRIMARY CARE
Has an occupational cause of symptoms been excluded?[1,2]
Yes
No
Non-occupational disease
Continue treatment
Do symptoms improve when away from work or deteriorate when at work?
No
Yes
ASTHMA
RHINITIS
Has the patient developed asthma?
Yes
Possible work-related asthma
Refer quickly to a chest physician or occupational physician [4,5]
Arrange serial PEF measurements [6]
Possible work-related rhinitis
Refer to an allergy specialist or occupational physician
Monitor for the development of asthma symptoms [3]
High risk work[2] includes:
baking
pastry making
spray painting
laboratory animal work
healthcare
dentalcare
food processing
welding
soldering
metalwork
woodwork
chemical processing
textile, plastics and rubber manufacture
farming and other jobs with exposure to dusts and fumes
1. At least 1 in 10 cases of new or reappearance of childhood asthma in adult life are attributable to occupation.
2. Enquire of adult patients with rhinitis or asthma about their job and the materials with which they work.
3. Rhino-conjunctivitis may precede IgE-associated occupational asthma; the risk of developing asthma being highest in the year after the onset of rhinitis.
4. The prognosis of occupational asthma is improved by early identification and early avoidance of further exposure to its cause
5. Confirm a diagnosis supported by objective criteria and not on the basis of a compatible history alone because of the potential implications for employment.
6. Arrange for workers whom you suspect of having work-related asthma to perform serial peak flow measurements at least four times a day.
Guidelines for the Identification, Management and Prevention of Occupational Asthma • www.bohrf.org.uk/content/asthma.htm
© British Occupational Health Research Foundation, 6 St Andrews Place, Regents Park, London NW1 4LB

Annex 10

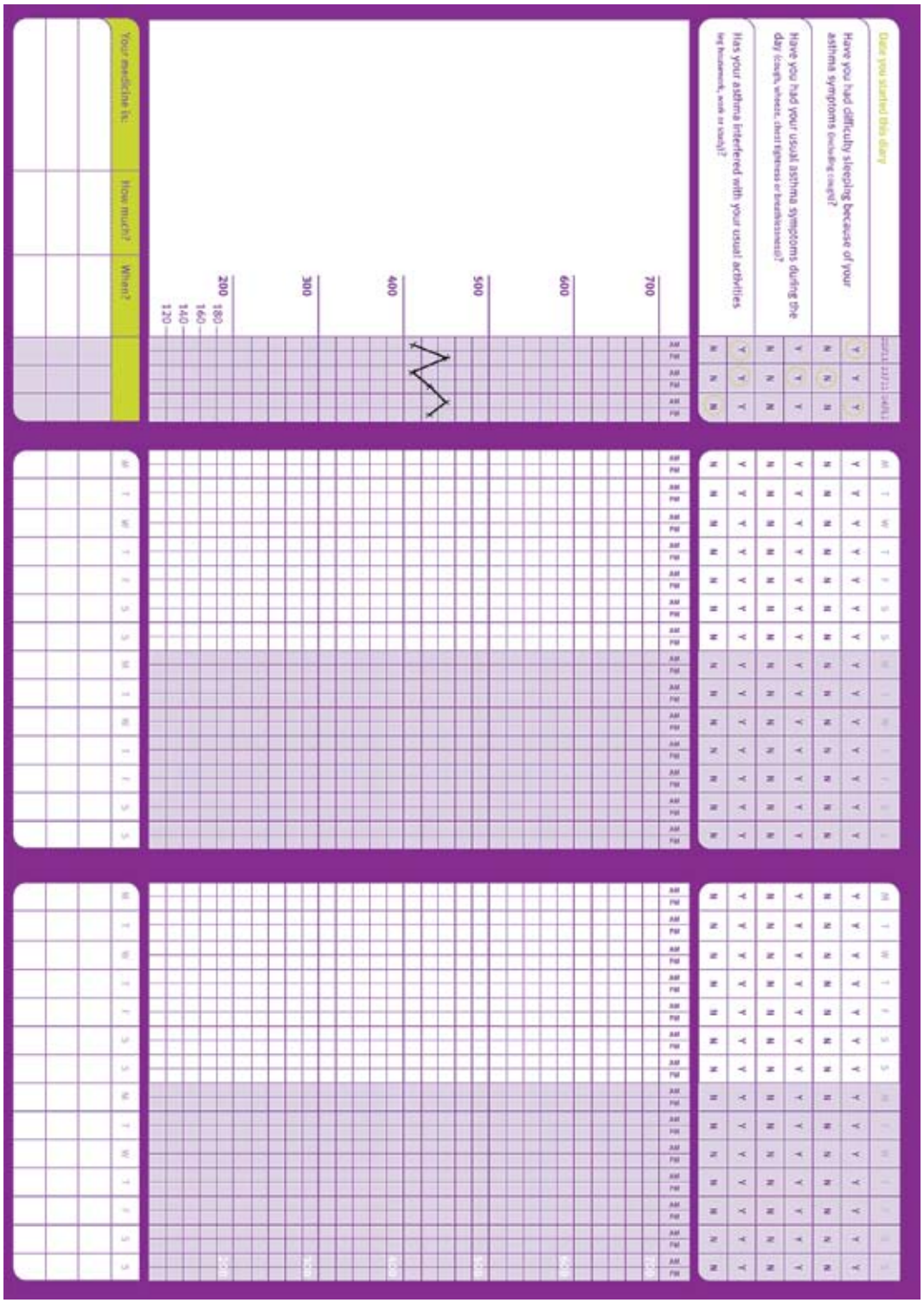


Adapted by Clement Clarke for use with EN13826 / EU scale peak flow meters
from Nunn AJ Gregg I, Br Med J 1989:298;1068-70

Annex 11

About your personal asthma action plan
This plan is intended to be used by people with asthma aged 12 and above.
Your doctor or nurse will fill in this plan with you and explain the different medicines that you should take to control your asthma. It shows you how to recognise when your asthma is getting worse and what you can do about it.
It is reassuring to know that by taking steps early, severe asthma attacks can usually be prevented.
Updating your personal asthma action plan
Because your asthma symptoms can change from day to day, your doctor or nurse may need to change your plan. You should have your asthma reviewed at least once a year.
If your medicine has been changed or increased, visit your doctor or nurse after one month to review your asthma.
Do not stop taking your asthma medicines without talking to your doctor or nurse first.
What to do in an asthma attack
An emergency is when any of the following happen:
1 Your reliever (blue) inhaler does not help
2 Your symptoms get worse (coughs, breathless, wheeze, tight chest)
3 You are too breathless to speak
What you must do during an attack:
1 Take your reliever (blue) inhaler
2 Sit up and loosen tight clothing
3 If no immediate improvement during an attack continue to take one puff of reliever inhaler every minute for five minutes or until symptoms improve
4 If your symptoms do not improve in five minutes – get it NOW (it is fatal – call 999 or a doctor urgently)
Asthma UK, Providence House, Providence Place, London N1 0NT
T 020 7226 2260 F 020 7704 0740
© 2004 Asthma UK Registered charity number 803554
Asthma UK Adviceline
Ask an asthma nurse specialist
08457 01 02 03
asthma.org.uk/adviceline
Asthma UK website
Read the latest independent advice and news on asthma
asthma.org.uk
Asthma UK membership
Become a member of Asthma UK and receive Asthma Magazine four times a year
020 7704 5888
membership@asthma.org.uk
Asthma UK publications
Request booklets, factsheets and other materials with independent, specialist information on every aspect of asthma.
020 7704 5888
info@asthma.org.uk
Personal asthma action plan
Be in control
Name
Name of next of kin
Relationship to you
Next of kin contact number
Doctor or nurse contact number
Best peak flow and date taken
Drug allergies
Date plan updated
Notes
Asthma medicine card
Name
Doctor or nurse contact number
Growing what asthma medicines to take and when to take them is a vital first step towards keeping your asthma symptoms to an absolute minimum.
Be in control
What you can do
Make sure you are taking your medicines as discussed with your doctor or nurse – this information should be written in this card.
Ask your doctor or nurse for a personal asthma action plan. This will help you to know what to do if your symptoms get worse or do not improve.

Annex 11 (contd)



References

1. British Guideline on the Management of Asthma. Thorax 2003;58(Suppl 1):i1-94.
2. Scottish Intercollegiate Guidelines Network. SIGN 50: A Guideline Developer's Handbook. Edinburgh: SIGN; 2008.
3. North of England Evidence Based Guideline Development Project. The primary care management of asthma in adults. Newcastle upon Tyne: University of Newcastle upon Tyne, Centre for Health Services Research; 1999. Report No. 97.
4. Cane RS, Ranganathan SC, McKenzie SA. What do parents of wheezy children understand by "wheeze"? Arch Dis Child 2000;82(4):327-32.
5. Dodge R, Martinez FD, Cline MG, Lebowitz MD, Burrows B. Early childhood respiratory symptoms and the subsequent diagnosis of asthma. J Allergy Clin Immunol 1996;98(1):48-54.
6. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. The Group Health Medical Associates. N Engl J Med 1995;332(3):133-8.
7. Park ES, Golding J, Carswell F, Stewart-Brown S. Preschool wheezing and prognosis at 10. Arch Dis Child 1986;61(7):642-6.
8. Sporik R, Holgate ST, Cogswell JJ. Natural history of asthma in childhood - a birth cohort study. Arch Dis Child 1991;66(9):1050-3.
9. Strachan DP, Butland BK, Anderson HR. Incidence and prognosis of asthma and wheezing illness from early childhood to age 33 in a national British cohort. BMJ 1996;312(7040):1195-9.
10. Castro-Rodriguez JA, Holberg CJ, Wright AL, Martinez FD. A clinical index to define risk of asthma in young children with recurrent wheezing. Am J Respir Crit Care Med 2000;162(4 Pt 1):1403-6.
11. Galant SP, Crawford LJ, Morphew T, Jones CA, Bassin S. Predictive value of a cross-cultural asthma case-detection tool in an elementary school population. Pediatrics 2004;114(3):e307-16.
12. Gerald LB, Grad R, Turner-Henson A, Hains C, Tang S, Feinstein R, et al. Validation of a multistage asthma case-detection procedure for elementary school children. Pediatrics. 2004;114(4):e459-68.
13. Ly NP, Gold DR, Weiss ST, Celedon JC. Recurrent wheeze in early childhood and asthma among children at risk for atopy. Pediatrics 2006;117(6):e1132-8.
14. Jones CA, Morphew T, Clement LT, Kimia T, Dyer M, Li M, et al. A school-based case identification process for identifying inner city children with asthma: the Breathmobile program. Chest 2004;125(3):924-34.
15. Kurukulaaratchy RJ, Matthews S, Holgate ST, Arshad SH. Predicting persistent disease among children who wheeze during early life. Eur Respir J. 2003;22(5):767-71.
16. Schonberger H, van Schayck O, Muris J, Bor H, van den Hoogen H, Knottnerus A, et al. Towards improving the accuracy of diagnosing asthma in early childhood. Eur J Gen Pract. 2004;10(4):138-45,51.
17. Marchant JM, Masters IB, Taylor SM, Cox NC, Seymour GJ, Chang AB. Evaluation and outcome of young children with chronic cough. Chest 2006;129(5):1132-41.
18. Marchant JM, Masters IB, Taylor SM, Chang AB. Utility of signs and symptoms of chronic cough in predicting specific cause in children. Thorax. 2006;61(8):694-8.
19. Saglani S, Nicholson AG, Scallan M, Balfour-Lynn I, Rosenthal M, Payne DN, et al. Investigation of young children with severe recurrent wheeze: any clinical benefit? Eur Respir J. 2006;27(1):29-35.
20. Kurukulaaratchy RJ, Matthews S, Arshad SH. Relationship between childhood atopy and wheeze: what mediates wheezing in atopic phenotypes? Ann Allergy Asthma Immunol. 2006;97(1):84-91.
21. Jenkins MA, Hopper JL, Bowes G, Carlin JB, Flander LB, Giles GG. Factors in childhood as predictors of asthma in adult life. BMJ 1994;309(6947):90-3.
22. Aberg N, Engstrom I. Natural history of allergic diseases in children. Acta Paediatr Scand. 1990;79(2):206-11.
23. Toelle BG, Xuan W, Peat JK, Marks GB. Childhood factors that predict asthma in young adulthood. Eur Respir J. 2004;23(1):66-70.
24. Anderson HR, Pottier AC, Strachan DP. Asthma from birth to age 23: incidence and relation to prior and concurrent atopic disease. Thorax 1992;47(7):537-42.
25. Barbee RA, Murphy S. The natural history of asthma. J Allergy Clin Immunol 1998;102(4 Pt 2):S65-72.
26. Blair H. Natural history of childhood asthma. 20-year follow-up. Arch Dis Child 1977;52(8):613-9.
27. Johnstone DE. A study of the natural history of bronchial asthma in children. Am J Dis Child 1968;115(2):213-6.
28. Laor A, Cohen L, Danon YL. Effects of time, sex, ethnic origin, and area of residence on prevalence of asthma in Israeli adolescents. BMJ 1993;307(6908):841-4.
29. Heaney LG, Conway E, Kelly C, Johnston BT, English C, Stevenson M, et al. Predictors of therapy resistant asthma: outcome of a systematic evaluation protocol. Thorax 2003;58(7):561-6.
30. Luyt DK, Burton PR, Simpson H. Epidemiological study of wheeze, doctor diagnosed asthma, and cough in preschool children in Leicestershire. BMJ 1993;306(6889):1386-90.
31. Martin AJ, McLennan LA, Landau LI, Phelan PD. The natural history of childhood asthma to adult life. BMJ 1980;280(6229):1397-400.
32. Robertson CF, Heycock E, Bishop J, Nolan T, Olinsky A, Phelan PD. Prevalence of asthma in Melbourne schoolchildren: changes over 26 years. BMJ 1991;302(6785):1116-8.
33. Roorda RJ. Prognostic factors for the outcome of childhood asthma in adolescence. Thorax 1996;51(Suppl 1):S7-12.
34. Sears MR, Holdaway MD, Flannery EM, Herbison GP, Silva PA. Parental and neonatal risk factors for atopy, airway hyper-responsiveness, and asthma. Arch Dis Child 1996;75(5):392-8.
35. Sherman CB, Tosteson TD, Tager IB, Speizer FE, Weiss ST. Early childhood predictors of asthma. Am J Epidemiol 1990;132(1):83-95.
36. Sigurs N, Bjarnason R, Sigurbergsson F, Kjellman B, Bjorksten B. Asthma and immunoglobulin E antibodies after respiratory syncytial virus bronchiolitis: a prospective cohort study with matched controls. Pediatrics 1995;95(4):500-5.
37. Tariq SM, Matthews SM, Hakim EA, Stevens M, Arshad SH, Hide DW. The prevalence of and risk factors for atopy in early childhood: a whole population birth cohort study. J Allergy Clin Immunol 1998;101(5):587-93.
38. Clough JB, Keeping KA, Edwards LC, Freeman WM, Warner JA, Warner JO. Can we predict which wheezy infants will continue to wheeze? Am J Respir Crit Care Med 1999;160(5 Pt 1):1473-80.
39. Reijonen TM, Kotaniemi-Syrjanen A, Korhonen K, Korppi M. Predictors of asthma three years after hospital admission for wheezing in infancy. Pediatrics 2000;106(6):1406-12.
40. Kotaniemi-Syrjanen A, Reijonen TM, Romppanen J, Korhonen K, Savolainen K, Korppi M. Allergen-specific immunoglobulin E antibodies in wheezing infants: the risk for asthma in later childhood. Pediatrics 2003;111(3):e255-61.
41. Sears MR, Herbison GP, Holdaway MD, Hewitt CJ, Flannery EM, Silva PA. The relative risks of sensitivity to grass pollen, house dust mite and cat dander in the development of childhood asthma. Clin Exp Allergy 1989;19(4):419-24.
42. Rona RJ, Duran-Tauleria E, Chinn S. Family size, atopic disorders inparents, asthma in children, and ethnicity. J Allergy Clin Immunol 1997;99(4):454-60.
43. Rusconi F, Galassi C, Corbo GM, Forastiere F, Biggeri A, Ciccone G, et al. Risk factors for early, persistent, and late-onset wheezing in young children. SIDRIA Collaborative Group. Am J Respir Crit Care Med 1999;160(5 Pt 1)):1617-22.
44. Yu IT, Wong TW, Li W. Using child reported respiratory symptoms to diagnose asthma in the community. Arch Dis Child. 2004;89(6):544-8.
45. Remes ST, Pekkanen J, Remes K, Salonen RO, Korppi M. In search of childhood asthma: questionnaire, tests of bronchial hyperresponsiveness, and clinical evaluation. Thorax 2002;57(2):120-6.
46. Bacharier LB, Strunk RC, Mauger D, White D, Lemanske Jr RF, Sorkness CA. Classifying asthma severity in children: Mismatch between symptoms, medication use, and lung function. Am J Respir Crit Care Med. 2004;170(4):426-32.
47. Brouwer AFJ, Roorda RJ, Brand PLP. Home spirometry and asthma severity in children. Eur Respir J. 2006;28(6):1131-7.
48. Verini M, Peroni DG, Rossi N, Nicodemo A, De Stradis R, Spagnolo C, et al. Functional assessment of allergic asthmatic children while asymptomatic. Allergy Asthma Proc 2006;27(4):359-64.
49. Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, et al. Interpretative strategies for lung function tests. Eur Respir J 2005;26(5):948-68.
50. Tantisira KG, Fuhlbrigge AL, Tonascia J, Van Natta M, Zeiger RS, Strunk RC, et al. Bronchodilation and bronchoconstriction: predictors of future lung function in childhood asthma. J Allergy Clin Immunol. 2006;117(6):1264-71.
51. Dundas I, Chan EY, Bridge PD, McKenzie SA. Diagnostic accuracy of bronchodilator responsiveness in wheezy children. Thorax 2005;60(1):13-6.
52. Arets HGM, Brackel HJL, van der Ent CK. Applicability of interrupter resistance measurements using the MicroRint in daily practice. Respir Med. 2003;97(4):366-74.
53. Olaguibel JM, Alvarez-Puebla MJ, Anda M, Gomez B, Garcia BE, Tabar AI, et al. Comparative analysis of the bronchodilator response measured by impulse oscillometry (IOS), spirometry and body plethysmography in asthmatic children. J Investig Allergol Clin Immunol. 2005;15(2):102-6.
54. Marotta A, Klinnert MD, Price MR, Larsen GL, Liu AH. Impulse oscillometry provides an effective measure of lung dysfunction in 4-year-old children at risk for persistent asthma. J Allergy Clin Immunol. 2003;112(2):317-22.
55. Joseph-Bowen J, de Klerk NH, Firth MJ, Kendall GE, Holt PG, Sly PD. Lung function, bronchial responsiveness, and asthma in a community cohort of 6-year-old children. Am J Respir Crit Care Med. 2004;169(7):850-4.

56. Abu-Hasan M, Tannous B, Weinberger M. Exercise-induced dyspnea in children and adolescents: if not asthma then what? Ann Allergy Asthma Immunol. 2005;94(3):366-71.
57. Lex C, Payne DN, Zacharasiewicz A, Li AM, Wilson NM, Hansel TT, et al. Sputum induction in children with difficult asthma: safety, feasibility, and inflammatory cell pattern. Pediatr Pulmonol. 2005;39(4):318-24.
58. Rytila P, Pelkonen AS, Metso T, Nikander K, Haahtela T, Turpeinen M. Induced sputum in children with newly diagnosed mild asthma: The effect of 6 months of treatment with budesonide or disodium cromoglycate. Allergy 2004;59(8):839-44.
59. Covar RA, Spahn JD, Martin RJ, Silkoff PE, Sundstrom DA, Murphy J, et al. Safety and application of induced sputum analysis in childhood asthma. J Allergy Clin Immunol. 2004;114(3):575-82.
60. Malmberg LP, Turpeinen H, Rytila P, Sarna S, Haahtela T. Determinants of increased exhaled nitric oxide in patients with suspected asthma. Allergy 2005;60(4):464-8.
61. Brussee JE, Smit HA, Kerkhof M, Koopman LP, Wijga AH, Postma DS, et al. Exhaled nitric oxide in 4-year-old children: relationship with asthma and atopy. Eur Respir J. 2005;25(3):455-61.
62. Barreto M, Villa MP, Monti F, Bohmerova Z, Martella S, Montesano M, et al. Additive effect of eosinophilia and atopy on exhaled nitric oxide levels in children with or without a history of respiratory symptoms. Pediatr Allergy Immunol. 2005;16(1):52-8.
63. Malmberg LP, Petays T, Haahtela T, Laatikainen T, Jousilahti P, Vartiainen E, et al. Exhaled nitric oxide in healthy nonatopic school-age children: Determinants and height-adjusted reference values. Pediatr Pulmonol. 2006;41(7):635-42.
64. Prasad A, Langford B, Stradling JR, Ho LP. Exhaled nitric oxide as a screening tool for asthma in school children. Respir Med. 2006;100(1):167-73.
65. Pijnenburg MW, Floor SE, Hop WC, De Jongste JC. Daily ambulatory exhaled nitric oxide measurements in asthma. Pediatr Allergy Immunol. 2006;17(3):189-93.
66. Chan EY, Dundas I, Bridge PD, Healy MJ, McKenzie SA. Skin-prick testing as a diagnostic aid for childhood asthma. Pediatr Pulmonol. 2005;39(6):558-62.
67. Eysink PE, ter Riet G, Aalberse RC, van Aalderen WM, Roos CM, van der Zee JS, et al. Accuracy of specific IgE in the prediction of asthma: development of a scoring formula for general practice. Br J Gen Pract. 2005;55(511):125-31.
68. Simpson A, Soderstrom L, Ahlstedt S, Murray CS, Woodcock A, Custovic A. IgE antibody quantification and the probability of wheeze in preschool children. J Allergy Clin Immunol. 2005;116(4):744-9.
69. Kurukulaaratchy RJ, Fenn M, Matthews S, Arshad SH. Characterisation of atopic and non-atopic wheeze in 10 year old children. Thorax 2004;59(7):563-8.
70. Hederos CA, Janson S, Andersson H, Hedlin G. Chest X-ray investigation in newly discovered asthma. Pediatr Allergy Immunol 2004;15(2):163-5.
71. Hunter CJ, Brightling CE, Woltmann G, Wardlaw AJ, Pavord ID. A comparison of the validity of different diagnostic tests in adults with asthma. Chest 2002;121(4):1051-7.
72. Joyce DP, Chapman KR, Kesten S. Prior diagnosis and treatment of patients with normal results of methacholine challenge and unexplained respiratory symptoms. Chest 1996;109(3):697-701.
73. Brand PL, Postma DS, Kerstjens HA, Koeter GH. Relationship of airway hyperresponsiveness to respiratory symptoms and diurnal peak flow variation in patients with obstructive lung disease. The Dutch CNSLD Study Group. Am Rev Respir Dis 1991;143(5 Pt 1):916-21.
74. Gibson PG, Fujimura M, Niimi A. Eosinophilic bronchitis: clinical manifestations and implications for treatment. Thorax 2002;57(2):178-82.
75. James AL, Finucane KE, Ryan G, Musk AW. Bronchial responsiveness, lung mechanics, gas transfer, and corticosteroid response in patients with chronic airflow obstruction. Thorax 1988;43(11):916-22.
76. Ramsdale EH, Morris MM, Roberts RS, Hargreave FE. Bronchial responsiveness to methacholine in chronic bronchitis: relationship to airflow obstruction and cold air responsiveness. Thorax 1984;39(12):912-8.
77. Goldstein MF, Veza BA, Dunsky EH, Dvorin DJ, Belecanech GA, Haralabatos IC. Comparisons of peak diurnal expiratory flow variation, postbronchodilator FEV(1) responses, and methacholine inhalation challenges in the evaluation of suspected asthma. Chest 2001;119(4):1001-10.
78. Smith AD, Cowan JO, Brassett KP, Filsell S, McLachlan C, Monti-Sheehan G, et al. Exhaled nitric oxide: a predictor of steroid response. Am J Respir Crit Care Med. 2005;172(4):453-9. .
79. Smith AD, Cowan JO, Filsell S, McLachlan C, Monti-Sheehan G, Jackson P, et al. Diagnosing asthma: comparisons between exhaled nitric oxide measurements and conventional tests. Am J Respir Crit Care Med. 2004;169(4):473-8. (34 ref).
80. Taylor DR, Pijnenburg MW, Smith AD, De Jongste JC. Exhaled nitric oxide measurements: clinical application and interpretation. Thorax 2006;61(9):817-27.
81. Brightling CE, Monteiro W, Ward R, Parker D, Morgan MD, Wardlaw AJ, et al. Sputum eosinophilia and short-term response to prednisolone in chronic obstructive pulmonary disease: a randomised controlled trial. Lancet 2000;356(9240):1480-5.
82. Chatkin JM, Ansarin K, Silkoff PE, McClean P, Gutierrez C, Zamel N, et al. Exhaled nitric oxide as a noninvasive assessment of chronic cough. Am J Respir Crit Care Med 1999;159(6):1810-3.
83. Pavord ID, Brightling CE, Woltmann G, Wardlaw AJ. Non-eosinophilic corticosteroid unresponsive asthma. Lancet 1999;353(9171):2213-4.
84. Green RH, Brightling CE, McKenna S, Hargadon B, Parker D, Bradding P, et al. Asthma exacerbations and sputum eosinophil counts: a randomised controlled trial. Lancet 2002;360(9347):1715-21.
85. Smith AD, Cowan JO, Brassett KP, Herbison GP, Taylor DR. Use of exhaled nitric oxide measurements to guide treatment in chronic asthma. N Engl J Med 2005;352(21):2163-73.
86. Jayaram L, Pizzichini MM, Cook RJ, Boulet LP, Lemiere C, Pizzichini E, et al. Determining asthma treatment by monitoring sputum cell counts: Effect on exacerbations. Eur Respir J. 2006;27(3):483-94.
87. Berry M, Hargadon B, Morgan A, Shelley M, Richter J, Shaw D, et al. Alveolar nitric oxide in adults with asthma: evidence of distal lung inflammation in refractory asthma. Eur Respir J 2005;25(6):986-91.
88. Quanjer PH, Lebowitz MD, Gregg I, Miller MR, Pedersen OF. Peak expiratory flow: conclusion and recommendations of a working party of the European Respiratory Society. Eur Respir J Suppl. 1997;24:2S-8S.
89. D'Alonzo GE, Steinijans VW, Keller A. Measurements of morning and evening airflow grossly underestimate the circadian variability of FEV1 and peak expiratory flow rate in asthma. Am J Respir Crit Care Med 1995;152(3):1097-9.
90. Chowienczyk PJ, Parkin DH, Lawson CP, Cochrane GM. Do asthmatic patients correctly record home spirometry measurements? BMJ 1994;309(6969):1618.
91. Higgins BG, Britton JR, Chinn S, Jones TD, Jenkinson D, Burney PG, et al. The distribution of peak flow variability in a population sample. Am Rev Respir Dis 1989;140(5):1368-72.
92. Higgins BG, Britton JR, Chinn S, Cooper S, Burney PG, Tattersfield AE. Comparison of bronchial reactivity and peak expiratory flow variability measurements for epidemiologic studies. Am Rev Respir Dis 1992;145(3):588-93.
93. Quackenboss JJ, Lebowitz MD, Krzyzanowski M. The normal range of diurnal changes in peak expiratory flow rates. Relationship to symptoms and respiratory disease. Am Rev Respir Dis 1991;143(2):323-30.
94. Lebowitz MD, Krzyzanowski M, Quackenboss JJ, O'Rourke MK. Diurnal variation of PEF and its use in epidemiological studies. Eur Respir J Suppl. 1997(24):49s-56s.
95. Boezen HM, Schouten JP, Postma DS, Rijcken B. Distribution of peak expiratory flow variability by age, gender and smoking habits in a random population sample aged 20-70 yrs. Eur Respir J 1994;7(10):1814-20.
96. Siersted HC, Hansen HS, Hansen NC, Hyldebrandt N, Mostgaard G, Oxhoj H. Evaluation of peak expiratory flow variability in an adolescent population sample. The Odense Schoolchild Study. Am J Respir Crit Care Med 1994;149(3 Pt 1):598-603.
97. Gannon PF, Newton DT, Belcher J, Pantin CF, Burge PS. Development of OASYS-2: a system for the analysis of serial measurement of peak expiratory flow in workers with suspected occupational asthma. Thorax 1996;51(5):484-9.
98. Crapo R. Guidelines for methacholine and exercise challenge testing-1999. Am J Respir Crit Care Med 2000;161(1):309-29.
99. Cockcroft DW, Killian DN, Mellon JJ, Hargreave FE. Bronchial reactivity to inhaled histamine: a method and clinical survey. Clin Allergy 1977;7(3):235-43.
100. Cockcroft DW, Murdock KY, Berscheid BA, Gore BP. Sensitivity and specificity of histamine PC20 determination in a random selection of young college students. J Allergy Clin Immunol 1992;89(1 Pt 1):23-30.
101. Joos GF, O'Connor B, Anderson SD, Chung F, Cockcroft DW, Dahlen B, et al. Indirect airway challenges. Eur Respir J 2003;21(6):1050-68.
102. Anderton RC, Cuff MT, Frith PA, Cockcroft DW, Morse JL, Jones NL, et al. Bronchial responsiveness to inhaled histamine and exercise. J Allergy Clin Immunol 1979;63(5):315-20.
103. American Thoracic Society, European Respiratory Society. ATS/ERS recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide. Am J Respir Crit Care Med 2005;171(8):912-30.
104. Pavord ID, Pizzichini MM, Pizzichini E, Hargreave FE. The use of induced sputum to investigate airway inflammation. Thorax 1997;52(6):498-501.
105. Brightling CE, Pavord ID. Eosinophilic bronchitis: an important cause of prolonged cough. Ann Med 2000;32(7):446-51.
106. Carney IK, Gibson PG, Murree-Allen K, Saltos N, Olson LG, Hensley MJ. A systematic evaluation of mechanisms in chronic cough. Am J Respir Crit Care Med 1997;156(1):211-6.
107. Bateman ED, Boushey HA, Bousquet J, Busse WW, Clark TJ, Pauwels RA, et al. Can guideline-defined asthma control be achieved? The Gaining Optimal Asthma ControL study. Am J Respir Crit Care Med 2004;170(8):836-44.

108. Sont JK, Willems LN, Bel EH, van Krieken JH, Vandenbroucke JP, Sterk PJ. Clinical control and histopathologic outcome of asthma when using airway hyperresponsiveness as an additional guide to long-term treatment. The AMPUL Study Group. Am J Respir Crit Care Med 1999;159(4 Pt 1):1043-51.
109. Pearson MG, CE B, editors. Measuring clinical outcome in asthma : a patient-focused approach London: Royal College of Physicians; 1999.
110. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. Eur Respir J 2005;26(2):319-38.
111. Tweeddale PM, Alexander F, McHardy GJ. Short term variability in FEV1 and bronchodilator responsiveness in patients with obstructive ventilatory defects. Thorax 1987;42:487-90.
112. Dekker FW, Schrier AC, Sterk PJ, Dijkman JH. Validity of peak expiratory flow measurement in assessing reversibility of airflow obstruction. Thorax 1992;47(3):162-6.
113. Juniper EF, Bousquet J, Abetz L, Bateman ED. Identifying ‚well-controlled' and ‚not well-controlled' asthma using the Asthma Control Questionnaire. Respir Med 2006;100(4):616-21.
114. Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. Eur Respir J 1999;14(4):902-7.
115. Juniper EF, Svensson K, Mork AC, Stahl E. Measurement properties and interpretation of three shortened versions of the asthma control questionnaire. Respir Med. 2005;99(5):553-8.
116. Nathan RA, Sorkness CA, Kosinski M, Schatz M, Li JT, Marcus P, et al. Development of the asthma control test: a survey for assessing asthma control. J Allergy Clin Immunol. 2004;113(1):59-65.
117. Schatz M, Sorkness CA, Li JT, Marcus P, Murray JJ, Nathan RA, et al. Asthma Control Test: reliability, validity, and responsiveness in patients not previously followed by asthma specialists. J Allergy Clin Immunol 2006;117(3):549-56.
118. Juniper EF, Guyatt GH, Ferrie PJ, Griffith LE. Measuring quality of life in asthma. Am Rev Respir Dis 1993;147(4):832-8.
119. Kharitonov SA, Gonio F, Kelly C, Meah S, Barnes PJ. Reproducibility of exhaled nitric oxide measurements in healthy and asthmatic adults and children. Eur Respir J. 2003;21(3):433-8.
120. Berry M, Shaw D, Green RH, Brightling CE, Wardlaw AJ, Pavord ID. The use of exhaled nitric oxide concentration to identify eosinophilic airway inflammation: an observational study in adults with asthma. Clin Exp Allergy 2005;35:1175-1179.
121. Belda J, Leigh R, Parameswaran K, O'Byrne PM, Sears MR, Hargreave FE. Induced sputum cell counts in healthy adults. Am J Respir Crit Care Med 2000;161(2 Pt 1):475-8.
122. Djukanovic R, Sterk PJ, Fahy JV, Hargreave FE. Standardised methodology of sputum induction and processing. Eur Respir J Suppl 2002;37:1s-2s.
123. Wahn U, Lau S, Bergmann R, Kulig M, Forster J, Bergmann K, et al. Indoor allergen exposure is a risk factor for sensitization during the first three years of life. J Allergy Clin Immunol 1997;99(6 Pt 1):763-9.
124. Corver K, Kerkhof M, Brussee JE, Brunekreef B, van Strien RT, Vos AP, et al. House dust mite allergen reduction and allergy at 4 yr: follow up of the PIAMA-study. Pediatr Allergy Immunol 2006;17(5):329-36.
125. Lau S, Illi S, Sommerfeld C, Niggemann B, Bergmann R, von Mutius E, et al. Early exposure to house-dust mite and cat allergens and development of childhood asthma: a cohort study. Multicentre Allergy Study Group. Lancet 2000;356(9239):1392-7.
126. Arshad SH, Bateman B, Matthews SM. Primary prevention of asthma and atopy during childhood by allergen avoidance in infancy: A randomised controlled study. Thorax 2003;58(6):489-93.
127. Sporik R, Holgate ST, Platts-Mills TA, Cogswell JJ. Exposure to house-dust mite allergen (Der p 1) and the development of asthma in childhood. N Engl J Med 1990;323:502-7.
128. Cullinan P, MacNeill SJ, Harris JM, Moffat S, White C, Mills P, et al. Early allergen exposure, skin prick responses, and atopic wheeze at age 5 in English children: a cohort study. Thorax 2004;59(10):855-61.
129. Chan-Yeung M, Ferguson A, Watson W, Dimich-Ward H, Rousseau R, Lilley M, et al. The Canadian Childhood Asthma Primary Prevention Study: Outcomes at 7 years of age. J Allergy Clin Immunol. 2005;116(1):49-55.
130. Horak F, Jr., Matthews S, Ihorst G, Arshad SH, Frischer T, Kuehr J, et al. Effect of mite-impermeable mattress encasings and an educational package on the development of allergies in a multinational randomized, controlled birth-cohort study -- 24 months results of the Study of Prevention of Allergy in Children in Europe. Clin Exp Allergy. 2004;34(8):1220-5.
131. Custovic A, Simpson BM, Simpson A, Kissen P, Woodcock A. Effect of environmental manipulation in pregnancy and early life on respiratory symptoms and atopy during the first year of life: a randomised trial. Lancet 2001;358(9277):188-93.
132. Woodcock A, Lowe LA, Murray CS, Simpson BM, Pipis SD, Kissen P, et al. Early life environmental control: effect on symptoms, sensitization, and lung function at age 3 years. Am J Respir Crit Care Med 2004;170(4):433-9.
133. Hesselmar B, Aberg N, Aberg B, Eriksson B, Bjorksten B. Does early exposure to cat or dog protect against later allergy development? Clin Exp Allergy 1999;29:611-7.
134. Remes ST, Castro-Rodriguez JA, Holberg CJ, Martinez FD, Wright AL. Dog exposure in infancy decreases the subsequent risk of frequent wheeze but not of atopy. J Allergy Clin Immunol 2001;108:509-15.
135. Muraro A, Dreborg S, Halken S, Host A, Niggemann B, Aalberse R, et al. Dietary prevention of allergic diseases in infants and small children. Part I: immunologic background and criteria for hypoallergenicity. Pediatr Allergy Immunol 2004;15(2):103-11.
136. Muraro A, Dreborg S, Halken S, Host A, Niggemann B, Aalberse R, et al. Dietary prevention of allergic diseases in infants and small children. Part III: Critical review of published peer-reviewed observational and interventional studies and final recommendations. Pediatr Allergy Immunol 2004;15(4):291-307.
137. Kramer MS, Kakuma R. Maternal dietary antigen avoidance during pregnancy or lactation, or both, for preventing or treating atopic disease in the child (Cochrane Review). In: The Cochrane Library, Issue 3, 2006. London: John Wiley & Sons Ltd138. Vance GH, Grimshaw KE, Briggs R, Lewis SA, Mullee MA, Thornton CA, et al. Serum ovalbumin-specific immunoglobulin G responses during pregnancy reflect maternal intake of dietary egg and relate to the development of allergy in early infancy. Clin Exp Allergy 2004;34(12):1855-61.
139. van Odijk J KI, Borres MP, Brandtzaeg P, Edberg U, Hanson LA, Host A, Kuitunen M. Ol;sen SF, Skerfving S, Sundell J, Willie S. Breast feeding and allergic disease: a multi-disciplinary review of the literature (1996-2001) on the mode of early feeding in infancy and its impact on later atopic manifestations. Allergy 2003;58(9):833-43.
140. Sears MR, Greene JM, Willan AR, Taylor DR, Flannery EM, Cowan JO, et al. Long-term relation between breastfeeding and development of atopy and asthma in children and young adults: a longitudinal study. Lancet. 2002;360(9337):901-7.
141. Osborn DA, Sinn J. Formulas containing hydrolysed protein for prevention of allergy and food intolerance in infants (Cochrane Review). In: The Cochrane Library, Issue 4, 2006.Chichester: John Wiley
142. Osborn DA, Sinn J. Soy formula for prevention of allergy and food intolerance in infants (Cochrane Review). In: The Cochrane Library, Issue 4, 2006. London: John Wiley & Sons Ltd.
143. Tricon S, Willers S, Smit HA, Burney PG, Devereux G, Frew AJ, et al. Nutrition and allergic disease. Clin Exp Allergy Reviews 2006;6(5):117-88.
144. Zutavern A, von Mutius E, Harris J, Mills P, Moffatt S, White C, et al. The introduction of solids in relation to asthma and eczema. Arch Dis Child. 2004;89(4):303-8. .
145. Dunstan JA, Mori TA, Barden A, Beilin LJ, Taylor AL, Holt PG, et al. Fish oil supplementation in pregnancy modifies neonatal allergen-specific immune responses and clinical outcomes in infants at high risk of atopy: a randomized, controlled trial. J Allergy Clin Immunol. 2003;112(6):1178-84.
146. Mihrshahi S, Peat JK, Webb K, Oddy W, Marks GB, Mellis CM, et al. Effect of omega-3 fatty acid concentrations in plasma on symptoms of asthma at 18 months of age. Pediatr Allergy Immunol. 2004;15(6):517-22.
147. Shaheen SO, Newson RB, Henderson AJ, Emmett PM, Sherriff A, Cooke M. Umbilical cord trace elements and minerals and risk of early childhood wheezing and eczema. Eur Respir J 2004;24(2):292-7.
148. Devereux G, Turner SW, Craig LC, McNeill G, Martindale S, Harbour PJ, et al. Low maternal vitamin E intake during pregnancy is associated with asthma in 5-year-old children. Am J Respir Crit Care Med 2006;174(5):499-507.
149. Holt PG, Sly PD, Bjorksten B. Atopic versus infectious diseases in childhood: a question of balance? Pediatr Allergy Immunol 1997;8(2):53-8.
150. Strachan DP. Family size, infection and atopy: the first decade of the "hygiene hypothesis". Thorax 2000;55(Suppl 1):S2-10.
151. Kalliomaki M, Salminen S, Arvilommi H, Kero P, Koskinen P, Isolauri E. Probiotics in primary prevention of atopic disease: a randomised placebo-controlled trial. Lancet 2001;357(9262):1076-9.
152. Moro G, Arslanoglu S, Stahl B, Jelinek J, Wahn U, Boehm G. A mixture of prebiotic oligosaccharides reduces the incidence of atopic dermatitis during the first six months of age. Arch Dis Child 2006;91(10):814-9.
153. Cook DG, Strachan DP. Health effects of passive smoking-10: Summary of effects of parental smoking on the respiratory health of children and implications for research. Thorax 1999;54(4):357-66.
154. Dezateau C, Stocks J, Dundas I, Fletcher ME. Impaired airway function and wheezing in infancy: the influence of maternal smoking and a genetic predisposition to asthma. Am J Respir Crit Care Med 1999;159(2):403-10.
155. Gilliland FD, Berhane K, McConnell R, Gauderman WJ, Vora H, Rappaport EB, et al. Maternal smoking during pregnancy, environmental tobacco smoke exposure and childhood lung function. Thorax 2000;55(4):271-6.

156. Lodrup Carlsen KC, Carlsen KH, Nafstad P, Bakketeig L. Perinatal risk factors for recurrent wheeze in early life. Pediatr Allergy Immunol 1999;10(2):89-95.
157. Arshad SH, Kurukulaaratchy RJ, Fenn M, Matthews S. Early life risk factors for current wheeze, asthma, and bronchial hyperresponsiveness at 10 years of age. Chest 2005;127(2):502-8.
158. Jaakkola JJ, Gissler M. Maternal smoking in pregnancy, fetal development, and childhood asthma. Am J Public Health 2004;94(1):136-40.
159. Kabesch M, Hoefler C, Carr D, Leupold W, Weiland SK, von Mutius E. Glutathione S transferase deficiency and passive smoking increase childhood asthma. Thorax 2004;59(7):569-73.
160. Belanger K, Beckett W, Triche E, Bracken MB, Holford T, Ren P, et al. Symptoms of wheeze and persistent cough in the first year of life: associations with indoor allergens, air contaminants, and maternal history of asthma. Am J Epidemiol 2003;158(3):195-202.
161. Lee YL, Lin YC, Lee YC, Wang JY, Hsiue TR, Guo YL. Glutathione S-transferase P1 gene polymorphism and air pollution as interactive risk factors for childhood asthma. Clin Exp Allergy 2004;34(11):1707-13.
162. Miller RL, Garfinkel R, Horton M, Camann D, Perera FP, Whyatt RM, et al. Polycyclic aromatic hydrocarbons, environmental tobacco smoke, and respiratory symptoms in an inner-city birth cohort. Chest 2004;126(4):1071-8.
163. Romieu I, Sienra-Monge JJ, Ramirez-Aguilar M, Moreno-Macias H, Reyes-Ruiz NI, Estela del Rio-Navarro B, et al. Genetic polymorphism of GSTM1 and antioxidant supplementation influence lung function in relation to ozone exposure in asthmatic children in Mexico City. Thorax 2004;59(1):8-10.
164. Purello-D'Ambrosio F, Gangemi S, Merendino RA, Isola S, Puccinelli P, Parmiani S, et al. Prevention of new sensitizations in monosensitized subjects submitted to specific immunotherapy or not. A retrospective study. Clin Exp Allergy 2001;31(8):1295-302.
165. Pajno GB, Barberio G, de Luca F, Morabito L, Parmiani S. Prevention of new sensitizations in asthmatic children monosensitized to house dust mite by specific immunotherapy. A six-year follow-up study. Clin Exp Allergy 2001;31(9):1392-7.
166. Des Roches A, Paradis L, Menardo JL, Bouges S, Daures JP, Bousquet J. Immunotherapy with standardized dermatophagoides pteronyssinus extract. VI. Specific immunotherapy prevents the onset of new sensitizations in children. J Allergy Clin Immunol 1997;99(4):450-3.
167. Moller C, Dreborg S, Ferdousi HA, Halken S, Host A, Jacobsen L, et al. Pollen immunotherapy reduces the development of asthma in children with seasonal rhinoconjunctivitis (the PAT-study). J Allergy Clin Immunol 2002;109(2):251-6.
168. Niggemann B, Staden U, Rolinck-Werninghaus C, Beyer K. Specific oral tolerance induction in food allergy. Allergy 2006;61(7):808-11.
169. Kemp A, Bjorksten B. Immune deviation and the hygiene hypothesis: a review of the epidemiological evidence. Pediatr Allergy Immunol 2003;14(2):74-80.
170. Martignon G, Oryszczyn MP, Annesi-Maesano I. Does childhood immunization against infectious diseases protect from the development of atopic disease? Pediatr Allergy Immunol 2005;16(3):193-200.
171. Peat JK, Salome CM, Woolcock AJ. Longitudinal changes in atopy during a 4-year period: relation to bronchial hyperresponsiveness and respiratory symptoms in a population sample of Australian schoolchildren. J Allergy Clin Immunol 1990;85(1 Pt 1):65-74.
172. Platts-Mills TA, Thomas WR, Aalberse RC, Vervloet D, Champman MD. Dust mite allergens and asthma: report of a second international workshop. J Allergy Clin Immunol 1992;89(5):1046-60.
173. Peroni DG, Boner AL, Vallone G, Antolini I, Warner JO. Effective allergen avoidance at high altitude reduces allergen-induced bronchial hyperresponsiveness. Am J Respir Crit Care Med 1994;149(6):1442-6.
174. Gøtzsche PC, Johansen HK, Schmidt LM, Burr ML. House dust mite control measures for asthma (Cochrane Review). In: The Cochrane Library, Issue 4, 2004. London: John Wiley & Sons Ltd.
175. Terreehorst I, Duivenvoorden HJ, Tempels-Pavlica Z, Oosting AJ, de Monchy JG, Bruijnzeel-Koomen CA, et al. The effect of encasings on quality of life in adult house dust mite allergic patients with rhinitis, asthma and/or atopic dermatitis. Allergy 2005;60(7):888-93.
176. Woodcock A, Forster L, Matthews E, Martin J, Letley L, Vickers M, et al. Control of exposure to mite allergen and allergen-impermeable bed covers for adults with asthma. N Engl J Med. 2003;349(3):225-36.
177. Halken S, Host A, Niklassen U, Hansen LG, Nielsen F, Pedersen S, et al. Effect of mattress and pillow encasings on children with asthma and house dust mite allergy. J Allergy Clin Immunol. 2003;111(1):169-76.
178. Van Den Bemt L, Van Knapen L, De Vries MP, Jansen M, Cloosterman S, Van Schayck CP. Clinical effectiveness of a mite allergen-impermeable bed-covering system in asthmatic mite-sensitive patients. J Allergy Clin Immunol. 2004;114(4):858-62.
179. Wood RA, Chapman MD, Adkinson NF Jr, Eggleston PA. The effect of cat removal on allergen content in household-dust samples. J Allergy Clin Immunol 1989;83(4):730-4.
180. Wood RA, Johnson EF, Van Natta ML, Chen PH, Eggleston PA. A placebo-controlled trial of a HEPA air cleaner in the treatment of cat allergy. Am J Respir Crit Care Med 1998;158(1):115-20.
181. Platts-Mills T, Vaughan J, Squillace S, Woodfolk J, Sporik R. Sensitisation, asthma, and a modified Th2 response in children exposed to cat allergen: a population-based cross-sectional study. Lancet 2001;357(9258):752-6.
182. Francis H, Fletcher G, Anthony C, Pickering C, Oldham L, Hadley E, et al. Clinical effects of air filters in homes of asthmatic adults sensitized and exposed to pet allergens. Clin Exp Allergy. 2003;33(1):101-5.
183. Popplewell EJ, Innes VA, Lloyd-Hughes S, Jenkins EL, Khdir K, Bryant TN, et al. The effect of high-efficiency and standard vacuum-cleaners on mite, cat and dog allergen levels and clinical progress. Pediatr Allergy Immunol 2000;11(3):142-8.
184. Carter MC, Perzanowski MS, Raymond A, Platts-Mills TA. Home intervention in the treatment of asthma among inner-city children. J Allergy Clin Immunol 2001;108(5):732-7.
185. Krieger JW, Takaro TK, Song L, Weaver M. The Seattle-King County Healthy Homes Project: A randomized, controlled trial of a community health worker intervention to decrease exposure to indoor asthma triggers. Am J Public Health. 2005;95(4):652-9.
186. Singh M, Bara A, Gibson P. Humidity control for chronic asthma (Cochrane Review). In: The Cochrane Library, Issue 1, 2002. London: John Wiley & Sons Ltd.
187. Chalmers GW, MacLeod KJ, Little SA, Thomson LJ, McSharry CP, Thomson NC. Influence of cigarette smoking on inhaled corticosteroid treatment in mild asthma. Thorax. 2002;57(3):226-30.
188. Ehrlich R, Jordaan E, Du TD, Potter P, Volmink J, Zwarenstein M, et al. Household smoking and bronchial hyperresponsiveness in children with asthma. J Asthma. 2001;38(3):239-51.
189. Gallefoss F, Bakke PS. Does smoking affect the outcome of patient education and self-management in asthmatics? Patient Educ Couns. 2003;49(1):91-7.
190. Mannino DM, Homa DM, Redd SC. Involuntary smoking and asthma severity in children: Data from the Third National Health and Nutrition Examination Survey. Chest. 2002;122(2):409-15.
191. Murray AB, Morrison BJ. The decrease in severity of asthma in children of parents who smoke since the parents have been exposing them to less cigarette smoke. J Allergy Clin Immunol 1993;91(1 Pt 1):102-10.
192. Wilson SR, Yamada EG, Sudhakar R, Roberto L, Mannino D, Mejia C, et al. A controlled trial of an environmental tobacco smoke reduction intervention in low-income children with asthma. Chest. 2001;120(5):1709-22.
193. Tonnesen P, Pisinger C, Hvidberg S, Wennike P, Bremann L, Westin A, et al. Effects of smoking cessation and reduction in asthmatics. Nicotine Tob Res 2005;7(1):139-48.
194. Wakefield M, Banham D, McCaul K, Martin J, Ruffin R, Badcock N, et al. Effect of feedback regarding urinary cotinine and brief tailored advice on home smoking restrictions among low-income parents of children with asthma: a controlled trial. Prev Med. 2002;34(1):58-65.
195. Irvine L, Crombie IK, Clark RA, Slane PW, Feyerabend C, Goodman KE, et al. Advising parents of asthmatic children on passive smoking: randomised controlled trial. BMJ 1999;318(7196):1456-9.
196. Hovell MF, Meltzer SB, Wahlgren DR, Matt GE, Hofstetter CR, Jones JA, et al. Asthma management and environmental tobacco smoke exposure reduction in Latino children: a controlled trial. Pediatrics. 2002;110(5):946-56.
197. Rasmussen F, Siersted HC, Lambrechtsen J, Hansen HS, Hansen NC. Impact of airway lability, atopy, and tobacco smoking on the development of asthma-like symptoms in asymptomatic teenagers. Chest 2000;117(5):1330-5.
198. Devalia JL, Rusznak C, Herdman MJ, Trigg CJ, Tarraf H, Davies RJ. Effect of nitrogen dioxide and sulphur dioxide on airway response of mild asthmatic patients to allergen inhalation. Lancet 1994;344(8938):1668-71.
199. Molfino NA, Wright SC, Katz I, Tarlo S, Silverman F, McClean PA, et al. Effect of low concentrations of ozone on inhaled allergen responses in asthmatic subjects. Lancet 1991;338(8761):199-203.
200. Committee on the Medical Effects of Air Pollutants. Asthma and outdoor air pollution. London: HMSO; 1995.
201. Lin M, Chen Y, Burnett RT, Villeneuve PJ, Krewski D. Effect of short-term exposure to gaseous pollution on asthma hospitalisation in children: A bi-directional case-crossover analysis. J Epidemiol Community Health. 2003;57(1):50-5.
202. Kaur B, Anderson HR, Austin J, Burr M, Harkins LS, Strachan DP, et al. Prevalence of asthma symptoms, diagnosis, and treatment in 12-14 year old children across Great Britain (international study of asthma and allergies in childhood, ISAAC UK). BMJ 1998;316(7125):118-24.
203. Norbäck D, Björnsson E, Janson C, Widstrom J, Boman G. Asthmatic symptoms and volatile organic compounds, formaldehyde, and carbon dioxide in dwellings. Occup Environ Med 1995;52(6):388-95.
204. Tunnicliffe WS, Burge PS, Ayres JG. Effect of domestic concentrations of nitrogen dioxide on airway responses to inhaled allergen in asthmatic patients. Lancet 1994;344(8939-40):1733-6.

205. Abramson MJ, Puy RM, Weiner JM. Allergen immunotherapy for asthma (Cochrane Review). In: The Cochrane Library, Issue 4, 2003. London: John Wiley & Sons Ltd.
206. Shaikh WA. Immunotherapy vs inhaled budesonide in bronchial asthma: an open, parallel, comparative trial. Clin Exp Allergy 1997;27(11):1279-84.
207. Durham SR, Walker SM, Varga EM, Jacobson MR, O'Brien F, Noble W, et al. Long-term clinical efficacy of grass-pollen immunotherapy. N Engl J Med 1999;341(7):468-75.
208. Calamita Z, Saconato H, Pela AB, Atallah AN. Efficacy of sublingual immunotherapy in asthma: systematic review of randomized-clinical trials using the Cochrane Collaboration method. Allergy 2006;61(10):1162-72.
209. Burney P. A diet rich in sodium may potentiate asthma. Epidemiologic evidence for a new hypothesis. Chest 1987;91(6 Suppl):143S-8S.
210. Burney PG. The causes of asthma–does salt potentiate bronchial activity? Discussion paper. J R Soc Med 1987;80(6):364-7.
211. Mickleborough TD, Lindley MR, Ray S. Dietary salt, airway inflammation, and diffusion capacity in exercise-induced asthma. Med Sci Sports Exerc. 2005;37(6):904-14.
212. Ardern KD, Ram FS. Dietary salt reduction or exclusion for allergic asthma (Cochrane Review). In: The Cochrane Library, Issue 4, 2001. London: John Wiley & Sons Ltd.
213. Britton J, Pavord I, Richards K, Wisniewski A, Knox A, Lewis S, et al. Dietary magnesium, lung function, wheezing, and airway hyperreactivity in a random adult population sample. Lancet 1994;344(8919):357-62.
214. Blitz M, Blitz S, Beasely R, Diner BM, Hughes R, Knopp JA, et al. Inhaled magnesium sulfate in the treatment of acute asthma (Cochrane Review). In: The Cochrane Library, Issue 2, 2005. London: John Wiley & Sons Ltd.2005;
215. Bede O, Suranyi A, Pinter K, Szlavik M, Gyurkovits K. Urinary magnesium excretion in asthmatic children receiving magnesium supplementation: a randomized, placebo-controlled, double-blind study. Magnes Res 2003;16(4):262-70.
216. Fogarty A, Lewis SA, Scrivener SL, Antoniak M, Pacey S, Pringle M, et al. Oral magnesium and vitamin C supplements in asthma: a parallel group randomized placebo-controlled trial. Clin Exp Allergy. 2003;33(10):1355-9.
217. Hill J. Magnesium and airway reactivity. Clin Sci 1998;95(2):111-2.
218. Prescott SL, Calder PC. N-3 polyunsaturated fatty acids and allergic disease. Curr Opin Clin Nutr Metab Care 2004;7(2):123-9.
219. Stephensen CB. Fish oil and inflammatory disease: is asthma the next target for n-3 fatty acid supplements? Nutr Rev 2004;62(12):486-9.
220. Woods RK, Thien FC, Abramson MJ. Dietary marine fatty acids (fish oil) for asthma (Cochrane Review). In: The Cochrane Library, Issue 3, 2001. London: John Wiley & Sons Ltd.
221. Allam MF, Lucane RA. Selenium supplementation for asthma (Cochrane Review). In: The Cochrane Library, Issue 2, 2004. London: John Wiley & Sons Ltd.
222. Pearson PJ, Lewis SA, Britton J, Fogarty A. Vitamin E supplements in asthma: a parallel group randomised placebo controlled trial. Thorax 2004;59(8):652-6.
223. Ram FS, Rowe BH, Kaur B. Vitamin C supplementation for asthma (Cochrane Review). In: The Cochrane Library, Issue 3, 2004. London: John Wiley & Sons Ltd.
224. Butland BK, Strachan DP, Anderson HR. Fresh fruit intake and asthma symptoms in young British adults: confounding or effect modification by smoking? Eur Respir J 1999;13(4):744-50.
225. Carey IM, Strachan DP, Cook DG. Effects of changes in fresh fruit consumption on ventilatory function in healthy British adults. Am J Respir Crit Care Med 1998;158(3):728-33.
226. Cook DG, Carey IM, Whincup PH, Papacosta O, Chirico S, Bruckdorfer KR, et al. Effect of fresh fruit consumption on lung function and wheeze in children. Thorax 1997;52(7):628-33.
227. Ellwood P, Asher MI, Bjorksten B, Burr M, Pearce N, Robertson CF. Diet and asthma, allergic rhinoconjunctivitis and atopic eczema symptom prevalence: an ecological analysis of the International Study of Asthma and Allergies in Childhood (ISAAC) data. ISAAC Phase One Study Group. Eur Respir J 2001;17(3):436-43.
228. Gilliland FD, Berhane KT, Li YF, Gauderman WJ, McConnell R, Peters J. Children's lung function and antioxidant vitamin, fruit, juice, and vegetable intake. Am J Epidemiol 2003;158(6):576-84.
229. Heinrich J, Holscher B, Bolte G, Winkler G. Allergic sensitization and diet: ecological analysis in selected European cities. Eur Respir J 2001;17(3):395-402.
230. Strachan DP, Cox BD, Erzinclioglu SW, Walters DE, Whichelow MJ. Ventilatory function and winter fresh fruit consumption in a random sample of British adults. Thorax 1991;46(9):624-9.
231. Castro-Rodriguez JA, Holberg CJ, Morgan WJ, Wright AL, Martinez FD. Increased incidence of asthmalike symptoms in girls who become overweight or obese during the school years. Am J Respir Crit Care Med. 2001;163(6):1344-9.
232. Chinn S, Jarvis D, Burney P. Relation of bronchial responsiveness to body mass index in the ECRHS. Thorax. 2002;57(12):1028-33.
233. Ford ES. The epidemiology of obesity and asthma. J Allergy Clin Immunol 2005;115(5):897-909.
234. Jarvis D, Chinn S, Potts J, Burney P, Community E. Association of body mass index with respiratory symptoms and atopy: results from the European Community Respiratory Health Survey. Clinical & Experimental Allergy. 2002;32(6):831-7.
235. Stenius-Aarniala B, Poussa T, Kvarnstrom J, Gronlund EL, Ylikahri M, Mustajoki P. Immediate and long term effects of weight reduction in obese people with asthma: randomised controlled study. BMJ 2000;320(7238):827-32.
236. Bjorksten B, Sepp E, Julge K, Voor T, Mikelsaar M. Allergy development and the intestinal microflora during the first year of life. J Allergy Clin Immunol 2001;108(4):516-20.
237. Helin T, Haahtela S, Haahtela T. No effect of oral treatment with an intestinal bacterial strain, Lactobacillus rhamnosus (ATCC 53103), on birch-pollen allergy: a placebo-controlled double-blind study. Allergy 2002;57(3):243-6.
238. Isolauri E, Arvola T, Sutas Y, Moilanen E, Salminen S. Probiotics in the management of atopic eczema. Clin Exp Allergy 2000;30(11):1604-10.
239. Wheeler JG, Shema SJ, Bogle ML, Shirrell MA, Burks AW, Pittler A, et al. Immune and clinical impact of Lactobacillus acidophilus on asthma. Annals of Allergy, Asthma, & Immunology 1997;79(3):229-33.
240. Gruber C, Illi S, Lau S, Nickel R, Forster J, Kamin W, et al. Transient suppression of atopy in early childhood is associated with high vaccination coverage. Pediatrics 2003;111(3):e282-8.
241. Gruber C, Meinlschmidt G, Bergmann R, Wahn U, Stark K. Is early BCG vaccination associated with less atopic disease? An epidemiological study in German preschool children with different ethnic backgrounds. Pediatr Allergy Immunol 2002;13(3):177-81.
242. Henderson J, North K, Griffiths M, Harvey I, Golding J. Pertussis vaccination and wheezing illnesses in young children: prospective cohort study. The Longitudinal Study of Pregnancy and Childhood Team. BMJ 1999;318(7192):1173-6.
243. Nilsson L, Kjellman NI, Bjorksten B. A randomized controlled trial of the effect of pertussis vaccines on atopic disease. Arch Pediatr Adolesc Med 1998;152(8):734-8.
244. Choi IS, Koh YI. Therapeutic effects of BCG vaccination in adult asthmatic patients: a randomized, controlled trial. Annals of Allergy, Asthma, & Immunology. 2002;88(6):584-91.
245. Arikan C, Bahceciler NN, Deniz G, Akdis M, Akkoc T, Akdis CA, et al. Bacillus Calmette-Guerin-induced interleukin-12 did not additionally improve clinical and immunologic parameters in asthmatic children treated with sublingual immunotherapy. Clinical & Experimental Allergy 2004;34(3):398-405.
246. Tsai JJ, Peng HJ, Shen HD. Therapeutic effect of Bacillus Calmette-Guerin with allergen on human allergic asthmatic patients. Journal of Microbiology, Immunology & Infection. 2002;35(2):99-102.
247. Nicholson KG, Nguyen-Van-Tam JS, Ahmed AH, Wiselka MJ, Leese J, Ayres J, et al. Randomised placebo-controlled crossover trial on effect of inactivated influenza vaccine on pulmonary function in asthma. Lancet 1998;351(9099):326-31.
248. Bueving HJ, Bernsen RM, de Jongste JC, van Suijlekom-Smit LW, Rimmelzwaan GF, Osterhaus AD, et al. Influenza vaccination in children with asthma: randomized double-blind placebo-controlled trial. American Journal of Respiratory & Critical Care Medicine 2004;169(4):488-93.
249. Bueving HJ, van der Wouden JC, Raat H, Bernsen RMD, de Jongste JC, van Suijlekom-Smith LWA, et al. Influenza vaccination in asthmatic children: Effects on quality of life and symptoms. European Respiratory Journal 2004;24(6):925-31.
250. Hanania NA, Sockrider M, Castro M, Holbrook JT, Tonascia J, Wise R, et al. Immune response to influenza vaccination in children and adults with asthma: effect of corticosteroid therapy. Journal of Allergy & Clinical Immunology 2004;113(4):717-24.
251. Sheikh A, Alves B, Dhami S. Pneumococcal vaccine for asthma (Cochrane Review). In: The Cochrane Library, Issue 1, 2002. London: John Wiley & Sons Ltd.
252. Steurer-Stey C, Russi EW, Steurer J. Complementary and alternative medicine in asthma: do they work? Swiss Med Wkly 2002;132(25-26):338-44.
253. Linde K, Jobst K, Panton J. Acupuncture for chronic asthma (Cochrane Review). In: The Cochrane Library, Issue 3, 2001. London: John Wiley & Sons Ltd.
254. Martin J, Donaldson AN, Villarroel R, Parmar MK, Ernst E, Higginson IJ. Efficacy of acupuncture in asthma: systematic review and meta-analysis of published data from 11 randomised controlled trials. Eur Respir J 2002;20(4):846-52.
255. Gruber W, Eber E, Malle-Scheid D, Pfleger A, Weinhandl E, Dorfer L, et al. Laser acupuncture in children and adolescents with exercise induced asthma. Thorax. 2002;57(3):222-5.

256. Malmstrom M, Ahlner J, Carlsson C, Schmekel B. No effect of chinese acupuncture on isocapnic hyperventilation with cold air in asthmatics, measured with impulse oscillometry. Acupuncture.in Medicine. 2002;20(2-3):66-73.
257. Blackhall K, Appleton S, Cates CJ. Ionisers for chronic asthma (Cochrane Review). In: The Cochrane Library, Issue 3, 2003. London: John Wiley & Sons Ltd.
258. Warner JA, Marchant JL, Warner JO. A double blind trial of ionisers in children with asthma sensitive to the house dust mite. Thorax 1993;48(4):330-3.
259. Holloway E, Ram FSF. Breathing exercises for asthma (Cochrane Review). In: The Cochrane Library, Issue 3, 2001. London: John Wiley & Sons Ltd.
260. Singh V, Wisniewski A, Britton J, Tattersfield A. Effect of yoga breathing exercises (pranayama) on airway reactivity in subjects with asthma. Lancet 1990;335(8702):1381-3.
261. Cooper S, Oborne J, Newton S, Harrison V, Thompson Coon J, Lewis S, et al. Effect of two breathing exercises (Buteyko and pranayama) in asthma: a randomised controlled trial. Thorax 2003;58(8):674-9.
262. McHugh P, Aitcheson F, Duncan B, Houghton F. Buteyko breathing technique for asthma: An effective intervention. N Z Med J 2003;116(1187):U710.
263. Bowler SD, Green A, Mitchell CA. Buteyko breathing techniques in asthma: a blinded randomised controlled trial. Med J Aust 1998;169(11-12):575-8.
264. Opat AJ, Cohen MM, Bailey MJ, Abramson MJ. A clinical trial of the Buteyko Breathing Technique in asthma as taught by a video. J Asthma 2000;37(7):557-64.
265. Huntley A, Ernst E. Herbal medicines for asthma: a systematic review. Thorax 2000;55(11):925-9.
266. Chan CK, Kuo ML, Shen JJ, See LC, Chang HH, Huang JL. Ding Chuan Tang, a Chinese herb decoction, could improve airway hyper-responsiveness in stabilized asthmatic children: a randomized, double-blind clinical trial. Pediatr Allergy Immunol 2006;17(5):316-22.
267. Hsu CH, Lu CM, Chang TT. Efficacy and safety of modified Mai-Men-Dong-Tang for treatment of allergic asthma. Pediatric Allergy & Immunology 2005;16(1):76-81.
268. Linde K, Jobst KA. Homeopathy for chronic asthma (Cochrane Review). In: The Cochrane Library, Issue 3, 2001. London: John Wiley & Sons Ltd.
269. White A, Slade P, Hunt C, Hart A, Ernst E. Individualised homeopathy as an adjunct in the treatment of childhood asthma: a randomised placebo controlled trial. Thorax 2003;58(4):317-21.
270. Huntley A, White AR, Ernst E. Relaxation therapies for asthma: a systematic review. Thorax 2002;57(2):127-31.
271. Hondras MA, Linde K, Jones AP. Manual therapy for asthma (Cochrane Review). In: The Cochrane Library, Issue 3, 2001. London: John Wiley & Sons Ltd.
272. Panton J, Barley EA. Family therapy for asthma in children (Cochrane Review). In: The Cochrane Library, Issue 2, 2000. London: John Wiley & Sons Ltd.
273. North of England Evidence Based Guideline Development Project. The primary care management of asthma in adults. Newcastle upon Tyne:: University of Newcastle upon Tyne, Centre for Health Services Research; 1999.
274. Pharmacological management of asthma. Evidence table 4.2: ipratopium bromide. Edinburgh: SIGN; 2002. Available from url: http://www.sign.ac.uk/guidelines/published/support/guideline63/index.html
275. Dennis SM, Sharp SJ, Vickers MR, Frost CD, Crompton GK, Barnes PJ, et al. Regular inhaled salbutamol and asthma control: the TRUST randomised trial. Therapy Working Group of the National Asthma Task Force and the MRC General Practice Research Framework. Lancet 2000;355(9216):1675-9.
276. Walters EH, Walters J. Inhaled short acting beta2-agonist use in asthma: regular versus as needed treatment (Cochrane Review). In: The Cochrane Library, Issue 3, 2001. London: John Wiley & Sons Ltd.
277. Pharmacological management of asthma. Evidence table 4.1: inhaled short acting beta 2 agonists. Edinburgh: SIGN; 2002. Available from url: http://www.sign.ac.uk/guidelines/published/support/guideline63/index.html
278. Pharmacological management of asthma. Evidence table 4.4a: inhaled corticosteroid vs theophylline. Edinburgh: SIGN; 2002. Available from url: http://www.sign.ac.uk/guidelines/published/support/guideline63/index.html
279. Pharmacological management of asthma. Evidence table 4.4c: inhaled corticosteroid vs leukotriene receptor antagonists. Edinburgh: SIGN; 2002. Available from url: http://www.sign.ac.uk/guidelines/published/support/guideline63/index.html
280. Adams N, Bestall J, Jones PW. Inhaled fluticasone proprionate for chronic asthma (Cochrane Review). In: The Cochrane Library, Issue 3, 2001. London: John Wiley & Sons Ltd.
281. Adams NP, Bestall JB, Jones PW. Inhaled beclometasone versus placebo for chronic asthma (Cochrane Review). In: The Cochrane Library, Issue 3, 2001. London: John Wiley & Sons Ltd.
282. Calpin C, Macarthur C, Stephens D, Feldman W, Parkin PC. Effectiveness of prophylactic inhaled steroids in childhood asthma: a systemic review of the literature. J Allergy Clin Immunol 1997;100(4):452-7.
283. Carlsen KCL SS, Kamin W, et al. The efficacy and safety of fluticasone propionate in very young children with persistent asthma symptoms. Respir Med 2005;99(11):1393-402.
284. Teper AM CA, Kofman CD, et al. Effects of Inhaled Fluticasone Propionate in Children Less Than 2 Years Old with Recurrent Wheezing. Pediatr Pulmonol 2004;37(2):111-5.
285. Teper AM KC, Szulman GA, et al. . Fluticasone improves pulmonary function in children under 2 years old with risk factors for asthma. Am J Respir Crit Care Med 2005;171(6):587-90.
286. Bisgaard H AD, Milanowski J, et al. . Twelve-month safety and efficacy of inhaled fluticasone propionate in children aged 1 to 3 years with recurrent wheezing. Pediatrics 2004;113(2):e87-94.
287. O'Byrne PM, Barnes PJ, Rodriguez-Roisin R, Runnerstrom E, Sandstrom T, Svensson K, et al. Low dose inhaled budesonide and formoterol in mild persistent asthma: the OPTIMA randomized trial.[comment]. American Journal of Respiratory & Critical Care Medicine. 2001;164(8 Pt 1):1392-7.
288. Pauwels RA PS, Busse WW, et al. Early intervention with budesonide in mild persistent asthma: a randomised, double-blind trial. Lancet 2003;361(9363):1071-6.
289. Pharmacological management of asthma. Evidence table 4.7: high dose step-down. Edinburgh: SIGN; 2002. Available from url: http://www.sign.ac.uk/guidelines/published/support/guideline63/index.html
290. Hodges IGC, Netherway TA. Once-daily fluticasone propionate is as effective as twice-daily treatment in stable, mild-to-moderate childhood asthma. Clin Drug Invest. 2005;25(1):13-22.
291. Ram FS, Jones A, Fay JK. Primary care based clinics for asthma (Cochrane Review). In: The Cochrane Library, Issue 1, 2003. London: John Wiley & Sons Ltd.
292. Sharek PJ, Bergman DA. The effect of inhaled steroids on the linear growth of children with asthma: a meta-analysis. Pediatrics 2000;106(1):E8.
293. Dunlop KA, Carson DJ, Steen HJ, McGovern V, McNaboe J, Shields MD. Monitoring growth in asthmatic children treated with high dose inhaled glucocorticoids does not predict adrenal suppression. Arch Dis Child 2004;89(8):713-6.
294. Bernstein D AD. Evaluation of tests of hypothalamic-pituitary-adrenal axis function used to measure effects of inhaled corticosteroids. Ann Allergy Asthma Immunol 2007;98(2):118-27.
295. Pharmacological management of asthma. Evidence table 4.25: budesonide vs beclometasone. Edinburgh: 2002. Available from url: http://www.sign.ac.uk/guidelines/published/support/guideline63/index.html
296. Pharmacological management of asthma. Evidence table 4.15: mometasone furoate dry powder inhalation evidence. Edinburgh: SIGN; 2002. Available from url: http://www.sign.ac.uk/guidelines/published/support/guideline63/index.html
297. Boulet LP, Drollmann A, Magyar P, Timar M, Knight A, Engelstatter R, et al. Comparative efficacy of once-daily ciclesonide and budesonide in the treatment of persistent asthma. Respir Med 2006;100(5):785-94.
298. Buhl R, Vinkler I, Magyar P, Gyori Z, Rybacki C, Middle MV, et al. Comparable efficacy of ciclesonide once daily versus fluticasone propionate twice daily in asthma. Pulm Pharmacol Ther 2006;19(6):404-12.
299. Niphadkar P, Jagannath K, Joshi JM, Awad N, Boss H, Hellbardt S, et al. Comparison of the efficacy of ciclesonide 160 microg QD and budesonide 200 microg BID in adults with persistent asthma: a phase III, randomized, double-dummy, open-label study. Clin Ther 2005;27(11):1752-63.
300. Pearlman DS, Berger WE, Kerwin E, Laforce C, Kundu S, Banerji D. Once-daily ciclesonide improves lung function and is well tolerated by patients with mild-to-moderate persistent asthma. J Allergy Clin Immunol 2005;116(6):1206-12.
301. Szefler S, Rohatagi S, Williams J, Lloyd M, Kundu S, Banerji D. Ciclesonide, a novel inhaled steroid, does not affect hypothalamic-pituitary-adrenal axis function in patients with moderate-to-severe persistent asthma. Chest 2005;128(3):1104-14.
302. Tomlinson JE, McMahon AD, Chaudhuri R, Thompson JM, Wood SF, Thomson NC. Efficacy of low and high dose inhaled corticosteroid in smokers versus non-smokers with mild asthma. Thorax 2005;60(4):282-7.
303. Salmeterol (Severant) and formoterol (Oxis) in asthma management. Curr Probl Pharmacovigilanc 2003;29(5).
304. Edwards A SM. The clinical efficacy of inhaled nedocromil sodium (Tilade) in the treatment of asthma. Eur Respir J 1993;6(1):35-41.
305. Pharmacological management of asthma. Evidence table 4.24a: Other preventor therapies - Chromones in children aged 5-12. Edinburgh: SIGN; 2005. Available from url: http://www.sign.ac.uk/guidelines/published/support/guideline63/index.html

306. Table 16: nedocromil and sodium cromoglycate studies not included in the nedocromil meta-analysis. In: North of England Evidence Based Guideline Development Project, editor. The primary care management of asthma in adults. Newcastle upon Tyne: University of Newcastle upon Tyne, Centre for Health Services Research; 1999. p.46-7.
307. Pharmacological management of asthma. Evidence table 4.4j: Do cromones works as first line preventor in children > 5 years? Edinburgh: SIGN; 2002. Available from url: http://www.sign.ac.uk/guidelines/published/support/guideline63/index.html
308. Pharmacological management of asthma. Evidence table 4.24b: Other preventor therapies - Chromones in children aged < 5. Edinburgh: SIGN; 2005. Available from url: Available from url: http://www.sign.ac.uk/guidelines/published/support/guideline63/index.html
309. Pharmacological management of asthma. Evidence table 4.4d: leukotriene receptor antagonists with short-acting beta-agonists. Edinburgh: SIGN; 2002. Available from url: http://www.sign.ac.uk/guidelines/published/support/guideline63/index.html
310. Ducharme FM. Inhaled glucocorticoids versus leukotriene receptor antagonists as single agent asthma treatment: systematic review of current evidence. BMJ 2003;362(7390):621.
311. Van Ganse E, Kaufman L, Derde MP, Yernault JC, Delaunois L, Vincken W. Effects of antihistamines in adult asthma: a meta-analysis of clinical trials. Eur Respir J 1997;10(10):2216-24.
312. Pharmacological management of asthma. Evidence table 4.11b: Add-on drugs for inhaled steroids: long acting or oral B2 agonists. Edinburgh: SIGN; 2002. Available from url: http://www.sign.ac.uk/guidelines/published/support/guideline63/index.html
313. Pharmacological management of asthma. Evidence table 4.11d: Add-on drugs for inhaled steroids: theophylline, beclometasone diproponate, budesonide. Edinburgh: SIGN; 2002. Available from url: http://www.sign.ac.uk/guidelines/published/support/guideline63/index.html
314. Pharmacological management of asthma. Evidence table 4.11c: Add-on drugs for inhaled steroids: anticholinergics. Edinburgh: SIGN; 2002. Available from url: http://www.sign.ac.uk/guidelines/published/support/guideline63/index.html
315. Pharmacological management of asthma. Evidence table 4.11a: Add-on drugs for inhaled steroids: cromones. Edinburgh: SIGN; 2002. Available from url: http://www.sign.ac.uk/guidelines/published/support/guideline63/index.html
316. Becker AB, Simons FE. Formoterol, a new long-acting selective beta 2-adrenergic receptor agonist: double-blind comparison with salbutamol and placebo in children with asthma. J Allergy Clin Immunol 1989;84(6 Pt 1):891-5.
317. Kips JC, Pauwels RA. Long-acting inhaled beta(2)-agonist therapy in asthma. Am J Respir Crit Care Med 2001;164(6):923-32.
318. Pharmacological management of asthma. Evidence table 4.22: Combined therapy of inhaled steroids and long acting B2 agonists. Edinburgh: SIGN; 2002. Available from url: http://www.sign.ac.uk/guidelines/published/support/guideline63/index.html
319. Pharmacological management of asthma. Evidence table 4.8c: Children with poor asthma control on ICS - is addition of leukotriene receptor antagonists helpful? Edinburgh: SIGN; 2002. Available from url: http://www.sign.ac.uk/guidelines/published/support/guideline63/index.html
320. Knorr B, Franchi LM, Bisgaard H, Vermeulen JH, LeSouef P, Santanello N, et al. Montelukast, a leukotriene receptor antagonist, for the treatment of persistent asthma in children aged 2 to 5 years. Pediatrics 2001;108(3):E48.
321. Westby M, Benson M, Gibson P. Anticholinergic agents for chronic asthma in adults (Cochrane Review). In: The Cochrane Library, Issue 3, 2004. London: John Wiley & Sons Ltd.
322. British Thoracic Society, National Asthma Campaign, Royal College of Physicians of London in association with the General Practitioner in Asthma Group, The British Association of Accident and Emergency Medicine, The British Paediatric Respiratory Society, Royal College of Paediatrics and Child Health. The British guidelines on asthma management 1995 review and position statement. Thorax 1997;52(Suppl 1):S1-S21.
323. Kuna P, Peters MJ, Manjra AI, Jorup C, Naya IP, Martinez-Jimenez NE, et al. Effect of budesonide/formoterol maintenance and reliever therapy on asthma exacerbations. Int J Clin Pract 2007;61(5):725-36.
324. O'Byrne PM, Bisgaard H, Godard PP, Pistolesi M, Palmqvist M, Zhu Y, et al. Budesonide/formoterol combination therapy as both maintenance and reliever medication in asthma. Am J Respir Crit Care Med 2005;171(2):129-36.
325. Rabe KF, Atienza T, Magyar P, Larsson P, Jorup C, Lalloo UG. Effect of budesonide in combination with formoterol for reliever therapy in asthma exacerbations: a randomised controlled, double-blind study. Lancet 2006;368(9537):744-53.
326. Scicchitano. Efficacy and safety of budesonide/formoterol single inhaler therapy versus a higher dose of budesonide in moderate to severe asthma. Current Medical Research and opinions 2004;20(9):1403-18.
327. Vogelmeier C, D'Urzo A, Pauwels R, Merino JM, Jaspal M, Boutet S, et al. Budesonide/formoterol maintenance and reliever therapy: an effective asthma treatment option? Eur Respir J 2005;26(5):819-28.
328. National Osteoporosis Society. Guidance on the prevention and management of corticosteroid induced osteoporosis. Bath: National Osteoporosis Society; 1998.
329. Nassif EG, Weinberger M, Thompson R, Huntley W. The value of maintenance theophylline in steroid-dependent asthma. N Engl J Med 1981;304(2):71-5.
330. Pharmacological management of asthma. Evidence table 4.13a: Immunosuppresive agents. Edinburgh: SIGN; 2002. Available from url: http://www.sign.ac.uk/guidelines/published/support/guideline63/index.html
331. O'Driscoll BR, Ruffles SP, Ayres JG, Cochrane GM. Long term treatment of severe asthma with subcutaneous terbutaline. Br J Dis Chest 1988;82(4):360-7.
332. Payne D, Balfour-Lynn I, Biggart E, Bush A, Rosenthal M. Subcutaneous terbutaline in children with chronic severe asthma. Pediatr Pulmonol. 2002;33(5):356-61.
333. Berry MA, Hargadon B, Shelley M, Parker D, Shaw DE, Green RH, et al. Evidence of a role of tumor necrosis factor alpha in refractory asthma N Engl J Med. 2006;354(7):697-708.
334. Hawkins G, McMahon AD, Twaddle S, Wood S, Ford I, NC. T. Stepping down inhaled corticosteroids in asthma: randomised controlled trial. BMJ 2003;326(7399):1115.
335. Pharmacological management of asthma. Evidence table 4.9: Exacerbation. Edinburgh: SIGN; 2002. Available from url: http://www.sign.ac.uk/guidelines/published/support/guideline63/index.html
336. Foresi A, Morelli MC, Catena E. Low-dose budesonide with the addition of an increased dose during exacerbations is effective in long-term asthma control. On behalf of the Italian Study Group. Chest 2000;117(2):440-6.
337. Henriksen JM, Agertoft L, Pedersen S. Protective effect and duration of action of inhaled formoterol and salbutamol on exercise-induced asthma in children. J Allergy Clin Immunol 1992;89(6):1176-82.
338. Pharmacological management of asthma. Evidence table 4.3a: Long acting B2 agonists in exercise induced asthma. Edinburgh: SIGN; 2002. Available from url: http://www.sign.ac.uk/guidelines/published/support/guideline63/index.html
339. Pharmacological management of asthma. Evidence table 4.3c: Theophyllines in exercise-induced asthma. Edinburgh: SIGN; 2002. Available from url: http://www.sign.ac.uk/guidelines/published/support/guideline63/index.html
340. Pharmacological management of asthma. Evidence table 4.3d: Leukotriene receptor antagonists in exercise induced asthma. Edinburgh: SIGN; 2002. Available from url: http://www.sign.ac.uk/guidelines/published/support/guideline63/index.html
341. Kelly K, Spooner CH, Rowe BH. Nedocromil sodium versus sodium cromoglycate for preventing exercise-induced bronchoconstriction in asthmatics (Cochrane Review). In: The Cochrane Library, Issue 3, 2001. London: John Wiley & Sons Ltd.
342. Pharmacological management of asthma. Evidence table 4.3g: Oral B2 agonists for exercise induced asthma. Edinburgh: SIGN; 2002. Available from url: http://www.sign.ac.uk/guidelines/published/support/guideline63/index.html
343. Pharmacological management of asthma. Evidence table 4.3f: Anticholinergic therapy for exercise-induced asthma. Edinburgh: SIGN; 2002. Available from url: http://www.sign.ac.uk/guidelines/published/support/guideline63/index.html
344. Pharmacological management of asthma. Evidence table 4.3b: Ketotifen for exercise-induced asthma. Edinburgh: SIGN; 2002. Available from url: http://www.sign.ac.uk/guidelines/published/support/guideline63/index.html
345. Pharmacological management of asthma. Evidence table 4.3e: Antihistamines for exercise-induced asthma. Edinburgh: SIGN; 2002. Available from url: http://www.sign.ac.uk/guidelines/published/support/guideline63/index.html
346. Pharmacological management of asthma. Evidence table 4.10: Rhinitis. Edinburgh: SIGN; 2002. Available from url: http://www.sign.ac.uk/guidelines/published/support/guideline63/index.html
347. Pharmacological management of asthma. Evidence table 4.19: Allergic bronchopulmonary aspergillosis. Edinburgh: SIGN; 2002. Available from url: http://www.sign.ac.uk/guidelines/published/support/guideline63/index.html
348. Wark PAB, Gibson PG, Wilson AJ. Azoles for allergic bronchopulmonary aspergillosis associated with asthma (Cochrane Review). In: The Cochrane Library, Issue 3, 2004. London: John Wiley & Sons Ltd.
349. Pharmacological management of asthma. Evidence table 4.21: Aspirin intolerant asthma. Edinburgh: SIGN; 2002. Available from url: http://www.sign.ac.uk/guidelines/published/support/guideline63/index.html
350. Coughlan J. Oesophagitis does not consistently improve asthma control: A systematic review. . Thorax 2001;56(3):198-204.
351. Gibson PG, Henry RL, Coughlan JL. Gastro oesophogeal reflux treatment for asthma in adults and children (Cochrane Review). In: The Cochrane Library, Issue 2, 2003. London: John Wiley & Sons Ltd.

352. Brocklebank D, Ram F, Wright J, Barry P, Cates C, Davies L, et al. Comparison of the effectiveness of inhaler devices in asthma and chronic obstructive airways disease: a systematic review of the literature. Health Technol Assess 2001;5(26):1-149.
353. Cates CJ, Rowe BH, Bara A, Crilly JA. Holding chambers versus nebulisers for beta-agonist treatment of acute asthma (Cochrane Review). In: The Cochrane Library, Issue 3, 2001. London: John Wiley & Sons Ltd.
354. Leversha AM, Campanella SG, Aickin RP, Asher MI. Costs and effectiveness of spacer versus nebuliser in young children with moderate and severe acute asthma. J Pediatr 2000;136(4):497-502.
355. Closa RM, Ceballos JM, Gomez-Papi A, Galiana AS, Gutierrez C, Marti-Henneber C. Efficacy of bronchodilators administered by nebulizers versus spacer devices in infants with acute wheezing. Pediatr Pulmonol 1998;26(5):344-8.
356. Delgado A, Chou KJ, Silver EJ, Crain EF. Nebulizers vs metered-dose inhalers with spacers for bronchodilator therapy to treat wheezing in children aged 2 to 24 months in a pediatric emergency department. Archives of Pediatrics & Adolescent.Medicine. 2003;157(1):76-80.
357. Ram FS, Wright J, Brocklebank D, White JE. Systematic review of clinical effectiveness of pressurised metered dose inhalers versus other hand held inhaler devices for delivering beta (2)agonists bronchodilators in asthma. BMJ 2001;323(7318):901-5.
358. Broeders M, Molema J, Hop WCJ, Vermue NA, Folgering HTM. Does the inhalation device affect the bronchodilatory dose response curve of salbutamol in asthma and chronic obstructive pulmonary disease patients? European Journal of Clinical Pharmacology 2003;59(5-6):449-55.
359. Hughes DA, Woodcock A, Walley T. Review of therapeutically equivalent alternatives to short acting beta(2) adrenoceptor agonists delivered via chlorofluorocarbon-containing inhalers. Thorax 1999;54(12):1087-92.
360. Farmer IS, Middle M, Savic J, Perri VL, Herdman MJ. Therapeutic equivalence of inhaled beclometasone dipropionate with CFC and non-CFC (HFA 134a) propellants both delivered via the Easibreathe inhaler for the treatment of paediatric asthma. Respir Med 2000;94(1):57-63.
361. De Benedictis FM, Boner A, Cavagni G, Caffarelli C, Ferraro L, Cantini L. Treating asthma in children with beclometasone dipropionate: Pulvinal versus Diskhaler. Journal of Aerosol Medicine 2000;13(1):35-41.
362. Adams N, Cates CJ, Bestall J. Holding chambers versus nebulisers for inhaled steroids in chronic asthma (Cochrane Review). In: The Cochrane Library, Issue 3, 2001. London: John Wiley & Sons Ltd.
363. Lumry W, Noveck R, Weinstein S, Barnhart F, Vandermeer A, Murray A, et al. Switching from Ventolin CFC to Ventolin HFA is well tolerated and effective in patients with asthma. Ann Allergy Asthma Immunol 2001;86(3):297-303.
364. Gross G, Cohen RM, Guy H. Efficacy response of inhaled HFA-albuterol delivered via the breath-actuated Autohaler inhalation device is comparable to dose in patients with asthma. Journal of Asthma 2003;40(5):487-95.
365. Gustafsson P, Kallman S, Whitehead PJ. Clinical equivalence between salbutamol hydrofluoroalkane pMDI and salbutamol Turbuhaler at the same cumulative microgram doses in paediatric patients. Respiratory Medicine 2002;96(11):957-9.
366. Hawksworth RJ, Sykes AP, Faris M, Mant T, Lee TH. Albuterol HFA is as effective as albuterol CFC in preventing exercise-induced bronchoconstriction. Annals of Allergy, Asthma, & Immunology 2002;88(5):473-7.
367. Shapiro G, Bronsky E, Murray A, Barnhart F, VanderMeer A, Reisner C. Clinical comparability of ventolin formulated with hydrofluoroalkane or conventional chlorofluorocarbon propellants in children with asthma. Arch Pediatr Adolescent Med 2000;154(12):1219-25.
368. Shapiro GS, Klinger NM, Ekholm BP, Colice GL. Comparable bronchodilation with hydrofluoroalkane-134a (HFA) albuterol and chlorofluorocarbons-11/12 (CFC) albuterol in children with asthma. Journal of Asthma 2000;37(8):667-75.
369. Anderson PB, Langley SJ, Mooney P, Jones J, Addlestone R, Rossetti A, et al. Equivalent efficacy and safety of a new HFA-134a formulation of BDP compared with the conventional CFC in adult asthmatics. J Investig Allergol Clin Immunol 2002;12(2):107-13.
370. Lee TL, Adler L, McLaren G, Rossetti A, Cantini L. Assessment of efficacy and systemic safety of a new chlorofluorocarbon-free formulation of inhaled beclometasone dipropionate in asthmatic children. Pediatr Asthma Allergy Immunol 2001;15(3):133-43.
371. Vondra V, Sladek K, Kotasova J, Terl M, Rossetti A, Cantini L. A new HFA-134a propellant in the administration of inhaled BDP via the Jet spacer: controlled clinical trial vs the conventional CFC. Respiratory Medicine 2002;96(10):784-9.
372. Ederle K, Multicentre Study Group. Improved control of asthma symptoms with a reduced dose of HFA-BDP extrafine aerosol: an open-label, randomised study. European Review for Medical & Pharmacological Sciences 2003;7(2):45-55.
373. Fireman P, Prenner BM, Vincken W, Demedts M, Mol SJ, Cohen RM. Long-term safety and efficacy of a chlorofluorocarbon-free beclometasone dipropionate extrafine aerosol. Annals of Allergy, Asthma, & Immunology 2001;86(5):557-65.
374. Pedersen S, Warner J, Wahn U, Staab D, Le Bourgeois M, Van Essen-Zandvliet E, et al. Growth, systemic safety, and efficacy during 1 year of asthma treatment with different beclometasone dipropionate formulations: an open-label, randomized comparison of extrafine and conventional aerosols in children. Pediatrics. 2002;109(6):e92.
375. Szefler SJ, Warner J, Staab D, Wahn U, Le Bourgeois M, van Essen-Zandvliet EE, et al. Switching from conventional to extrafine aerosol beclometasone dipropionate therapy in children: a 6-month, open-label, randomized trial. Journal of Allergy & Clinical Immunology 2002;110(1):45-50.
376. Ayres JG, Millar AB, Sykes AP. Clinical efficacy and safety of fluticasone propionate 1 mg twice daily administered via a HFA 134a pressurized metered dose inhaler to patients with severe asthma. Respiratory Medicine 2000;94(Suppl B):S42-S50.
377. Fowler SJ, Orr LC, Sims EJ, Wilson AM, Currie GP, McFarlane L, et al. Therapeutic ratio of hydrofluoroalkane and chlorofluorocarbon formulations of fluticasone propionate. Chest. 2002;122(2):618-23.
378. Langley SJ, Holden J, Derham A, Hedgeland P, Sharma RK, Woodcock A. Fluticasone propionate via the Diskhaler or hydrofluoroalkane-134a metered-dose inhaler on methacholine-induced airway hyperresponsiveness. Chest. 2002;122(3):806-11.
379. Lyttle B, Gilles J, Panov M, Emeryk A, Wixon C. Fluticasone propionate 100 microg bid using a non-CFC propellant, HFA 134a, in asthmatic children. Canadian Respiratory Journal 2003;10(2):103-9.
380. Perruchoud AP, Lundback B, Yigla M, Sykes AP. Clinical efficacy and safety of fluticasone propionate 1 mg per day administered via a HFA 134a pressurized metered dose inhaler to patients with moderate to severe asthma. Resp Med 2000;94(Suppl B):S35-S41.
381. Accuracy of death certificates in bronchial asthma. Accuracy of certification procedures during the confidential inquiry by the British Thoracic Association. A subcommittee of the BTA Research Committee. Thorax 1984;39(7):505-9.
382. Bucknall CE, Slack R, Godley CC, Mackay TW, Wright SC. Scottish Confidential Inquiry into Asthma Deaths (SCIAD), 1994-6. Thorax 1999;54(11):978-84.
383. Burr ML, Davies BH, Hoare A, Jones A, Williamson IJ, Holgate SK, et al. A confidential inquiry into asthma deaths in Wales. Thorax 1999;54(11):985-9.
384. Mohan G, Harrison BD, Badminton RM, Mildenhall S, Wareham NJ. A confidential enquiry into deaths caused by asthma in an English health region: implications for general practice. Br J Gen Pract 1996;46(410):529-32.
385. Wareham NJ, Harrison BD, Jenkins PF, Nicholls J, Stableforth DE. A district confidential enquiry into deaths due to asthma. Thorax 1993;48(11):1117-20.
386. Harrison BDW, Slack R, Berrill WT, Burr ML, Stableforth DE, Wright SC. Results of a national confidential enquiry into asthma deaths. Asthma J 2000;5(4):180-6.
387. Spitzer WO, Suissa S, Ernst P, Horwitz RI, Habbick B, Cockcroft D, et al. The use of beta-agonists and the risk of death and near death from asthma. N Engl J Med 1992;326(8):501-6.
388. Suissa S, Blais L, Ernst P. Patterns of increasing beta-agonist use and the risk of fatal or near-fatal asthma. Eur Respir J 1994;7(9):1602-9.
389. Jalaludin BB, Smith MA, Chey T, Orr NJ, Smith WT, Leeder SR. Risk factors for asthma deaths: A population-based, case-control study. Aust NZ J Pub Health 1999;23(6):595-600.
390. Rea HH, Scragg R, Jackson R, Beaglehole R, Fenwick J, Sutherland DC. A case-control study of deaths from asthma. Thorax 1986;41(11):833-9.
391. Campbell MJ, Cogman GR, Holgate ST, Johnston SL. Age specific trends in asthma mortality in England and Wales, 1983-95: results of an observational study. BMJ 1997;314(7092):1439-41.
392. Richards GN, Kolbe J, Fenwick J, Rea HH. Demographic characteristics of patients with severe life threatening asthma: comparison with asthma deaths. Thorax 1993;48(11):1105-9.
393. Innes NJ, Reid A, Halstead J, Watkin SW, Harrison BD. Psychosocial risk factors in near-fatal asthma and in asthma deaths. J R Coll Phys Lond 1998;32(5):430-4.
394. Khot A, Evans N, Lenney W. Seasonal trends in childhood asthma in south east England. Br Med J (Clin Res Ed) 1983;287(6401):1257-8.
395. Barr RG, Woodruff PG, Clark S, Camargo CA Jr. Sudden-onset asthma exacerbations: clinical features, response to therapy, and 2-week follow-up. Multicenter Airway Research Collaboration (MARC) investigators. Eur Respir J 2000;15(2):266-73.
396. Kolbe J, Fergusson W, Garrett J. Rapid onset asthma: a severe but uncommon manifestation. Thorax 1998;53(4):241-7.
397. Kolbe J, Fergusson W, Vamos M, Garrett J. Case-control study of severe life threatening asthma (SLTA) in adults: demographics, health care, and management of the acute attack. Thorax 2000;55(12):1007-15.
398. Rodrigo GJ, Rodrigo C. Rapid-onset asthma attack: a prospective cohort study about characteristics and response to emergency department treatment. Chest 2000;118(6):1547-52.

399. Turner MO, Noertjojo K, Vedal S, Bai T, Crump S, Fitzgerald JM. Risk factors for near-fatal asthma. A case-control study in hospitalized patients with asthma. Am J Respir Crit Care Med 1998;157(6 Pt 1):1804-9.
400. Woodruff PG, Emond SD, Singh AK, Camargo CA Jr. Sudden-onset severe acute asthma: clinical features and response to therapy. Acad Emerg Med 1998;5(7):695-701.
401. Scottish Intercollegiate Guidelines Network. Emergency management of acute asthma. Edinburgh: SIGN; 1999.
402. International consensus report on the diagnosis and treatment of asthma. National Heart, Lung, and Blood Institute, National Institutes of Health. Bethesda, Maryland 20892. Publication no. 92-3091, March 1992. Eur Respir J 1992;5(5):601-41.
403. Neville E, Gribbin H, Harrison BD. Acute severe asthma. Respir Med 1991;85(6):463-74.
404. Brenner B, Kohn MS. The acute asthmatic patient in the ED: to admit or discharge. Am J Emerg Med 1998;16(1):69-75.
405. Boulet LP, Becker A, Berube D, Beveridge R, Ernst P. Canadian asthma consensus report, 1999. Canadian asthma consensus group. Canadian Medical Association Journal 1999;161(11 Suppl):S1-61.
406. Nunn AJ, Gregg I. New regression equations for predicting peak expiratory flow in adults. BMJ 1989;298(6680):1068-70.
407. Gibson PG, Powell H, Coughlan J, Wilson AJ, Abramson M, Haywood P, et al. Self-management education and regular practitioner review for adults with asthma (Cochrane Review). In: The Cochrane Library, Issue 1, 2003. London: John Wiley & Sons Ltd.
408. Abramson MJ, Bailey MJ, Couper FJ, Driver JS, Drummer OH, Forbes AB, et al. Are asthma medications and management related to deaths from asthma? Am J Respir Crit Care Med 2001;163(1):12-8.
409. Robinson SM, Harrison BD, Lambert MA. Effect of a preprinted form on the management of acute asthma in an accident and emergency department. J Accid Emerg Med 1996;13(2):93-7.
410. Shim CS, Williams MH Jr. Evaluation of the severity of asthma: patients versus physicians. Am J Med 1980;68(1):11-3.
411. Emerman CL, Cydulka RK. Effect of pulmonary function testing on the management of acute asthma. Arch Intern Med 1995;155(20):2225-8.
412. Standardized lung function testing. Report working party. Bull Eur Physiopathol Respir 1983;19(Suppl 5):1-95.
413. Carruthers DM, Harrison BD. Arterial blood gas analysis or oxygen saturation in the assessment of acute asthma? Thorax 1995;50(2):186-8.
414. Pearson MG, Spence DP, Ryland I, Harrison BD. Value of pulsus paradoxus in assessing acute severe asthma. British Thoracic Society Standards of Care Committee. BMJ 1993;307(6905):659.
415. McFadden ER Jr, Lyons HA. Arterial-blood gas tension in asthma. N Engl J Med 1968;278(19):1027-32.
416. Rebuck AS, Read J. Assessment and management of severe asthma. Am J Med 1971;51(6):788-98.
417. Jenkins PF, Benfield GF, Smith AP. Predicting recovery from acute severe asthma. Thorax 1981;36(11):835-41.
418. Molfino NA, Nannini LJ, Martelli AN, Slutsky AS. Respiratory arrest in near-fatal asthma. N Engl J Med 1991;324(5):285-8.
419. Gleeson JG, Green S, Price JF. Air or oxygen as driving gas for nebulised salbutamol. Arch Dis Child 1988;63(8):900-4.
420. Douglas JG, Rafferty P, Fergusson RJ, Prescott RJ, Crompton GK, Grant IW. Nebulised salbutamol without oxygen in severe acute asthma: how effective and how safe? Thorax 1985;40(3):180-3.
421. McFadden ER Jr. Critical appraisal of the therapy of asthma - an idea whose time has come. Am Rev Respir Dis 1986;133(5):723-4.
422. Rossing TH, Fanta CH, Goldstein DH, Snapper JR, McFadden ER Jr. Emergency therapy of asthma: comparison of the acute effects of parenteral and inhaled sympathomimetics and infused aminophylline. Am Rev Respir Dis 1980;122(3):365-71.
423. Siegel D, Sheppard D, Gelb A, Weinberg PF. Aminophylline increases the toxicity but not the efficacy of an inhaled beta-adrenergic agonist in the treatment of acute exacerbations of asthma. Am Rev Respir Dis 1985;132(2):283-6.
424. Travers A, Jones AP, Kelly K, Barker SJ, Camargo CA, Rowe BH. Intravenous beta2-agonists for acute asthma in the emergency department (Cochrane Review). In: The Cochrane Library, Issue 3, 2001. London: John Wiley & Sons Ltd.
425. Lin RY, Sauter D, Newman T, Sirleaf J, Walters J, Tavakol M. Continuous versus intermittent albuterol nebulization in the treatment of acute asthma. Ann Emerg Med 1993;22(12):1847-53.
426. Rudnitsky GS, Eberlein RS, Schoffstall JM, Mazur JE, Spivey WH. Comparison of intermittent and continuously nebulized albuterol for treatment of asthma in an urban emergency department. Ann Emerg Med 1993;22(12):1842-6.
427. Shrestha M, Bidadi K, Gourlay S, Hayes J. Continuous vs intermittent albuterol, at high and low doses, in the treatment of severe acute asthma in adults. Chest 1996;110(1):42-7.
428. Rowe BH, Spooner C, Ducharme FM, Bretzlaff JA, Bota GW. Early emergency department treatment of acute asthma with systemic corticosteroids (Cochrane Review). In: The Cochrane Library, Issue 3, 2001. London: John Wiley & Sons Ltd.
429. Rowe BH, Spooner CH, Ducharme FM, Bretzlaff JA, Bota GW. Corticosteroids for preventing relapse following acute exacerbations of asthma (Cochrane Review). In: The Cochrane Library, Issue 3, 2001. London: John Wiley & Sons Ltd.
430. Manser R, Reid D, Abramson M. Corticosteroids for acute severe asthma in hospitalised patients (Cochrane Review). In: The Cochrane Library, Issue 3, 2001. London: John Wiley & Sons Ltd.
431. Hatton MQ, Vathenen AS, Allen MJ, Davies S, Cooke NJ. A comparison of ‚abruptly stopping' with ‚tailing off' oral corticosteroids in acute asthma. Respir Med 1995;89(2):101-4.
432. O'Driscoll BR, Kalra S, Wilson M, Pickering CA, Carroll KB, Woodcock AA. Double-blind trial of steroid tapering in acute asthma. Lancet 1993;341(8841):324-7.
433. Edmonds ML, Camargo CA, Saunders LD, Brenner BE, Rowe BH. Inhaled steroids in acute asthma following emergency department discharge (Cochrane Review). In: The Cochrane Library, Issue 3, 2001. London: John Wiley & Sons Ltd.
434. Lanes SF, Garrett JE, Wentworth CE 3rd, Fitzgerald JM, Karpel JP. The effect of adding ipratropium bromide to salbutamol in the treatment of acute asthma: a pooled analysis of three trials. Chest 1998;114(2):365-72.
435. Rodrigo G, Rodrigo C, Burschtin O. A meta-analysis of the effects of ipratropium bromide in adults with acute asthma. Am J Med 1999;107(4):363-70.
436. Stoodley RG, Aaron SD, Dales RE. The role of ipratropium bromide in the emergency management of acute asthma exacerbation: a metaanalysis of randomized clinical trials. Ann Emerg Med 1999;34(1):8-18.
437. Rowe BH, Bretzlaff JA, Bourdon C, Bota GW, Camargo CA Jr. Magnesium sulfate for treating exacerbations of acute asthma in the emergency department (Cochrane Review). In: The Cochrane Library, Issue 3, 2001. London: John Wiley & Sons Ltd.
438. Parameswaran K, Belda J, Rowe BH. Addition of intravenous aminophylline to beta2-agonists in adults with acute asthma (Cochrane Review). In: The Cochrane Library, Issue 3, 2001. London: John Wiley & Sons Ltd.
439. Graham VA, Milton AF, Knowles GK, Davies RJ. Routine antibiotics in hospital management of acute asthma. Lancet 1982;1(8269):418-20.
440. Kass JE, Terregino CA. The effect of heliox in acute severe asthma: a randomized controlled trial. Chest 1999;116(2):296-300.
441. Henderson SO, Acharya P, Kilaghbian T, Perez J, Korn CS, Chan LS. Use of heliox-driven nebulizer therapy in the treatment of acute asthma. Ann Emerg Med 1999;33(2):141-6.
442. Meduri GU, Cook TR, Turner RE, Cohen M, Leeper KV. Noninvasive positive pressure ventilation in status asthmaticus. Chest 1996;110(3):767-74.
443. Lim KL, Harrison BD. A criterion based audit of inpatient asthma care. Closing the feedback loop. J R Coll Physicians Lond 1992;26(1):71-5.
444. McFadden ER Jr, Elsanadi N, Dixon L, Takacs M, Deal EC, Boyd KK, et al. Protocol therapy for acute asthma: therapeutic benefits and cost savings. Am J Med 1995;99(6):651-61.
445. Goldberg R, Chan L, Haley P, Harmata-Booth J, Bass G. Critical pathway for the emergency department management of acute asthma: effect on resource utilization. Ann Emerg Med 1998;31(5):562-7.
446. Udwadia ZF, Harrison BD. An attempt to determine the optimal duration of hospital stay following a severe attack of asthma. J R Coll Physicians Lond 1990;24(2):112-4.
447. Pearson MG, Ryland I, Harrison BD. National audit of acute severe asthma in adults admitted to hospital. Standards of Care Committee, British Thoracic Society. Qual Health Care 1995;4(1):24-30.
448. Emerman CL, Woodruff PG, Cydulka RK, Gibbs MA, Pollack CV Jr, Camargo CA Jr. Prospective multicenter study of relapse following treatment for acute asthma among adults presenting to the emergency department. MARC investigators. Multicenter Asthma Research Collaboration. Chest 1999;115(4):919-27.
449. Cowie RI, Revitt SG, Underwood MF, Field SK. The effect of a peak flow-based action plan in the prevention of exacerbations of asthma. Chest 1997;112(6):1534-8.
450. Connett GJ, Lenney W. Use of pulse oximetry in the hospital management of acute asthma in childhood. Pediatr Pulmonol 1993;15(6):345-9.
451. Geelhoed GC, Landau LI, Le Seouf PN. Evaluation of SaO2 as a predictor of outcome in 280 children presenting with acute asthma. Ann Emerg Med 1994;23(6):1236-41.
452. Schuh S, Johnson D, Stephens D, Callahan S, Canny G. Hospitalization patterns in severe acute asthma in children. Pediatr Pulmonol 1997;23(3):184-92.
453. Wright RO, Santucci KA, Jay GD, Steele DW. Evaluation of pre- and posttreatment pulse oximetry in acute childhood asthma. Acad Emerg Med 1997;4(2):114-7.
454. Brooks LJ, Cloutier MM, Afshani E. Significance of roentgenographic abnormalities in children hospitalized for asthma. Chest 1982;82(3):315-8.
455. Gershel JC, Goldman HS, Stein RE, Shelov SP, Zirprkowski M. The usefulness of chest radiographs in first asthma attacks. N Engl J Med 1983;309(6):336-9.

456. McDowell KM, Chatburn RL, Myers TR, O'Riordan MA, Kercsmar CM. A cost-saving algorithm for children hospitalized for status asthmaticus. Arch Paediatr Adolesc Med 1998;152(10):977-84.
457. Schuh S, Parkin P, Rajan A, Canny G, Healy R, Rieder M, et al. High- versus low-dose, frequently administered, nebulised albuterol in children with severe, acute asthma. Pediatrics 1989;83(4):513-8.
458. Schuh S, Reider MJ, Canny G, Pender E, Forbes T, Tan YK, et al. Nebulized albuterol in acute childhood asthma: comparison of two doses. Pediatrics 1990;86(4):509-13.
459. Robertson CF, Smith F, Beck R, Levison H. Response to frequent low doses of nebulized salbutamol in acute asthma. J Pediatr 1985;106(4):672-4.
460. Schuh S, Johnson DW, Stephens D, Callahan S, Winders P, Canny GJ. Comparison of albuterol delivered by a metered dose inhaler with spacer versus a nebuliser in children with mild acute asthma. J Pediatr 1999;135(1):22-7.
461. Dewar AL, Stewart A, Cogswell JJ, Connett GJ. A randomised controlled trial to assess the relative benefits of large volume spacers and nebulisers to treat acute asthma in hospital. Arch Dis Child 1999;80(5):421-3.
462. Powell CV, Maskell GR, Marks MK, South M, Robertson CF. Successful implementation of spacer treatment guideline for acute asthma. Arch Dis Child 2001;84(2):142-6.
463. Khine H, Fuchs SM, Saville AL. Continuous vs intermittent nebulized albuterol for emergency management of asthma. Acad Emerg Med 1996;3(11):1019-24.
464. Papo MC, Frank J, Thompson AE. A prospective, randomized study of continuous versus intermittent nebulized albuterol for severe status asthmaticus in children. Crit Care Med 1993;21(10):1479-86.
465. Becker JM, Arora A, Scarfone RJ, Spector ND, Fontana-Penn ME, Gracely E, et al. Oral versus intravenous corticosteroids in children hospitalized with asthma. J Allergy Clin Immunol 1999;103(4):586-90.
466. Barnett PL, Caputo GL, Baskin M, Kuppermann N. Intravenous versus oral corticosteroids in the management of acute asthma in children. Ann Emerg Med 1997;29(2):212-7.
467. Langton Hewer S, Hobbs J, Reid F, Lenney W. Prednisolone in acute childhood asthma: clinical responses to three dosages. Respir Med 1998;92(3):541-6.
468. Edmonds ML, Camargo CA, Pollack CV, Rowe BH. Early use of inhaled corticosteroids in the emergency department treatment of acute asthma (Cochrane Review). In: The Cochrane Library, Issue 3, 2001. London: John Wiley & Sons Ltd.
469. McKean M, Ducharme F. Inhaled steroids for episodic viral wheeze of childhood (Cochrane Review). In: The Cochrane Library, Issue 3, 2001. London: John Wiley & Sons Ltd.
470. Schuh S, Reisman J, Alshehri M, Dupuis A, Corey M, Arseneault R, et al. A comparison of inhaled fluticasone and oral prednisone for children with severe acute asthma. N Engl J Med 2000;343(10):689-94.
471. Plotnick LH, Ducharme FM. Combined inhaled anticholinergic agents and beta-2-agonists for initial treatment of acute asthma in children (Cochrane Review). In: The Cochrane Library, Issue 3, 2001. London: John Wiley & Sons Ltd.
472. Goodman DC, Littenberg B, O'Connor GT, Brooks JG. Theophylline in acute childhood asthma: a meta-analysis of its efficacy. Pediatr Pulmonol 1996;21(4):211-8.
473. Yung M, South M. Randomised controlled trial of aminophylline for severe acute asthma. Arch Dis Child 1998;79(5):405-10.
474. Graham V, Lasserson T, Rowe BH. Antibiotics for acute asthma (Cochrane Review). In: The Cochrane Library, Issue 3, 2001. London: John Wiley & Sons Ltd.
475. Ciarallo L, Brousseau D, Reinert S. Higher-dose intravenous magnesium therapy for children with moderate to severe acute asthma. Arch Pediatr Adolesc Med 2000;154(10):979-83.
476. Stormon MO, Mellis CM, Van Asperen PP, Kilham HA. Outcome evaluation of early discharge of asthmatic children from hospital: a randomized control trial. J Qual Clin Pract 1999;19(3):149-54.
477. Fox GF, Marsh MJ, Milner AD. Treatment of recurrent acute wheezing episodes in infancy with oral salbutamol and prednisolone. Eur J Pediatr 1996;155(6):512-6.
478. LeSouef PN. Aerosol delivery to wheezy infants: a comparison between a nebulizer and two small volume spacers. Pediatr Pulmonol 1997;23(3):212-6.
479. Rubilar L, Castro-Rodriguez JA, Girardi G. Randomized trial of salbutamol via metered-dose inhaler with spacer versus nebulizer for acute wheezing in children less than 2 years of age. Pediatr Pulmonol 2000;29(4):264-9.
480. Daugbjerg P, Brenoe E, Forchhammer H, Frederiksen B, Glazowski MJ, Ibsen KK, et al. A comparison between nebulized terbutaline, nebulized corticosteroid and systemic corticosteroid for acute wheezing in children up to 18 months of age. Acta Paediatrica 1993;82(6-7):547-51.
481. Bentur L, Canny GJ, Shields MD, Kerem E, Schuh S, Reisman JJ, et al. Controlled trial of nebulized albuterol in children younger than 2 years of age with acute asthma. Pediatrics 1992;89(1):133-7.
482. Prahl P, Petersen NT, Hornsleth A. Beta 2-agonists for the treatment of wheezy bronchitis? Ann Allergy 1986;57(6):439-41.
483. Tal A, Levy N, Bearman JE. Methylprednisolone therapy for acute asthma in infants and toddlers: a controlled clinical trial. Pediatrics 1990;86(3):350-6.
484. Everard ML, Bara A, Kurian M, Elliott TM, Ducharme F. Anticholinergic drugs for wheeze in children under the age of two years (Cochrane Review). In: The Cochrane Library, Issue 3, 2001. London: John Wiley & Sons Ltd.
485. Chung KF, Godard P, Adelroth E, Ayres J, Barnes N, Barnes P, et al. Difficult/therapy-resistant asthma: The need for an integrated approach to define clinical phenotypes, evaluate risk factors, understand pathophysiology and find novel therapies. European Respiratory Journal 1999;13(5):1198-208.
486. Prys-Picard CO, Campbell SM, Ayres JG, Miles JF, Niven RM, Consensus on Difficult Asthma Consortium UK. Defining and investigating difficult asthma: developing quality indicators. Respiratory Medicine 2006;100(7):1254-61.
487. Bratton DL, Price M, Gavin L, Glenn K, Brenner M, Gelfand EW, et al. Impact of a multidisciplinary day program on disease and healthcare costs in children and adolescents with severe asthma: a two-year follow-up study. Pediatric Pulmonology 2001;31(3):177-89.
488. Robinson DS, Campbell DA, Durham SR, Pfeffer J, Barnes PJ, Chung KF, et al. Systematic assessment of difficult-to-treat asthma. European Respiratory Journal 2003;22(3):478-83.
489. Weinstein AG, McKee L, Stapleford J, Faust D. An economic evaluation of short-term inpatient rehabilitation for children with severe asthma. Journal of Allergy & Clinical Immunology. Vol. 1996;98(2):264-73.
490. Ranganathan SC, Payne DN, Jaffe A, McKenzie SA. Difficult asthma: defining the problems. Pediatr Pulmonol 2001;31(2):114-20.
491. Vamos M, Kolbe J. Psychological factors in severe chronic asthma. Aust N Z J Psychiatry. 1999;33(4):538-44.
492. Vila G, Nollet-Clemencon C, De Blic J, Mouren-Simeoni MC, Scheinmann P. Asthma severity and psychopathology in a tertiary care department for children and adolescent. Eur Child Adolesc Psychiatry. 1998;7(3):137-44.
493. Wainwright NWJ, Surtees PG, Wareham NJ, Harrison BDW. Psychosocial factors and incident asthma hospital admissions in the EPIC-Norfolk cohort study. Allergy. 2007;62(5):554-60.
494. Wamboldt MZ, Weintraub P, Krafchick D, Wamboldt FS. Psychiatric family history in adolescents with severe asthma. Journal of the American Academy of Child & Adolescent Psychiatry 1996;35(8):1042-9.
495. Miles JF, Garden GM, Tunnicliffe WS, Cayton RM, Ayres JG. Psychological morbidity and coping skills in patients with brittle and non-brittle asthma: a case-control study. Clinical & Experimental Allergy 1997;27(10):1151-9.
496. Ten Brinke A, Ouwerkerk ME, Bel EH, Spinhoven P. Similar psychological characteristics in mild and severe asthma. J Psychosom Res. 2001;50(1):7-10.
497. Wamboldt MZ, Fritz G, Mansell A, McQuaid EL, Klein RB. Relationship of asthma severity and psychological problems in children. J Amer Acad Child Adolescent Psychiatr 1998;37(9):943-50.
498. McQuaid EL, Kopel SJ, Nassau JH. Behavioral adjustment in children with asthma: A meta-analysis. J Dev Behav Pediatr. 2001;22(6):430-9.
499. Brown ES, Vigil L, Khan DA, Liggin JD, Carmody TJ, Rush AJ. A randomized trial of citalopram versus placebo in outpatients with asthma and major depressive disorder: a proof of concept study. Biological psychiatry 2005;58(11):865-70.
500. Godding V, Kruth M, Jamart J. Joint consultation for high-risk asthmatic children and their families, with pediatrician and child psychiatrist as co-therapists: model and evaluation. Family Process 1997;36(3):265-80.
501. Smith JR, Mildenhall S, Noble MJ, Shepstone L, Koutantji M, Mugford M, et al. The Coping with Asthma Study: a randomised controlled trial of a home based, nurse led psychoeducational intervention for adults at risk of adverse asthma outcomes. Thorax 2005;60(12):1003-11.
502. Smith JR, Mugford M, Holland R, Candy B, Noble MJ, Harrison BDW, et al. A systematic review to examine the impact of psycho-educational interventions on health outcomes and costs in adults and children with difficult asthma. Health Technology Assessment 2005;9(23):iii-iv,1-167.
503. Position statement. Environmental allergen avoidance in allergic asthma. Ad Hoc Working Group on Environmental Allergens and Asthma. J Allergy Clin Immunol 1999;103(2 Pt 1):203-5.
504. O'Driscoll BR, Hopkinson LC, Denning DW. Mold sensitization is common amongst patients with severe asthma requiring multiple hospital admissions. BMC Pulmonary Medicine 2005;5(4).
505. Zureik M, Neukirch C, Leynaert B, Liard R, Bousquet J, Neukirch F, et al. Sensitisation to airborne moulds and severity of asthma: cross sectional study from European Community respiratory health survey. BMJ 2002;325(7361):411-4.
506. Black PN, Udy AA, Brodie SM. Sensitivity to fungal allergens is a risk factor for life-threatening asthma. Allergy 2000;55(5):501-4.

507. O'Hollaren MT, Yunginger JW, Offord KP, Somers MJ, O'Connell EJ, Ballard DJ, et al. Exposure to an aeroallergen as a possible precipitating factor in respiratory arrest in young patients with asthma. N Engl J Med 1991;324(6):359-63.
508. Chlumsky J, Striz I, Terl M, Vondracek J. Strategy aimed at reduction of sputum eosinophils decreases exacerbation rate in patients with asthma. J Int Med Res 2006;34(2):129-39.
509. Fahy JV, Boushey HA, Lazarus SC, Mauger EA, Cherniack RM, Chinchilli VM, et al. Safety and reproducibility of sputum induction in asthmatic subjects in a multicenter study. Am J Respir Crit Care Med. 2001;163(6):1470-5.
510. Grootendorst DC, van den Bos JW, Romeijn JJ, Veselic-Charvat M, Duiverman EJ, Vrijlandt EJ, et al. Induced sputum in adolescents with severe stable asthma. Safety and the relationship of cell counts and eosinophil cationic protein to clinical severity. Eur Respir J 1999;13(3):647-53.
511. Loh LC, Kanabar V, D'Amato M, Barnes NC, O'Connor BJ. Sputum induction in corticosteroid-dependant asthmatics: risks and airway cellular profile. Asian Pacific Journal of Allergy & Immunology 2005;23(4):189-96.
512. Tarodo de la Fuente P, Romagnoli M, Carlsson L, Godard P, Bousquet J, Chanez P. Eosinophilic inflammation assessed by induced sputum in corticosteroid-dependent asthma. Respiratory Medicine. 1999;93(3):183-9.
513. Pijnenburg MW, Hofhuis W, Hop WC, De Jongste JC. Exhaled nitric oxide predicts asthma relapse in children with clinical asthma remission. Thorax 2005;60(3):215-8.
514. Shaw DE, Berry MA, Thomas M, Green RH, Brightling CE, Wardlaw AJ, Pavord ID. The use of exhaled nitric oxide to guide asthma management: A randomised controlled trial. Am J Respir Crit Care Med 2007;176:231-7
515. Schatz M, Harden K, Forsythe A, Chillingar L, Hoffman C, Sperling W, et al. The course of asthma during pregnancy, post partum, and with successive pregnancies: a prospective analysis. J Allergy Clin Immunol 1988;81(3):509-17.
516. Schatz M, Zeiger RS, Hoffman CP, Harden K, Forsythe A, Chilingar L, et al. Perinatal outcomes in the pregnancies of asthmatic women: a prospective controlled analysis. Am J Respir Crit Care Med 1995;151(4):1170-4.
517. Wendel PJ, Ramin SM, Barnett-Hamm C, Rowe TF, Cunningham FG. Asthma treatment in pregnancy: a randomized controlled study. Am J Obstet Gynecol 1996;175(1):150-4.
518. Juniper EF, Newhouse MT. Effect of pregnancy on asthma - a systematic review and meta-analysis. In: Schatz M, Zeiger RS, Claman HC, editors. Asthma and immunological diseases in pregnancy and early infancy. New York: Marcel Dekker; 1993. p.401-27.
519. Stenius-Aarniala BS, Hedman J, Terano KA. Acute asthma during pregnancy. Thorax 1996;51(4):411-4.
520. Stenius-Aarniala B, Piirila P, Teramo K. Asthma and pregnancy: a prospective study of 198 pregnancies. Thorax 1988;43(1):12-8.
521. Schatz M. Interrelationships between asthma and pregnancy: a literature review. J Allergy Clin Immunol 1999;103(2 Pt 2):S330-6.
522. Fitzsimons R, Greenberger PA, Patterson R. Outcome of pregnancy in women requiring corticosteroids for severe asthma. J Allergy Clin Immunol 1986;78(2):349-53.
523. Perlow JH, Montogomery D, Morgan MA, Towers CV, Porto M. Severity of asthma and perinatal outcome. Am J Obstet Gynecol 1992;167(4 Pt 4):964-7.
524. Schatz M, Zeiger RS, Hoffman CP. Intrauterine growth is related to gestational pulmonary function in pregnant asthmatic women. Kaiser-Permanente Asthma and Pregnancy Study Group. Chest 1990;98(2):389-92.
525. Demissie K, Breckenbridge MB, Rhoads GG. Infant and maternal outcomes in the pregnancies of asthmatic women. Am J Respir Crit Care Med 1998;158(4):1091-5.
526. Kallen B, Rydhstroem H, Aberg A. Asthma during pregnancy-a population based study. Eur J Epidemiol 2000;16(2):167-71.
527. Cydulka RK, Emerman CL, Schreiber D, Molander KH, Woodruff PG, Carmargo CA Jr. Acute asthma among pregnant women presenting to the emergency department. Am J Respir Crit Care Med 1999;160(3):887-92.
528. Department of Health. Why mothers die. Confidential enquiries into maternal deaths in the United Kingdom 1994-96. London: The Stationery Office; 1998. [cited 06 Mar 2008]. Available from url: http://www.archive.official-documents.co.uk/document/doh/wmd/wmd-hm.htm
529. Lewis G, editor. Why mothers die 1997-1999. The fifth report of the confidential enquiries into maternal deaths in the United Kingdom 1997-99. London: RCOG Press; 2001.
530. Schatz M, Zeiger RS, Harden K, Hoffman CC, Chilingar L, Petitti D. The safety of asthma and allergy medications during pregnancy. J Allergy Clin Immunol 1997;100(3):301-6.
531. Rayburn WF, Atkinson BD, Gilbert K, Turnbull GL. Short-term effects of inhaled albuterol on maternal and fetal circulations. Am J Obstet Gynecol 1994;171(3):770-3.
532. Schatz M, Zeiger RS, Harden KM, Hoffman CP, Forsythe AB, Chillingar LM, et al. The safety of inhaled beta-agonist bronchodilators during pregnancy. J Allergy Clin Immunol 1988;82(4):686-95.
533. Mann RD, Kubota K, Pearce G, Wilton L. Salmeterol: a study by prescription-event monitoring in a UK cohort of 15,407 patients. J Clin Epidemiol 1996;49(2):247-50.
534. Greenberger PA, Patterson R. Beclometasone diproprionate for severe asthma during pregnancy. Ann Intern Med 1983;98(4):478-80.
535. Dombrowski M, Thom E, McNellis D. Maternal-Fetal Medicine Units (MFMU) studies of inhaled corticosteroids during pregnancy. J Allergy Clin Immunol 1999;103(2 Pt 2):S356-9.
536. Dombrowski MP, Brown CL, Berry SM. Preliminary experience with triamcinolone acetonide in pregnancy. J Matern Fetal Med 1996;5(6):310-3.
537. Kallen B, Rydhstroem H, Aberg A. Congenital malformations after the use of inhaled budesonide in early pregnancy. Obstet Gynecol 1999;93(3):392-5.
538. Stenius-Aarniala B, Riikonen S, Teramo K. Slow-release theophylline in pregnant asthmatics. Chest 1995;107(3):642-7.
539. Schatz M. Asthma during pregnancy: interrelationships and management. Ann Allergy 1992;68(2):123-33.
540. Czeizel AE, Rockenbauer M. Population-based case-control study of teratogenic potential of corticosteroids. Teratology 1997;56(5):335-40.
541. Park-Wyllie L, Mazzotta P, Pastuszak A, Moretti ME, Beique L, Junnisett L, et al. Birth defects after maternal exposure to corticosteroids: prospective cohort study and meta-analysis of epidemiological studies. Teratology 2000;62(6):385-92.
542. Rodriguez-Pinilla E, Martinez-Frias ML. Corticosteroids during pregnancy and oral clefts: a case-control study. Teratology 1998;58(1):2-5.
543. The use of newer asthma and allergy medications during pregnancy. The American College of Obstetricians and Gynecologists (ACOG) and The Americal College of Allergy, Asthma and Immunology (ACAAI). Ann Allergy Asthma Immunol 2000;84(5):475-80.
544. Mabie WC, Barton JR, Wasserstrum N, Sibai BM. Clinical observations on asthma in pregnancy. J Matern Fetal Med 1992;1(1):45-50.
545. Lao TT, Huengsburg M. Labour and delivery in mothers with asthma. Eur J Obstet Gynecol Reprod Biol 1990;35(2-3):183-90.
546. Arad I, Landau H. Adrenocortical reserve of neonates born of long-term, steroid-treated mothers. Eur J Pediatr 1984;142(4):279-80.
547. Turner ES, Greenberger PA, Patterson R. Management of the pregnant asthmatic patient. Ann Intern Med 1980;93(6):905-18.
548. Ost L, Wettrell G, Bjorkhem I, Rane A. Prednisolone excretion in human milk. J Paediatr 1985;106(6):1008-11.
549. McKenzie SA, Selley JA, Agnew JE. Secretion of prednisolone into breast milk. Arch Dis Child 1975;50(11):894-6.
550. Greenberger PA, Odeh YK, Frederiksen MC, Atkinson AJ Jr. Pharmocokinetics of prednisolone transfer to breast milk. Clin Pharmacol Ther 1993;53(3):324-8.
551. Meredith S, Nordman H. Occupational asthma: measures of frequency from four countries. Thorax 1996;51(4):435-40.
552. Blanc PD, Toren K. How much adult asthma can be attributed to occupational factors? Am J Med 1999;107(6):580-7.
553. Balmes J, Becklake M, Blanc P, Henneberger P, Kreiss K, Mapp C, et al. American Thoracic Society Statement: Occupational contribution to the burden of airway disease. Am J Respir Crit Care Med 2003;167(5):787-97.
554. Ross DJ. Ten years of the SWORD project. Surveillance of Work-related and Occupational Respiratory Disease. Clin Exp Allergy 1999;29(6):750-3.
555. Hendrick DJ, Burge PS. Asthma. In: Hendrick DJ, Beckett W, Burge PS, Churg A, editors. Occupational disorders of the lung. Recognition, management and prevention. London: WB Saunders; 2002. p.33-76.
556. Banks DE, Wang ML. Occupational asthma: „the big picture". Occup Med 2000;15(2):335-58.
557. Ameille J, Pauli G, Calastreng-Crinquand A, Vervloet D, Iwatsubo Y, Popin E, et al. Reported incidence of occupational asthma in France, 1996-99: the ONAP programme. Occup Environ Med 2003;60(2):136-41.
558. Brhel P. Occupational respiratory diseases in the Czech Republic. Ind Health 2003;41(2):121-3.
559. Cortona G, Pisati G, Dellabianca A, Moscato G. Respiratory occupational allergies: the experience of the Hospital Operative Unit of Occupational Medicine in Lombardy from 1990 to 1998 [Italian]. G Ital Med Lav Ergon 2001;23(1):64-70.
560. Gannon PF, Burge PS. The SHIELD scheme in the West Midlands Region, United Kingdom. Midland Thoracic Society Research Group. Br J Ind Med 1993;50(9):791-6.
561. Hnizdo E, Esterhuizen TM, Rees D, Lalloo UG. Occupational asthma as identified by the Surveillance of Work-related and Occupational Respiratory Diseases programme in South Africa. Clin Exp Allergy 2001;31(1):32-9.

562. McDonald JC, Keynes HL, Meredith SK. Reported incidence of occupational asthma in the United Kingdom, 1989-97. Occup Environ Med 2000;57(12):823-9.
563. Meyer JD, Holt DL, Cherry NM, McDonald JC. SWORD ,98: surveillance of work-related and occupational respiratory disease in the UK. Occup Med (Oxf) 1999;49(8):485-9.
564. Sallie BA, Ross DJ, Meredith SK, McDonald JC. SWORD ,93. Surveillance of work-related and occupational respiratory disease in the UK. Occup Med (Oxf) 1994;44(4):177-82.
565. Toren K, Jarvholm B, Brisman J, Hagberg S, Hermansson BA, Lillienberg L. Adult-onset asthma and occupational exposures. Scand J Work Environ Health 1999;25(5):430-5.
566. Meredith SK, Taylor VM, McDonald JC. Occupational respiratory disease in the United Kingdom 1989: a report to the British Thoracic Society and the Society of Occupational Medicine by the SWORD project group. Br J Ind Med 1991;48(5):292-8.
567. Karjalainen A, Kurppa K, Martikainen R, Karjalainen J, Klaukka T. Exploration of asthma risk by occupation--extended analysis of an incidence study of the Finnish population. Scand J Work Environ & Health 2002;28(1):49-57.
568. Reijula K, Haahtela T, Klaukka T, Rantanen J. Incidence of occupational asthma and persistent asthma in young adults has increased in Finland. Chest 1996;110(1):58-61.
569. Jaakkola JJ, Piipari R, Jaakkola MS. Occupation and asthma: a population-based incident case-control study. Am J Epidemiol 2003;158(10):981-7.
570. Johnson AR, Dimich-Ward HD, Manfreda J, Becklake MR, Ernst P, Sears MR, et al. Occupational asthma in adults in six Canadian communities. Am J Respir Crit Care Med 2000;162(6):2058-62.
571. Kogevinas M, Anto JM, Soriano JB, Tobias A, Burney P. The risk of asthma attributable to occupational exposures. A population-based study in Spain. Spanish Group of the European Asthma Study. Am J Respir Crit Care Med 1996;154(1):137-43.
572. Kogevinas M, Anto JM, Sunyer J, Tobias A, Kromhout H, Burney P. Occupational asthma in Europe and other industrialised areas: a population-based study. European Community Respiratory Health Survey Study Group. Lancet 1999;353(9166):1750-4.
573. Lundh T, Stahlbom B, Akesson B. Dimethylethylamine in mould core manufacturing: exposure, metabolism, and biological monitoring. Br J Ind Med 1991;48(3):203-7.
574. Burge PS, Pantin CF, Newton DT, Gannon PF, Bright P, Belcher J, et al. Development of an expert system for the interpretation of serial peak expiratory flow measurements in the diagnosis of occupational asthma. Midlands Thoracic Society Research Group. Occup Environ Med 1999;56(11):758-64.
575. Bright P, Newton DT, Gannon PF, Pantin CF, Burge PS. OASYS-3: improved analysis of serial peak expiratory flow in suspected occupational asthma. Monaldi Arch Chest Dis 2001;56(3):281-8.
576. Burge PS. Occupational asthma in electronics workers caused by colophony fumes: follow-up of affected workers. Thorax 1982;37(5):348-53.
577. Cote J, Kennedy S, Chan-Yeung M. Sensitivity and specificity of PC20 and peak expiratory flow rate in cedar asthma. J Allergy Clin Immunol 1990;85(3):592-8.
578. Leroyer C, Perfetti L, Trudeau C, L'Archeveque J, Chan-Yeung M, Malo JL. Comparison of serial monitoring of peak expiratory flow and FEV1 in the diagnosis of occupational asthma. Am J Respir Crit Care Med 1998;158(3):827-32.
579. Liss GM, Tarlo SM. Peak expiratory flow rates in possible occupational asthma. Chest 1991;100(1):63-9.
580. Malo JL, Cote J, Cartier A, Boulet LP, L'Archeveque J, Chan-Yeung M. How many times per day should peak expiratory flow rates be assessed when investigating occupational asthma? Thorax 1993;48(12):1211-7.
581. Malo JL, Ghezzo H, L'Archeveque J, Lagier F, Perrin B, Cartier A. Is the clinical history a satisfactory means of diagnosing occupational asthma? Am Rev Respir Dis 1991;143(3):528-32.
582. Axon EJ, Beach JR, Burge PS. A comparison of some of the characteristics of patients with occupational and non-occupational asthma. Occup Med (Oxf) 1995;45(2):109-11.
583. Koskela H, Taivainen A, Tukiainen H, Chan HK. Inhalation challenge with bovine dander allergens: who needs it? Chest 2003;124(1):383-91.
584. Malo JL, Ghezzo H, L'Archeveque J, Lagier F, Perrin B, Cartier A. Is the clinical history a satisfactory means of diagnosing occupational asthma? Am Rev Respir Dis 1991;143(3):528-32.
585. Malo JL, Lemiere C, Desjardins A, Cartier A. Prevalence and intensity of rhinoconjunctivitis in subjects with occupational asthma. Eur Respir J 1997;10(7):1513-5.
586. Ricciardi L, Fedele R, Saitta S, Tigano V, Mazzeo L, Fogliani O, et al. Occupational asthma due to exposure to iroko wood dust. Ann Allergy Asthma Immunol 2003;91(4):393-7.
587. Vandenplas O, Binard-Van Cangh F, Brumagne A, Caroyer JM, Thimpont J, Sohy C, et al. Occupational asthma in symptomatic workers exposed to natural rubber latex: evaluation of diagnostic procedures. J Allergy Clin Immunol 2001;107(3):542-7.
588. Cote J, Kennedy S, Chan-Yeung M. Quantitative versus qualitative analysis of peak expiratory flow in occupational asthma. Thorax 1993;48(1):48-51.
589. Perrin B, Lagier F, L'Archeveque J, Cartier A, Boulet LP, Cote J, et al. Occupational asthma: validity of monitoring of peak expiratory flow rates and non-allergic bronchial responsiveness as compared to specific inhalation challenge. Eur Respir J 1992;5(1):40-8.
590. Baldwin DR, Gannon P, Bright P, Newton DT, Robertson A, Venables K, et al. Interpretation of occupational peak flow records: level of agreement between expert clinicians and Oasys-2. Thorax 2002;57(10):860-4.
591. Baur X, Huber H, Degens PO, Allmers H, Ammon J. Relation between occupational asthma case history, bronchial methacholine challenge, and specific challenge test in patients with suspected occupational asthma. Am J Ind Med 1998;33(2):114-22.
592. Anees W, Huggins V, Pavord ID, Robertson AS, Burge PS. Occupational asthma due to low molecular weight agents: eosinophilic and non-eosinophilic variants. Thorax 2002;57(3):231-6.
593. Brisman J, Lillienberg L, Belin L, Ahman M, Jarvholm B. Sensitisation to occupational allergens in bakers' asthma and rhinitis: a case-referent study. Int Arch Occup Environ Health 2003;76(2):167-70.
594. Cartier A, Grammer L, Malo JL, Lagier F, Ghezzo H, Harris K, et al. Specific serum antibodies against isocyanates: association with occupational asthma. J Allergy Clin Immunol 1989;84(4 Pt 1):507-14.
595. Hargreave FE, Ramsdale EH, Pugsley SO. Occupational asthma without bronchial hyperresponsiveness. Am Rev Respir Dis 1984;130(3):513-5.
596. Lemiere C, Cartier A, Malo JL, Lehrer SB. Persistent specific bronchial reactivity to occupational agents in workers with normal nonspecific bronchial reactivity. Am J Respir Crit Care Med 2000;162(3 Pt 1):976-80.
597. Lin FJ, Chen H, Chan-Yeung M. New method for an occupational dust challenge test. Occup Environ Med 1995;52(1):54-6.
598. Merget R, Schultze-Werninghaus G, Bode F, Bergmann EM, Zachgo W, Meier-Sydow J. Quantitative skin prick and bronchial provocation tests with platinum salt. Br J Ind Med 1991;48(12):830-7.
599. Merget R, Dierkes A, Rueckmann A, Bergmann EM, Schultze-Werninghaus G. Absence of relationship between degree of nonspecific and specific bronchial responsiveness in occupational asthma due to platinum salts. Eur Respir J 1996;9(2):211-6.
600. Moscato G, Dellabianca A, Vinci G, Candura SM, Bossi MC. Toluene diisocyanate-induced asthma: clinical findings and bronchial responsiveness studies in 113 exposed subjects with work-related respiratory symptoms. J Occup Med 1991;33(6):720-5.
601. Tarlo SM, Broder I. Outcome of assessments for occupational asthma. Chest 1991;100(2):329-35.
602. Vandenplas O, Delwiche JP, Evrard G, Aimont P, van der Brempt X, Jamart J, et al. Prevalence of occupational asthma due to latex among hospital personnel. Am J Respir Crit Care Med 1995;151(1):54-60.
603. Burge PS, O'Brien IM, Harries MG. Peak flow rate records in the diagnosis of occupational asthma due to colophony. Thorax 1979;34(3):308-16.
604. Burge PS, O'Brien IM, Harries MG. Peak flow rate records in the diagnosis of occupational asthma due to isocyanates. Thorax 1979;34(3):317-23.
605. Chan-Yeung M, Lam S, Koener S. Clinical features and natural history of occupational asthma due to western red cedar (Thuja plicata). Am J Med 1982;72(3):411-5.
606. Merget R, Schulte A, Gebler A, Breitstadt R, Kulzer R, Berndt ED, et al. Outcome of occupational asthma due to platinum salts after transferral to low-exposure areas. Int Arch Occup Environ Health 1999;72(1):33-9.
607. Moscato G, Dellabianca A, Perfetti L, Brame B, Galdi E, Niniano R, et al. Occupational asthma: a longitudinal study on the clinical and socioeconomic outcome after diagnosis. Chest 1999;115(1):249-56.
608. Pisati G, Baruffini A, Zedda S. Toluene diisocyanate induced asthma: outcome according to persistence or cessation of exposure. Br J Ind Med 1993;50(1):60-4.
609. Rosenberg N, Garnier R, Rousselin X, Mertz R, Gervais P. Clinical and socio-professional fate of isocyanate-induced asthma. Clin Allergy 1987;17(1):55-61.
610. Tarlo SM, Banks D, Liss G, Broder I. Outcome determinants for isocyanate induced occupational asthma among compensation claimants. Occup Environ Med 1997;54(10):756-61.
611. Valentino M, Pizzichini MA, Monaco F, Governa M. Latex-induced asthma in four healthcare workers in a regional hospital. Occup Med (Oxf) 1994;44(3):161-4.
612. Valentino M, Rapisarda V. Course of isocyanate-induced asthma in relation to exposure cessation: longitudinal study of 50 subjects [Italian]. G Ital Med Lav Ergon 2002;24(1):26-31.

613. Vandenplas O, Delwiche JP, Depelchin S, Sibille Y, Vande Weyer R, Delaunois L. Latex gloves with a lower protein content reduce bronchial reactions in subjects with occupational asthma caused by latex. Am J Respir Crit Care Med 1995;151(3 Pt 1):887-91.
614. Chan-Yeung M, MacLean L, Paggiaro PL. Follow-up study of 232 patients with occupational asthma caused by western red cedar (Thuja plicata). J Allergy Clin Immunol 1987;79(5):792-6.
615. Malo JL, Cartier A, Ghezzo H, Lafrance M, McCants M, Lehrer SB. Patterns of improvement in spirometry, bronchial hyperresponsiveness, and specific IgE antibody levels after cessation of exposure in occupational asthma caused by snow-crab processing. Am Rev Respir Dis 1988;138(4):807-12.
616. Gannon PF, Weir DC, Robertson AS, Burge PS. Health, employment, and financial outcomes in workers with occupational asthma. Brit J Ind Med 1993;50(6):491-6.
617. Cannon J, Cullinan P, Newman Taylor A. Consequences of occupational asthma. BMJ 1995;311(7005):602-3.
618. Larbanois A, Jamart J, Delwiche JP, Vandenplas O. Socioeconomic outcome of subjects experiencing asthma symptoms at work. Eur Respir J 2002;19(6):1107-13.
619. Ross DJ, McDonald JC. Health and employment after a diagnosis of occupational asthma: a descriptive study. Occup Med (Oxf) 1998;48(4):219-25.
620. Ameille J, Pairon JC, Bayeux MC, Brochard P, Choudat D, Conso F, et al. Consequences of occupational asthma on employment and financial status: a follow-up study. Eur Respir J 1997;10(1):55-8.
621. Gannon PF, Weir DC, Robertson AS, Burge PS. Health, employment, and financial outcomes in workers with occupational asthma. Br J Ind Med 1993;50(6):491-6.
622. Marabini A, Dimich-Ward H, Kwan SY, Kennedy SM, Waxler-Morrison N, Chan-Yeung M. Clinical and socioeconomic features of subjects with red cedar asthma. A follow-up study. Chest 1993;104(3):821-4.
623. Vandenplas O, Jamart J, Delwiche JP, Evrard G, Larbanois A. Occupational asthma caused by natural rubber latex: outcome according to cessation or reduction of exposure. J Allergy Clin Immunol 2002;109(1):125-30.
624. Venables KM, Davison AG, Newman Taylor AJ. Consequences of occupational asthma. Respir Med 1989;83(5):437-40.
625. Clark NM, Gong M, Schork MA, Evans D, Roloff D, Hurwitz M, et al. Impact of education for physicians on patient outcomes. Pediatrics 1998;101(5):831-6.
626. Feder G, Griffiths C, Highton C, Eldridge S, Spena M, Southgate L. Do clinical guidelines introduced with practice based education improve care of asthmatic and diabetic patients? A randomised controlled trial in general practitioners in east London. BMJ 1995;311(7018):1473-8.
627. Battleman DS, Callahan MA, Silber S, Munoz CI, Santiago L, Abularrage J, et al. Dedicated asthma center improves the quality of care and resource utilization for pediatric asthma: a multicenter study. Academic Emergency Medicine. 2001;8(7):709-15.
628. Premaratne UN, Sterne JA, Marks GB, Webb JR, Azima H, Burney PG. Clustered randomised trial of an intervention to improve the management of asthma: Greenwich asthma study. BMJ 1999;318(7193):1251-5.
629. Charlton I, Charlton G, Broomfield J, Mullee MA. Audit of the effect of a nurse run asthma clinic on workload and patient morbidity in a general practice. Br J Gen Pract 1991;41(347):227-31.
630. Hoskins G, Neville RG, Smith B, Clark RA. Focus on asthma. The link between nurse training and asthma outcomes. Br J Comm Nursing 1999;4(5):222-8.
631. Heard AR, Richards IJ, Alpers JH, Pilotto LS, Smith BJ, Black JA. Randomised controlled trial of general practice based asthma clinics. Med J Aust 1999;171(2):68-71.
632. Bryce FP, Neville RG, Crombie IK, Clark RA, McKenzie P. Controlled trial of an audit facilitator in diagnosis and treatment of childhood asthma in general practice. BMJ 1995;310(6983):838-42.
633. Dickinson J, Hutton S, Atkin A, Jones K. Reducing asthma morbidity in the community: the effect of a targeted nurse-run asthma clinic in an English general practice. Respir Med 1997;91(10):634-40.
634. Lindberg M, Ahlner J, Moller M, Ekstrom T. Asthma nurse practice - a resource-effective approach in asthma management. Respir Med 1999;93(8):584-8.
635. Sondergaard J, Andersen M, Vach K, Kragstrup J, Maclure M, Gram LF. Detailed postal feedback about prescribing to asthma patients combined with a guideline statement showed no impact: a randomised controlled trial. European Journal of Clinical Pharmacology. 2002;58(2):127-32.
636. Pinnock H, Bawden R, Proctor S, Wolfe S, Scullion J, Price D, et al. Accessibility, acceptability, and effectiveness in primary care of routine telephone review of asthma: pragmatic, randomised controlled trial. BMJ 2003;326(7387):477-9.
637. Smeele IJ, Grol RP, van Schayck CP, van den Bosch WJ, van den Hoogen HJ, Muris JW. Can small group education and peer review improve care for patients with asthma/chronic obstructive pulmonary disease? Qual Health Care 1999;8(2):92-8.
638. Paterson C, Britten N. Organising primary health care for people with asthma: the patient's perspective. Br J Gen Pract. 2000;50(453):299-303.
639. Barnes G, Partridge MR. Community asthma clinics: 1993 survey of primary care by the National Asthma Task Force. Qual Health Care 1994;3(3):133-6.
640. Ng TP. Validity of symptom and clinical measures of asthma severity for primary outpatient assessment of adult asthma. Br J Gen Pract 2000;50(450):7-12.
641. Gibson PG, Wilson AJ. The use of continuous quality improvement methods to implement practice guidelines in asthma. J Qual Clin Pract 1996;16(2):87-102.
642. Neville RG, Hoskins G, Smith B, Clark RA. Observations on the structure, process and clinical outcomes of asthma care in general practice. Br J Gen Pract 1996;46(411):583-7.
643. Eccles M, McColl E, Steen N, Rousseau N, Grimshaw J, Parkin D, et al. Effect of computerised evidence based guidelines on management of asthma and angina in adults in primary care: cluster randomised controlled trial. BMJ. 2002;325(7370):941.
644. Neville R. Two approaches to effective asthma audit. Practitioner 1995;239(1548):203-5.
645. Jones K, Cleary R, Hyland M. Predictive value of a simple asthma morbidity index in a general practice population. Br J Gen Pract 1999;49(438):23-6.
646. Worral G, Chaulk P, Freake D. The effects of clinical practice guidelines on patient outcomes in primary care: a systematic review. Canadian Medical Association Journal 1997;156(12):1705-12.
647. Effectiveness of routine self monitoring of peak flow in patients with asthma. Grampian Asthma Study of Integrated Care (GRASSIC). BMJ 1994;308(6928):564-7.
648. Bernsten C, Bjorkman I, Caramona M, Crealey G, Frokjaer B, Grundberger E, et al. Integrated care for asthma: a clinical, social, and economic evaluation. Grampian Asthma Study of Integrated Care (GRASSIC). BMJ 1994;308(6928):559-64.
649. Osman LM, Abdalla MI, Russell IT, Fiddes J, Friend JA, Legge JS, et al. Integrated care for asthma: matching care to the patient. Eur Respir J 1996;9(3):444-8.
650. Buckingham K, Drummond N, Cameron I, Meldrum P, Douglas G. Costing shared care. Health Serv Manage 1994;90(2):22-5.
651. Bernsten C, Bjorkman I, Caramona M, Crealey G, Frokjaer B, Grundberger E, et al. Improving the well-being of elderly patients via community pharmacy-based provision of pharmaceutical care: a multicentre study in seven European countries. Drugs & Aging 2001;18(1):63-77.
652. Schulz M, Verheyen F, Muhlig S, Muller JM, Muhlbauer K, Knop-Schneickert E, et al. Pharmaceutical care services for asthma patients: a controlled intervention study. Journal of Clinical Pharmacology. 2001;41(6):668-76.
653. Cordina M, McElnay JC, Hughes CM. Assessment of a community pharmacy-based program for patients with asthma. Pharmacotherapy. 2001;21(10):1196-203.
654. Burr ML, Verrall C, Kaur B. Social deprivation and asthma. Respir Med 1997;91(10):603-8.
655. Rona RJ. Asthma and poverty. Thorax 2000;55(3):239-44.
656. Carey OJ, Cookson JB, Britton J, Tattersfield AE. The effect of lifestyle on wheeze, atopy, and bronchial hyperreactivity in Asian and white children. Am J Respir Crit Care Med 1996;154(2 Pt 1):537-40.
657. Mielck A, Reitmeir P, Wjst M. Severity of childhood asthma by socioeconomic status. Int J Epidemiol 1996;25(2):388-93.
658. Griffiths C, Kaur G, Gantley M, Feder G, Hillier S, Goddard J, et al. Influences on hospital admission for asthma in south Asian and white adults: qualitative interview study. BMJ 2001;323(7319):962-6.
659. Evans D, Mellins R, Lobach K, Ramos-Bonoan C, Pinkett-Heller M, Wiesemann S, et al. Improving care for minority children with asthma: professional education in public health clinics. Pediatrics 1997;99(2):157-64.
660. Higgins BG, Britton JR. Geographical and social class effects on asthma mortality in England and Wales. Respir Med 1995;89(5):341-6.
661. Mowat DHR, McCowan C, Neville RG, Crombie IK, Thomas G, Ricketts IW, et al. Socio-economic status and childhood asthma. Asthma Gen Pract 1998;6(1):9-11.
662. Partridge MR. In what way may race, ethnicity or culture influence asthma outcomes? Thorax 2000;55(3):175-6.
663. Williams MV, Baker DW, Honig EG, Lee TM, Nowlan A. Inadequate literacy is a barrier to asthma knowledge and self-care. Chest 1999;114(4):1008-15.
664. Griffiths C, Naish J, Sturdy P, Pereira F. Prescribing and hospital admissions for asthma in east London. BMJ 1996;312(7029):481-2.
665. Gibson PG, Henry RL, Vimpani GV, Halliday J. Asthma knowledge, attitudes, and quality of life in adolescents. Arch Dis Child 1995;73(4):321-6.
666. Neville RG, McCowan C, Hoskins G, Thomas G. Cross-sectional observations on the natural history of asthma. Br J Gen Pract 2001;51(466):361-5.
667. Dyer CA, Hill SL, Stockley RA, Sinclair AJ. Quality of life in elderly subjects with a diagnostic label of asthma from general practice registers. Eur Respir J 1999;14(1):39-45.

668. Enright PL, McClelland RL, Newman AB, Gottlieb DJ, Lebowitz MD. Underdiagnosis and undertreatment of asthma in the elderly. Cardiovascular Health Study Research Group. Chest 1999;116(3):603-13.
669. Bucknall CE, Robertson C, Moran F, Stevenson RD. Management of asthma in hospital: a prospective audit. Br Med J (Clin Res Ed) 1988;296(6637):1637-9.
670. Vollmer WM, O'Hollaren M, Ettinger KM, Stibolt T, Wilkins J, Buist AS, et al. Specialty differences in the management of asthma. A cross-sectional assessment of allergists' patients and generalists' patients in a large HMO. Arch Intern Med 1997;157(11):1201-8.
671. Grant C, Nicholas R, Moore L, Salisbury C. An observational study comparing quality of care in walk-in centres with general practice and NHS Direct using standardised patients. BMJ 2002;324(7353):1556.
672. Pearson MG, Ryland I, Harrison BD. Comparison of the process of care of acute severe asthma in adults admitted to hospital before and 1yr after the publication of national guidelines. Respir Med 1996;90(9):539-45.
673. Beasley R, Miles J, Fishwick D, Leslie H. Management of asthma in the hospital emergency department. Br J Hosp Med 1996;55(5):253-7.
674. Neville RG, Clark RC, Hoskins G, Smith B. National asthma attack audit 1991-2. General Practitioners in Asthma Group. BMJ 1993;306(6877):559-62.
675. Neville RG, Hoskins G, Smith B, Clark RA. How general practitioners manage acute asthma attacks. Thorax 1997;52(2):153-6.
676. McDermott MF, Murphy DG, Zalenski RJ, Rydman RJ, McCarren M, Marder D, et al. A comparison between emergency diagnostic and treatment unit and inpatient care in the management of acute asthma. Arch Intern Med 1997;157(18):2055-62.
677. Crompton GK, Grant IW. Edinburgh emergency asthma admission service. BMJ 1975;4(5998):680-2.
678. Madge P, McColl J, Paton J. Impact of a nurse-led home management training programme in children admitted to hospital with acute asthma: a randomised controlled study. Thorax 1997;52(3):223-8.
679. Wesseldine LJ, McCarthy P, Silverman M. Structured discharge procedure for children admitted to hospital with acute asthma: a randomised controlled trial of nursing practice. Arch Dis Child 1999;80(2):110-4.
680. Levy ML, Robb M, Allen J, Doherty C, Bland JM, Winter RJ. A randomized controlled evaluation of specialist nurse education following accident and emergency department attendance for acute asthma. Respir Med 2000;94(9):900-8.
681. Smith E, Alexander V, Booker C, McCowan C, Ogston S, Mukhopadhyay S. Effect of hospital asthma nurse appointment on inpatient asthma care. Respir Med 2000;94(1):82-6.
682. Osman LM, Calder C, Godden DJ, Friend JA, McKenzie L, Legge JS, et al. A randomised trial of self-management planning for adult patients admitted to hospital with acute asthma. Thorax. 2002;57(10):869-74.
683. Stevens CA, Wesseldine LJ, Couriel JM, Dyer AJ, Osman LM, Silverman M. Parental education and guided self-management of asthma and wheezing in the pre-school child: a randomised controlled trial.[comment]. Thorax. 2002;57(1):39-44.
684. Baren JM, Shofer FS, Ivey B, Reinhard S, DeGeus J, Stahmer SA, et al. A randomized, controlled trial of a simple emergency department intervention to improve the rate of primary care follow-up for patients with acute asthma exacerbations. Annals of Emergency.Medicine. 2001;38(2):115-22.
685. Sin DD, Bell NR, Svenson LW, Man SF. The impact of follow-up physician visits on emergency readmissions for patients with asthma and chronic obstructive pulmonary disease: a population-based study. Am J Med. 2002;112(2):120-5.
686. Boudreaux ED, Clark S, Camargo CA Jr. Telephone follow-up after the emergency department visit: experience with acute asthma. Ann Emerg Med 2000;35(6):555-63.
687. O'Brien MA, Rogers S, Jamtvedt G, Oxman AD, Odgaard-Jensen J, Kristoffersen DT, et al. Educational outreach visits: effects on professional practice and health care outcomes (Cochrane Review). In: The Cochrane Library, Issue 1, 2003. London: John Wiley & Sons Ltd.
688. Pharmacological management of asthma. Evidence table: Audit and asthma. Edinburgh: SIGN; 2002. Available from url: http://www.sign.ac.uk/guidelines/published/support/guideline63/index.html
689. Bart and the London School for Medicine and Dentistry. Centre for Health Sciences. Clinical Effectiveness Group. . Available from http://www.ihse.qmul.ac.uk/chs/nhs/ceg/index.html: [Accessed. 6 March. 2008.]
690. Cote J, Bowie DM, Robichaud P, Parent JG, Battisti L, Boulet LP. Evaluation of two different educational interventions for adult patients consulting with an acute asthma exacerbation. Am J Respir Crit Care Med 2001;163(6):1415-9.
691. Cote J, Cartier A, Robichaud P, Boutin H, Malo JL, Rouleau M, et al. Influence of asthma education on asthma severity, quality of life and environmental control. Can Respir J 2000;7(5):395-400.
692. Gallefoss F, Bakke PS. Impact of patient education and self-management on morbidity in asthmatics and patients with chronic obstructive pulmonary disease. Respir Med 2000;94(3):279-87.
693. Gallefoss F, Bakke PS, Rsgaard PK. Quality of life assessment after patient education in a randomized controlled study on asthma and chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1999;159(3):812-7.
694. George MR, O'Dowd LC, Martin I, Lindell KO, Whitney F, Jones M, et al. A comprehensive educational program improves clinical outcome measures in inner-city patients with asthma. Arch Intern Med 1999;159(15):1710-6.
695. Ghosh CS, Ravindran P, Josh M, Stearns SC. Reductions in hospital use from self-management training for chronic asthmatics. Soc Sci Med 1998;46(8):1087-93.
696. Ignacio-Garcia JM, Gonzalez-Santos P. Asthma self-management education program by home monitoring of peak expiratory flow. Am J Respir Crit Care Med 1995;151(2 Pt 1):353-9.
697. Lahdensuo A, Haahtela T, Herrala J, Kava T, Kiviranta K, Kuusisto P, et al. Randomised comparison of guided self management and traditional treatment of asthma over one year. BMJ 1996;312(7033):748-52.
698. Moudgil H, Marshall T, Honeybourne D. Asthma education and quality of life in the community: a randomised controlled study to evaluate the impact on white European and Indian subcontinent ethnic groups from socioeconomically deprived areas in Birmingham, UK. Thorax 2000;55(3):177-83.
699. Cicutto L, Murphy S, Coutts D, O'Rourke J, Lang G, Chapman C, et al. Breaking the access barrier: Evaluating an asthma center's efforts to provide education to children with asthma in schools. Chest 2005;128(4):1928-35.
700. Guendelman S, Meade K, Benson M, Chen YQ, Samuels S. Improving asthma outcomes and self-management behaviors of inner-city children: a randomized trial of the Health Buddy interactive device and an asthma diary.[comment]. Archives of Pediatrics & Adolescent Medicine. 2002;156(2):114-20.
701. Shah S, Peat JK, Mazurski EJ, Wang H, Sindhusake D, Bruce C, et al. Effect of peer led programme for asthma education in adolescents: cluster randomised controlled trial.[comment]. BMJ. 2001;322(7286):583-5.
702. Thoonen BP, Schermer TR, Van den BG, Molema J, Folgering H, Akkermans RP, et al. Self-management of asthma in general practice, asthma control and quality of life: a randomised controlled trial. Thorax. 2003;58(1):30-6.
703. Wolf FM, Guevara JP, Grum CM, Clark NM, Cates CJ. Educational interventions for asthma in children (Cochrane Review). In: The Cochrane Library, Issue 1, 2003. London: John Wiley & Sons Ltd.
704. Greineder DK, Loane KC, Parks P. A randomized controlled trial of a pediatric asthma outreach program. J Allergy Clin Immunol 1999;103(3 Pt 1):436-40.
705. Griffiths C, Foster G, Barnes N, Eldridge S, Tate H, Begum S, et al. Specialist nurse intervention to reduce unscheduled asthma care in a deprived multiethnic area: the east London randomised controlled trial for high risk asthma (ELECTRA). BMJ 2004;328(7432):144.
706. Guendelman S, Meade K, Chen YQ, Benson M. Asthma control and hospitalizations among inner-city children: Results of a randomized trial. Telemedicine Journal & E Health 2004;10(2):235-44.
707. Liu C, Feekery C. Can asthma education improve clinical outcomes? An evaluation of a pediatric asthma education program. J Asthma 2001;38(3):269-78.
708. Magar Y, Vervloet D, Steenhouwer F, Smaga S, Mechin H, Rocca Serra JP, et al. Assessment of a therapeutic education programme for asthma patients: „un souffle nouveau". Patient Education & Counseling 2005;58(1):41-6.
709. Shames RS, Sharek P, Mayer M, Robinson TN, Hoyte EG, Gonzalez-Hensley F, et al. Effectiveness of a multicomponent self-management program in at-risk, school-aged children with asthma. Annals of Allergy, Asthma, & Immunology. 2004;92(6):611-8.
710. Urek MC, Tudoric N, Plavec D, Urek R, Koprivc-Milenovic T, Stojic M. Effect of educational programs on asthma control and quality of life in adult asthma patients. Patient Education & Counseling 2005;58(1):47-54.
711. Osman LM, Abdalla MI, Beattie JA, Ross SJ, Russell IT, Friend JA, et al. Reducing hospital admission through computer supported education for asthma patients. BMJ 1994;308(6928):568-71.
712. Yoon R, McKenzie DK, Bauman A, Miles DA. Controlled trial evaluation of an asthma education programme for adults. Thorax 1993;48(11):1110-6.
713. Allen RM, Jones MP, Oldenburg B. Randomised trial of an asthma self-management programme for adults. Thorax 1995;50(7):731-8.
714. Bartholomew LK, Gold RS, Parcel GS, Czyzewski DI, Sockrider MM, Fernandez M, et al. Watch, Discover, Think, and Act: evaluation of computer-assisted instruction to improve asthma self-management in inner-city children. Patient Educ Couns 2000;39(2-3):269-80.
715. Charlton I, Antoniou AG, Atkinson J, Campbell MJ, Chapman E, Mackintosh T, et al. Asthma at the interface: bridging the gap between general practice and a district general hospital. Arch Dis Child 1994;70(4):313-8.

716. Clark NM, Feldman CH, Evans D, Levison MJ, Wasilewski Y, Mellins RB. The impact of health education on frequency and cost of health care use by low income children with asthma. J Allergy Clin Immunol 1986;78(1 Pt 1):108-15.
717. Cote J, Cartier A, Robichaud P, Boutin H, Malo JL, Rouleau M, et al. Influence on asthma morbidity of asthma education programs based on self-management plans following treatment optimization. Am J Respir Crit Care Med 1997;155(5):1509-14.
718. Couturaud F, Proust A, Frachon I, Dewitte JD, Oger E, Quiot JJ, et al. Education and self-management: a one-year randomized trial in stable adult asthmatic patients. J Asthma. 2002;39(6):493-500.
719. Cowie RL, Underwood MF, Little CB, Mitchell I, Spier S, Ford GT. Asthma in adolescents: a randomized, controlled trial of an asthma program for adolescents and young adults with severe asthma. Canadian Respiratory Journal. 2002;9(4):253-9.
720. Dolinar RM, Kumar V, Coutu-Wakulczyk G, Rowe BH. Pilot study of a home-based asthma health education program. Patient Educ Couns 2000;40(1):93-102.
721. Kauppinen R, Vilkka V, Sintonen H, Klaukka T, Tukiainen H. Long-term economic evaluation of intensive patient education during the first treatment year in newly diagnosed adult asthma. Respiratory Medicine. 2001;95(1):56-63.
722. Klein JJ, van der PJ, Uil SM, Zielhuis GA, Seydel ER, van Herwaarden CL. Benefit from the inclusion of self-treatment guidelines to a self-management programme for adults with asthma. European Respiratory Journal. 2001;17(3):386-94.
723. Marabini A, Brugnami G, Curradi F, Casciola G, Stopponi R, Pettinari L, et al. Short-term effectiveness of an asthma educational program: results of a randomized controlled trial. Respiratory Medicine. 2002;96(12):993-8.
724. Morice AH, Wrench C. The role of the asthma nurse in treatment compliance and self-management following hospital admission. Respiratory Medicine. 2001;95(11):851-6.
725. Perneger TV, Sudre P, Muntner P, Uldry C, Courteheuse C, Naef AF, et al. Effect of patient education on self-management skills and health status in patients with asthma: a randomized trial. American Journal of Medicine. 2002;113(1):7-14.
726. van der Palen J, Klein JJ, Zielhuis GA, van Herwaarden CL, Seydel ER. Behavioural effect of self-treatment guidelines in a self-management program for adults with asthma. Patient Educ Couns 2001;43(2):161-9.
727. Wilson SR, Scamagas P, German DF, Hughes GW, Lulla S, Coss S, et al. A controlled trial of two forms of self-management education for adults with asthma. Am J Med 1993;94(6):564-76.
728. Lefevre F, Piper M, Weiss K, Mark D, Clark N, Aronson N. Do written action plans improve patient outcomes in asthma? An evidence-based analysis. J Fam Pract. 2002;51(10):842-48.
729. Sudre P, Jacquemet S, Uldry C, Perneger TV. Objectives, methods and content of patient education programmes for adults with asthma: systematic review of studies published between 1979 and 1998. Thorax 1999;54(8):681-7.
730. Gibson PG, Powell H. Written action plans for asthma: an evidence-based review of the key components. Thorax 2004;59(2):94-9.
731. Toelle BG, Ram FS. Written individualised management plans for asthma in children and adults (Cochrane Review). In: The Cochrane Library, Issue 2, 2004. London: John Wiley & Sons Ltd.
732. Adams RJ, Boath K, Homan S, Campbell DA, Ruffin RE. A randomized trial of peak-flow and symptom-based action plans in adults with moderate-to-severe asthma. Respirology. 2001;6(4):297-304.
733. Ayres JG, Campbell LM. A controlled assessment of an asthma self-management plan involving a budesonide dose regimen. OPTIONS Research Group. Eur Respir J 1996;9(5):886-92.
734. Charlton I, Charlton G, Broomfield J, Mullee MA. Evaluation of peak flow and symptoms only self management plans for control of asthma in general practice. BMJ 1990;301(6765):1355-9.
735. Yoos HL, Kitzman H, McMullen A, Henderson C, Sidora K. Symptom monitoring in childhood asthma: a randomized clinical trial comparing peak expiratory flow rate with symptom monitoring. Annals of Allergy, Asthma, & Immunology. 2002;88(3):283-91.
736. Brown JV, Bakeman R, Celano MP, Demi AS, Kobrynski L, Wilson SR. Home-based asthma education of young low-income children and their families. J Pediatr Psychol. 2002;27(8):677-88.
737. Colland VT. Learning to cope with asthma: a behavioural self-management program for children. Patient Educ Couns 1993;22(3):141-52.
738. Wilson SR, Latini D, Starr NJ, Fish L, Loes LM, Page A, et al. Education of parents of infants and very young children with asthma: a developmental evaluation of the Wee Wheezers program. J Asthma 1996;33(4):239-54.
739. Ronchetti R, Indinnimeo L, Bonci E, Corrias A, Evans D, Hindi-Alexander M, et al. Asthma self-management programmes in a population of Italian children: a multicentric study. Italian Study Group on Asthma Self-Management Programmes. Eur Respir J 1997;10(6):1248-53.
740. Bailey WC, Kohler CL, Richards JM Jr, Windsor RA, Brooks CM, Gerald LB, et al. Asthma self-management: do patient education programs always have an impact? Arch Intern Med 1999;159(20):2422-8.
741. Glasgow NJ, Ponsonby AL, Yates R, Beilby J, Dugdale P. Proactive asthma care in childhood: general practice based randomised controlled trial. BMJ 2003;327(7416):659.
742. Homer C, Susskind O, Alpert HR, Owusu M, Schneider L, Rappaport LA, et al. An evaluation of an innovative multimedia educational software program for asthma management: report of a randomized, controlled trial. Pediatrics 2000;106(1 Pt 2):210-5.
743. Rubin DH, Leventhal JM, Sadock RT, Letovsky E, Schottland P, Clemente I, et al. Educational intervention by computer in childhood asthma: a randomized clinical trial testing the use of a new teaching intervention in childhood asthma. Pediatrics 1986;77(1):1-10.
744. van Es SM, Nagelkerke AF, Colland VT, Scholten RJ, Bouter LM. An intervention programme using the ASE-model aimed at enhancing adherence in adolescents with asthma. Patient Educ Couns. 2001;44(3):193-203.
745. Haby MM, Waters E, Roberston CF, Gibson PG, Ducharme FM. Interventions for educating children who have attended the emergency room for asthma (Cochrane Review). In: The Cochrane Library, Issue 3, 2001. London: John Wiley & Sons Ltd.
746. Klinnert MD, Liu AH, Pearson MR, Ellison MC, Budhiraja N, Robinson JL. Short-term impact of a randomized multifaceted intervention for wheezing infants in low-income families. Archives of Pediatrics & Adolescent Medicine 2005;159(1):75-82.
747. Royal Pharmaceutical Society of Great Britain. From compliance to concordance: achieving shared goals in medicine taking. London: The Society; 1997.
748. Hand CH, Bradley C. Health beliefs of adults with asthma: toward an understanding of the difference between symptomatic and preventive use of inhaler treatment. J Asthma 1996;33(5):331-8.
749. Byer B, Myers, LB. Psychological correlates of adherence to medication in asthma. Psychol Health Med 2000;5(4):389-93.
750. Garrett J, Fenwick JM, Taylor G, Mitchell E, Rea H. Peak expiratory flow meters (PEFMs)--who uses them and how and does education affect the pattern of utilisation? Aust N Z J Med 1994;24(5):521-9.
751. Redline S, Wright EC, Kattan M, Kercsmar C, Weiss K. Short-term compliance with peak flow monitoring: results from a study of inner city children with asthma. Pediatr Pulmonol 1996;21(4):203-10.
752. Burkhart PV, Dunbar-Jacob JM, Fireman P, Rohay J. Children's adherence to recommended asthma self-management. Pediatr Nurs. 2002;28(4):409-14.
753. Kamps AW, Roorda RJ, Brand PL. Peak flow diaries in childhood asthma are unreliable. Thorax. 2001;56(3):180-2.
754. Berg J, Dunbar-Jacob J, Sereika SM. An evaluation of a self-management program for adults with asthma. Clin Nurs Res 1997;6(3):225-38.
755. Cochrane MC, Bala MV, Downs KE, Mauskopf J, Ben-Joseph RH. Inhaled corticosteroids for asthma therapy: patient compliance, devices, and inhalation technique. Chest 2000;117(2):542-50.
756. Jonasson G, Carlsen KH, Sodal A, Jonasson C, Mowinckel P. Patient compliance in a clinical trial with inhaled budesonide in children with mild asthma. Eur Respir J 1999;14(1):150-4.
757. Braunstein GL, Trinquet G, Harper AE. Compliance with nedocromil sodium and a nedocromil sodium/salbutamol combination. Compliance Working Group. Eur Respir J 1996;9(5):893-8.
758. Haynes RB, McDonald H, Garg AX, Montague P. Interventions for helping patients to follow prescriptions for medications (Cochrane Review). In: The Cochrane Library, Issue 3, 2001. London: John Wiley & Sons Ltd.
759. Gibson PG, Shah S, Mamoon HA. Peer-led asthma education for adolescents: impact evaluation. J Adolesc Health 1998;22(1):66-72.
760. Schraa JC, Dirks JF. Improving patient recall and comprehension of the treatment regimen. J Asthma 1982;19(3):159-62.
761. Huss K, Salerno M, Huss RW. Computer-assisted reinforcement of instruction: effects on adherence in adult atopic asthmatics. Res Nurs Health 1991;14(4):259-67.
762. Rasmussen LM, Phanareth K, Nolte H, Backer V. Internet-based monitoring of asthma: A long-term, randomized clinical study of 300 asthmatic subjects. Journal of Allergy & Clinical Immunology 2005;115(6):1137-42.
763. Delaronde S, Peruccio DL, Bauer BJ. Improving asthma treatment in a managed care population. Am J Manag Care. 2005;11(6):361-8.
764. Feifer RA, Verbrugge RR, Khalid M, Levin R, O'Keefe GB, Aubert RE. Improvements in asthma pharmacotherapy and self-management: An example of a population-based disease management program. Dis Manag Health Outcomes 2004;12(2):93-102.
765. Homer CJ, Forbes P, Horvitz L, Peterson LE, Wypij D, Heinrich P. Impact of a quality improvement program on care and outcomes for children with asthma. Arch Pediatr Adolesc Med 2005;159(5):464-9.
766. Kemple T, Rogers C. A mailed personalised self-management plan improves attendance and increases patients' understanding of asthma. Prim Care Respir J 2003;12(4):110-4.

New references

767. Berger W. Budesonide inhalation suspension for the treatment of asthma in infants and children. Drugs 2005;65(14):1973-89.
768. Sorkness CA, Lemanske Jr RF, Mauger DT, Boehmer SJ, Chinchilli VM, Martinez FD, et al. Long-term comparison of 3 controller regimens for mild-moderate persistent childhood asthma: The Pediatric Asthma Controller Trial. Journal of Allergy and Clinical Immunology 2007;119(1):64-72.
769. Szefler SJ, Baker JW, Uryniak T, Goldman M, Silkoff PE. Comparative study of budesonide inhalation suspension and montelukast in young children with mild persistent asthma. The Journal of allergy and clinical immunology 2007;120:1043-50.
770. Chen Y-Z, Busse WW, Pedersen S, Tan W, Lamm C-J, O'Byrne PM. Early intervention of recent onset mild persistent asthma in children aged under 11 yrs: the Steroid Treatment As Regular Therapy in early asthma (START) trial. Pediatric Allergy & Immunology 2006;17 Suppl(17):7-13.
771. Kelly A, Tang R, Becker S, Stanley CA. Poor specificity of low growth hormone and cortisol levels during fasting hypoglycemia for the diagnoses of growth hormone deficiency and adrenal insufficiency. Pediatrics 2008;122(3):e522-8.
772. Brémont F, Moisan V, Dutau G. Continuous subcutaneous infusion of beta 2-agonists in infantile asthma. Pediatr Pulmonol 1992;12(2):81-3.
773. Payne D, Balfour-Lynn IM, Biggart EA, Bush A, Rosenthal M. Subcutaneous terbutaline in children with chronic severe asthma. Pediatr Pulmonol 2002;33(5):356-61.
774. Bousquet J, P. C, N. B, R. B, S. H, S. W, et al. The effect of treatment with omalizumab, an anti-IgE antibody, on asthma exacerbations and emergency medical visits in patients with severe persistent asthma. Allergy 2005;60(3):302-8.
775. Holgate S, Chuchalin AG, Hébert J, Lötvall J, Persson GB, Chung KF, et al. Efficacy and safety of a recombinant anti-immunoglobulin E antibody (omalizumab) in severe allergic asthma. Clin Exp Allergy. 2004;34(4):632-8.
776. Humbert M, Beasley R, Ayres J, Slavin R, Hebert J, Bousquet J, et al. Benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): INNOVATE. Allergy 2005;60(3):309-16.
777. Robertson C, Price D, Henry R et al Short course montelukast for intermittent asthma in children: A randomized controlled trial Am J Resp Crit Care Med 2007;175:323-9.
778. Vuillermin PJ, Robertson CF, South M. Parent-initiated oral corticosteroid therapy for intermittent wheezing illnesses in children: Systematic review. Journal of Paediatrics and Child Health 2007;43(6):438-42.
779. Stelmach I, Grzelewski T, Majak P, Jerzynska J, Stelmach W, Kuna P. Effect of different antiasthmatic treatments on exercise-induced bronchoconstriction in children with asthma. Journal of Allergy & Clinical Immunology 2008;121(2):383-9.
780. Sturdy PM, Butland BK, Anderson HR, Ayres JG, Bland JM, Harrison BD, et al. Deaths certified as asthma and use of medical services: a national case-control study. Thorax 2005;60(11):909-15.
781. Harrison B, Slack R, Berrill WT, Burr ML, Stableforth DE, Wright SC. Results of a national confidential enquiry into asthma deaths. Asthma J 2000;5:180-6.
782. Arnold DH, Gebretsadik T, Minton PA, Higgins S, Hartert TV. Clinical measures associated with FEV1 in persons with asthma requiring hospital admission. American Journal of Emergency Medicine 2007;25(4):425-9.
783. British Thoracic Society. Guideline for emergency oxygen use in adult patients. Thorax 2008;63(suppl. 6):68.
784. Carruthers D, Harrison BD. Arterial blood gas analysis or oxygen saturation in the assessment of acute asthma? Thorax 1995;50:186-8.
785. Rodrigo G, Nannini L. Comparison between nebulized adrenaline and beta2 agonists for the treatment of acute asthma. a meta-analysis of randomized trials. American Journal of Emergency Medicine 2006;24(2):217-22.
786. Cates CJ, Crilly JA, Rowe BH. Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma. Cochrane Database of Systematic Reviews 2006, Issue 2.
787. Lahn M, Bijur P, Gallagher EJ. Randomized clinical trial of intramuscular vs oral methylprednisolone in the treatment of asthma exacerbations following discharge from an emergency department. Chest 2004;126(2):362-8.
788. Edmonds ML, Camargo CA, Jr., Pollack CV, Jr., Rowe BH. Early use of inhaled corticosteroids in the emergency department treatment of acute asthma.[update of Cochrane Database Syst Rev. 2001;(1):CD002308; PMID: 11279763]. Cochrane Database of Systematic Reviews 2003, Issue 3.
789. Rodrigo GJ. Rapid effects of inhaled corticosteroids in acute asthma: an evidence-based evaluation. Chest 2006;130(5):1301-11.
790. Mohammed S, Goodacre S. Intravenous and nebulised magnesium sulphate for acute asthma: systematic review and meta-analysis. Emergency Medicine Journal 2007;24(12):823-30.
791. Blitz M, Blitz S, Beasely R, Diner BM, Hughes R, Knopp JA, et al. Inhaled magnesium sulfate in the treatment of acute asthma. Cochrane Database of Systematic Reviews 2005, Issue 4.
792. Blitz M, Blitz S, Hughes R, Diner B, Beasley R, Knopp J, et al. Aerosolized magnesium sulfate for acute asthma: a systematic review. Chest 2005;128(1):337-44.
793. Rodrigo G, Pollack C, Rodrigo C, Rowe BH. Heliox for nonintubated acute asthma patients.[update of Cochrane Database Syst Rev. 2003;(4):CD002884; PMID: 14583955]. Cochrane Database of Systematic Reviews 2006, Issue 4.
794. Rodrigo GJ, Rodrigo C, Pollack CV, Rowe B. Use of helium-oxygen mixtures in the treatment of acute asthma: a systematic review. Chest 2003;123(3):891-6.
795. Yen ZS, Chen SC. Best evidence topic report. Nebulised furosemide in acute adult asthma. Emergency Medicine Journal 2005;22(9):654-5.
796. Ram FS, Wellington S, Rowe B, Wedzicha JA. Non-invasive positive pressure ventilation for treatment of respiratory failure due to severe acute exacerbations of asthma. Cochrane Database of Systematic Reviews 2005, Issue 3.
797. Tapp S, Lasserson TJ, Rowe B. Education interventions for adults who attend the emergency room for acute asthma. Cochrane Database of Systematic Reviews 2007, Issue 3.
798. Nathan JA, Pearce L, Field C, Dotesio-Eyres N, Sharples LD, Cafferty F, et al. A randomized controlled trial of follow-up of patients discharged from the hospital following acute asthma: best performed by specialist nurse or doctor? Chest 2006;130(1):51-7.
799. Baren JM, Boudreaux ED, Brenner BE, Cydulka RK, Rowe BH, Clark S, et al. Randomized controlled trial of emergency department interventions to improve primary care follow-up for patients with acute asthma. Chest 2006;129(2):257-65.
800. Davies G, Paton JY, Beaton SJ, Young D, Lenney W. Children admitted with acute wheeze/asthma during November 1998-2005: a national UK audit. Arch Dis Child 2008 93(11):952-8.
801. Cunningham S, Logan C, Lockerbie L, Dunn MJG, McMurray A, Prescott RJ. Effect of an Integrated Care Pathway on Acute Asthma/Wheeze in Children Attending Hospital: Cluster Randomized Trial. Journal of Pediatrics 2008;152(3):315-20.
802. Harmanci K, Bakirtas A, Turktas I, Degim T. Oral montelukast treatment of preschool-aged children with acute asthma. Annals of allergy, asthma & immunology 2006;96(5):731-5.
803. Nelson KA, Smith SR, Trinkaus K, Jaffe DM. Pilot study of oral montelukast added to standard therapy for acute asthma exacerbations in children aged 6 to 14 years. Pediatric emergency care 2008;24(1):21-7.
804. Wheeler DS, Jacobs BR, Kenreigh CA, Bean JA, Hutson TK, Brilli RJ. Theophylline versus terbutaline in treating critically ill children with status asthmaticus: a prospective, randomized, controlled trial. Pediatric critical care medicine 2005;6(2):142-7.
805. Roberts G, Newsom D, Gomez K, Raffles A, Saglani S, Begent J, et al. Intravenous salbutamol bolus compared with an aminophylline infusion in children with severe asthma: a randomised controlled trial. Thorax 2003;58(4):306-10.
806. Scottish Intercollegiate Guidelines Network: Bronchiolitis in children. Edinburgh: SIGN; 2006. (SIGN guideline 91). Available from url: http://www.sign.ac.uk/pdf/sign91.pdf
807. Dombrowski MP, Schatz M, Wise R, Momirova V, Landon M, Mabie W, et al. Asthma during pregnancy. Obstetrics and Gynecology 2004;103(1):5-12.
808. Gluck JC, Gluck PA. The effect of pregnancy on the course of asthma. Immunology & Allergy Clinics of North America 2006;26(1):63-80.
809. Kwon HL, Belanger K, Bracken MB. Effect of pregnancy and stage of pregnancy on asthma severity: a systematic review. American Journal of Obstetrics and Gynecology. 2004;190(5):1201-10. (56 ref).
810. Bracken MB, Triche EW, Belanger K, Saftlas A, Beckett WS, Leaderer BP. Asthma symptoms, severity, and drug therapy: a prospective study of effects on 2205 pregnancies. Obstetrics & Gynecology 2003;102(4):739-52.
811. Murphy VE, Clifton VL, Gibson PG. Asthma exacerbations during pregnancy: incidence and association with adverse pregnancy outcomes. Thorax 2006;61(2):169-76.
812. Schatz M, Dombrowski MP, Wise R, Momirova V, Landon M, Mabie W, et al. Spirometry is related to perinatal outcomes in pregnant women with asthma. American Journal of Obstetrics & Gynecology 2006;194(1):120-6.
813. Lewis G, editor. The Confidential Enquiry into Maternal and Child Health (CEMACH). Why mothers die: the sixth report of the confidential enquiries into maternal deaths in the UK. London: Royal College of Obstetricians and Gynaecologists; 2004.

814. Lewis G, editor. The Confidential Enquiry into Maternal and Child Health (CEMACH). Saving mothers' lives: reviewing maternal deaths to make motherhood safer 2003-2005. The seventh report on confidential enquiries into maternal deaths in the UK. London: Confidential Enquiry into Maternal and Child Health; 2007.
815. Campbell L, Klocke RA. Implications for the pregnant patient. Am J Respir Crit Care Med 2001;163(5).
816. Templeton A, Kelman GR. Maternal blood-gases, (PAO2--PaO2), physiological shunt and VD/VT in normal pregnancy. Br J Anaesth. 1976;48(10):1001-4.
817. Van Hook J, Harvey CJ, Anderson GD. Effect of pregnancy on maternal oxygen saturation values: use of reflectance pulse oximetry during pregnancy. South Med J 1996;89(12):1188-92.
818. Altman D, Carroli G, Duley L, Farrell B, Moodley J, Neilson J, et al. Do women with pre-eclampsia, and their babies, benefit from magnesium sulphate? The magpie trial: a randomised placebo-controlled trial. Lancet 2002;359(9321):1877-90.
819. Gee J, Packer B, Millen J, Robin E. Pulmonary mechanics during pregnancy. J Clin Invest. 1967;46(6):945-52.
820. Izci B, Riha R, Martin S, Vennelle M, Liston W, Dundas K, et al. The upper airway in pregnancy and pre-eclampsia. Am J Respir Crit Care Med. 2003;167(2):137-40.
821. Chambers C. Safety of asthma and allergy medications in pregnancy. Immunology & Allergy Clinics of North America 2006;26(1):13-28.
822. Tata L, Lewis S, McKeever T, Smith C, Doyle P, Smeeth L, et al. Effect of maternal asthma, exacerbations and asthma medication use on congenital malformations in offspring: a UK population-based study. Thorax 2008;63(11).
823. Schatz M, Dombrowski M, Wise R, Momirova V, Landon M, Mabie W, et al. The relationship of asthma medication use to perinatal outcomes. J Allergy Clin Immunol 2004 113(6).
824. Wilton L, Shakir SA. A post-marketing surveillance study of formoterol (Foradil): its use in general practice in England. Drug Safety 2002;25(3):213-23.
825. Gluck JC, Gluck PA. Asthma controller therapy during pregnancy. American Journal of Obstetrics & Gynecology 2005;192(2):369-80.
826. Nelson H, Weiss S, Bleecker E, Yancey S, Dorinsky P. The salmeterol multicenter asthma research trial (SMART Study Group): a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol. Chest 2006;129(1):15-26.
827. Perrio M, Wilton L, Shakir S. A modified prescription-event monitoring study to assess the introduction of Seretide Evohaler in England: an example of studying risk monitoring in pharmacovigilance. Drug Saf. 2007;30(8):681-95.
828. Silverman M, Sheffer A, Diaz PV, Lindmark B, Radner F, Broddene M, et al. Outcome of pregnancy in a randomized controlled study of patients with asthma exposed to budesonide. Annals of Allergy, Asthma, & Immunology 2005;95(6):566-70.
829. Rahimi R, Nikfar S, Abdollahi M. Meta-analysis finds use of inhaled corticosteroids during pregnancy safe: a systematic meta-analysis review. Human & Experimental Toxicology 2006;25(8):447-52.
830. Källén B. Maternal drug use and infant cleft lip/palate with special reference to corticoids. Cleft Palate Craniofac J 2003;40(6):624-8.
831. Carmichael SL, Shaw GM, Ma C, Werler MM, Rasmussen SA, Lammer EJ. Maternal corticosteroid use and orofacial clefts. Am J Obstet Gynecol 2007;197(6):585 e1-7; discussion 683-4, e1-7.
832. Bakhireva LN, Schatz M, Chambers CD. Effect of maternal asthma and gestational asthma therapy on fetal growth. Journal of Asthma 2007;44(2):71-6.
833. Twaites BR, Wilton LV, Shakir SA. Safety of zafirlukast: results of a postmarketing surveillance study on 7976 patients in England. Drug Safety 2007;30(5):419-29.

ISBN 978 1 905813 28 5

British Thoracic Society
17 Doughty Street, London WC1N 2PL
www.brit-thoracic.org.uk

Scottish Intercollegiate Guidelines Network
Elliott House, 8 -10 Hillside Crescent, Edinburgh EH7 5EA
www.sign.ac.uk

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken:

Question: 1 of 100

Which of the following statements regarding bariatric surgery is correct?

(Please select 1 option)

- Associated with a significant post-operative mortality
- Associated with nutritional deficiencies
- Contraindicated in adolescents
- Indicated in patients with a BMI <35 kg/m^2
- Reduces cardiovascular mortality

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 16 mins 6 secs

Question: 10 of 100

A 39-year-old female presents with lethargy, nausea, and muscle cramps; and she has passed 450 ml of urine in the last 24 hours.

She was recently started on a new medication.

Serum sodium	128 mmol/l	(137-144)
Plasma osmolality	272 mosmol/l	(275-290)
Urine osmolality	380 mosmol/l	(350-1000)

Which of the following recently prescribed drugs accounts for the findings?

(Please select 1 option)

- Aspirin
- Fluoxetine
- Furosemide
- Lithium
- Metoprolol

Submit answer | Skip question | Tag Question | Remove question

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 4 hrs 30 mins 30 secs

Question: 100 of 100

A 39-year-old male presents with gynaecomastia.

Which of the following is the most likely cause of his gynaecomastia?

(Please select 1 option)

○	Congenital adrenal hyperplasia (CAH)
○	Hypopituitarism
○	Hypothyroidism
○	Prolactinoma
○	Seminoma

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Question: 100 of 100

A 39-year-old male presents with gynaecomastia.

Which of the following is the most likely cause of his gynaecomastia?

(Please select 1 option)

○	Congenital adrenal hyperplasia (CAH)
○	Hypopituitarism
◉	Hypothyroidism ✕ Incorrect answer selected
○	Prolactinoma
○	Seminoma ← This is the correct answer

Gynaecomastia is due to a perturbation in the testosterone to oestradiol ratio.

Neither hyperprolactinaemia nor hypopituitarism disturb this ratio and are rarely associated with gynaecomastia.

Unlike hyperthyroidism, hypothyroidism is not a cause.

CAH is not a cause.

However, gynaecomastia may be a presenting symptom of a seminoma and may arise due to human chorionic gonadotropin (HCG) secretion.

Finish | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Plasma osmolality	272 mosmol/l	(275-290)
Urine osmolality	380 mosmol/l	(350-1000)

Which of the following recently prescribed drugs accounts for the findings?

(Please select 1 option)

◉	Aspirin ✕ Incorrect answer selected
○	Fluoxetine ← This is the correct answer
○	Furosemide
○	Lithium
○	Metoprolol

This lady has

- Hyponatraemia
- Hypotonicity (low serum osmolality) and
- Inappropriately concentrated urine

which is consistent with syndrome of inappropriate antidiuretic hormone (ADH).

Of the drugs listed, fluoxetine is the most likely cause of syndrome of inappropriate secretion of antidiuretic hormone (SIADH).

Further reading:
SIADH eMedicine

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 17 mins 32 secs

Question: 11 of 100

A 60-year-old patient with metastatic breast carcinoma attends clinic complaining of pain in the jaw and ulceration within the oral cavity which has persisted for four weeks following a dental extraction. She has had a course of antibiotic therapy for suspected secondary infection of the ulceration.

On examination there is ulceration within the oral cavity which extends as far as the underlying mandible.

Which of the following drugs is likely to be responsible for her presentation?

(Please select 1 option)

- Anastrozole
- Diclofenac
- Prednisolone
- Tamoxifen
- Zoledronic acid

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Which of the following drugs is likely to be responsible for her presentation?

(Please select 1 option)

○	Anastrozole
○	Diclofenac
○	Prednisolone
○	Tamoxifen
◉	Zoledronic acid ✓ Correct

The likely causative agent is the nitrogen containing bisphosphonate zoledronic acid.

The clinical scenario suggests a diagnosis of bisphosphonate associated osteonecrosis of the jaw. This is a recently recognised adverse effect of bisphosphonate therapy. This is a consequence of potent anti-resorptive action of the nitrogen containing bisphosphonates.

Most cases have been associated with zoledronic acid and pamidronate given intravenously for metastatic bone disease. The reported incidence in patients with malignancy treated with these drugs is between 1.3-4.0%.

Dental disease is a recognised predisposing factor.

The lesions usually heal with minimal surgical debridement, chlorhexidine mouthwashes, antibiotics and analgesia.

Further reading:
Bisphosphonates and osteonecrosis of the jaw NHS Evidence

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 18 mins 46 secs

Question: 12 of 100

A 64-year-old retired Caucasian solicitor attends the surgery. He is overweight and takes little exercise.

He has been treated for hypertension for five years and is controlled on 5 mg of ramipril. He also takes 20 mg of simvastatin for hypercholesterolaemia. A 75g oral glucose tolerance test was recently performed and gave a result consistent with impaired glucose tolerance (IGT) with a two hour plasma glucose concentration of 9.3 mmol/L (3.0-6.0). The patient is keen to know what would be his risk of developing type 2 diabetes.

What do you tell him?

(Please select 1 option)

○	6% over 6 years
○	10% over 6 years
○	33% over 6 years
◉	60% over 6 years
○	100% over 6 years

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Scores
- Community
- Help
- Shop

He has been treated for hypertension for five years and is controlled on 5 mg of ramipril. He also takes 20 mg of simvastatin for hypercholesterolaemia. A 75g oral glucose tolerance test was recently performed and gave a result consistent with impaired glucose tolerance (IGT) with a two hour plasma glucose concentration of 9.3 mmol/L (3.0-6.0). The patient is keen to know what would be his risk of developing type 2 diabetes.

What do you tell him?

(Please select 1 option)

○	6% over 6 years
○	10% over 6 years
◉	33% over 6 years ✓ Correct
○	60% over 6 years
○	100% over 6 years

Individuals with IGT are at significant risk of progression to type 2 diabetes.

A number of studies have looked at the absolute risk of progression from IGT to type 2 diabetes. The large and widely quoted Hoorn study which looked at 1342 Caucasian non-diabetic subjects found that 33.8% progressed to type 2 diabetes over six years follow up.

This increased to 64.5% if individuals had both IGT and IFG. A similar rate of progression for individuals with IGT was Vaccaro who studied a Caucasian group in Italy.

Intensive lifestyle changes involving diet changes, regular exercise and weight loss have been shown to reduce the rate of progression to type 2 diabetes.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 21 mins 18 secs

Question: 13 of 100

A 52-year-old male with a history of dyslipidaemia and hypertension attends the surgery for a 75 g oral glucose tolerance test (OGTT) as part of his cardiovascular risk assessment and screening for Type 2 diabetes. He is overweight with a BMI of 29 kg/m^2, his blood pressure is 135/85 mmHg on a combination of amlodipine and perindopril.

His venous plasma OGTT result is as follows:

0 minutes	6.3
120 minutes	10.4

Which of the following is the correct interpretation of these results?

(Please select 1 option)

- ○ Impaired fasting glucose (IFG)
- ○ Impaired fasting glucose and impaired glucose tolerance
- ○ Impaired glucose tolerance (IGT)
- ○ Normal glucose tolerance.
- ○ Type 2 diabetes

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Which of the following is the correct interpretation of these results?

(Please select 1 option)

○	Impaired fasting glucose (IFG)
◉	Impaired fasting glucose and impaired glucose tolerance ✓ Correct
○	Impaired glucose tolerance (IGT)
○	Normal glucose tolerance.
○	Type 2 diabetes

The World Health Organisation recommend the use of the OGTT for the diagnosis of Type 2 diabetes as it incorporates the fasting and two hour post-glucose load which can identify different sub-groups of diabetic patients and different categories of individuals at risk of Type 2 diabetes.

The diagnostic criteria are:

Venous plasma glucose	Fasting (mmol/l)	2 hour post glucose (mmol/l)
Diabetic	> 7.0	> 11.1
IGT	<7.0	7.8-11.0
IFG	6.1-6.9	<7.8

In the absence of marked hyperglycaemia and symptoms such as weight loss, polyuria or polydipsia these results should be confirmed by a repeat test on another day.

Next question

Tag Question | Remove question

Work Smart Session - MRCP Part 1

Question: 14 of 100

A 26-year-old man presented with polydipsia and polyuria for the last two years.

Investigations reveal:

Serum urea	8.4 mmol/L (2.5-7.5)
Serum creatinine	108 mol/L (60-110)
Serum corrected calcium	2.82 mmol/L (2.2-2.6)
Serum phosphate	0.73 mmol/L (0.8-1.4)
Plasma parathyroid hormone	6.8 pmol/L (0.9-5.4)

Which of the following is directly responsible for his increased intestinal calcium reabsorption?

(Please select 1 option)

- 1,25 Dihydroxy vitamin D
- 25 Hydroxy vitamin D
- Calcitonin
- Hypophosphataemia
- Parathyroid hormone

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Investigations reveal:

Serum urea	8.4 mmol/L (2.5-7.5)
Serum creatinine	108 mol/L (60-110)
Serum corrected calcium	2.82 mmol/L (2.2-2.6)
Serum phosphate	0.73 mmol/L (0.8-1.4)
Plasma parathyroid hormone	6.8 pmol/L (0.9-5.4)

Which of the following is directly responsible for his increased intestinal calcium reabsorption?

(Please select 1 option)

- (●) 1,25 Dihydroxy vitamin D ✓ Correct
- ( ) 25 Hydroxy vitamin D
- ( ) Calcitonin
- ( ) Hypophosphataemia
- ( ) Parathyroid hormone

This patient has hypercalcaemia due to hyperparathyroidism.

However, the intestinal absorption of calcium is facilitated by 1,25 dihydroxy-vitamin D, which stimulates the microvillous membrane of the enterocyte to synthesise the calcium-binding carrier protein necessary for active calcium ion absorption .

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Question: 15 of 100

A 45-year-old male presents concerned about his risk of developing diabetes. His family history reveals that his mother and maternal uncle both have diabetes.

He has central obesity with a waist measurement of 110 cm.

On examination, his blood pressure is 130/82 mmHg, his BMI is 30.2 kg/m^2 .

His investigations reveal:

Fasting cholesterol	5.2 mmol/L	(<5.2)
Triglycerides	1.4 mmol/L	(0.45-1.69)
HDL cholesterol	1.1 mmol/L	(> 1.55)
Fasting glucose	6.2 mmol/L	(3.0-6.0)

In addition to his waist measurement which of this man's observations fulfills the criteria for the diagnosis of the metabolic syndrome?

(Please select 1 option)

- ○ Blood pressure of 130/82 mmHg
- ○ BMI of 30.2 kg/m^2
- ○ Fasting plasma glucose of 6.2 mmol/l
- ○ HDL concentration of 1.1 mmol/l
- ○ Triglyceride concentration of 1.4 mmol/l

Submit answer | Skip question | Tag Question | Remove question

syndrome?

(Please select 1 option)

○	Blood pressure of 130/82 mmHg
○	BMI of 30.2 kg/m^2
◉	Fasting plasma glucose of 6.2 mmol/l ✓ Correct
○	HDL concentration of 1.1 mmol/l
○	Triglyceride concentration of 1.4 mmol/l

The metabolic syndrome is becoming hugely important as a cluster of features associated with increased cardiovascular and diabetes risk.

The condition is defined by various criteria the latest of which is the global definition for the IDF as central obesity (>=94cm for men, >=80 cm for women) plus any two of the following:

- Hypertriglyceridaemia >1.7 mmol/l
- Low HDL concentration <1.03 mmol/l male, <1.29 mmol/l female
- BP > or = 130/85 mmHg, or on treatment for hypertension
- Fasting glucose > or = 5.6 mmol/l, or known to have type 2 diabetes.

Thus, in our patient's case the elevated fasting glucose of 6.3 mmol/l fulfills this diagnostic criterion.

The BMI is not a function of the diagnostic criteria as the waist circumference appears to be a far more powerful predictor of risk.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 28 mins 18 secs

Question: 16 of 100

A 29-year-old female with Turner syndrome is referred by the GP concerned about her blood pressure which he has found to be persistently elevated at between 140-160/90 mmHg.

On examination she is noted to have a blood pressure of 148/92 mmHg, with no radio-femoral delay and no murmur audible.

Which of the following is the most likely cause of her hypertension?

(Please select 1 option)

- Coarctation of the aorta
- Essential hypertension
- Primary hyperaldosteronism
- Renal artery stenosis
- Single horseshoe kidney

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 29 mins 18 secs

Question: 16 of 100

A 29-year-old female with Turner syndrome is referred by the GP concerned about her blood pressure which he has found to be persistently elevated at between 140-160/90 mmHg.

On examination she is noted to have a blood pressure of 148/92 mmHg, with no radio-femoral delay and no murmur audible.

Which of the following is the most likely cause of her hypertension?

(Please select 1 option)

◉	Coarctation of the aorta ✕ Incorrect answer selected
○	Essential hypertension ← This is the correct answer
○	Primary hyperaldosteronism
○	Renal artery stenosis
○	Single horseshoe kidney

Hypertension is quite common in Turner syndrome (10%) and is typically idiopathic - essential.

In a small proportion causes can include coarctation of the aorta and renal dysfunction due to horseshoe kidney.

In this case, essential hypertension is the most likely cause, but in the absence of specific features of coarctation this would again be the most appropriate option.

Next question

Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 29 mins 18 secs

Question: 17 of 100

A 41-year-old male on routine risk factor screening is noted to have a blood pressure of 146/86 mm/Hg.

His investigations reveal:

Fasting plasma glucose	5.8 mmol/L	(3.0-6.0)
Total cholesterol	6.2 mmol/L	(<5.2)
Triglyceride	12.8 mmol/L	(0.45-1.69)
HDL-cholesterol	0.8 mmol/L	(>1.55)

Which is the most appropriate treatment for his lipid profile?

(Please select 1 option)

- ○ Ezetimibe
- ○ Fenofibrate
- ○ Nicotinic acid slow release
- ○ Rosuvastatin
- ○ Simvastatin

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Shop

Triglyceride	12.8 mmol/L	(0.45-1.69)
HDL-cholesterol	0.8 mmol/L	(>1.55)

Which is the most appropriate treatment for his lipid profile?

(Please select 1 option)

- Ezetimibe
- Fenofibrate
- Nicotinic acid slow release ← This is the correct answer
- Rosuvastatin
- Simvastatin ✕ Incorrect answer selected

This patient is likely to have type V hyperlipoproteinaemia characterised by an excess of triglyceride containing lipoproteins and an increased risk of pancreatitis.

Nicotinic acid primarily reduces plasma TG levels via inhibition of hepatic TG synthesis suppressing FFA supply to the liver. It is currently the most effective TG reducing pharmacotherapy producing reductions of up to 30% in plasma TG at a dose of 2 g a day.

Its use is limited by side effects mainly flushing and an exacerbation of insulin resistance. The flushing may be diminished by gradual dose escalation, consumption following a low fat snack and concomitant aspirin use.

Alternative therapies in the event of intolerance to nicotinic acid include fenofibrate as a good second choice or alternatively omega-3 fatty acids.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Question: 18 of 100

During routine investigation of a healthy couple for primary subfertility semen analysis reveals azoospermia.

On examination of the male there are no abnormalities on general examination and testicular examination shows a normal testicular volume.

Investigations reveal:

LH	5.1 IU/L	(2-10)
FSH	4.3 IU/L	(2-10)
Testosterone	15.3 nmol/L	(9-30)

Which of the following is the most likely cause of his azoospermia?

(Please select 1 option)

- Androgen insensitivity
- Genital tract obstruction
- Idiopathic testicular failure
- Kallman's Syndrome
- Sperm autoimmunity

Submit answer | Skip question | Tag Question | Remove question

Investigations reveal:

LH	5.1 IU/L	(2-10)
FSH	4.3 IU/L	(2-10)
Testosterone	15.3 nmol/L	(9-30)

Which of the following is the most likely cause of his azoospermia?

(Please select 1 option)

- Androgen insensitivity
- Genital tract obstruction ← This is the correct answer
- Idiopathic testicular failure
- Kallman's Syndrome
- Sperm autoimmunity ✕ Incorrect answer selected

The normal FSH and testosterone would exclude a primary testicular cause of the azoospermia and therefore would suggest obstruction such as agenesis of the vas as seen in cystic fibrosis.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 33 mins 14 secs

Question: 19 of 100

A 48-year-old woman presents with a history of intestinal polyps and multiple lipomas on the arms and back. She now has a small palpable nodule in her neck. Thyroid function tests and thyroid antibodies are normal.

Which of the following tumours is she at increased risk of developing?

(Please select 1 option)

- Anaplastic carcinoma of the thyroid
- Follicular carcinoma of the thyroid
- Medullary carcinoma of the thyroid
- Papillary carcinoma of the thyroid
- Thyroid lymphoma

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 34 mins 45 secs

Question: 19 of 100

A 48-year-old woman presents with a history of intestinal polyps and multiple lipomas on the arms and back. She now has a small palpable nodule in her neck. Thyroid function tests and thyroid antibodies are normal.

Which of the following tumours is she at increased risk of developing?

(Please select 1 option)

○	Anaplastic carcinoma of the thyroid
○	Follicular carcinoma of the thyroid
○	Medullary carcinoma of the thyroid
○	Papillary carcinoma of the thyroid ← This is the correct answer
◉	Thyroid lymphoma ✕ Incorrect answer selected

This lady has Gardener's syndrome, or familial adenomatous polyposis, characterised by multiple small and large intestinal tumours and lipomas. Osteomata and fibromas are also seen.

It is a rare familial condition, when arising from mutations of the APC gene is inherited in an autosomal dominant fashion.

Gardener's syndrome carries an increased risk of papillary carcinoma of the thyroid with a preponderance for female patients.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 1 mins 21 secs

Question: 1 of 100

Which of the following statements regarding bariatric surgery is correct?

(Please select 1 option)

○	Associated with a significant post-operative mortality
◉	Associated with nutritional deficiencies ✓ Correct
○	Contraindicated in adolescents
○	Indicated in patients with a BMI <35 kg/m^2
○	Reduces cardiovascular mortality

Bariatric surgery is a major gastrointestinal procedure. Bariatric surgery in adolescents raises social, psychological and developmental issues, but adolescents are not excluded from surgery, and some hospitals have specialised programmes for younger patients.

Potential candidates for surgery are those with a body mass index (BMI) exceeding 40, or BMI >35 with serious co-morbidities (e.g. sleep apnoea, type 2 diabetes). Post-operative mortality ranges from 0.1-2%.

Vomiting is a risk associated with bariatric surgery, as is dumping syndrome and nutritional deficiencies. There is no evidence as yet, that bariatric surgery reduces cardiovascular mortality in patients.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 mins 21 secs

Question: 2 of 100

Whilst hospitalised after a hip replacement, a patient with acute intermittent porphyria (AIP) has an epileptic seizure. The seizure was thought to have been due to alcohol withdrawal.

The patient requires large amounts of analgesia. Six days post-operatively she suffers a porphyric attack.

Which of the following drugs on her prescription is likely to have been responsible?

(Please select 1 option)

- Aspirin
- Augmentin
- Oramorph
- Paracetamol
- Sodium valproate

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 34 mins 45 secs

Question: 20 of 100

A patient with type 2 diabetes being treated with gliclazide presents with sweating and dizziness.

He is on treatment for hypertension, atrial fibrillation, joint pain and indigestion.

Blood glucose was 1.9 mmol/L (3.0-6.0).

Which of the following drugs is responsible?

(Please select 1 option)

○	Aspirin
○	Atenolol
○	Digoxin
○	Fluconazole
○	Ranitidine

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

○	Fluconazole ← This is the correct answer
◉	Ranitidine ✕ Incorrect answer selected

Gliclazide is highly bound to plasma proteins, about 94%. Its free plasma level increases on displacement by aspirin given for joint pains.

As a result of drug interaction hypoglycaemia may be potentiated when a sulfonylurea is used concurrently with agents such as

- Long-acting sulfonamides
- Tuberculostatics
- Phenylbutazone
- Clofibrate
- Monoamine oxidase (MAO) inhibitors
- Coumarin derivatives
- Salicylates
- Probenecid
- Propranolol
- Cimetidine
- Disopyramide
- Angiotensin converting enzyme inhibitors.

Plasma protein binding of fluconazole is low and its excreted by kidney.

Gliclazide is a sulphonylurea drug with an intermediate half life of around 11 hours. It is extensively metabolised within the liver by CYP2C9.

Renal clearance accounts for only 4% of total drug clearance.

- Long-acting sulfonamides
- Tuberculostatics
- Phenylbutazone
- Clofibrate
- Monoamine oxidase (MAO) inhibitors
- Coumarin derivatives
- Salicylates
- Probenecid
- Propranolol
- Cimetidine
- Disopyramide
- Angiotensin converting enzyme inhibitors.

Plasma protein binding of fluconazole is low and its excreted by kidney.

Gliclazide is a sulphonylurea drug with an intermediate half life of around 11 hours. It is extensively metabolised within the liver by CYP2C9.

Renal clearance accounts for only 4% of total drug clearance.

As fluconazole is a potent inhibitor of CYP2C8 and CYP2C9 it may also interact with the sulphonylureas (for example, glimepiride and gliclazide).

Thus the best answer in this scenario would be likely to be fluconazole.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Question: 21 of 100

A 52-year-old schoolteacher attends with weight loss and sweats.

She is clinically thyrotoxic with a diffuse goitre.

Subsequent investigations show:

Free T4	40 pmol/l	(9-23)
Free T3	9.8 nmol/l	(3.5-6)
TSH	6.1 mU/l	(0.5-5)

A repeat TFT is similar.

What is the most appropriate investigation for this patient?

(Please select 1 option)

- FNA of thyroid gland
- MRI scan pituitary gland
- Radio-isotope uptake scan of thyroid gland
- Repeat TFT checking for antibody interference
- Thyroid auto antibodies

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Subsequent investigations show:

Free T4	40 pmol/l	(9-23)
Free T3	9.8 nmol/l	(3.5-6)
TSH	6.1 mU/l	(0.5-5)

A repeat TFT is similar.

What is the most appropriate investigation for this patient?

(Please select 1 option)

- ○ FNA of thyroid gland
- ◉ MRI scan pituitary gland ✓ Correct
- ○ Radio-isotope uptake scan of thyroid gland
- ○ Repeat TFT checking for antibody interference
- ○ Thyroid auto antibodies

This patient is thyrotoxic; however, as the non-suppressed thyroid-stimulating hormone (TSH) suggests that this is due to excessive TSH production by the pituitary gland, the possibility of a thyrotroph adenoma must be pursued.

In primary hyperthyroidism the TSH should always be suppressed by negative feedback, which is not the case here.

TSH-omas are indeed very rare, but the giveaway would be the normal or elevated TSH with thyrotoxicosis.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 38 mins 20 secs

Question: 22 of 100

In a study healthy volunteers are given 50 mls of 50% dextrose solution by one of two routes. Route A is intravenous and Route B is via a nasogastric tube.

Every 15 minutes the plasma insulin level and glucose are measured and plotted on a graph.

Which of the following statements would best describe the likely results comparing Route A to Route B in this experiment?

(Please select 1 option)

- Insulin and glucose the same in Route A and Route B
- Insulin higher, glucose higher in Route A
- Insulin higher, glucose higher in Route B
- Insulin higher, glucose lower in Route A
- Insulin higher, glucose lower in Route B

Submit answer | Skip question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

(Please select 1 option)

○	Insulin and glucose the same in Route A and Route B
○	Insulin higher, glucose higher in Route A
○	Insulin higher, glucose higher in Route B
○	Insulin higher, glucose lower in Route A
◉	Insulin higher, glucose lower in Route B ✓ Correct

Glucose given via the gut elicits a greater insulin response as compared to the same quantity given intravenously even though the plasma glucose peak is higher when it is given IV. This phenomenon is called the 'incretin effect'.

The incretin effect denominates the phenomenon that oral glucose elicits a higher insulin response than does intravenous glucose.

The two hormones responsible for the incretin effect, glucose-dependent insulinotropic hormone (GIP) and glucagon-like peptide-1 (GLP-1), are secreted after oral glucose loads and augment insulin secretion in response to hyperglycaemia.

Gastric Inhibitory Polypeptide and Glucagon-Like Peptide-1 in the Pathogenesis of Type 2 Diabetes. Diabetes 53:S190-S196, 2004

The investigation of the incretin effect is not usually performed using the same quantity of glucose as in this question. An 'isoglycaemic study' is often used where an infusion of glucose is designed to copy exactly the blood glucose profile generated in an individual or animal by a certain enteral glucose load.

Exenatide (synthetic exendin-4) is a new agent for the treatment of type 2 diabetes. Exendin-4 occurs naturally in the saliva venom of the North American lizard called the Gila Monster. It mimics the action of the gut hormone GLP-1 (Glucagon-like peptide 1).

Next question | Remove Tag | Remove question

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 40 mins 29 secs

Question: 23 of 100

A 54-year-old male who is a HGV driver and has a 10 year history of type 2 diabetes is seen on annual review.

His glycaemic control is poor with a HBA1c of 10.5% on maximal oral hypoglycaemic therapy (3.8-6.4).

You suggest switching to insulin but he refuses to do this as he would lose his HGV licence. He also refuses to inform the DVLA himself.

What is the most appropriate action in this case?

(Please select 1 option)

- Continue to review patient in clinic and accept that he continues to drive
- Discharge him from clinic as there is nothing more that you can do
- Inform his employer that he must stop driving and suggest administrative work
- Inform the DVLA even if the patient withholds his consent
- Tell his next of kin that they should inform the DVLA that he is nol onger fit to drive

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

His glycaemic control is poor with a HBA1c of 10.5% on maximal oral hypoglycaemic therapy (3.8-6.4).

You suggest switching to insulin but he refuses to do this as he would lose his HGV licence. He also refuses to inform the DVLA himself.

What is the most appropriate action in this case?

(Please select 1 option)

◉	Continue to review patient in clinic and accept that he continues to drive ✓ Correct
○	Discharge him from clinic as there is nothing more that you can do
○	Inform his employer that he must stop driving and suggest administrative work
○	Inform the DVLA even if the patient withholds his consent
○	Tell his next of kin that they should inform the DVLA that he is nol onger fit to drive

In this particular case, the patient has poor glycaemic control, but otherwise has no features whatsoever that preclude him from driving such as retinopathy, neuropathy or hypoglycaemic episodes.

You cannot therefore force this patient to switch to insulin and neither can you stop him driving.

He will continue to need a regular medical every three years for his continued HGV licence.

Further reading:

Driver and Vehicle Licensing Agency

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 42 mins 53 secs

Question: 24 of 100

A 33-year-old female presents with a one year history of galactorrhoea and amenorrhoea. She informs you that she does not want to become pregnant. On examination there is galactorrhoea to expression and visual fields are normal to confrontation.

Investigations confirm the diagnosis of a macroprolactinoma, with a prolactin concentration of 10,500 mu/l (50-500) and MRI of the pituitary revealing a 1.5 cm tumour with some suprasellar extension.

What is the most appropriate treatment for this woman?

(Please select 1 option)

- Cabergoline therapy
- Combined oral contraceptive
- Pituitary surgery
- Somatostatin analogue therapy
- Stereotactic pituitary irradiation

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

pituitary revealing a 1.5 cm tumour with some suprasellar extension.

What is the most appropriate treatment for this woman?

(Please select 1 option)

◉	Cabergoline therapy ✓ Correct
○	Combined oral contraceptive
○	Pituitary surgery
○	Somatostatin analogue therapy
○	Stereotactic pituitary irradiation

This young woman has a macroprolactinoma and these are exquisitely sensitive to dopamine agonist therapy and rapid tumour reduction with restoration of menses and cessation of galactorrhoea expected.

Pituitary surgery is rarely required in prolactinomas and is generally reserved for patients intolerant or resistant to dopamine agonist therapy.

Even with large tumours that compress the chiasm, these can be treated with dopamine agonists with rapid reduction in size and relief of pressure.

The fact that she does not want to become pregnant is a bit of an irrelevance. One would still treat her with dopamine agonist therapy and suggest use of appropriate contraception which could include the OCP.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

A 28-year-old female is referred with a three month history of tiredness and weakness.

On examination, pulse is 82 bpm and blood pressure is 128/72 mmHg. No specific abnormalities are evident on examination of the cardiovascular, respiratory, abdominal or neurological systems.

Investigations reveal:

Serum sodium	142 mmol/l	(137-144)
Serum potassium	3.0 mmol/l	(3.5-4.9)
Serum urea	4.2 mmol/l	(2.5-7.5)
Serum creatinine	82 µmol/l	(60-110)
Serum chloride	73 mmol/l	(95-107)
Plasma glucose	5.5 mmol/l	(3.0-6.0)
Urinary chloride	60 mmol/l	(20-350)

Which of the following is the likely diagnosis?

(Please select 1 option)

- Bartter's syndrome
- Conn's syndrome
- Drug ingestion
- Liddle's syndrome
- Non-classical congenital adrenal hyperplasia (CAH)

(Please select 1 option)

◉	Bartter's syndrome ✗ Incorrect answer selected
○	Conn's syndrome
○	Drug ingestion ← This is the correct answer
○	Liddle's syndrome
○	Non-classical congenital adrenal hyperplasia (CAH)

This young woman has hypokalaemia and hypochloraemia.

The normal blood pressure would exclude a diagnosis of Conn's, CAH, or Liddle's syndrome (apparent mineralocorticoid excess). Similarly, drug ingestion associated with hypokalaemia liquorice/carbenoxolone is associated with hypertension (and low urinary chloride less than 20 mmol/l).

Bartter's syndrome is a rare, recessive condition associated with weakness, lethargy and growth retardation and is found in youngsters. Hypokalaemic hypochloraemic alkalosis is seen in the condition but symptoms would be more apparent at a much younger age than this woman.

If Gitelman's syndrome were offered then that would be a better option.

Therefore the most likely diagnosis as the symptoms have arisen only over the last three months and no other features are apparent on examination, is diuretic abuse.

Further reading:
Postgrad Med J 2001;77:e4 BMJ

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Question: 26 of 100

A 19-year-old male presents with concerns regarding his pubertal development.

On examination he is 1.8 m tall, thin and has little pubic and axillary hair. Both testes are approximately 5 ml in volume (NR 15 ml). No other abnormalities are encountered.

Investigations reveal:

LH	3.3 mU/l	(3-10)
FSH	5.5 mU/l	(3-10)
Testosterone	5.5 nmol/l	(9-30)

Which of the following is the most likely diagnosis?

(Please select 1 option)

- Anorexia nervosa
- Craniopharyngioma
- Kallmann's syndrome
- Klinefelter's syndrome
- Primary testicular failure

Submit answer | Skip question | Tag Question | Remove question

(Please select 1 option)

○	Anorexia nervosa
○	Craniopharyngioma
○	Kallmann's syndrome ← This is the correct answer
◉	Klinefelter's syndrome ✕ Incorrect answer selected
○	Primary testicular failure

This young male has delayed puberty with hypogonadotrophic hypogonadism. The most likely explanation would be Kallmann's syndrome.

Klinefelter's would be associated with elevated luteinising hormone/follicle stimulating hormone (LH/FSH), as would primary testicular failure.

His height of 1.8 m, suggesting that he is tall, would argue against this being anorexia despite his thin appearance. If anorexia had preceded puberty then his stature should also have been affected.

The only other possibility is craniopharyngioma, but this is probably less likely in an otherwise well man, and other possible features should be included to suggest this diagnosis, for example, visual fields.

You may wish to cry foul at this point, and say that anosmia should be given as a clue to Kallmann's; however, in reality how often do you ask about sense of smell, let alone test for it?!

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Question: 27 of 100

A 24-year-old female presents with a two week history of polyuria and polydipsia together with frequent nocturia.

Investigations show

Serum sodium	144 mmol/L (137-144)
Serum potassium	3.3 mmol/L (3.5-4.9)
Serum calcium	2.6 mmol/L (2.2-2.6)
Plasma glucose	6.8 mmol/L (3.0-6.0)
Serum osmolality	310 mOsmol/L (275-295)

What is the diagnosis?

(Please select 1 option)

- Diabetes insipidus
- Diabetes mellitus
- Drug abuse
- Primary hyperparathyroidism
- Primary polydipsia

Submit answer | Skip question | Tag Question | Remove question

- Shop

Plasma glucose	6.8 mmol/L (3.0-6.0)
Serum osmolality	310 mOsmol/L (275-295)

What is the diagnosis?

(Please select 1 option)

◉	Diabetes insipidus ✕ Incorrect answer selected
○	Diabetes mellitus
○	Drug abuse ← This is the correct answer
○	Primary hyperparathyroidism
○	Primary polydipsia

This patient has polyuria and polydipsia of relatively recent onset and has an elevated plasma osmolality with a high calcium and glucose concentration.

These features would be unlikely in DI and are more in keeping with thiazide diuretic abuse - high calcium, glucose and hypokalaemia.

Similarly, the serum osmolality would be low in association with primary polydipsia.

There may be plenty of variations purely by alteration of the biochemistry of this question in the examination.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Question: 28 of 100

A 25-year-old female presents with weight gain, oligomenorrhoea and primary infertility. She has a history of bipolar disorder for which she takes lithium.

On examination she has a BMI of 32 kg/m^2.

Investigations reveal:

Free T4	6.4 pmol/l	(10-22)
TSH	42 mU/l	(0.4-5)
Prolactin	980 mU/l	(50-450)

What is the most appropriate treatment for this patient?

(Please select 1 option)

- Cabergoline
- Cabergoline plus thyroxine
- Metformin
- Stop lithium
- Thyroxine

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

(Please select 1 option)

○	Cabergoline
○	Cabergoline plus thyroxine
○	Metformin
○	Stop lithium
◉	Thyroxine ✓ Correct

This patient has primary hypothyroidism which would explain the increasing weight and the associated hyperprolactinaemia.

The latter occurs as a consequence of reduced dopaminergic tone.

Lithium may be the cause of this but stopping it is not usually attempted since it may dangerously exacerbate the psychiatric illness. There is an excellent review by John Lazarus on this topic[1] where he says, "The common clinical side effects of the drug are goitre in up to 40% and hypothyroidism in about 20%. Lithium increases thyroid autoimmunity if present before therapy. Treatment with levothyroxine is effective and lithium therapy should not be stopped."

The most appropriate treatment for her would be thyroxine which would, through euthyroidism, be expected to normalise prolactin concentration.

In turn this may improve weight, menstrual function and fertility.

Reference:

1. Lazarus JH. Lithium and thyroid. Best Pract. Res. Clin. Endocrinol. Metab. 2009;23(6):723-733.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 54 mins 46 secs

Question: 29 of 100

A 65-year-old male undergoes a CT headscan after falling from a ladder and knocking himself out.

The CT report reveals that he has a 1.3 cm macroadenoma which does not encroach upon the optic chiasm. On recovery he is perfectly well and examination is entirely normal, including full viusal fields to confrontation.

Investigations reveal normal thyroid function, testosterone concentration and short Synacthen test results. His prolactin concentration is 550 mU/L (50-450).

What is the most appropriate treatment for this patient?

(Please select 1 option)

- Advise trans-sphenoidal hypophysectomy
- Arrange pituitary radiotherapy
- Arrange serial imaging
- No further investigation/treatment required
- Treat with cabergoline

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

perfectly well and examination is entirely normal, including full viusal fields to confrontation.

Investigations reveal normal thyroid function, testosterone concentration and short Synacthen test results. His prolactin concentration is 550 mU/L (50-450).

What is the most appropriate treatment for this patient?

(Please select 1 option)

○	Advise trans-sphenoidal hypophysectomy
○	Arrange pituitary radiotherapy
○	Arrange serial imaging ← This is the correct answer
○	No further investigation/treatment required
◉	Treat with cabergoline ✕ Incorrect answer selected

This man has a co-incidentally detected pituitary macroadenoma.

The small elevation in prolactin probably reflects stalk compression and does not indicate that this is a prolactinoma. In macroprolactinomas, the prolactin concentration is greater than 2000 mU/L.

In this man's case, with no visual field defects and the tumour being distant from the chiasm, the most appropriate treatment would be observation with serial scanning to assess for any change in size that would then merit surgical intervention.

However, this man who is eupituitary may never encounter any growth in this co-incidentally detected non-functional pituitary tumour.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Which of the following drugs on her prescription is likely to have been responsible?

(Please select 1 option)

○	Aspirin
○	Augmentin
○	Oramorph
○	Paracetamol
◉	Sodium valproate ✓ Correct

AIP is an autosomal dominant disease resulting from defects in production or activity of the enzyme porphobilinogen (PBG) deaminase.

Attacks may be precipitated by fasting, and by many drugs, such as

- Phenobarbitone
- Alcohol
- Sulphonylureas
- Oestrogens.

Amoxicillin and opiates are thought to be safe in porphyria.

Further reading:
Porphyria, Acute Intermittent eMedicine

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Question: 3 of 100

A 25-year-old is admitted on the medical intake. She is ten weeks post partum and has been generally unwell for two weeks with malaise sweats and anxiety.

On examination she is haemodynamically stable and clinically euthyroid.

TFTs show the following:

Free T4	33 pmol/l	(9-23)
Free T3	8 nmol/l	(3.5-6)
TSH	<0.02 mU/l	(0.5-5)

What is the appropriate management?

(Please select 1 option)

- Carbimazole 40 mg/day
- Lugol's iodine
- Propranolol 20 mg tds
- Propylthiouracil 50 mg/tds
- Radioactive iodine therapy

Submit answer | Skip question | Tag Question | Remove question

Work Smart Session - MRCP Part 1

Time taken: 55 mins 59 secs

Question: 30 of 100

Which of the following statements is correct concerning the relationship between type 2 diabetes and colonic cancer?

(Please select 1 option)

◉	Increased concentrations of C-peptide are a marker of increased colorectal cancer risk
○	Insulin treatment increases recurrence free survival after treatment of colonic cancer
○	The increased risk of colorectal cancer in diabetes is related to BMI
○	The increased risk of colorectal cancer in diabetes is related to total cholesterol
○	Type 1 diabetes has similar risks of colonic cancer as does type 2 diabetes

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 57 mins 3 secs

Question: 30 of 100

Which of the following statements is correct concerning the relationship between type 2 diabetes and colonic cancer?

(Please select 1 option)

◉	Increased concentrations of C-peptide are a marker of increased colorectal cancer risk ✓ Correct
○	Insulin treatment increases recurrence free survival after treatment of colonic cancer
○	The increased risk of colorectal cancer in diabetes is related to BMI
○	The increased risk of colorectal cancer in diabetes is related to total cholesterol
○	Type 1 diabetes has similar risks of colonic cancer as does type 2 diabetes

Type 2 diabetes is associated with a 40-60% increase in the risk of cancer of the large bowel. This increase is linked to changes in HbA1c.

Type 2 diabetes is associated with significantly higher rates of overall mortality and reduced disease free and recurrence free survivals after chemotherapy/radiotherapy, and insulin has not been shown to have any effects on mortality.

No association has been found between colonic malignancy and type 1 diabetes, nor gestational diabetes.

For a discussion see BMJ 2005;330:551-2.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 57 mins 3 secs

Question: 31 of 100

A 26-year-old female with no previous history of diabetes presents with a first episode of diabetic ketoacidosis. There is no evidence of infection but she has recently commenced a new medication.

Which of the following drugs is implicated in precipitating diabetic ketoacidosis?

(Please select 1 option)

○	Olanzapine
○	Omeprazole
○	Progestogen only contraceptive pill
○	Sodium valproate
○	Venlafaxine

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 58 mins 38 secs

Question: 31 of 100

A 26-year-old female with no previous history of diabetes presents with a first episode of diabetic ketoacidosis. There is no evidence of infection but she has recently commenced a new medication.

Which of the following drugs is implicated in precipitating diabetic ketoacidosis?

(Please select 1 option)

○	Olanzapine ← This is the correct answer
○	Omeprazole
◉	Progestogen only contraceptive pill ✕ Incorrect answer selected
○	Sodium valproate
○	Venlafaxine

The atypical antipsychotics such as olanzapine have been implicated in precipitating diabetes as well as diabetic ketoacidosis.

Other drugs implicated include thiazide diuretics, beta sympathomimetics and steroids.

Next question

Remove Tag

Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 58 mins 38 secs

Question: 32 of 100

A 22-year-old female student presents acutely unwell with vomiting and dehydration. She has a two month history of weight loss and thirst.

Investigations confirm a diagnosis of diabetic ketoacidosis with a glucose of 29.3 mmol/L (3.0-6.0), a pH of 7.12 (7.36-7.44) on blood gas analysis and urinalysis reveals +++ ketones.

What percentage of type 1 diabetics are initially diagnosed following presentation with diabetic ketoacidosis?

(Please select 1 option)

○	5%
○	10%
○	15%
○	25%
○	40%

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 18 secs

Question: 32 of 100

A 22-year-old female student presents acutely unwell with vomiting and dehydration. She has a two month history of weight loss and thirst.

Investigations confirm a diagnosis of diabetic ketoacidosis with a glucose of 29.3 mmol/L (3.0-6.0), a pH of 7.12 (7.36-7.44) on blood gas analysis and urinalysis reveals +++ ketones.

What percentage of type 1 diabetics are initially diagnosed following presentation with diabetic ketoacidosis?

(Please select 1 option)

○	5%
○	10%
○	15%
○	25% ← This is the correct answer
◉	40% ✕ Incorrect answer selected

Approximately 25% of patients with type 1 diabetes will first present in diabetic ketoacidosis although often there are symptoms such as thirst, polyuria and weight loss which have been ignored.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Show tools

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 18 secs

Question: 33 of 100

Which of the following percentages most accurately reflects the mortality associated with the modern management of diabetic ketoacidosis?

(Please select 1 option)

○	0.5%
○	1%
○	2-3%
○	5-6%
○	8-10%

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 51 secs

Question: 33 of 100

Which of the following percentages most accurately reflects the mortality associated with the modern management of diabetic ketoacidosis?

(Please select 1 option)

○	0.5%
○	1%
◉	2-3% ✓ Correct
○	5-6%
○	8-10%

Despite the advances in the management of diabetes in general and the improvements in intensive care, studies reveal that the mortality associated with diabetic ketoacidosis remains stubbornly around the 2-5% since the 1970s.

Specifically, mortality relates to cerebral oedema.

Next question

Tag Question

Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 51 secs

Question: 34 of 100

A 30-year-old female who is 24 weeks pregnant presents with a blood pressure on three separate occasions of approximately 160/110 mmHg.

Her liver function tests (LFTs) show:

Aspartate transaminase	150 U/l	(5-45)
Alkaline phosphatase	213 U/l	(50-120)
Bilirubin	31 µmol/l	(0-18)

Which antihypertensive is indicated?

(Please select 1 option)

- Atenolol
- Irbesartan
- Labetalol
- Methyldopa
- Ramipril

Submit answer | Skip question | Tag Question | Remove question

Her liver function tests (LFTs) show:

Aspartate transaminase	150 U/l	(5-45)
Alkaline phosphatase	213 U/l	(50-120)
Bilirubin	31 µmol/l	(0-18)

Which antihypertensive is indicated?

(Please select 1 option)

- (●) Atenolol ✗ Incorrect answer selected
- ( ) Irbesartan
- ( ) Labetalol ← This is the correct answer
- ( ) Methyldopa
- ( ) Ramipril

Angiotensin-converting enzyme inhibitors are contraindicated in pregnancy as they cause renal dysgenesis in the fetus. For this reason A2RBs are also not recommended for use in pregnancy.

There is a theoretical risk of intrauterine growth retardation with the use of atenolol in pregnancy although the studies which showed this effect were done with very large doses of atenolol.

One would not utilise methyldopa in a patient with abnormal LFTs.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 3 mins 21 secs

Question: 35 of 100

A 25-year-old nurse presents with fatigue, tremulousness and a 7 kg weight loss over the past one month. On examination she has a tachycardia but no other abnormal findings.

Thyroid function tests show:

Free thyroxine	40 pmol/L (10-23)
TSH	<0.01 mU/L (0.5-5.0)

Which one of the following would confirm the diagnosis of thyroiditis?

(Please select 1 option)

- Elevated free T3 concentration
- Failure of TSH to rise following IV TRH
- High titre of thyroid peroxidase antibodies
- Negligible four hour radioiodine thyroid uptake
- Raised ESR

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Thyroid function tests show:

Free thyroxine	40 pmol/L (10-23)
TSH	<0.01 mU/L (0.5-5.0)

Which one of the following would confirm the diagnosis of thyroiditis?

(Please select 1 option)

- Elevated free T3 concentration
- Failure of TSH to rise following IV TRH
- High titre of thyroid peroxidase antibodies
- Negligible four hour radioiodine thyroid uptake ← This is the correct answer
- Raised ESR ✕ Incorrect answer selected

This test result and symptoms may be consistent with thyroiditis such as DeQuervain's and an elevated ESR with negligible uptake of RAI (as thyroid cells are attacked and hence release stored T4 but fail to synthesise T4) would be expected.

In Graves' disease you would expect homogenous uptake whereas a toxic nodule would show a solitary area of high uptake.

Antibodies such as TPO, and TSH receptor antibodies are found in autoimmune thyroid disease.

The TRH test is seldom used except in thyroid oncology.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 5 mins 16 secs

Question: 36 of 100

A 32-year-old male with type 1 diabetes undergoes a 24 hour urine collection.

Which of the following urine albumin concentrations signify microalbuminuria?

(Please select 1 option)

○	10 mg/day
○	50 mg/day
○	500 mg/day
○	1 g/day
○	3.5 g/day

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

A 32-year-old male with type 1 diabetes undergoes a 24 hour urine collection.

Which of the following urine albumin concentrations signify microalbuminuria?

(Please select 1 option)

○	10 mg/day
◉	50 mg/day ✓ Correct
○	500 mg/day
○	1 g/day
○	3.5 g/day

Microalbuminuria is defined as a urine albumin excretion of between 30-300 mg per 24 hours.

A concentration above 300 mg/24 hours signifies albuminuria and a concentration above 3.5 g/24 hours signifies overt proteinuria.

Microalbuminuria is not just an indictor of early renal involvement but it also identifies increased cardiovascular risk with an approximate two- fold cardiovascular risk above the already increased risk in the diabetic population.

A useful surrogate of the total albumin excretion is the albumin: creatinine ratio. The urinary albumin:creatinine ratio is measured using the first morning urine sample where practicable.

Microalbuminuria is indicated where there is an albumin:creatinine ratio ≥2.5 mg/mmol (men) or 3.5 mg/mmol (women).

Proteinuria is indicated by a ratio of ≥30 mg/mmol.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 6 mins 2 secs

Question: 37 of 100

A 43-year-old male is diagnosed with diabetic nephropathy. If this patient had type 1 diabetes his chances of progressing to end stage renal disease (ESRD) would be approximately 50%.

What percentage of patients with type 2 diabetes with diabetic nephropathy would be expected to progress to ESRD?

(Please select 1 option)

- 15%
- 30%
- 45%
- 50%
- 55%

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Question: 37 of 100

A 43-year-old male is diagnosed with diabetic nephropathy. If this patient had type 1 diabetes his chances of progressing to end stage renal disease (ESRD) would be approximately 50%.

What percentage of patients with type 2 diabetes with diabetic nephropathy would be expected to progress to ESRD?

(Please select 1 option)

○	15% ← This is the correct answer
○	30%
○	45%
○	50%
◉	55% ✕ Incorrect answer selected

Although the incidence of diabetic nephropathy is less in type 2 diabetics as approximately 90-95% of all diabetics are type 2s, the majority of patients with diabetic nephropathy are type 2 diabetics.

There are a number of stages in the development of nephropathy with glomerular hyperfiltration being an early feature. Nephropathy itself is signalled by the excretion of trace amounts of protein in the urine microalbuminuria.

The progression of the disease may be attenuated by stringent blood pressure control (with an angiotensin-converting enzyme inhibitor [ACEi]) and strict glycaemic control.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 7 mins 41 secs

Question: 38 of 100

A 62-year-old female with a six year history of type 2 diabetes attends for annual review. Her HbA1c is 10% (3.8-6.4).

Into what average plasma glucose concentration does her HbA1c translate?

(Please select 1 option)

- 7.5 mmol/l
- 10 mmol/l
- 12.5 mmol/l
- 15.5 mmol/l
- 19 mmol/l

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

(Please select 1 option)

○	7.5 mmol/l
○	10 mmol/l
◉	12.5 mmol/l ✗ Incorrect answer selected
○	15.5 mmol/l ← This is the correct answer
○	19 mmol/l

The HbA1c is an important reflection of control over a three month period (life expectancy of the erythrocyte).

There is a good relationship between the rise in glucose and its ability to glycosylate the Hb molecule (there is a difference between average plasma glucose and blood glucose).

Thus a HbA1c of 7% would translate into an average **plasma** (higher than value of **blood** glucose) glucose of 9.5 mmol/l and a HbA1c of 10% into 15.5 mmol/l.

This is the reason why so much emphasis is placed on controlling HbA1c rather than the specific glucose measurements, as these vary so much throughout the day.

This is a difficult question and it is very unlikely that you would be asked to translate average blood glucose into an exact HbA1c figure; however it is useful to realise that the numerical values are not the same.

Further reading:
Laboratory medicine in primary care: Glycated haemoglobin (HbA1c) monitoring Student BMJ

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 9 mins 19 secs

Question: 39 of 100

An 18-year-old woman presented with a history of 15 kg weight loss in the previous four months. She has been amenorrheic for some months.

On examination she had fine lanugo hair and a blood pressure of 110/60 mmHg.

Which one of the following laboratory results would support the most likely clinical diagnosis?

(Please select 1 option)

- ○ High plasma follicle stimulating hormone (FSH) concentration
- ○ Low plasma testosterone concentration
- ○ High serum ferritin concentration
- ○ Low plasma cortisol concentration
- ○ Suppressed thyroid stimulating hormone (TSH) concentration

Submit answer | Skip question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

some months.

On examination she had fine lanugo hair and a blood pressure of 110/60 mmHg.

Which one of the following laboratory results would support the most likely clinical diagnosis?

(Please select 1 option)

○	High plasma follicle stimulating hormone (FSH) concentration
○	Low plasma testosterone concentration
○	High serum ferritin concentration
○	Low plasma cortisol concentration
◉	Suppressed thyroid stimulating hormone (TSH) concentration ✓ Correct

The question alludes to a patient with anorexia nervosa.

Anorexia is associated with functional hypogonadotrophic hypogonadism with low FSH and luteinising hormone (LH) levels.

Cortisol levels may be increased but are typically within the 'normal range'. They may however, may fail to suppress with dexamethasone.

Plasma testosterone levels are normal in females with anorexia.

Basal levels of TSH may be depressed in anorexia, though T4 and T3 may be normal.

Ferritin levels are low in a state of malnutrition.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

TSH	<0.02 mU/l	(0.5-5)

What is the appropriate management?

(Please select 1 option)

- Carbimazole 40 mg/day
- Lugol's iodine
- Propranolol 20 mg tds ✓ Correct
- Propylthiouracil 50 mg/tds
- Radioactive iodine therapy

The diagnosis here is likely to be post partum thyroiditis which tends to occur within the three months of delivery, followed by a hypothyroid phase at three to six months, followed by spontaneous recovery in one third of cases.

In the remaining two-thirds a single-phase pattern or the reverse occurs.

Management is centred on symptomatic treatment using beta-blockers for relief of tremor or anxiety, and observation for the development of persistent hypo- or hyperthyroidism.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 5 mins 18 secs

Question: 4 of 100

A 70-year-old woman is referred by her GP with a breast lump.

She was asymptomatic but her investigations reveal:

Corrected calcium	2.72 mmol/L (2.2-2.6)
Phosphate	0.80 mmol/L (0.8-1.4)
Alkaline phosphatase	110 U/L (45-105)
PTH concentration	5.1 pmol/L (0.9-5.4)

What is the most likely diagnosis?

(Please select 1 option)

- Bony metastases
- Chronic vitamin D excess
- Ectopic PTH related peptide (PTHrp) secretion
- Multiple myeloma
- Primary hyperparathyroidism

Submit answer | Skip question | Tag Question | Remove question

Work Smart Session - MRCP Part 1

Question: 40 of 100

A 73-year-old woman presented with thirst and polyuria of six months duration.

She had suffered several episodes of lower back pain. She was on no medication. On examination she looked well, had a dorsal kyphosis and a blood pressure of 170/95 mmHg.

Investigations revealed:

Erythrocyte sedimentation rate	15 mm/1st hour (0-30)
Serum urea	11.9 mmol/L (2.5-7.5)
Serum creatinine	175 µmol/L (60-110)
Serum albumin	40 g/L (37-49)
Serum total calcium	2.98 mmol/L (2.2-2.6)

What is the most likely cause of this lady's hypercalcaemia?

(Please select 1 option)

- Metastatic breast cancer
- Myeloma
- Osteoporosis
- Primary hyperparathyroidism
- Sarcoidosis

Submit answer | Skip question | Tag Question | Remove question

Serum total calcium	2.98 mmol/L (2.2-2.6)

What is the most likely cause of this lady's hypercalcaemia?

(Please select 1 option)

- Metastatic breast cancer
- Myeloma
- Osteoporosis
- Primary hyperparathyroidism ✓ Correct
- Sarcoidosis

The prevalence of hyperparathyroidism is said to be four per 1000 in women over 60, and is two to three times more common in women than men.

The lower back pain may be loin pain due to renal colic caused by renal calculi or due to osteoporosis. The renal impairment may be associated with renal calculi, perhaps due to calculi-induced hydronephrosis in extreme cases. Renal impairment in hyperparathyroidism is not uncommon. Chronic hypercalcaemia can compromise the renal concentrating ability leading to polydipsia and polyuria.

The kyphosis may be due to osteoporosis which is commonly seen in conjunction with hyperparathyroidism. Classically, hypertension has been associated with hyperparathyroidism.

Associated with myeloma one would expect a drop in albumin concentration together with a markedly elevated ESR.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 12 mins 52 secs

Question: 41 of 100

A 40-year-old man is undergoing investigation for acromegaly.

MRI of the pituitary fossa is normal, but a routine chest x ray reveals a large centrally based mass. The patient is a non-smoker.

What is the most likely type of this lung tumour?

(Please select 1 option)

- Adenocarcinoma
- Carcinoid
- Large cell
- Small cell
- Squamous cell

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 21 mins 56 secs

Question: 41 of 100

A 40-year-old man is undergoing investigation for acromegaly.

MRI of the pituitary fossa is normal, but a routine chest x ray reveals a large centrally based mass. The patient is a non-smoker.

What is the most likely type of this lung tumour?

(Please select 1 option)

○	Adenocarcinoma
○	Carcinoid ← This is the correct answer
○	Large cell
◉	Small cell ✕ Incorrect answer selected
○	Squamous cell

A central based mass in a non-smoker showing clinical evidence of neuroendocrine cell origin is consistent with a carcinoid and surgery offers a very high chance of cure.

Next question

Remove Tag

Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 21 mins 56 secs

Question: 42 of 100

Which of the following hormones acts through cyclic AMP as the second messenger?

(Please select 1 option)

- Insulin
- Oestradiol
- PTH
- TRH
- Triiodothyronine

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

◉	PTH ✓ Correct
○	TRH
○	Triiodothyronine

Unlike steroids (progesterone, testosterone, oestradiol and cortisol) other ionic hormones such as:

- Adrenaline
- Growth hormone-releasing hormone (GHRH)
- Glucagon
- Luteinising hormone (LH)
- Follicle stimulating hormone (FSH)
- Parathyroid hormone (PTH)
- Thyroid-stimulating hormone (TSH)

are unable to pass the plasma membrane acting upon cell surface receptors and then through cyclic adenosine monophosphate (cAMP) as the second messenger.

Insulin acts through mitogen-activated protein (MAP) kinase pathway, as does growth hormone (GH) and prolactin.

- Thyroid releasing hormone (TRH)
- Gonadatrophin-releasing hormone (GnRH)
- Antidiuretic hormone (ADH)

act through calcium/phosphoinositide.

Nitric oxide and atrial natriuretic peptide (ANP) act through cyclic guanosine monophosphate (cGMP).

Triiodothyronine (T3) acts by binding to intracellular receptors.

Unlike steroids (progesterone, testosterone, oestradiol and cortisol) other ionic hormones such as:

- Adrenaline
- Growth hormone-releasing hormone (GHRH)
- Glucagon
- Luteinising hormone (LH)
- Follicle stimulating hormone (FSH)
- Parathyroid hormone (PTH)
- Thyroid-stimulating hormone (TSH)

are unable to pass the plasma membrane acting upon cell surface receptors and then through cyclic adenosine monophosphate (cAMP) as the second messenger.

Insulin acts through mitogen-activated protein (MAP) kinase pathway, as does growth hormone (GH) and prolactin.

- Thyroid releasing hormone (TRH)
- Gonadatrophin-releasing hormone (GnRH)
- Antidiuretic hormone (ADH)

act through calcium/phosphoinositide.

Nitric oxide and atrial natriuretic peptide (ANP) act through cyclic guanosine monophosphate (cGMP).

Triiodothyronine (T3) acts by binding to intracellular receptors.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Question: 43 of 100

A 60-year-old man is admitted with a productive cough with flecks of blood in his sputum.

Chest x ray reveals a mass lesion in the right mid zone.

Investigations reveal:

Sodium	110 mmol/L (137-144)
Potassium	4.0 mmol/L (3.5-4.9)
Bicarbonate	24 mmol/L (20-28)
Urea	3.0 mmol/L (2.5-7.5)
Creatinine	80 µmol/L (60-110)

Which of the following findings suggest a diagnosis of the syndrome of inappropriate ADH (SIADH) secretion?

(Please select 1 option)

- ○ Plasma osmolality 236 mosmol/kg (278-305)
- ○ Presence of ascites
- ○ Urine flow rate 20 mL/hour
- ○ Urine osmolality 250 mosmol/kg (350-1000)
- ○ Urine sodium 110 mmol/L

EN 7:36 PM 2/21/2011

Sodium	110 mmol/L (137-144)
Potassium	4.0 mmol/L (3.5-4.9)
Bicarbonate	24 mmol/L (20-28)
Urea	3.0 mmol/L (2.5-7.5)
Creatinine	80 µmol/L (60-110)

Which of the following findings suggest a diagnosis of the syndrome of inappropriate ADH (SIADH) secretion?

(Please select 1 option)

- ○ Plasma osmolality 236 mosmol/kg (278-305)
- ○ Presence of ascites
- ○ Urine flow rate 20 mL/hour
- ◉ Urine osmolality 250 mosmol/kg (350-1000) ✕ Incorrect answer selected
- ○ Urine sodium 110 mmol/L ← This is the correct answer

The serum osmolality associated with hyponatraemia is generally low and so would not in itself suggest SIADH.

However, in the context of the low plasma osmolality a high urine osmolality (2x that of the plasma osmolality) with an elevated urine sodium (above 20 mmol/L) is suggestive of this diagnosis.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 25 mins 4 secs

Question: 44 of 100

A 23-year-old woman with type 1 diabetes (T1DM) of three years duration, presents for annual review with weight loss.

She had normal menstrual cycles and bowel habit was unchanged.

On examination her BMI was 23 kg/m^2 and investigations revealed a haemoglobin of 7 g/dL (11.5-16.5) and a MCV of 69 fL (80-96).

Which of the following is the most likely diagnosis?

(Please select 1 option)

- Anorexia nervosa
- Bacterial overgrowth
- Beta-thalassaemia minor
- Coeliac disease
- Crohn's disease

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Question: 44 of 100

A 23-year-old woman with type 1 diabetes (T1DM) of three years duration, presents for annual review with weight loss.

She had normal menstrual cycles and bowel habit was unchanged.

On examination her BMI was 23 kg/m^2 and investigations revealed a haemoglobin of 7 g/dL (11.5-16.5) and a MCV of 69 fL (80-96).

Which of the following is the most likely diagnosis?

(Please select 1 option)

○	Anorexia nervosa
○	Bacterial overgrowth
○	Beta-thalassaemia minor
◉	Coeliac disease ✓ Correct
○	Crohn's disease

Coeliac disease is the likely option as this patient has autoimmune disease (T1DM), an iron deficiency anaemia and little in the way of symptoms.

Bacterial overgrowth is associated with profuse diarrhoea and a macrocytosis due to vitamin B12 consumption.

Crohn's disease again would be expected to be symptomatic.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 26 mins 24 secs

Question: 45 of 100

A 47-year-old schoolteacher presents to her GP with fatigue.

The GP noted her to be hypercalcaemic with an albumin of 39 g/L (37-49), globulin of 28g/L and Ca^{++} of 2.80 mmol/l (2.2-2.6).

Which of the following statements is true?

(Please select 1 option)

○	24 hour urinary calcium assay is of no use at all.
○	Modern assays for PTH and PTHrp may cross-react so assays are unreliable.
○	Primary hyperparathyroidism will be diagnosed only if the PTH is at least three times the normal range.
○	The most likely diagnosis is myeloma.
○	The patient could have surgery if renal stones are found on ultrasound

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Which of the following statements is true?

(Please select 1 option)

○	24 hour urinary calcium assay is of no use at all.
○	Modern assays for PTH and PTHrp may cross-react so assays are unreliable.
○	Primary hyperparathyroidism will be diagnosed only if the PTH is at least three times the normal range.
○	The most likely diagnosis is myeloma.
◉	The patient could have surgery if renal stones are found on ultrasound ✓ Correct

Twenty four hour urinary calcium may be useful if used in comparison to the serum calcium in order to distinguish familial hypocalciuric hypercalcaemia from primary hyperparathyroidism.

Parathyroid hormone (PTH) may be less than twice the upper limit of normal in primary hyperparathyroidism.

Several indications for surgery exist including:

- Calcium more than1 mg/dl above upper normal limit
- Greater than 30% decline in renal function
- Renal stones
- Age less than 50
- Unwillingness of patient to follow advice of medical surveillance.

Myeloma is unlikely given the normal immunoglobulins.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 28 mins 53 secs

Question: 46 of 100

These are the blood gas results obtained from a 20-year-old female admitted to hospital.

Hydrogen ion concentration	35 nmol/l	(35-45)
pH	7.45	(7.36-7.44)
pCO_2	6.8 kPa	(4.7-6.0)
Bicarbonate	32 mmol/l	(20-28)

Which of the following is the most likely cause of this patient's acid-base derangement?

(Please select 1 option)

- Amitriptyline overdose
- Cushing's syndrome
- Hepatic failure
- Pregnancy
- Salicylate poisoning

Submit answer | Skip question | Tag Question | Remove question

Hydrogen ion concentration	35 nmol/l	(35-45)
pH	7.45	(7.36-7.44)
pCO_2	6.8 kPa	(4.7-6.0)
Bicarbonate	32 mmol/l	(20-28)

Which of the following is the most likely cause of this patient's acid-base derangement?

(Please select 1 option)

- ○ Amitriptyline overdose
- ○ Cushing's syndrome
- ○ Hepatic failure
- ◉ Pregnancy ✓ Correct
- ○ Salicylate poisoning

This patient has a mild metabolic alkalosis with what appears to be respiratory compensation as reflected by the elevated pCO_2.

Amitriptyline overdose is associated with acidosis as is salicylate poisoning.

Hepatic failure usually presents with acidosis.

This type of picture is associated with prolonged vomiting (as in pregnancy), diarrhoea, diuretic therapy and in Cushing's syndrome, or in those receiving high dose corticosteroids. With no other information provided for this case, common things being common, one should select pregnancy as the best answer for a 20-year-old female.

Next question | Tag Question | Remove question

Question: 47 of 100

An 80-year-old male presents with a brief history of weakness and giddiness following an episode of diarrhoea.

He has been taking bendroflumethiazide for the last three years.

On examination his pulse is 100 beats per minute with a blood pressure of 130/80 mmHg (lying) and 100/70 mmHg (standing).

Investigations reveal:

Sodium	120 mmol/L (137-144)
Potassium	5.5 mmol/L (3.5-4.9)
Urea	13 mmol/L (2.5-7.5)
Creatinine	130 µmol/L (60-110)
Random plasma glucose	13 mmol/L (<11.1)

What is the most likely cause of the hyponatraemia?

(Please select 1 option)

- ○ Bendroflumethiazide
- ○ Diarrhoea
- ○ Hyperglycaemia
- ○ Inappropriate secretion of antidiuretic hormone
- ○ Renal tubular acidosis

Random plasma glucose	13 mmol/L (<11.1)

What is the most likely cause of the hyponatraemia?

(Please select 1 option)

- Bendroflumethiazide
- Diarrhoea
- Hyperglycaemia
- Inappropriate secretion of antidiuretic hormone
- Renal tubular acidosis ✓ Correct

The patient has diabetes as reflected by the elevated random glucose, has hyponatraemia, renal impairment and mild hyperkalaemia which appears to have been precipitated following diarrhoea.

Hypoadrenalism is unlikely as he has hyperglycaemia and the hyperglycaemia would itself be expected to cause a dehydration and hence hypernatraemia.

This sort of picture in an elderly male with diabetes is typical of hyporeninaemic hypoaldosteronsim - type IV RTA - and could be exacerbated both by the diarrhoea and by the diuretic.

It is unlikely that the diarrhoea alone has caused the hyponatraemia.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 32 mins 42 secs

Question: 48 of 100

You have been called to the ward by the senior nurse, to review a repeat calcium result. The repeat result is 3.9 mmol/l (2.2-2.6), the previous result four hours earlier was 3.2.

The patient has a disseminated malignancy with an unknown primary.

Which of the following statements is most correct when considering the hypercalcaemia of malignancy?

(Please select 1 option)

- A prolonged QT interval is associated with hypercalcaemia
- Bisphosphonates inhibit osteoblast function thereby lowering calcium
- Calcitonin is of greater benefit than bisphosphonates in the treatment of hypercalcaemia of malignancy
- NSAIDs are indicated for bone pain in this patient
- On neurological examination, hyporeflexia may be exhibited

Submit answer | Skip question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

The patient has a disseminated malignancy with an unknown primary.

Which of the following statements is most correct when considering the hypercalcaemia of malignancy?

(Please select 1 option)

○	A prolonged QT interval is associated with hypercalcaemia
○	Bisphosphonates inhibit osteoblast function thereby lowering calcium
◉	Calcitonin is of greater benefit than bisphosphonates in the treatment of hypercalcaemia of malignancy ✕ Incorrect answer selected
○	NSAIDs are indicated for bone pain in this patient
○	On neurological examination, hyporeflexia may be exhibited ← This is the correct answer

This is an oncological emergency.

Hyporeflexia is a common clinical sign in patients with hypercalcaemia.

Non-steroidal anti-inflammatory drugs (NSAIDs) should not be prescribed in patients with hypercalcaemia as they reduce renal blood flow thus inhibiting urinary calcium excretion.

Bisphosphonates inhibit bone resorption by osteoclasts, and are the first line pharmacological treatment of hypercalcaemia of malignancy; calcitonin use is limited by its association with anaphylaxis.

Electrocardiogram changes in hypercalcaemia include bradycardia, prolonged PR interval, short QT interval, widened T waves and arrhythmias.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 38 mins 42 secs

Question: 49 of 100

Which of the following statements concerning transferrin is correct?

(Please select 1 option)

- In the absence of anaemia transferrin is 80% saturated with iron
- Levels are elevated in haemochromatosis
- Levels are elevated in patients on the oral contraceptive pill
- Transferrin binds ferrous iron
- Transferrin levels fall during pregnancy

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 39 mins 37 secs

Question: 49 of 100

Which of the following statements concerning transferrin is correct?

(Please select 1 option)

○	In the absence of anaemia transferrin is 80% saturated with iron
○	Levels are elevated in haemochromatosis
◉	Levels are elevated in patients on the oral contraceptive pill ✓ Correct
○	Transferrin binds ferrous iron
○	Transferrin levels fall during pregnancy

Pregnancy and the oral contraceptive pill (OCP) both increase transferrin levels. Iron is carried in the blood bound to transferrin. Fe^{2+} (ferrous iron) is oxidised to Fe^{3+} (ferric iron) by caeruloplasmin to bind to transferrin which is about one third saturated with iron.

The saturation of transferrin (plasma iron concentration/TIBC x 100) is used as a measure of iron stores. A value below 16% is indicative of iron deficiency.

The transferrin level and the TIBC rise in iron deficiency. Pregnancy and the OCP both increase transferrin levels; whereas transferrin and TIBC fall in iron overload, percentage saturation is increased in haemochromatosis.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Corrected calcium	2.72 mmol/L (2.2-2.6)
Phosphate	0.80 mmol/L (0.8-1.4)
Alkaline phosphatase	110 U/L (45-105)
PTH concentration	5.1 pmol/L (0.9-5.4)

What is the most likely diagnosis?

(Please select 1 option)

- (●) Bony metastases ✗ Incorrect answer selected
- ( ) Chronic vitamin D excess
- ( ) Ectopic PTH related peptide (PTHrp) secretion
- ( ) Multiple myeloma
- ( ) Primary hyperparathyroidism ← This is the correct answer

This patient has hypercalcaemia with a borderline low phosphate concentration but an inappropriately normal parathyroid hormone (PTH) concentration.

This suggests hyperparathyroidism, which is a relatively common disorder amongst elderly females.

The story of the breast lump in this case is endeavouring to throw the candidate.

Vitamin D excess would be expected to cause an elevated phosphate.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 8 mins 14 secs

Question: 5 of 100

Which of the following statements regarding individuals with porphobilinogen (PBG) deaminase deficiency is correct?

(Please select 1 option)

○	Excrete faecal PBG between acute attacks
○	Experience significant photosensitivity
○	Have a greater than 75% chance of remaining asymptomatic throughout their lives
○	Have markedly increased faecal protoporphyrin excretion during attacks
○	When manifesting clinical disease generally present within the first decade of life

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Question: 50 of 100

A 40-year-old female who has been prescribed thyroid replacement therapy has routine thyroid function tests.

On examination she appeared clinically euthyroid with no abnormal findings.

Her thyroid function tests revealed:

TSH	3.2 mU/L (0.4-5.0)
Total T_4	20 nmol/L (55-144)
Free T_4	2.6 pmol/L (10-22)
Total T_3	2.5 nmol/L (0.9-2.8)

Which one of the following statements is correct?

(Please select 1 option)

- Her thyroid hormone replacement is adequate
- Investigation of pituitary function is required
- She has a thyroiditis
- She has sick euthyroid syndrome
- She has tertiary hypothyroidism

Submit answer | Skip question | Tag Ques

Avira
Guard: Autorun blocked
Date/Time: 18/03/32, 07:22:49
Type: Autorun blocked
Access to the file 'G:\autorun.inf' was blocked for your security.
Additional information on this is available in the help.
OK

Which one of the following statements is correct?

(Please select 1 option)

○	Her thyroid hormone replacement is adequate ← This is the correct answer
○	Investigation of pituitary function is required
◉	She has a thyroiditis ✕ Incorrect answer selected
○	She has sick euthyroid syndrome
○	She has tertiary hypothyroidism

This question is extremely poorly presented as no one, except for the RCP, measures total thyroid hormone concentrations.

However, this patient has normal TSH, low total T_4 with normal total T_3 and really low free T_4 which would suggest that she is taking T3 as replacement therapy. This may explain why no fT_3 figures are provided.

Consequently she is receiving adequate replacement as reflected by the normal thyroid-stimulating hormone (TSH).

She does not have sick euthyroidism as it states in the run in that these measurements were routine. Although TSH is normal and tT_4 and fT_4 low, secondary/tertiary hypothyroidism would not explain the plum normal total T_3 concentration.

She may well have had a thyroiditis such as Hashimoto's to have given her the hypothyroidism originally but she is now on replacement therapy and the former would not explain her thyroid function tests.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 1 mins 40 secs

Question: 51 of 100

Which of the following cell types are linked with the substance they synthesise ?

(Please select 1 option)

○	Gastric chief cells - intrinsic factor
○	Islet A cells - somatostatin
◉	Islet B cells - amylin ✓ Correct
○	Islet D cells - pancreatic polypeptide
○	Islet F cells - glucagon

Islet beta cells produce insulin and amylin, as well as C-peptide, pro-insulin and gamma-aminobutyric acid (GABA).

- Islet D cells produce somatostatin
- F cells produce pancreatic polypeptide and
- A cells produce glucagon
- Gastric chief cells produce pepsinogen whilst
- Gastric parietal cells produce acid and intrinsic factor.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

http://my.onexamination.com/Assessment/Que
Questions Set : REF4605
Demonoid.me

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 1 mins 40 secs

Question: 52 of 100

A patient with type 1 diabetes displays typical symptoms of hypoglycaemic unawareness.

Which of the following statements regarding hypoglycaemic unawareness is correct?

(Please select 1 option)

○	Alcohol inhibits gluconeogenesis in patients with hypoglycaemia unawareness
○	Glucose sensing occurs in the locus caeruleus
○	Recurrent hypoglycaemia has no long term consequences on higher cerebral function
○	Recurrent hypoglycaemia is most commonly associated with poor diabetic control
○	Selective beta-blockers are an important cause of hypoglycaemia unawareness

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Question: 52 of 100

A patient with type 1 diabetes displays typical symptoms of hypoglycaemic unawareness.

Which of the following statements regarding hypoglycaemic unawareness is correct?

(Please select 1 option)

◉	Alcohol inhibits gluconeogenesis in patients with hypoglycaemia unawareness ✓ Correct
○	Glucose sensing occurs in the locus caeruleus
○	Recurrent hypoglycaemia has no long term consequences on higher cerebral function
○	Recurrent hypoglycaemia is most commonly associated with poor diabetic control
○	Selective beta-blockers are an important cause of hypoglycaemia unawareness

Alcohol

- Inhibits gluconeogenesis
- Decreases peripheral hypoglycaemic responses and
- Impairs perception of symptoms of hypoglycaemia.

There is no evidence to suggest that beta-blockers cause hypoglycaemic unawareness.

Glucose sensing occurs in the hypothalamus, and there is evidence to suggest that chronic, and recurrent hypoglycaemia may have deleterious effects on higher cerebral function.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 3 mins 2 secs

Question: 53 of 100

Which of the following is not a feature of zinc deficiency?

(Please select 1 option)

- Dwarfism
- Geophagia
- Hepatosplenomegaly
- Hypertelorism
- Hypogonadism

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Question: 53 of 100

Which of the following is not a feature of zinc deficiency?

(Please select 1 option)

○	Dwarfism
○	Geophagia
○	Hepatosplenomegaly
◉	Hypertelorism ✓ Correct
○	Hypogonadism

Zinc deficiency is associated with

- Dwarfism
- Hypogonadism
- Hepatosplenomegaly
- Rough and dry skin
- Mental lethargy and
- Geophagia.

Zinc supplementation has also been shown to improve neuropsychological function in Chinese children, and zinc deficiency is associated with adverse pregnancy outcomes.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Question: 54 of 100

A 55-year-old male presents with anorexia and weight loss of 12 months duration. Over this year he has had two deep vein thromboses (DVTs) and had the last whilst his INR was 2 (less than 1.4).

He remains on long term warfarin therapy with an INR above 2.6. Examination reveals that he is pigmented and has a postural drop in his blood pressure of 15 mmHg.

Investigations are as follows:

Sodium	131 mmol/l	(137-144)
Potassium	5.0 mmol/l	(3.5-4.9)
INR	3.0	(<1.4)

A short Synacthen test reveals a baseline cortisol concentration at time 0 of 120 nmol/l which rises to 155 nmol/l after 30 minutes (normal response greater than 550 nmol/l).

Which single diagnosis would explain this patient's illness?

(Please select 1 option)

- Addison's disease
- Antiphospholipid syndrome
- Autoimmune polyendocrine syndrome (Schmidt's disease)
- Pituitary infarction
- Protein S deficiency

http://my.onexamination.com/Assessment/Que
Questions Set : REF4392
Torrent list - Demonoid

(Please select 1 option)

○	Addison's disease
◉	Antiphospholipid syndrome ✓ Correct
○	Autoimmune polyendocrine syndrome (Schmidt's disease)
○	Pituitary infarction
○	Protein S deficiency

With a history of recurrent DVT and confirmed hypoadrenalism, this patient is likely to have the antiphospholipid syndrome. Antiphospholipid syndrome is a primary diagnosis or may co-exist with systemic lupus erythematosus.

Anticardiolipin antibodies or lupus anticoagulant may be present.

It is associated with arterial and venous thrombosis and has a predilection for the adrenal veins causing adrenal infarction with consequent hypoadrenalism.

Addison's disease is an autoimmune phenomenon and is not associated with DVT.

The pigmentation (due to increased adrenocorticotropic hormone [ACTH] in hypoadrenalism) would exclude pituitary infarction as the cause of the hypoadrenalism.

Hypoadrenalism is not associated with protein S deficiency.

Autoimmune polyendocrine syndrome is associated with

- Hypothyroidism
- Type 1 diabetes
- Addison's disease.

EN 7:08 PM 2/21/2011

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 33 mins 16 secs

Question: 55 of 100

A 55-year-old female undergoes a DEXA scan which reveals a bone mineral density (BMD) T score of -2.55 at the hip and lumbar spine.

Which of the following may contribute to such a result?

(Please select 1 option)

○	Acromegaly
○	Delayed menopause
○	Hypothyroidism
○	Myeloma
○	Obesity

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

◉	Myeloma ✓ Correct
○	Obesity

This patient has osteoporosis as defined by her abnormally low T score.

Endocrine diseases associated with osteoporosis are

- Cushing's disease
- Vitamin D deficiency
- Thyrotoxicosis and
- Hypogonadism.

Myeloma and lymphoma are also associated with reduced BMD.

Other associates include

- Rheumatoid arthritis
- Renal failure
- Corticosteroids
- Early menopause
- Slender habitus
- Smoking
- Lack of exercise
- Family history
- Age/sex and
- Excess alcohol.

http://my.onexamination.com/Assessment/Que
Questions Set : REF4321
File Edit View Favorites Tools Help

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 36 mins 7 secs

Question: 56 of 100

With which of the following is hyperprolactinaemia associated?

(Please select 1 option)

- Cabergoline therapy
- Depression
- Fluoxetine therapy
- Hyperthyroidism
- Sheehan's syndrome

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

With which of the following is hyperprolactinaemia associated?

(Please select 1 option)

○	Cabergoline therapy
◉	Depression ✗ Incorrect answer selected
○	Fluoxetine therapy ← This is the correct answer
○	Hyperthyroidism
○	Sheehan's syndrome

Hyperprolactinaemia may manifest as a milky discharge from the breasts.

The causes include:

- Prolactinoma
- Hypothyroidism (far increased thyrotropin-releasing hormone [TRH])
- Non-functional tumour with stalk compression and
- Drugs, in particular dopamine antagonists such as chlorpromazine, haloperidol and domperidone.

Pregnancy is a particularly common cause of hyperprolactinaemia.

Other drugs that are occasionally reported include selective serotonin reuptake inhibitors (SSRIs).

Polycystic ovary syndrome (PCOs) is often associated with idiopathic hyperprolactinaemia.

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 37 mins 25 secs

Question: 57 of 100

A 36-year-old male with insulin-dependent diabetes mellitus (IDDM) of three years duration presented with decreased libido and erectile dysfunction since diagnosis. No abnormalities were noted on genital examination.

Investigations revealed:

plasma testosterone	6.0 nmol/L (9 - 35)
plasma follicle stimulating hormone	1.0 u/L (1-8)

Which of the following investigations is the most appropriate next step?

(Please select 1 option)

- ○ Autonomic function testing
- ○ Doppler studies of penile artery
- ○ Nerve conduction studies
- ◉ Serum ferritin
- ○ Serum prolactin

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

○	Autonomic function testing
○	Doppler studies of penile artery
○	Nerve conduction studies
◉	Serum ferritin ✓ Correct
○	Serum prolactin

This IDDM patient appears to have hypogonadotrophic hypogonadism (HH) as reflected by low testosterone and low follicle-stimulating hormone (FSH).

The combination is compatible with a diagnosis of haemochromatosis and measuring ferritin would be a reasonable investigation.

Haemochromatosis typically causes hypogonadotrophic hypogonadism as a consequence of the ferritin deposition within the pituitary rather than primary testicular dysfunction.

Autonomic nerve dysfunction is one of the commoner causes of impotence in a person with diabetes but in this case is not the cause of his HH.

For similar reasons, both nerve conduction studies and Doppler studies are irrelevant.

Prolactin would be a sensible measurement but probably if you were looking to confirm a diagnosis that incorporates the diabetes as well, ferritin would be the investigation of choice.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 48 mins 25 secs

Question: 58 of 100

Which of the following is not associated with hyponatraemia and hyperkalaemia?

(Please select 1 option)

○	Acute hypoadrenalism
○	Carbenoxolone therapy
○	Co-amilofruse therapy
○	Congestive cardiac failure.
○	Type IV renal tubular acidosis

Submit answer | Skip question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 49 mins 8 secs

Question: 58 of 100

Which of the following is not associated with hyponatraemia and hyperkalaemia?

(Please select 1 option)

○	Acute hypoadrenalism
○	Carbenoxolone therapy ← This is the correct answer
○	Co-amilofruse therapy
○	Congestive cardiac failure.
◉	Type IV renal tubular acidosis ✕ Incorrect answer selected

Carbenoxolone therapy may be associated with hypokalaemia and salt retention due to pseudohypoaldosteronism through inhibition of the enzyme 11 beta hydroxysteroid dehydrogenase.

Type IV renal tubular acidosis is associated with hyporeninaemic hypoaldosteronism and both hyponatraemia and hyperkalaemia can occur.

Hypoadrenalism is associated with hyperkalaemia and hyponatraemia as is cardiac failure, hepatic and renal failure.

Co-amilofruse the combination of amiloride and furosemide may also produce this biochemical picture.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 49 mins 8 secs

Question: 59 of 100

A 21-year-old woman is known to suffer from anorexia nervosa.

Which of the following metabolic disturbances would be a characteristic finding?

(Please select 1 option)

○	A decrease in cortisol levels
○	An increase in LH levels
○	Hyperkalaemia
○	Impaired glucose tolerance
○	Raised androgen levels

Submit answer | Skip question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

○	A decrease in cortisol levels
○	An increase in LH levels
○	Hyperkalaemia
◉	Impaired glucose tolerance ✓ Correct
○	Raised androgen levels

Malnutrition is another cause of diabetes. (Can you name the others? ... Type 1 and Type 2 OK ... but what about gestational or post pancreatitis / pancreatectomy ... do you know the others? Read more ...).

Cortisol and growth hormone levels are elevated.

Luteinising hormone (LH) and follicle-stimulating hormone (FSH) would be low and LH response to luteinising-hormone releasing hormone (LHRH) is impaired when weight loss is severe.

Hypokalaemia (not hyperkalaemia) may be seen.

Also there may be

- Hypoalbuminaemia
- Anaemia
- Leukopenia
- Raised serum carotene.

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 9 mins 23 secs

Question: 5 of 100

Which of the following statements regarding individuals with porphobilinogen (PBG) deaminase deficiency is correct?

(Please select 1 option)

○	Excrete faecal PBG between acute attacks
○	Experience significant photosensitivity
○	Have a greater than 75% chance of remaining asymptomatic throughout their lives ← This is the correct answer
◉	Have markedly increased faecal protoporphyrin excretion during attacks ✕ Incorrect answer selected
○	When manifesting clinical disease generally present within the first decade of life

Porphobilinogen (PBG) deaminase deficiency is the basis of acute intermittent porphyria (AIP).

Photosensitivity is unusual in AIP and patients excrete urinary PBG between and during acute attacks.

Faecal porphyrin excretion is usually normal or slightly increased.

Clinical disease is manifested more frequently in females, and only rarely presents before puberty: 90% of affected individuals remain asymptomatic throughout their lives.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Show tools

Work Smart Session - MRCP Part 1

Question: 6 of 100

A 40-year-old man was referred to the endocrine clinic for his resistant hypertension.

He is taking the following medications: atenolol 50 mg once daily, ramipril 10 mg once daily, doxazosin 4 mg daily, amlodipine 10 mg daily and bendroflumethiazide 2.5 mg daily.

On examination his pulse was 64 beats per minute, his blood pressure was 162/96 mmHg, heart sounds were normal and there were no cushingoid features.

Investigations showed:

Serum urea	4.4 mmol/L	(2.5-7.5)
Serum creatinine	88 µmol/L	(60-110)
Serum potassium	3.6 mmol/L	(3.5-4.9)

Which is the most important medication to be discontinued before testing his aldosterone/plasma renin activity ratio?

(Please select 1 option)

- Amlodipine
- Atenolol
- Bendroflumethiazide
- Doxazosin
- Ramipril

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 49 mins 56 secs

Question: 60 of 100

A 73-year-old female is diagnosed with Cushing's disease.

Which of the following is correct?

(Please select 1 option)

○	Adrenalectomy would be the treatment of choice.
○	op-DDD is a treatment if unfit for surgery
○	Ketoconazole may be used as a treatment if unfit for surgery
○	Recurrence of Cushing's disease after transphenoidal surgery is less than 5%
○	Yttrium implantation is an effective treatment

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

A 73-year-old female is diagnosed with Cushing's disease.

Which of the following is correct?

(Please select 1 option)

○	Adrenalectomy would be the treatment of choice.
○	op-DDD is a treatment if unfit for surgery
○	Ketoconazole may be used as a treatment if unfit for surgery ← This is the correct answer
◉	Recurrence of Cushing's disease after transphenoidal surgery is less than 5% ✕ Incorrect answer selected
○	Yttrium implantation is an effective treatment

Transphenoidal hypophysectomy/ adenomectomy would be the initial treatment of choice.

Laparoscopic adrenalectomy would be advised where pituitary surgery has failed.

Ketoconazole may be an effective treatment for patients unfit for surgery.

opDDD is used for adrenal carcinomas.

Yttrium implantation has been abandoned even for acromegaly as it is pretty useless.

The recurrence rate for Cushing's disease after surgery is of the order of 20-30% in most series and depends on the size of the tumour with macroadenomas having a higher rate of relapse.

Next question

Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 51 mins 9 secs

Question: 61 of 100

Which of the following compounds has a vasodilating effect?

(Please select 1 option)

- Antidiuretic hormone (ADH)
- Calcitonin gene related peptide
- Endothelin
- Renin
- Somatostatin

Submit answer | Skip question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 51 mins 56 secs

Question: 61 of 100

Which of the following compounds has a vasodilating effect?

(Please select 1 option)

○	Antidiuretic hormone (ADH)
◉	Calcitonin gene related peptide ✓ Correct
○	Endothelin
○	Renin
○	Somatostatin

ADH acts on the vasopressor receptors to cause vasoconstriction.

Endothelin is also a vasoconstrictor as is renin.

Somatostatin is also recognised to produce vasoconstriction of the splanchnic system.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 51 mins 56 secs

Question: 62 of 100

Which of the following suggests a diagnosis of familial combined hyperlipidaemia (FCHL) rather than heterozygous familial hypercholesterolaemia (FH)?

(Please select 1 option)

○	Absence of hyperuricaemia
○	Presence of arcus senilus
○	Presence of glucose intolerance
○	Strong family history of premature coronary artery disease
○	Tendon xanthomas

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Help
- Shop

○	Presence of arcus senilus
○	Presence of glucose intolerance ← This is the correct answer
○	Strong family history of premature coronary artery disease
◉	Tendon xanthomas ✕ Incorrect answer selected

The genetic dislipidaemias occur in one third of patients who have suffered from their first myocardial infarction below the age of 50 years in men.

The commonest is familial combined hyperlipidaemia (two thirds), with a fifth due to familial hypercholesterolaemia. The former can be diagnosed only on family studies, and there is elevation of fasting plasma tricglycerides not associated with hypercylomicronaemia.

It is autosomal dominant, and some family members may have hypercylomicronaemia.

Only 20% of children have elevated triglycerides before the age of 25.

Obesity, insulin resistance, hyperinsulinaemia, glucose intolerance, and hyperuricaemia are associated.

Heterozygous familial hypercholesterolaemia is dominantly inherited, and results from defects in the low-density lipoprotein (LDL) receptor. The most important clinical manifestation is premature coronary artery disease, particularly with onset between the third or fourth decade.

Tendon xanthomata and arcus cornea are rarely present in children, but are very important signs to identify.

Copyright © 2002 Dr Colin Melville

Next question | Remove Tag | Remove question

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 52 mins 36 secs

Question: 63 of 100

Which one of the following concerning insulin is correct?

(Please select 1 option)

- Acts via a similar mechanism to steroid receptors
- Can be detected in the lymph
- Causes an increased glucose-protein transport on the endoplasmic reticulum
- Interacts with the nuclear membrane
- Is synthesised in the alpha cells of Islets of Langerhans

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 53 mins 30 secs

Question: 63 of 100

Which one of the following concerning insulin is correct?

(Please select 1 option)

○	Acts via a similar mechanism to steroid receptors
○	Can be detected in the lymph ← This is the correct answer
○	Causes an increased glucose-protein transport on the endoplasmic reticulum
◉	Interacts with the nuclear membrane ✕ Incorrect answer selected
○	Is synthesised in the alpha cells of Islets of Langerhans

Insulin acts via cell surface receptors.

Insulin binding to its receptor results in receptor autophosphorylation on tyrosine residues and the tyrosine phosphorylation of insulin receptor substrates (IRS-1, IRS-2 and IRS-3) by the insulin receptor tyrosine kinase.

Insulin is synthesised in the beta cells of the Islets of Langerhans not the alpha cells.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Show tools

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 53 mins 30 secs

Question: 64 of 100

Which of the following concerning diabetic retinopathy is correct?

(Please select 1 option)

○	Improved glycaemic control is more effective than hypertensive control in reducing progression of disease.
○	Is unusual in patients with type 2 diabetes
○	Normal visual acuity is seen in proliferative retinopathy.
○	Progression may be reduced with statin therapy
○	Soft exudates are a feature of background retinopathy.

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Question: 64 of 100

Which of the following concerning diabetic retinopathy is correct?

(Please select 1 option)

○	Improved glycaemic control is more effective than hypertensive control in reducing progression of disease.
○	Is unusual in patients with type 2 diabetes
◉	Normal visual acuity is seen in proliferative retinopathy. ✓ Correct
○	Progression may be reduced with statin therapy
○	Soft exudates are a feature of background retinopathy.

Diabetic retinopathy occurs in both type 1 and 2 DM and may be a presenting feature in type 2 as the condition may have existed for many years prior to diagnosis.

Progression may be slowed with improved glycaemic and hypertensive control but the latter has been shown to be more effective at reducing progression (UKPDS).

There are no data at present to suggest that statin therapy reduces disease progression.

Soft exudates are a feature of pre-proliferative Rn and despite quite marked new vessel disease the visual acuity may be normal.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 54 mins 28 secs

Question: 65 of 100

Which of the following is true concerning a 68-year-old male with type 2 diabetes diagnosed with type IV renal tubal acidosis (RTA)?

(Please select 1 option)

○	Aminoaciduria would be expected
○	Fludrocortisone treatment is effective
○	Increased glomerular filtration rate (GFR) is expected
○	Increased urinary bicarbonate would be expected
○	Normal renal handling of K^+ and H^+

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 55 mins 37 secs

Question: 65 of 100

Which of the following is true concerning a 68-year-old male with type 2 diabetes diagnosed with type IV renal tubal acidosis (RTA)?

(Please select 1 option)

○	Aminoaciduria would be expected
◉	Fludrocortisone treatment is effective ✓ Correct
○	Increased glomerular filtration rate (GFR) is expected
○	Increased urinary bicarbonate would be expected
○	Normal renal handling of K^+ and H^+

H^+ secretion, sodium reabsorption and ammonia production diminishes.

RTA 4 is, in effect, hyporeninaemic hypoaldosteronism or failure of aldosterone action, and thus helped treated with mineralocorticoids. It is usually seen in chronic renal disease and hence low GFR and particularly.

Aminoaciduria and increased urine bicarbonate are features of RTA types 1 and 2.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Show tools

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 55 mins 37 secs

Question: 66 of 100

Which one of the following is a recognised feature of achondroplasia?

(Please select 1 option)

○	Autosomal recessive inheritance
○	May be diagnosed radiologically at birth
○	Increased liability to pathological fractures
○	Shortened spine
○	Subfertility

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Question: 66 of 100

Which one of the following is a recognised feature of achondroplasia?

(Please select 1 option)

◉	Autosomal recessive inheritance ✕ Incorrect answer selected
○	May be diagnosed radiologically at birth ← This is the correct answer
○	Increased liability to pathological fractures
○	Shortened spine
○	Subfertility

Achondroplasia an autosomal dominant condition and one of the commonest forms of inherited dwarfism.

Epiphyseal dysplasia - thin zone of cartilage cells, diminished columnar arrangement short thick bones, spinal length almost always normal.

Features - short limbs, normal trunk, large head, saddle nose, exagerrated lumbar lordosis normal mental and sexual development, spinal problems.

Homozygotes - neonatal death.

(Harrisons)

Next question

Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 56 mins 31 secs

Question: 67 of 100

Which one of the following is true concerning antidiuretic hormone (ADH)?

(Please select 1 option)

- Carbamazepine potentiates its release
- Ethanol potentiates its release
- It circulates in the blood bound to neurohypophysin
- It is a cyclic octapeptide
- It is synthesised in the posterior pituitary

Submit answer | Skip question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Question: 67 of 100

Which one of the following is true concerning antidiuretic hormone (ADH)?

(Please select 1 option)

○	Carbamazepine potentiates its release ← This is the correct answer
◉	Ethanol potentiates its release ✗ Incorrect answer selected
○	It circulates in the blood bound to neurohypophysin
○	It is a cyclic octapeptide
○	It is synthesised in the posterior pituitary

ADH is a nonapeptide manufactured in the paraventricular and supra-optic nuclei of the hypothalamus and released from the posterior pituitary.

It acts on the collecting ducts improving water permeability and hence water retention.

Carbamazepine as well as other agents such as thiazides and selective serotin reuptake inhibitors (SSRIs) may potentiate its release.

Ethanol usually inhibits release.

http://acbrown.com/kidney/Lectures/RnWatr/RnWatrAntiTrmn.htm

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 57 mins 9 secs

Question: 68 of 100

Which of the following is a feature of pseudohypoparathyroidism?

(Please select 1 option)

○	Increased urinary phosphate and cAMP with PTH infusion
○	Low serum calcium and high serum phosphate
○	Low serum calcium and low serum phosphate
○	Low serum PTH
○	Shortened second and third metacarpals

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 59 mins 11 secs

Question: 68 of 100

Which of the following is a feature of pseudohypoparathyroidism?

(Please select 1 option)

○	Increased urinary phosphate and cAMP with PTH infusion
◉	Low serum calcium and high serum phosphate ✓ Correct
○	Low serum calcium and low serum phosphate
○	Low serum PTH
○	Shortened second and third metacarpals

The biochemistry shows a hypocalcaemia with hyperphosphataemia being usual but elevated parathyroid hormone (PTH) due to resistance to PTH.

This is due to mutation of the PTH receptor with abnormality of the Gsalpha subunit with reduced cyclic adenosine monophosphate (cAMP) production following a PTH infusion.

There are associated phenotypic signs including short stature, low IQ and shortened fourth and fifth metacarpals.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 59 mins 11 secs

Question: 69 of 100

A 19-year-old woman became breathless while travelling on an aeroplane.

Which one of the following features most strongly supports a diagnosis of acute hyperventilation related to a panic disorder?

(Please select 1 option)

○	Carpal spasm
○	Finger paraesthesia
○	Hypotension
○	Light-headedness
○	Loss of conciousness

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

A 19-year-old woman became breathless while travelling on an aeroplane.

Which one of the following features most strongly supports a diagnosis of acute hyperventilation related to a panic disorder?

(Please select 1 option)

○	Carpal spasm ← This is the correct answer
◉	Finger paraesthesia ✗ Incorrect answer selected
○	Hypotension
○	Light-headedness
○	Loss of conciousness

We need to distinguish between the signs that may be expected in the tachypnoea associated with the hypoxia from a pulmonary embolism (PE) or any other serious respiratory problem and the hyperventilation with increased pO_2 in a panic attack.

A carpal spasm would be most likely to reflect this.

Finger paraesthesia can occur with PE, as can hypotension, light-headedness and loss of conciousness.

Carpal spasm is found in association with hyperventilation due to the respiratory alkalosis which results in a reduction in ionised calcium concentration.

Next question

Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Shop

Investigations showed:

Serum urea	4.4 mmol/L	(2.5-7.5)
Serum creatinine	88 µmol/L	(60-110)
Serum potassium	3.6 mmol/L	(3.5-4.9)

Which is the most important medication to be discontinued before testing his aldosterone/plasma renin activity ratio?

(Please select 1 option)

- ○ Amlodipine
- ○ Atenolol ← This is the correct answer
- ○ Bendroflumethiazide
- ○ Doxazosin
- ◉ Ramipril ✕ Incorrect answer selected

Beta-blockers and spironolactone need to be discontinued prior to measuring aldosterone and renin concentrations.

Beta-blockers cause an elevation of the renin concentrations and hence produce a spuriously low PRA:aldosterone ratio.

Angiotensin-converting enzyme (ACE) inhibitors on the other hand may actually improve the sensitivity of the test.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Question: 7 of 100

A 26-year-old woman was being treated in the outpatient clinic for autoimmune hypothyroidism.

She was taking 150µg of thyroxine and 200 mg of amiodarone.

Investigations reveal:

Plasma prolactin	654 mU/L	(<360)
Plasma free T4	24 pmol/L	(10-22)
Plasma free T3	5.2 pmol/L	(5-10)
Plasma thyroid-stimulating hormone	68 mU/L	(0.4-5)

What is the most likely explanation for her high TSH levels?

(Please select 1 option)

- Amiodarone effect
- Hyperprolactinaemia
- Poor compliance with medications
- Thyroid hormone resistance
- TSH producing pituitary adenoma

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

http://my.onexamination.com/Assessment/Que
Questions Set : REF3909
My Account
Sign Out
Work Smart
Work Hard
Saved Tests
Revision Advice
Tagged Questions

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 59 mins 56 secs

Question: 70 of 100

A 50-year-old man presents with a diagnosis of acromegaly but has normal visual fields.

Which of the following is the most appropriate treatment for this patient?

(Please select 1 option)

○	Bromocriptine
○	Cabergoline
○	Radiotherapy
○	Somatostatin analogue therapy
○	Trans-sphenoidal hypophysectomy

Submit answer | Skip question | Tag Question | Remove question

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 3 hrs 31 secs

Question: 71 of 100

A 41-year-old woman presented asking for treatment to prevent osteoporosis. She was one year post-menopausal, is aware of flushes at night and has a family history of osteoporosis.

Which one of the following therapies would be most appropriate?

(Please select 1 option)

- ○ Calcium and vitamin D supplements
- ○ Continuous oestrogen
- ○ Cyclical etidronate and calcium
- ○ Cyclical oestrogen and progestogen
- ○ Vitamin D supplements

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Which one of the following therapies would be most appropriate?

(Please select 1 option)

◉	Calcium and vitamin D supplements ✕ Incorrect answer selected
○	Continuous oestrogen
○	Cyclical etidronate and calcium
○	Cyclical oestrogen and progestogen ← This is the correct answer
○	Vitamin D supplements

This patient with a family history of osteoporosis is one year post-menopausal and has symptoms.

Calcium and vitamin D supplements with a good diet would be unnecessary and are unproven in this age group.

There is no suggestion that she has had a hysterectomy and so an unopposed oestrogen would be contra-indicated.

Etidronate is licensed for the prevention of further osteoporotic fractures, prophylaxis against corticosteroid induced osteoporosis and use when hormone replacement therapy (HRT) is contra-indicated.

In this patient's case, and in the absence of any specific contra-indications - thromboembolic disease, breast cancer - combined HRT would be the treatment of choice despite the recent literature indicating increased risk of vascular disease. One would use HRT in the symptomatic (menopausal symptoms) but not in the asymptomatic where possibly bisphosphonates would be preferred.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Dashboard
Questions
Scores
Community
Help
Shop

Work Smart Session - MRCP Part 1

Time taken: 3 hrs 6 mins 2 secs

Question: 72 of 100

A 55-year-old man presents with gynaecomastia. He is receiving treatment for heart failure and gastro-oesophageal reflux.

Which of the following drug he takes is most likely to be responsible for his gynaecomastia?

(Please select 1 option)

- Amitryptiline
- Carvedilol
- Furosemide
- Omeprazole
- Ramipril

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Which of the following drug he takes is most likely to be responsible for his gynaecomastia?

(Please select 1 option)

○	Amitryptiline
○	Carvedilol
○	Furosemide
◉	Omeprazole ✓ Correct
○	Ramipril

Like cimetidine, omeprazole is associated with gynaecomastia.

The other agents are not associated.

Other causes of gynaecomastia include

- spironolactone
- amiloride
- to a lesser extent eplerenone
- digoxin
- luteinising hormone-releasing hormone (LHRH) analogues
- finasteride.

Next question

Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 3 hrs 6 mins 42 secs

Question: 73 of 100

A previously fit 47-year-old male presents with lower back pain from a vertebral collapse due to osteoporosis.

Which of the following investigations would be the most appropriate for this man?

(Please select 1 option)

- Oestrogen concentration
- Prolactin concentration
- Prostate-specific antigen concentration
- Testosterone concentration
- Thyroid function tests

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

A previously fit 47-year-old male presents with lower back pain from a vertebral collapse due to osteoporosis.

Which of the following investigations would be the most appropriate for this man?

(Please select 1 option)

○	Oestrogen concentration
○	Prolactin concentration
○	Prostate-specific antigen concentration
○	Testosterone concentration ← This is the correct answer
◉	Thyroid function tests ✕ Incorrect answer selected

Osteoporosis in a young male would be unusual.

Any symptoms or features of hypogonadism or hypercalcaemia should be elicited.

Hyperprolactinaemia causes hypogonadism so a testosterone concentration would be far more relevant.

Hyperthryoidism would need to be present for a considerable length of time before producing osteoporosis.

Hypogonadism often goes unnoticed.

Prostate malignancy does not cause osteoporosis.

Next question

Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 3 hrs 7 mins 38 secs

Question: 74 of 100

Which of the following suggests a poorer prognosis for thyroid cancer?

(Please select 1 option)

○	Age less than 30.
○	Cold nodule on thyroid uptake scan
○	High TSH concentration
○	Male sex.
○	Papillary thyroid cancer with cervical node involvement.

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 3 hrs 8 mins 21 secs

Question: 74 of 100

Which of the following suggests a poorer prognosis for thyroid cancer?

(Please select 1 option)

○	Age less than 30.
○	Cold nodule on thyroid uptake scan
○	High TSH concentration
◉	Male sex. ✓ Correct
○	Papillary thyroid cancer with cervical node involvement.

Factors that suggest a poor prognosis in thyroid cancer include

- Increasing age
- Male sex
- Poorly diffferentiated histological features and
- Distant spread.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 3 hrs 8 mins 21 secs

Question: 75 of 100

A 50-year-old man with a history of diabetis mellitus and hypertension attends an ophthalmic clinic for regular assessment.

On fundoscopy he is diagnosed to have preproliferative diabetic retinopathy.

Which of the following is characteristic of preproliferative diabetic retinopathy?

(Please select 1 option)

- Hard exudates
- Macular oedema
- Microaneurysms
- New vessels at the disc
- Venous beading

Submit answer | Skip question | Tag Question | Remove question

Dashboard
Questions
Scores
Community
Help
Shop

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

A 50-year-old man with a history of diabetis mellitus and hypertension attends an ophthalmic clinic for regular assessment.

On fundoscopy he is diagnosed to have preproliferative diabetic retinopathy.

Which of the following is characteristic of preproliferative diabetic retinopathy?

(Please select 1 option)

◉	Hard exudates ✗ Incorrect answer selected
○	Macular oedema
○	Microaneurysms
○	New vessels at the disc
○	Venous beading ← This is the correct answer

Microaneurysms and hard exudates are features of background diabetic retinopathy.

Macular oedema is associated with microaneurysms and hard exudates and is due to fluid leakage but is not necessarily a feature pre-proliferative or proliferative retinopathy although it may still require laser photocoagulation.

Venous beading, loops and soft exudates (cotton wool spots) are characteristic of the ischaemia associated with preproliferative diabetic retinopathy.

New vessels suggest proliferative retinopathy.

Next question

Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 3 hrs 9 mins 44 secs

Question: 76 of 100

When considering diabetic retinopathy which of the following statements is most accurate?

(Please select 1 option)

- A. Microaneurysms (MA) represent sacular dilatation of retinal arterioles
- B. Hard exudates (HE) represent calcium deposites in the retina
- C. Cotton wool spots (CWS) represent infarcts of the nerve fibre layer of the retina
- D. Haemorrhages close to the fovea are not potentially sight threatening
- E. Laser photocoagulation is applied directly to new vessels to destroy them

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 3 hrs 10 mins 48 secs

Question: 76 of 100

When considering diabetic retinopathy which of the following statements is most accurate?

(Please select 1 option)

◉	A. Microaneurysms (MA) represent sacular dilatation of retinal arterioles ✕ Incorrect answer selected
○	B. Hard exudates (HE) represent calcium deposites in the retina
○	C. Cotton wool spots (CWS) represent infarcts of the nerve fibre layer of the retina ← This is the correct answer
○	D. Haemorrhages close to the fovea are not potentially sight threatening
○	E. Laser photocoagulation is applied directly to new vessels to destroy them

A. MAs are capillary aneurysms.

B. HEs are collections of exudated lipid and protein.

C. This is correct, multiple CWS are a pre-proliferative sign.

D. Haemorrhages (or HEs) close to the fovea represent a risk of macular oedema and are therefore sight threatening.

E. Laser destroys ischaemic but viable retina to reduce the secretion of angiogenic growth factors and allow new vesel regression, it is not applied directly to new vessels as this would cause bleeding.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 3 hrs 10 mins 48 secs

Question: 77 of 100

You are consulted by a 52-year-old man with type 2 diabetes diagnosed for a year.

His blood pressure is 156/88 mmHg, his cholesterol is 5.3 mmol/L (<5.2), he has a BMI of 29 and does not smoke. His HbA1c is 7.9% (3.8-6.4), he currently takes only metformin 500mg bd.

Which of the following is the single intervention most likely to reduce his overall risk of microvascular and macrovascular events?

(Please select 1 option)

- Antihypertensive therapy
- Aspirin therapy
- Statin therapy
- Sulphonylurea therapy
- Weight reduction

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Which of the following is the single intervention most likely to reduce his overall risk of microvascular and macrovascular events?

(Please select 1 option)

○	Antihypertensive therapy ← This is the correct answer
○	Aspirin therapy
○	Statin therapy
○	Sulphonylurea therapy
◉	Weight reduction ✕ Incorrect answer selected

The UKPDS showed that effective antihypertensive therapy reduced the risk of cardiovascular events and microvascular complications.

Lowering HbA1c only resulted in a significant reduction in microvascular events.

Lipid lowering therapy benefits patients with diabetes as much as those without diabetes in preventing macrovascular events in sub group analyses but has no effect on microvascular events demonstrated so far.

Aspirin is recommended to type 2 patients with one other cardiovascular risk factor but there is little trial evidence of efficacy.

Weight reduction may reduce progression to overt diabetes from states of impaired glucose tolerance but has not been demonstrated to reduce microvascular risk in diabetes.

Next question

Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 3 hrs 12 mins 21 secs

Question: 78 of 100

A 19-year-old female is concerned following exposure to meningococcal meningitis. Her flatmate contracted meningococcal meningitis and she now wants preventative treatment. She is generally well without any past medical history. She takes Logynon as a contraceptive agent and uses a salbutamol inhaler infrequently.

Which prophylactic anti-microbial treatment would you select?

(Please select 1 option)

- Augmentin
- Ciprofloxacin
- Clarithromycin
- Doxycycline
- Rifampicin

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 3 hrs 13 mins 52 secs

Question: 78 of 100

A 19-year-old female is concerned following exposure to meningococcal meningitis. Her flatmate contracted meningococcal meningitis and she now wants preventative treatment. She is generally well without any past medical history. She takes Logynon as a contraceptive agent and uses a salbutamol inhaler infrequently.

Which prophylactic anti-microbial treatment would you select?

(Please select 1 option)

○	Augmentin
○	Ciprofloxacin ← This is the correct answer
○	Clarithromycin
○	Doxycycline
◉	Rifampicin ✕ Incorrect answer selected

Rifampicin is a reasonable choice as prophylaxis against meningococcal infection but in this 19-year-old sexually active student may be expected to reduce the efficacy of the oral contraceptive through liver enzyme induction.

Therefore Ciproxin would be the most appropriate agent from the above list as it does not induce cytochrome p450.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 3 hrs 13 mins 52 secs

Question: 79 of 100

Which of the following is a glycoprotein hormone?

(Please select 1 option)

- Cortisol
- Growth hormone releasing hormone
- Oxytocin
- Thyrotropin (TSH)
- Thyrotropin releasing hormone (TRH)

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 3 hrs 14 mins 48 secs

Question: 79 of 100

Which of the following is a glycoprotein hormone?

(Please select 1 option)

○	Cortisol
○	Growth hormone releasing hormone
○	Oxytocin
○	Thyrotropin (TSH) ← This is the correct answer
◉	Thyrotropin releasing hormone (TRH) ✕ Incorrect answer selected

Thyrotropin is glycosylated, cortisol is a steroid hormone and the others are peptide hormones/neuropeptides which as a group are rarely glycosylated.

Next question

Remove Tag

Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Plasma free T4	24 pmol/L	(10-22)
Plasma free T3	5.2 pmol/L	(5-10)
Plasma thyroid-stimulating hormone	68 mU/L	(0.4-5)

What is the most likely explanation for her high TSH levels?

(Please select 1 option)

- Amiodarone effect
- Hyperprolactinaemia
- Poor compliance with medications ✓ Correct
- Thyroid hormone resistance
- TSH producing pituitary adenoma

This young woman has a slightly elevated thyroxine (T4) and an elevated thyroid-stimulating hormone (TSH).

The most probable explanation is poor compliance. This also explains the slightly high prolactin concentration too; a consequence of reduced dopaminergic tone on the lactotrophs.

The typical scenario is that the patients take their medication in the days before the clinic.

This is a classic MRCP question and is highly discriminating. Consider this one carefully and try to understand fully why this is not an effect of amiodarone.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 13 mins 27 secs

Question: 8 of 100

A 40-year-old female presents with fatigue.

She has a six month history of secondary amenorrhoea and galactorrhoea.

Examination shows an obese lady with a BMI of 36 kg/m^2. Neurological examination is normal. A prolactin is measured at 3124 mU/L (normal <550mU/L) and thyroid function tests reveal a free T4 of 7.5 nmol/l and a TSH of 120 mU/l . A CT scan shows a bulky pituitary gland.

Which of the following is the likely diagnosis?

(Please select 1 option)

○	Cushing's syndrome
○	Hypothyroidism
○	Macroprolactinoma
○	Microprolactinoma
○	Type 2 diabetes

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 3 hrs 14 mins 48 secs

Question: 80 of 100

The thyroid hormone receptor is:

(Please select 1 option)

- A cell surface receptor
- A cytoplasmic protein
- A gated ion channel
- A G-protein coupled receptor
- A nuclear receptor

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 3 hrs 17 mins 59 secs

Question: 80 of 100

The thyroid hormone receptor is:

(Please select 1 option)

○	A cell surface receptor
○	A cytoplasmic protein
○	A gated ion channel
○	A G-protein coupled receptor
◉	A nuclear receptor ✓ Correct

The thyroid hormone receptor is a nuclear receptor.

When it binds T3 it is able to bind to the thyroid hormone response element (TRE) in the promoter region of thyroid hormone responsive genes and initiates transcription.

Next question

Tag Question

Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 3 hrs 17 mins 59 secs

Question: 81 of 100

A 75-year-old man is admitted with a blood sugar of 40 mmol/l and lobar pneumonia and dies despite treatment.

Post-mortem examination reports the presence of amyloid polypeptide on pancreatic histology.

Which of the following would be suggested by this?

(Please select 1 option)

- That he has chronic pancreatitis as a cause of diabetes
- That he has diabetes secondary to amyloidosis
- That he has type 1 diabetes
- That he has type 2 diabetes
- This can be a non-specific finding

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 3 hrs 20 mins 32 secs

Question: 81 of 100

A 75-year-old man is admitted with a blood sugar of 40 mmol/l and lobar pneumonia and dies despite treatment.

Post-mortem examination reports the presence of amyloid polypeptide on pancreatic histology.

Which of the following would be suggested by this?

(Please select 1 option)

○	That he has chronic pancreatitis as a cause of diabetes
○	That he has diabetes secondary to amyloidosis
○	That he has type 1 diabetes
◉	That he has type 2 diabetes ✓ Correct
○	This can be a non-specific finding

The presence of amyloid polypeptide on pancreatic histology is highly suggestive of type 2 diabetes.

Although the primary defect in type 2 diabetes is insulin resistance, loss of insulin secretory function over time does occur in patients with type 2 diabetes and reduction in beta cell mass due to amyloid deposition may partly account for this.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 3 hrs 20 mins 32 secs

Question: 82 of 100

A 32-year-old male physical education teacher has a three year history of type 1 diabetes.

At the last annual review his HbA1c was 6.8% but he complains of hypoglycaemic events particularly during exercise. He has been commenced on the insulin analogue - Lispro insulin.

Compared with conventional short-acting insulins what is the advantage of insulin analogue therapy?

(Please select 1 option)

- Longer duration of action
- Reduces the incidence of hypoglycaemic events
- Reduces the incidence of long term diabetic complications
- Reduces post-prandial glucose concentrations
- Significant improvement in HbA1c

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Question: 82 of 100

A 32-year-old male physical education teacher has a three year history of type 1 diabetes.

At the last annual review his HbA1c was 6.8% but he complains of hypoglycaemic events particularly during exercise. He has been commenced on the insulin analogue - Lispro insulin.

Compared with conventional short-acting insulins what is the advantage of insulin analogue therapy?

(Please select 1 option)

○	Longer duration of action
○	Reduces the incidence of hypoglycaemic events
○	Reduces the incidence of long term diabetic complications
◉	Reduces post-prandial glucose concentrations ✓ Correct
○	Significant improvement in HbA1c

The short acting insulin analogue, Lispro, has a rapid onset of action and a shorter duration of action than conventional short acting soluble insulins.

Consequently studies reveal reduced post-prandial glucose concentrations versus soluble insulin and potentially a reduced incidence of hypoglycaemia although the evidence for this is lacking.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 3 hrs 24 mins 3 secs

Question: 83 of 100

A 29-year-old female presents with headaches.

She is noted to be hypertensive with a blood pressure of 180/100 mmHg and initial investiagtions reveal a hypokalaemia of 2.9 mmol/L (3.5-4.9). On closer questioning she is found to consume a large quantity of licquorice.

Inhibition of which enzyme is responsible for the pseudohyperaldosteronism associated with liquorice?

(Please select 1 option)

○	17 Alpha hydroxylase (17aOH)
○	5 Alpha-reductase
○	11 Beta hydroxylase (11 bOH)
○	11 Beta hydroxysteroid dehydrogenase (11 bHSD)
○	21 Hydroxylase

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Question: 83 of 100

A 29-year-old female presents with headaches.

She is noted to be hypertensive with a blood pressure of 180/100 mmHg and initial investiagtions reveal a hypokalaemia of 2.9 mmol/L (3.5-4.9). On closer questioning she is found to consume a large quantity of licquorice.

Inhibition of which enzyme is responsible for the pseudohyperaldosteronism associated with liquorice?

(Please select 1 option)

○	17 Alpha hydroxylase (17aOH)
○	5 Alpha-reductase
○	11 Beta hydroxylase (11 bOH)
◉	11 Beta hydroxysteroid dehydrogenase (11 bHSD) ✓ Correct
○	21 Hydroxylase

11bHSD is responsible for the conversion of cortisol to the inactive cortisone, preventing activation of the mineralocorticoid receptor by cortisol but permitting activation by aldosterone.

Both liquorice and carbenoxolone inhibit 11bHSD and produce pseudohyperaldosteronism with hypertension and hypokalaemia yet appropriately low renin and aldosterone concentrations.

Much research is focused upon this enzyme of late.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 3 hrs 26 mins 12 secs

Question: 84 of 100

A 33-year-old female presents with tiredness and lethargy.

Five years previously she had undergone a frontal surgery for a craniopharyngioma following presentation with amenorrhoea and headache. Post-operatively she developed seizures and was treated with sodium valproate.

She was demonstrated to be hypopituitary and receives hydrocortisone, thyroxine, oestrogen replacement therapy and desmopressin.

Which of the following investigations would you select to confirm a growth hormone deficiency (GHD)?

(Please select 1 option)

○	Clonidine test
○	GHRH/arginine test
○	IGF-1 concentration
○	Insulin tolerance test
○	L-dopa test

Submit answer | Skip question | Tag Question | Remove question

A 33-year-old female presents with tiredness and lethargy.

Five years previously she had undergone a frontal surgery for a craniopharyngioma following presentation with amenorrhoea and headache. Post-operatively she developed seizures and was treated with sodium valproate.

She was demonstrated to be hypopituitary and receives hydrocortisone, thyroxine, oestrogen replacement therapy and desmopressin.

Which of the following investigations would you select to confirm a growth hormone deficiency (GHD)?

(Please select 1 option)

○	Clonidine test
○	GHRH/arginine test ← This is the correct answer
○	IGF-1 concentration
◉	Insulin tolerance test ✕ Incorrect answer selected
○	L-dopa test

This patient is more than likely to be GH deficient which would explain the lethargy but this requires confirmation before initiating treatment.

Although an insulin tolerance test is the gold standard for the diagnosis of GHD, it is contraindicated due to the epilepsy.

Therefore GHRH/arginine is regarded as a suitable alternative.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 3 hrs 27 mins 41 secs

Question: 85 of 100

A 72-year-old male presents with a two month history of weight loss and weakness.

Examination reveals a BMI of 24.5 kg/m^2 and a blood pressure of 146/90 mmHg.

Examination of the lower limbs reveals a bilateral weakness of knee extension. He is unable to rise from the squatting position. There is absence of the knee reflex but the ankle reflexes are preserved and both plantars are flexor. There are no abnormalities on sensory examination.

Which of the following tests may be diagnostic?

(Please select 1 option)

○	Oral glucose tolerance test
○	Thyroid function test
○	Urine free cortisol concentration
○	Vitamin B12 concentration
○	Vitamin D concentration

Submit answer | Skip question | Tag Question | Remove question

Examination reveals a BMI of 24.5 kg/m^2 and a blood pressure of 146/90 mmHg.

Examination of the lower limbs reveals a bilateral weakness of knee extension. He is unable to rise from the squatting position. There is absence of the knee reflex but the ankle reflexes are preserved and both plantars are flexor. There are no abnormalities on sensory examination.

Which of the following tests may be diagnostic?

(Please select 1 option)

○	Oral glucose tolerance test ← This is the correct answer
○	Thyroid function test
○	Urine free cortisol concentration
◉	Vitamin B12 concentration ✕ Incorrect answer selected
○	Vitamin D concentration

This patient presents with weight loss, and reduced quadriceps strength, bilaterally with absent knee reflexes. This is a typical presentation of diabetic amyotrophy.

Osteomalacia, hyperthyroidism and Cushing's would be unlikely as the proximal myopathy involves quadriceps and hamstrings and knee reflexes would be preserved.

Subacute combined degeneration of the cord does not present with such features.

Next question

Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 3 hrs 32 mins 44 secs

Question: 86 of 100

A 17-year-old with type 1 diabetes presents for annual review.

He takes three times daily short acting insulin with evening dose long acting insulin. His glycaemic control is good as reflected by an HbA1c of 6.5% (3.8-6.4).

He seeks advice regarding his ability to pursue a future career.

Which one of the following occupations would he be able to pursue?

(Please select 1 option)

- A chef in the army catering corps
- An oil rig engineer
- A police officer
- A steward on board a cruise liner
- An airline steward

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

A 17-year-old with type 1 diabetes presents for annual review.

He takes three times daily short acting insulin with evening dose long acting insulin. His glycaemic control is good as reflected by an HbA1c of 6.5% (3.8-6.4).

He seeks advice regarding his ability to pursue a future career.

Which one of the following occupations would he be able to pursue?

(Please select 1 option)

◉	A chef in the army catering corps ✗ Incorrect answer selected
○	An oil rig engineer
○	A police officer
○	A steward on board a cruise liner
○	An airline steward ← This is the correct answer

Careers opportunities are affected by insulin use in diabetes mellitus and it is important to know these restrictions in order that you can provide appropriate advice to your patient.

Any employment in the armed forces, fire service or police force is not permissible unless already a member of the armed forces.

Offshore work also is not an option.

Next question

Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 3 hrs 54 mins 56 secs

Question: 87 of 100

A 60-year-female presents with vague aches and pains and has a family history of osteoporosis. She is 10 years post-menopausal but has not taken any female HRT.

Dual energy x ray absorptiometry (DEXA) is requested.

Which of the following values of bone mineral density measured by DEXA would signify osteopenia at a measured site?

(Please select 1 option)

○	A T score of -2.6
○	A T score of -1.8
○	A Z score of -2.0
○	A z score of -1.5
○	A T score of -0.9

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

A 60-year-female presents with vague aches and pains and has a family history of osteoporosis. She is 10 years post-menopausal but has not taken any female HRT.

Dual energy x ray absorptiometry (DEXA) is requested.

Which of the following values of bone mineral density measured by DEXA would signify osteopenia at a measured site?

(Please select 1 option)

○	A T score of -2.6
◉	A T score of -1.8 ✓ Correct
○	A Z score of -2.0
○	A z score of -1.5
○	A T score of -0.9

Osteopenia is defined as a T score of between -1 and -2.5 standard deviations below the bone mineral density of a young female.

Osteoporosis is defined as <-2.5 SD.

These measurements are important as they signify a greatly increased risk of fracture.

Z scores refer to the bone mineral density compared with that of a 'normal' age matched subject.

Next question

Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 3 hrs 56 mins 40 secs

Question: 88 of 100

Wich of the following is correct concerning nitric oxide?

(Please select 1 option)

○	Acts via cAMP as the second messenger
○	Inhibits platelet aggregation
○	Is inactivated by superoxide dismutase
○	Is manufactured from glycine
○	Is synthesised principally by the vascular smooth muscle

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 3 hrs 57 mins 58 secs

Question: 88 of 100

Wich of the following is correct concerning nitric oxide?

(Please select 1 option)

○	Acts via cAMP as the second messenger
○	Inhibits platelet aggregation ← This is the correct answer
○	Is inactivated by superoxide dismutase
○	Is manufactured from glycine
◉	Is synthesised principally by the vascular smooth muscle ✕ Incorrect answer selected

Nitric oxide is a free radical that is produced from l-arginine by nitric oxide synthase in the vascular endothelium.

It is anti-atherogenic, causing vasorelaxation, inhibiting platelet aggregation and foam cell formation.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 3 hrs 57 mins 58 secs

Question: 89 of 100

Which of the following is correct regarding the peroxisome proliferator activated receptor gamma (PPAR gamma)?

(Please select 1 option)

- Is a G-protein coupled receptor
- Is a member of the cytokine receptor superfamily
- Is activated by free fatty acid as the endogenous ligand
- Is antagonised by low density lipoprotein (LDL).
- Is antagonised by thiazolinediones

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

http://my.onexamination.com/Assessment/Que
onexamination.com

Work Smart Session - MRCP Part 1

Time taken: 4 hrs 36 secs

Question: 89 of 100

Which of the following is correct regarding the peroxisome proliferator activated receptor gamma (PPAR gamma)?

(Please select 1 option)

○	Is a G-protein coupled receptor
○	Is a member of the cytokine receptor superfamily
○	Is activated by free fatty acid as the endogenous ligand ← This is the correct answer
○	Is antagonised by low density lipoprotein (LDL).
◉	Is antagonised by thiazolinediones ✕ Incorrect answer selected

PPAR gamma is an intracellular receptor that is activated by free fatty acids (which are the natural endogenous ligands) and the thiazolinediones such as pioglitazone.

On ligand binding it associates with the retinoid X receptor and couples with DNA producing downstream gene activation with protein synthesis that controls adipocyte differentiaition and function and is also related to cellular anti-inflammatory effects.

Two licensed medications existed in the thiazolidinedione class, rosiglitazone and pioglitazone, but rosiglitazone has been suspended from the european market due to concerns about its benefit risk ratio.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

(normal <550mU/L) and thyroid function tests reveal a free T4 of 7.5 nmol/l and a TSH of 120 mU/l . A CT scan shows a bulky pituitary gland.

Which of the following is the likely diagnosis?

(Please select 1 option)

○	Cushing's syndrome
○	Hypothyroidism ← This is the correct answer
◉	Macroprolactinoma ✕ Incorrect answer selected
○	Microprolactinoma
○	Type 2 diabetes

Hypothyroidism is not an uncommon cause of hyperprolactinaemia and should be part of the work up of all patients with an elevated prolactin.

The clinical scenario here would be consistent with a diagnosis of hypothyroidism.

Macroprolactin may masquerade as hyperprolactinaemia and most laboratories now carry out this assay if requested in patients with hyperprolactinaemia. Cabergoline or bromocriptine should only be commenced if a macroprolactinoma is confirmed.

A bulky pituitary gland on CT scan is not a significant finding and an MRI of the pituitary is required to delineate the anatomy of the pituitary gland.

Bitemporal hemianopia would be a feature of a macroprolactinoma impinging on the optic chiasm.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 15 mins 7 secs

Question: 9 of 100

A 55-year-old man with type 2 diabetes has noticed elevation of his blood glucose levels on a new treatment for his lipids.

He says his diet and exercise levels are unchanged his HbA1c has also deteriorated by about 0.5%.

Which one of the following drugs is the likely cause?

(Please select 1 option)

- Cholestyramine
- Ezetimibe
- Fenofibrate
- Nicotinic acid
- Rosuvastatin

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 4 hrs 36 secs

Question: 90 of 100

In randomised clinical studies which of the following is correct regarding post-menopausal hormone replacement therapy (HRT)?

(Please select 1 option)

◉	Causes regression of coronary plaques.
○	Increases plasma LDL concentrations.
○	Increases plasma triglycerides
○	Reduces cardiovascular mortality.
○	Reduces the incidence of stroke

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 4 hrs 3 mins

Question: 90 of 100

In randomised clinical studies which of the following is correct regarding post-menopausal hormone replacement therapy (HRT)?

(Please select 1 option)

◉	Causes regression of coronary plaques. ✕ Incorrect answer selected
○	Increases plasma LDL concentrations.
○	Increases plasma triglycerides ← This is the correct answer
○	Reduces cardiovascular mortality.
○	Reduces the incidence of stroke

In randomised controlled trials (RCTs), HRT has not been shown to reduce cardiovascular (CV) mortality or the incidence of stroke (heart [o]estrogen replacement study - HERS), nor does it cause regression of coronary plaques ([o]estrogen replacement and angiography study - ERA).

In fact HRT has been shown to have an increased CV morbidity in the WHI study.

It does not produce a raised low density lipoprotein (LDL) but may increase high density lipoprotein (HDL) concentrations. Similarly it frequently produces a rise in triglyceride concentrations.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 4 hrs 3 mins

Question: 91 of 100

Which of the following is true of IGF-1 concentrations?

(Please select 1 option)

- Concentrations are elevated in diabetes mellitus
- Concentrations are elevated in hepatic cirrhosis
- Concentrations are reduced in pregnancy
- Concentrations are reduced in starvation
- Concentrations are usually elevated in adult growth hormone deficiency (GHD)

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 4 hrs 3 mins 53 secs

Question: 91 of 100

Which of the following is true of IGF-1 concentrations?

(Please select 1 option)

○	Concentrations are elevated in diabetes mellitus
○	Concentrations are elevated in hepatic cirrhosis
○	Concentrations are reduced in pregnancy
○	Concentrations are reduced in starvation ← This is the correct answer
◉	Concentrations are usually elevated in adult growth hormone deficiency (GHD) ✕ Incorrect answer selected

IGF-1 concentrations are often increased in pregnancy.

Reduced IGF-1 is typically found in adult GHD.

Cirrhosis of the liver is due to reduced synthesis, diabetes mellitus and starvation.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 4 hrs 3 mins 53 secs

Question: 92 of 100

Causes of hypoadrenalism include:

(Please select 1 option)

- Hughes' syndrome (anti-phospholipid antibody)
- McArdle's syndrome
- MEN type 2a
- Pendred's syndrome
- Von Hippel-Lindau

Submit answer | Skip question | Tag Question | Remove question

Dashboard
Questions
Scores
Community
Help
Shop

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 4 hrs 5 mins 7 secs

Question: 92 of 100

Causes of hypoadrenalism include:

(Please select 1 option)

◉	Hughes' syndrome (anti-phospholipid antibody) ✓ Correct
○	McArdle's syndrome
○	MEN type 2a
○	Pendred's syndrome
○	Von Hippel-Lindau

The anti-phospholipid syndrome is one of the more common causes of hypoadrenalism and may precipitate adrenal infarction and haemorrhage through adrenal vein thrombosis.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 4 hrs 5 mins 7 secs

Question: 93 of 100

A 35-year-old female is found to have a solitary mass on the chest x- ray.

Biopsy confirms this to be a carcinoid tumour of the lung.

Which of the following are likely to be associated with this lesion?

(Please select 1 option)

○	Carcinoid syndrome
○	Cushing's syndrome
○	Hyponatraemia
○	Pellagra
○	Pulmonary hypertension

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Which of the following are likely to be associated with this lesion?

(Please select 1 option)

○	Carcinoid syndrome
○	Cushing's syndrome ← This is the correct answer
○	Hyponatraemia
○	Pellagra
◉	Pulmonary hypertension ✕ Incorrect answer selected

Carcinoid tumours of the foregut (such as lung), unlike tumours of the midgut, are not associated with carcinoid syndrome, but may secrete corticotropin-releasing hormone/adrenocorticotropic hormone (CRF/ACTH) resulting in ectopic Cushing's syndrome.

Other associated conditions where foregut carcinoid tumours are found in the pancreas are associated with Zollinger-Ellison syndrome and VIPoma.

A bronchial carcinoid tumour has rarely been reported in association with acromegaly (ectopic growth hormone-releasing hormone [GHRH]).

They may also be found in association with multiple endocrine neoplasia (MEN) Type 1 where pancreatic neuroendocrine tumours predominate.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 4 hrs 18 mins 59 secs

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Question: 94 of 100

A 52-year-old female presents with tiredness.

There are no specific abnormalities noted on examination, but investigations reveal:

T4	21.1 pmol/L (10-22)
T3	5.2 pmol/L (5-10)
TSH	0.05 mU/L (0.4-5)

Thyroid autoantibody titres are all undetectable.

Of what do these results suggest a diagnosis?

(Please select 1 option)

- DeQuervain's thyroidits
- Graves' disease
- Hashimoto's thyroiditis
- Sick euthyroid syndrome
- Solitary toxic nodule

Submit answer | Skip question | Tag Question | Remove question

There are no specific abnormalities noted on examination, but investigations reveal:

T4	21.1 pmol/L (10-22)
T3	5.2 pmol/L (5-10)
TSH	0.05 mU/L (0.4-5)

Thyroid autoantibody titres are all undetectable.

Of what do these results suggest a diagnosis?

(Please select 1 option)

○	DeQuervain's thyroidits
◉	Graves' disease ✕ Incorrect answer selected
○	Hashimoto's thyroiditis
○	Sick euthyroid syndrome
○	Solitary toxic nodule ← This is the correct answer

This patient has subclinical hyperthyroidism and, in the absence of thyroid auto-antibodies, the most probable explanation of these thyroid function abnormalities is a solitary toxic nodule.

Next question

Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 4 hrs 22 mins 1 secs

Question: 95 of 100

Which of the following is associated with a GH secreting pituitary tumour?

(Please select 1 option)

- Gs alpha subunit mutation
- H-ras mutation
- p53 mutation
- Pit-1 mutation
- Rb 1 mutation

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 4 hrs 27 mins 6 secs

Question: 95 of 100

Which of the following is associated with a GH secreting pituitary tumour?

(Please select 1 option)

◉	Gs alpha subunit mutation ✓ Correct
○	H-ras mutation
○	p53 mutation
○	Pit-1 mutation
○	Rb 1 mutation

A stimulatory mutation of the Gs protein alpha subunit has been noted in approximately 30% of growth hormone (GH) secreting pituitary tumours.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 4 hrs 27 mins 6 secs

Question: 96 of 100

Adult growth hormone deficiency (GHD) is confirmed by which of the following?

(Please select 1 option)

○	A low IGF-1 concentration
○	A low IGF binding protein-3 (IGFBP3) concentration
○	A peak growth hormone concentration of 6 mU/l (2 microg/l) with insulin induced hypoglycaemia
○	An undetectable random growth hormone concentration.
○	Suppression of GH below 2 mU/l (1.3 microg/l) with an oral glucose tolerance test

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 4 hrs 28 mins 22 secs

Question: 96 of 100

Adult growth hormone deficiency (GHD) is confirmed by which of the following?

(Please select 1 option)

○	A low IGF-1 concentration
○	A low IGF binding protein-3 (IGFBP3) concentration
◉	A peak growth hormone concentration of 6 mU/l (2 microg/l) with insulin induced hypoglycaemia ✓ Correct
○	An undetectable random growth hormone concentration.
○	Suppression of GH below 2 mU/l (1.3 microg/l) with an oral glucose tolerance test

The diagnosis of adult GHD depends on a peak GH response of less than 9 mU/l to insulin induced hypoglycaemia.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 4 hrs 28 mins 22 secs

Question: 97 of 100

Which of the following techniques would be most useful in the differential diagnosis between ectopic Cushing's syndrome and pituitary dependent Cushing's disease?

(Please select 1 option)

○	ACTH concentrations
○	CRF test
○	High dose dexamethasone suppression test
○	Inferior petrosal sinus sampling
○	Urine free cortisol

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 4 hrs 28 mins 57 secs

Question: 97 of 100

Which of the following techniques would be most useful in the differential diagnosis between ectopic Cushing's syndrome and pituitary dependent Cushing's disease?

(Please select 1 option)

○	ACTH concentrations
○	CRF test
○	High dose dexamethasone suppression test
◉	Inferior petrosal sinus sampling ✓ Correct
○	Urine free cortisol

Inferior petrosal sinus sampling with an elevated central adrenocorticotropic hormone (ACTH) concentration compared with the peripheral value is the most valuable test in the differential diagnosis of either Cushing's disease or ectopic Cushing's syndrome.

The other tests are far less useful in comparison.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Show tools

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 4 hrs 28 mins 57 secs

Question: 98 of 100

Primary hyperparathyroidism may occur in association with which of the following conditions?

(Please select 1 option)

- Autoimmune polyendocrine syndrome
- Chronic renal failure (CRF)
- Gastrinoma
- Sjogren's syndrome
- Vitamin D deficiency

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 4 hrs 29 mins 45 secs

Question: 98 of 100

Primary hyperparathyroidism may occur in association with which of the following conditions?

(Please select 1 option)

◉	Autoimmune polyendocrine syndrome ✕ Incorrect answer selected
○	Chronic renal failure (CRF)
○	Gastrinoma ← This is the correct answer
○	Sjogren's syndrome
○	Vitamin D deficiency

The association of primary hyperparathyroidism and a gastrinoma would suggest a diagnosis of multiple endocrine neoplasia type 1.

CRF causes secondary or tertiary hyperparathyroidism, with vitamin D deficiency causing secondary hyperparathyroidism.

There is no association with Sjogren's.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 4 hrs 29 mins 45 secs

Question: 99 of 100

Osteomalacia may be expected in:

(Please select 1 option)

- Auto-immune adrenalitis
- Mercury poisoning
- Pernicious anaemia
- Pseudo-hypoparathyroidism
- Sarcoidosis

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 4 hrs 30 mins 30 secs

Question: 99 of 100

Osteomalacia may be expected in:

(Please select 1 option)

○	Auto-immune adrenalitis
○	Mercury poisoning ← This is the correct answer
○	Pernicious anaemia
○	Pseudo-hypoparathyroidism
◉	Sarcoidosis ✗ Incorrect answer selected

Osteomalacia may occur with vitamin D deficiency.

Mercury poisoning or any heavy metal poisoning causes an acquired Fanconi syndrome with distal renal tubular acidosis.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

A 55-year-old man with type 2 diabetes has noticed elevation of his blood glucose levels on a new treatment for his lipids.

He says his diet and exercise levels are unchanged his HbA1c has also deteriorated by about 0.5%.

Which one of the following drugs is the likely cause?

(Please select 1 option)

○	Cholestyramine
○	Ezetimibe
○	Fenofibrate
○	Nicotinic acid ← This is the correct answer
◉	Rosuvastatin ✕ Incorrect answer selected

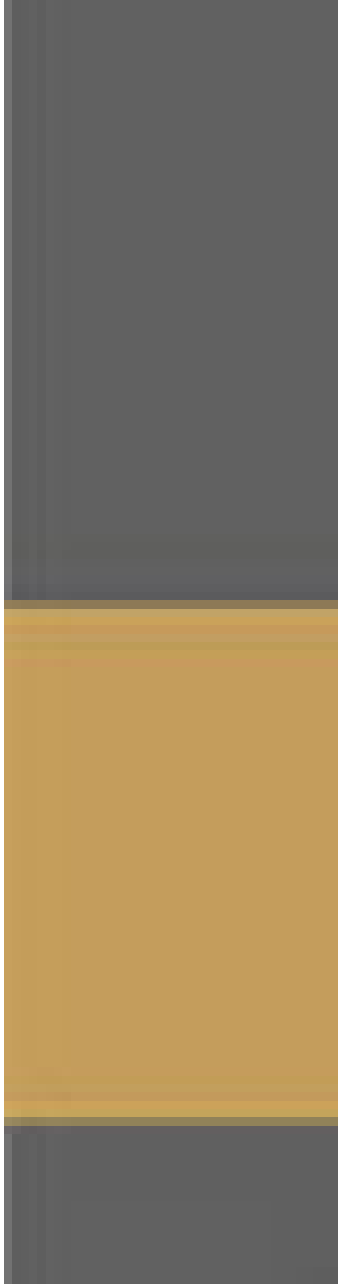
The mechanism of the effect of nicotinic acid on glucose is not entirely clear but, in some patients, it may increase blood glucose. For the majority of patients with diabetes it has a minimal effect.

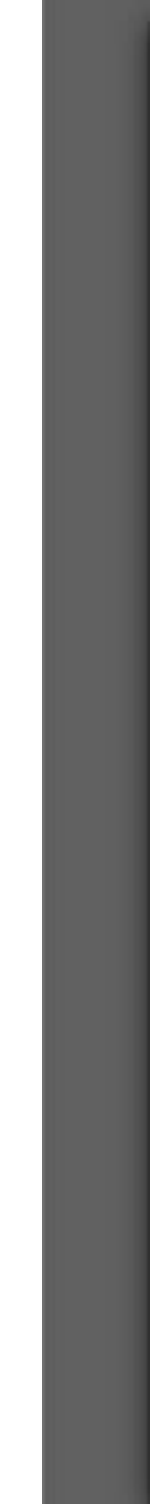
"Since nicotinic acid inhibits hepatic triglyceride synthesis the increased availability of free fatty acids may stimulate hepatic glucose output, either directly or indirectly. Free fatty acids are known to stimulate gluconeogenesis. Alternatively, free fatty acids may replace glucose as a primary energy source, enhancing glucose output by the liver. Another theory holds that free fatty acids rebound above baseline levels following initial suppression by nicotinic acid, blocking glucose uptake by skeletal muscle. Direct effects on beta-cell function have also been postulated, although there is no evidence to support this."

British Journal of Diabetes & Vascular Disease 2004;4:7885

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A





ASMBS American Society for Metabolic & Bariatric Surgery

Questions Set : REF4814 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
MSN.com | Questions Set : RE... | how to take a screens... | Learn how to make a ... | How to Take a Screen... | How to Take a Screen...
Page Safety Tools

Work Smart Session - MRCP Part 1

Time taken: 3 hrs 46 mins 41 secs

Question: 59 of 100

An 81-year-old frail man admitted with a stroke becomes increasingly drowsy after receiving nasogastric (NG) feeding for five days.

Which biochemical abnormality is the most likely cause of his drowsiness?

(Please select 1 option)

- ○ Hyperglycaemia
- ○ Hypermagnesaemia
- ○ Hypernatraemia
- ○ Hypocalcaemia
- ○ Hypophosphataemia

Submit answer | Skip question | Tag Question | Remove question

Done
Internet | Protected Mode: On
125%

Questions Set : REF4814 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
MSN.com | Questions Set : RE... | how to take a screens... | Learn how to make a ... | How to Take a Screen... | How to Take a Screen...
Page Safety Tools

Work Smart Session - MRCP Part 1

Time taken: 3 hrs 46 mins 41 secs

Question: 59 of 100

An 81-year-old frail man admitted with a stroke becomes increasingly drowsy after receiving nasogastric (NG) feeding for five days.

Which biochemical abnormality is the most likely cause of his drowsiness?

(Please select 1 option)

- Hyperglycaemia
- Hypermagnesaemia
- Hypernatraemia
- Hypocalcaemia
- Hypophosphataemia

Submit answer | Skip question | Tag Question | Remove question

Internet | Protected Mode: On
125%
EN
07:53 ص
2/10/2011

Questions Set : REF4813 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF4813
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 3 hrs 52 mins 49 secs

Question: 60 of 100

A 65-year-old woman presented with a malabsorption syndrome.

She had a past history of radiotherapy for cervical cancer.

Small intestine biopsy reveals

- villous atrophy and crypt hypertrophy

- chronic inflammatory cell infiltrate of the lamina propria together with

- increase in intra-epithelial lymphocytes.

What is the most likely diagnosis?

(Please select 1 option)

- Bacterial overgrowth
- Coeliac disease
- Crohn's disease
- Mesenteric ischaemia
- Radiation enteropathy

Submit answer | Skip question | Tag Question | Remove question

Internet | Protected Mode: On
100%
EN
08:05 ص
2/10/2011

Which biochemical abnormality is the most likely cause of his drowsiness?

(Please select 1 option)

○	Hyperglycaemia
○	Hypermagnesaemia
○	Hypernatraemia
○	Hypocalcaemia
◉	Hypophosphataemia ✓ Correct

The chronology of his presentation five days after receiving NG feeds suggests hypophosphataemia associated with the re-feeding syndrome.

This is well described in elderly frail subjects who may have prior poor nutrition.

However, other electrolyte abnormalities are also described in association with NG feeds, for example, hypernatraemia.

But with this briefest of histories and the five days it is likely that the examiner is looking for hypophosphataemia.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd. All rights reserved. Terms and conditions. Privacy policy.

Questions Set : REF4813 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF4813
Page
Safety
Tools

- increase in intra-epithelial lymphocytes.

What is the most likely diagnosis?

(Please select 1 option)

○	Bacterial overgrowth
○	Coeliac disease ← This is the correct answer
○	Crohn's disease
○	Mesenteric ischaemia
◉	Radiation enteropathy ✕ Incorrect answer selected

Do not be put off by the description of the case; these histological features are typical of coeliac disease with

- villous atrophy

- crypt hyperplasia/hypertrophy

- inflammatory infiltrate of the lamina propria and

- intra-epithelial lymphocytes.

Useful serology includes anti-TTG antibodies which would be expected in over 90% of cases.

Treatment of this case would therefore entail gluten-free diet.

Next question

Tag Question

Remove question

Done
Internet | Protected Mode: On
100%

Questions Set : REF4727 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF4727
Page Safety Tools

Work Smart Session - MRCP Part 1

Time taken: 3 hrs 57 mins 34 secs

Question: 61 of 100

A 29-year-old male presents with symptoms of severe gastro-oesophageal reflux.

Which one of the following is most useful in assessing the role of surgery?

(Please select 1 option)

- Cardiac sphincter manometry
- Gastric emptying study
- Intragastric pH monitoring off therapy
- Oesophageal motility study
- Oesophageal pH monitoring on therapy

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
100%

Questions Set : REF4727 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
File Edit View Favorites Tools Help
Favorites Suggested Sites Get More Add-ons
Questions Set : REF4727
Page Safety Tools
Work Smart Session - MRCP Part 1
Question: 61 of 100
Show

Questions Set : REF4705 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF4705
Page Safety Tools

Work Smart Session - MRCP Part 1

Time taken: 3 hrs 58 mins 51 secs

Question: 62 of 100

A 65-year-old man is referred with abnormal liver function and undergoes a liver biopsy.

Which of the following count against hepatic cirrhosis?

(Please select 1 option)

- Fibrous septa formation
- Granuloma formation
- Liver cell necrosis
- Nodular regeneration
- Subendothelial fibrosis

Questions Set : REF4705 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF4705
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 3 hrs 58 mins 51 secs

Question: 62 of 100

A 65-year-old man is referred with abnormal liver function and undergoes a liver biopsy.

Which of the following count against hepatic cirrhosis?

(Please select 1 option)

- Fibrous septa formation
- Granuloma formation
- Liver cell necrosis
- Nodular regeneration
- Subendothelial fibrosis

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
100%

Questions Set : REF4705 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF4705
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 4 hrs 2 mins 26 secs

Question: 62 of 100

A 65-year-old man is referred with abnormal liver function and undergoes a liver biopsy.

Which of the following count against hepatic cirrhosis?

(Please select 1 option)

- Fibrous septa formation
- Granuloma formation ✓ Correct
- Liver cell necrosis
- Nodular regeneration
- Subendothelial fibrosis

Granuloma formation is not classically seen in cirrhosis, which can be micro- or macronodular in type.

In the micronodular form, the nodules are less than 3 mm across with uniform liver involvement - seen in alcohol or biliary disease.

In the macronodular form, there are larger nodules, classically seen in chronic viral hepatitis.

Further reading:
Liver cirrhosis Loyola University Chicago Stritch School of Medicine

Done
Internet | Protected Mode: On
100%

Questions Set : REF4704 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF4704
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 4 hrs 2 mins 26 secs

Question: 63 of 100

Which of the following cell types are linked with the substance they synthesise ?

(Please select 1 option)

- Gastric chief cells - intrinsic factor
- Islet A cells - somatostatin
- Islet B cells - amylin
- Islet D cells - pancreatic polypeptide
- Islet F cells - glucagon

Submit answer | Skip question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms & Conditions

Avira
The application C:\PROGRA~1\Raptr\raptr.exe has been blocked to access the internet
Don't show this message again
OK

Done
Internet | Protected Mode: On
100%

Questions Set : REF4704 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites | Suggested Sites | Get More Add-ons
Questions Set : REF4704
Page | Safety | Tools

Work Smart Session - MRCP Part 1

Time taken: 4 hrs 3 mins 37 secs

Question: 63 of 100

Which of the following cell types are linked with the substance they synthesise ?

(Please select 1 option)

○	Gastric chief cells - intrinsic factor
○	Islet A cells - somatostatin
◉	Islet B cells - amylin ✓ Correct
○	Islet D cells - pancreatic polypeptide
○	Islet F cells - glucagon

Islet beta cells produce insulin and amylin, as well as C-peptide, pro-insulin and gamma-aminobutyric acid (GABA).

- Islet D cells produce somatostatin
- F cells produce pancreatic polypeptide and
- A cells produce glucagon
- Gastric chief cells produce pepsinogen whilst
- Gastric parietal cells produce acid and intrinsic factor.

Done
Internet | Protected Mode: On
100%

Questions Set : REF4640 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF4640
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 4 hrs 3 mins 37 secs

Question: 64 of 100

Which of the following statements regarding the genetic and immunological basis of coeliac disease is correct?

(Please select 1 option)

- 50% of patients are HLA-DQ 2 or HLA-DQ 8 positive
- Alpha-gliadin specific CD8 cells can be identified in the intestinal wall of untreated patients with coeliac disease
- Cow's milk proteins may precipitate an immune-related enteropathy indistinguishable from coeliac disease
- Tissue transglutaminase generates the antigenic epitopes present in alpha-gliadin
- TNF-alpha plays a critical role in the inflammatory response in the intestinal wall of patients with untreated celiac disease

Submit answer | Skip question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
100%

Questions Set : REF4640 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF4640
Page
Safety
Tools

Question: 64 of 100

Which of the following statements regarding the genetic and immunological basis of coeliac disease is correct?

(Please select 1 option)

○	50% of patients are HLA-DQ 2 or HLA-DQ 8 positive
○	Alpha-gliadin specific CD8 cells can be identified in the intestinal wall of untreated patients with coeliac disease
○	Cow's milk proteins may precipitate an immune-related enteropathy indistinguishable from coeliac disease
○	Tissue transglutaminase generates the antigenic epitopes present in alpha-gliadin ← This is the correct answer
◉	TNF-alpha plays a critical role in the inflammatory response in the intestinal wall of patients with untreated celiac disease ✕ Incorrect answer selected

The prevalence of coeliac disease is 1% in western societies, and is thus one of the commonest immune-mediated diseases.

It arises as a result of genetic predisposition, at least 95% of patients are HLA-DQ2 or HLA-DQ8 positive, and also from the specific immune response to the alpha-gliadin component of gluten.

Cow's milk can produce an immunologically mediated enteropathy, but the condition is rare and transient.

The action of tissue transglutaminase on alpha-gliadin generates epitopes to CD4+ T-lymphocytes, which provoke an inflammatory response in the intestinal wall.

In untreated individuals, alpha-gliadin specific CD4+ T cells can be found producing interferon-gamma in the intestinal wall.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
100%

Questions Set : REF4482 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF4482
Page Safety Tools

Work Smart Session - MRCP Part 1

Time taken: 4 hrs 14 mins 12 secs

Question: 65 of 100

A new diagnostic test for malabsorption has been analysed and the results have yielded the following 2x2 contingency table.

	Disease present	
test result	yes	no
+ve	0.9	0.1
-ve	0.2	0.8

Applying this test to a case of chronic diarrhoea from a patient group where the prevalence of malabsorption is known to be 20% (probability = 0.2) what is the probability of a patient having malabsorption if they have a positive test?

(Please select 1 option)

- 0.16
- 0.24
- 0.48
- 0.64
- 0.8

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
100%

Questions Set : REF4482 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF4482
Page Safety Tools

	(A)	positive (B)
-ve	false negative (C)	true negative (D)

Sensitivity (how much a test is positive in disease) = A / (A + C)
Specificity (how much a test is negative in health) = D / (B + D)
Positive Predictive Value = A / (A + B)
Negative Predictive value = D / (C + D)
Pre-test odds = the odds of having the disease before you do the test (e.g. your rule-of-thumb guestimate or the prevalence of the disease in the population or based on clinical findings etc.)
Post-test odds = the odds of having the disease after you did the test
Systematic Error = (A + B) / (A + C) = good statistic for - 1) breaking the ice at a party of epidemiologists, 2) confusing your fellow SpRs at meetings
Likelihood Ratio (LR) + (the ratio of the chance of having a +ve test if the disease is present to the chance of having a positive test if the disease is absent) = sensitivity / (1 - specificity)
LR- = (1 - sensitivity) / specificity
WHAT? ... Aghh! I knew I hated stats. Of what use is an LR?
Likelihood Ratios are good for

- Directly calculating post-test odds
- Tests with multiple levels (i.e. not just +ve or -ve). Calculate the LR at each level by taking the ratio of true +ves to false +ves both expressed as percentages of the total number tested.
- Diseases requiring multiple tests. The post-test odds after one test is the pre-test odds for the next.
- Bluffing your way in statistics, especially when talking to Evidence Based Medicine boffins

Next question
Tag Question
Remove question
© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A
Internet | Protected Mode: On
100%

Questions Set : REF4482 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF4482
Page Safety Tools

○	0.48
○	0.64 ← This is the correct answer
◉	0.8 ✕ Incorrect answer selected

This is tough but the College are putting more and more Evidence Based Medicine Questions into the exam. This question tests understanding of pre-test and post-test odds, likelihood ratios, sensitivity and specificity. The calculation is as follows.

Sensitivity = 0.9/(0.9 + 0.2) = 0.818

Specificity = 0.8 / (0.1 + 0.8) = 0.889

Likelihood ratio for a postivie test (LR+) = 0.818 / (1 - 0.889) = 7.2

Pre-test **odds** = 0.2 / (1 - 0.2) = 0.25

Post-test odds = pre-test odds X LR+ = 0.25 X 7.2 = 1.8

Post-test **probability** = 1.8 / (1.8 + 1) = 0.64

	Disease present	
test result	yes	no
+ve	true positive (A)	false positive (B)
-ve	false negative (C)	true negative (D)

Internet | Protected Mode: On 100%

Questions Set : REF4420 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites | Suggested Sites | Get More Add-ons
Questions Set : REF4420
Page | Safety | Tools

Work Smart Session - MRCP Part 1

Time taken: 4 hrs 16 mins 55 secs

Question: 66 of 100

A 56-year-old man from Thailand presented with abdominal pain and a mass in the right upper quadrant. He reported that he had been diagnosed with viral hepatitis several years previously.

Investigations showed:

Serum alpha-fetoprotein	13,500 IU/L	(< 10)

What is the most likely underlying viral infection?

(Please select 1 option)

- Hepatitis A virus
- Hepatitis B virus
- Hepatitis C virus
- Hepatitis D virus
- Hepatitis E virus

Submit answer | Skip question | Tag Question | Remove question

Done
Internet | Protected Mode: On
100%

Questions Set : REF4420 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF4420
Page Safety Tools

A 56-year-old man from Thailand presented with abdominal pain and a mass in the right upper quadrant. He reported that he had been diagnosed with viral hepatitis several years previously.

Investigations showed:

Serum alpha-fetoprotein	13,500 IU/L	(< 10)

What is the most likely underlying viral infection?

(Please select 1 option)

- Hepatitis A virus
- Hepatitis B virus ✓ Correct
- Hepatitis C virus
- Hepatitis D virus
- Hepatitis E virus

Very difficult! The patient has chronic viral hepatitis and presents with a hepatoma.

The underlying cause must be either hepatitis B virus (HBV) or hepatitis C virus (HCV).

There is a higher prevalence of HBV in the Far East and since his country of origin is the only other detail that gives a clue to the cause of his hepatitis, the most likely viral agent is HBV.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A
Internet | Protected Mode: On 100%

Questions Set : REF4414 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF4414
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 4 hrs 18 mins 47 secs

Question: 67 of 100

A 60-year-old woman with known alcoholic liver cirrhosis presents with vague abdominal pains, malaise and nausea.

She has been abstinent since she was diagnosed eight months ago.

On examination she had moderate ascites and mild, generalised abdominal tenderness.

Investigations:

Haemoglobin	11.2 g/dL (11.5-16.5)
WCC	15 $x10^9$/L (4-11 $x10^9$)
Prothrombin time	21 secs (11.5-15.5)
Serum albumin	28 g/L (37-49)
Serum total bilirubin	56 µmol/L (1-22)
Ascitic fluid protein	26 g/L
Ascitic fluid amylase	Normal
Ascitic fluid white cell count	500 $x10^9$/L

What is the most likely reason for her current problem?

(Please select 1 option)

Hepatic vein thrombosis

Done
Internet | Protected Mode: On
100%

Questions Set : REF4414 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF4414
Page
Safety
Tools

Haemoglobin	11.2 g/dL (11.5-16.5)
WCC	15 x10^9/L (4-11 x10^9)
Prothrombin time	21 secs (11.5-15.5)
Serum albumin	28 g/L (37-49)
Serum total bilirubin	56 µmol/L (1-22)
Ascitic fluid protein	26 g/L
Ascitic fluid amylase	Normal
Ascitic fluid white cell count	500 x10^9/L

What is the most likely reason for her current problem?

(Please select 1 option)

- Hepatic vein thrombosis
- Pancreatic pseudocyst rupture
- Portal vein thrombosis (PVT)
- Primary liver cancer
- Spontaneous bacterial peritonitis

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd. All rights reserved. Terms and conditions. Privacy policy.

Done
Internet | Protected Mode: On
100%

Questions Set : REF4414 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF4414
Page Safety Tools

Serum albumin	28 g/L (37-49)
Serum total bilirubin	56 µmol/L (1-22)
Ascitic fluid protein	26 g/L
Ascitic fluid amylase	Normal
Ascitic fluid white cell count	500 x10^9/L

What is the most likely reason for her current problem?

(Please select 1 option)

- ○ Hepatic vein thrombosis
- ○ Pancreatic pseudocyst rupture
- ○ Portal vein thrombosis (PVT)
- ○ Primary liver cancer
- ◉ Spontaneous bacterial peritonitis ✓ Correct

The high white cell count in the ascites makes spontaneous bacterial peritonitis (SBP) much more likely than Budd-Chiari syndrome (BCS), PVT, hepatocellular carcinoma (HCC), or a ruptured pancreatic pseudocyst.

Abdominal pain is often only mild, or even absent in SBP, with patients often presenting with otherwise unexplained hepatic decompensation.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A
Done
Internet | Protected Mode: On
100%

Questions Set : REF4413 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF4413
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 4 hrs 29 mins 21 secs

Question: 68 of 100

A 28-year-old lady develops abdominal pain, jaundice and ascites worsening over a week.

She drinks ten units of alcohol each week and takes the oral contraceptive pill.

Which of the following findings would make a diagnosis of hepatic vein thrombosis (Budd-Chiari syndrome [BCS]) most likely?

(Please select 1 option)

○	Acute liver failure
○	Alanine aminotransferase (ALT) of 345 U/L (5 - 35)
○	Ankle oedema
○	Ascites fluid protein of 38 g/L
◉	Tender enlarged liver ✓ Correct

The most common causes of an acute severe liver injury in a young woman are:

- Viruses (including hepatitis A virus [HAV], hepatitis B virus [HBV])
- Drugs (particularly paracetamol overdose)
- Autoimmune hepatitis and
- Hepatic vein thrombosis (often precipitated by pregnancy or oral contraceptive pill [OCP] use).

The presence of liver failure, ankle oedema, and an exudative ascites do not help differentiate between these aetiologies.

The ALT of 345 is moderately elevated and compatible with BCS. With viral or drug related hepatitis the peak ALT is usually much higher than this; the ALT

Done
Internet | Protected Mode: On
100%

Questions Set : REF4341 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF4341
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 4 hrs 29 mins 21 secs

Question: 69 of 100

Which one of the following statements is true of autoimmune hepatitis?

(Please select 1 option)

- It is associated with hypogammaglobulinaemia
- It may be associated with keratoconjunctivitis sicca
- It rarely interferes with menstruation except in later stages
- It rarely presents before 20 years of age
- It usually presents as an acute hepatitis

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
100%

Questions Set : REF4341 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF4341
Page Safety Tools

Work Smart Session - MRCP Part 1

Time taken: 4 hrs 30 mins 51 secs

Question: 69 of 100

Which one of the following statements is true of autoimmune hepatitis?

(Please select 1 option)

- It is associated with hypogammaglobulinaemia
- It may be associated with keratoconjunctivitis sicca ← This is the correct answer
- It rarely interferes with menstruation except in later stages
- It rarely presents before 20 years of age
- (●) It usually presents as an acute hepatitis ✕ Incorrect answer selected

It occurs frequently in young (10-20 years) and middle-aged women.

25% present as acute hepatitis, but usually the onset is insidious.

Some may be asymptomatic for years and then are found to have signs of chronic liver disease.

Amenorrhoea is common.

It is associated with hyperglobulinaemia and other autoimmmune disease.

60% are associated with HLA-B8, DR3 and Dw3.

The sicca syndrome (xerostomia/dry eyes, keratoconjunctivitis sicca) may occur.

Done
Internet | Protected Mode: On
100%

Questions Set : REF4339 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF4339
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 4 hrs 30 mins 51 secs

Question: 70 of 100

Which of the following is true of spontaneous bacterial peritonitis (SBP)?

(Please select 1 option)

- A survival rate of over 50% is expected at one year
- Gentamicin is the treatment of choice
- Is characteristically caused by aerobic bacteria.
- Is diagnosed by culture of ascitic fluid.
- Is due to intestinal perforation

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
100%

Questions Set : REF4339 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF4339
Page Safety Tools

Work Smart Session - MRCP Part 1

Time taken: 4 hrs 32 mins 2 secs

Question: 70 of 100

Which of the following is true of spontaneous bacterial peritonitis (SBP)?

(Please select 1 option)

- A survival rate of over 50% is expected at one year
- Gentamicin is the treatment of choice
- Is characteristically caused by aerobic bacteria. ✓ Correct
- Is diagnosed by culture of ascitic fluid.
- Is due to intestinal perforation

SBP is a frequent complication of the ascites of cirrhosis. It is diagnosed by ascitic fluid examination which reveals a PMN count of >250/ml.

SBP has poor prognostic significance with a one year survival after a diagnosis of between 30-50%.

It is, as the name suggests, a spontaneous event that is not a consequence of intestinal perforation. It is speculated that the infective organism may leak into the ascitic fluid via the blood or from intestinal overgrowth.

Organisms should be cultured by directly collecting into blood culture bottles.

It is typically caused by aerobic Gram-negative bacteria. Hence cefotaxime is regarded as the drug of choice for treatment.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
100%

Questions Set : REF4334 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF4334
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 4 hrs 32 mins 2 secs

Question: 71 of 100

Which of the following is correct regarding infection with *Salmonella typhi*?

(Please select 1 option)

- A. Children are particularly likely to become carriers
- B. Most carriers are female
- C. Faecal culture is almost always positive during the first week of illness
- D. Relapse does not occur if antibiotics are taken for two weeks
- E. Vaccinated individuals who develop the disease will have a mild illness

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
100%

Questions Set : REF4334 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF4334
Page Safety Tools

Dashboard
Questions
Scores
Community
Help
Shop

Work Smart Session - MRCP Part 1

Time taken: 4 hrs 33 mins 15 secs

Question: 71 of 100

Which of the following is correct regarding infection with *Salmonella typhi*?

(Please select 1 option)

- A. Children are particularly likely to become carriers
- B. Most carriers are female ✓ Correct
- C. Faecal culture is almost always positive during the first week of illness
- D. Relapse does not occur if antibiotics are taken for two weeks
- E. Vaccinated individuals who develop the disease will have a mild illness

Children are rarely chronic carriers of the organism although for some unknown reason females are more commonly long-term carriers than males (remember Typhoid Mary).

C. Only 50% of cases.

E. Higher threshold but same disease.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
100%

Questions Set : REF4293 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF4293
Page Safety Tools

Dashboard
Questions
Scores
Community
Help
Shop

Work Smart Session - MRCP Part 1

Time taken: 4 hrs 33 mins 15 secs

Question: 72 of 100

A routine ultrasound at 18 weeks' gestation in a diabetic mother reveals a male fetus with an endocardial cushion defect. Other abnormalities include increased nuchal thickening and a 'double bubble' sign.

Which of the following conditions is most likely to have contributed to this set of findings?

(Please select 1 option)

- Congenital syphilis
- Marfan syndrome
- Maternal folate deficiency
- Maternal use of ACE inhibitor
- Trisomy 21

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
100%

Questions Set : REF4293 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF4293
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 4 hrs 34 mins 17 secs

Question: 72 of 100

A routine ultrasound at 18 weeks' gestation in a diabetic mother reveals a male fetus with an endocardial cushion defect. Other abnormalities include increased nuchal thickening and a 'double bubble' sign.

Which of the following conditions is most likely to have contributed to this set of findings?

(Please select 1 option)

- Congenital syphilis
- Marfan syndrome
- Maternal folate deficiency
- Maternal use of ACE inhibitor
- Trisomy 21 ✓ Correct

Diabetic mothers are more likely to have children with congenital abnormalities depending on pre-conception, and first trimester blood sugar control.

40% of Down syndrome babies have atrioventricular septal defects, as in this fetus.

The double bubble sign suggests duodenal atresia, which again suggests Down syndrome.

GI malformations occur in 6% of Down's patients - most commonly duodenal atresia and Hirschsprung's disease.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
100%

Questions Set : REF4149 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF4149
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 4 hrs 34 mins 17 secs

Question: 73 of 100

A 24-year-old man with chronic diarrhoea and malabsorption is suspected of having coeliac disease. A jejunal biopsy is taken. Which of the following findings would be expected in coeliac disease?

(Please select 1 option)

- Shows leaf-shaped villi
- Shows flattening of the crypts
- Appearances may resemble severe tropical sprue
- Shows fissures penetrating into the submucosa
- Characteristically shows epithelial cells distended with fat globules

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
100%

Questions Set : REF4149 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF4149
Page Safety Tools

Work Smart Session - MRCP Part 1

Time taken: 4 hrs 51 mins 18 secs

Question: 73 of 100

A 24-year-old man with chronic diarrhoea and malabsorption is suspected of having coeliac disease. A jejunal biopsy is taken. Which of the following findings would be expected in coeliac disease?

(Please select 1 option)

- Shows leaf-shaped villi
- Shows flattening of the crypts
- Appearances may resemble severe tropical sprue ← This is the correct answer
- Shows fissures penetrating into the submucosa ✕ Incorrect answer selected
- Characteristically shows epithelial cells distended with fat globules

In coeliac disease, the villi are shortened and the crypts lengthened with increased lymphocytic infiltrate. Tropical sprue may also cause subtotal villous atrophy. Fissures are not found and epithelial cells are normal.

Copyright © 2002 Dr Colin Melville

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Internet | Protected Mode: On 100%

Questions Set : REF4147 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF4147
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 4 hrs 51 mins 18 secs

Question: 74 of 100

In the diarrhoea associated with cholera toxin, there is activation of which of the following enzyme systems?

(Please select 1 option)

- Adenosine triphosphate (ATP).
- Adenylate cyclase.
- Guanylate cyclase.
- Na-glucose co-transporter.
- Na+/K+ ATPase pump.

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
100%

Questions Set : REF4147 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites | Suggested Sites | Get More Add-ons
Questions Set : REF4147
Page | Safety | Tools

Work Smart Session - MRCP Part 1

Time taken: 4 hrs 52 mins

Question: 74 of 100

In the diarrhoea associated with cholera toxin, there is activation of which of the following enzyme systems?

(Please select 1 option)

- Adenosine triphosphate (ATP).
- Adenylate cyclase. ✓ Correct
- Guanylate cyclase.
- Na-glucose co-transporter.
- Na+/K+ ATPase pump.

Cholera toxin has two parts, A and B.

B binds while A activates G protein, which activates adenylate cyclase.

Elevated cyclic adenosine monophosphate (CAMP) results in unrestricted chloride secretion from villous crypts.

Copyright © 2002 Dr Colin Melville

Next question | Tag Question | Remove question

Done
Internet | Protected Mode: On
100%

Questions Set : REF4090 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF4090
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 4 hrs 52 mins

Question: 75 of 100

Which of the following statements regarding colon cancer is correct?

(Please select 1 option)

- A. In non-familial cases gene mutations in the cancer cells are unusual
- B. In familial cases the inheritance pattern is typically autosomal recessive
- C. It occurs most commonly in the ascending colon
- D. It is a characteristic feature of the Peutz-Jegher syndrome
- E. In familial polyposis coli the increased cancer risk is due to inheritance of a mutated suppressor gene

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
100%

Questions Set : REF4090 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF4090
Page
Safety
Tools

Question: 75 of 100

Which of the following statements regarding colon cancer is correct?

(Please select 1 option)

○	A. In non-familial cases gene mutations in the cancer cells are unusual
○	B. In familial cases the inheritance pattern is typically autosomal recessive
○	C. It occurs most commonly in the ascending colon
○	D. It is a characteristic feature of the Peutz-Jegher syndrome
◉	E. In familial polyposis coli the increased cancer risk is due to inheritance of a mutated suppressor gene ✓ Correct

A. Quantitative and qualitative alterations in gene expression accumulate in colorectal cancer cells. These include alterations of pro-oncogene expression and chromosomal abnormalities (deletions at 17p and 18q are seen in 70% of colorectal carcinomas).

B. Both familial polyposis coli and Gardner's syndrome are autosomal dominant.

C. The rectum and sigmoid colon are the commonest sites.

D. Peutz-Jegher's syndrome is dominantly inherited pigmentation of skin and mucous membranes and hamartomatous polyps in the stomach and larger intestine. The polyps only rarely undergo malignant change.

E. An allelic deletion of a putative tumour suppressor gene located 5q21-q22. Familial adenomatous polyposis FAP is an autosomal dominant disorder causing extensive adenomatous polyps of the colon and early onset colorectal cancer.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
100%

Questions Set : REF4087 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF4087
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 4 hrs 53 mins 2 secs

Question: 76 of 100

Which of the following is activated by cholera toxin?

(Please select 1 option)

- Adenylate cyclase
- Guanlyate cyclase
- Peroxisome proliferator receptor (PPAR) gamma
- Sodium/potassium ATPase
- The glucose-sodium transporter

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
100%

Questions Set : REF4087 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF4087
Page Safety Tools

Dashboard
Questions
Scores
Community
Help
Shop

Work Smart Session - MRCP Part 1

Time taken: 4 hrs 53 mins 45 secs

Question: 76 of 100

Which of the following is activated by cholera toxin?

(Please select 1 option)

- (●) Adenylate cyclase ✓ Correct
- ( ) Guanlyate cyclase
- ( ) Peroxisome proliferator receptor (PPAR) gamma
- ( ) Sodium/potassium ATPase
- ( ) The glucose-sodium transporter

Cholera toxin activates adenylate cyclase with generation of cyclic adenosine monophosphate (cAMP).

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
100%

Questions Set : REF4043 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF4043
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 4 hrs 53 mins 45 secs

Question: 77 of 100

Which of the following concerning the conjugation of bilirubin is correct?

(Please select 1 option)

- A. It is catalysed by a glucuronyl transferase
- B. It occurs in the Kupfer cells of the liver
- C. It is increased by valproate
- D. It is inhibited by rifampicin
- E. It is impaired in Dubin-Johnson syndrome

Submit answer | Skip question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
100%

Questions Set : REF4043 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF4043
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 4 hrs 54 mins 20 secs

Question: 77 of 100

Which of the following concerning the conjugation of bilirubin is correct?

(Please select 1 option)

- A. It is catalysed by a glucuronyl transferase ✓ Correct
- B. It occurs in the Kupfer cells of the liver
- C. It is increased by valproate
- D. It is inhibited by rifampicin
- E. It is impaired in Dubin-Johnson syndrome

B. Bilirubin is conjugated in the hepatocytes.

C. Sodium valproate is an enzyme inhibitor.

D. Rifampicin is an enzyme inducer.

E. In Dubin-Johnson syndrome, conjugation is normal, but excretion from the hepatocyte into the bile is impaired, resulting in a conjugated bilirubinaemia.

(In Gilbert's syndrome, bilirubin cannot enter the hepatocyte and unconjugated bilirubinaemia occurs, as it does in Crigler-Najjar syndrome, where bilirubin does not conjugate due to malproduced bilirubin glucuronyl transeferase.)

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
100%

Questions Set : REF4029 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF4029
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 4 hrs 54 mins 20 secs

Question: 78 of 100

A 68-year-old male presents with alcoholic cirrhosis complicated by mild ascites.

Which of the following features is likely in this patient?

(Please select 1 option)

- Increased serum sodium
- Increased vascular resistance
- Reduced renin concentrations
- Reduced urinary potassium excretion
- Reduced urinary sodium excretion

Submit answer | Skip question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
100%

Questions Set : REF4029 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites | Suggested Sites | Get More Add-ons
Questions Set : REF4029
Page | Safety | Tools

Work Smart Session - MRCP Part 1

Time taken: 4 hrs 55 mins 25 secs

Question: 78 of 100

A 68-year-old male presents with alcoholic cirrhosis complicated by mild ascites.

Which of the following features is likely in this patient?

(Please select 1 option)

- Increased serum sodium
- Increased vascular resistance ✕ Incorrect answer selected
- Reduced renin concentrations
- Reduced urinary potassium excretion
- Reduced urinary sodium excretion ← This is the correct answer

Remember that he has secondary hyperaldosteronism which results in sodium retention with consequent potassium loss.

There is decreased vascular resistance, increased plasma volume and low serum sodium.

Next question | Tag Question | Remove question

Show tools

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
100%

Questions Set : REF3970 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF3970
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 4 hrs 55 mins 25 secs

Question: 79 of 100

A 35-year-old woman with alcoholic cirrhosis is admitted with deteriorating encephalopathy and abdominal discomfort.

An ascitic tap revealed a polymorphonuclear cell count of 350 cells per mm^3.

Which of the following is the most appropriate therapy?

(Please select 1 option)

- Intravenous amoxicillin
- Intravenous cefotaxime
- Intravenous metronidazole
- Oral neomycin
- Oral norfloxacin

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
100%

Questions Set : REF3970 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF3970
Page Safety Tools

A 35-year-old woman with alcoholic cirrhosis is admitted with deteriorating encephalopathy and abdominal discomfort.

An ascitic tap revealed a polymorphonuclear cell count of 350 cells per mm^3.

Which of the following is the most appropriate therapy?

(Please select 1 option)

- Intravenous amoxicillin
- Intravenous cefotaxime ✓ Correct
- Intravenous metronidazole
- Oral neomycin
- Oral norfloxacin

This lady has spontaneous bacterial peritonitis as suggested by the typical history, ascites and raised polymorphonuclear count within the ascitic tap.

It is most commonly seen in alcoholic cirrhosis and the causative organism is usually *Escherichia coli*, *Klebsiella*, *S pneumoniae* or *Enterococci*. (Compare this with the mixed growth seen in other forms of peritonitis).

Sending some ascitic fluid in blood culture bottles increases the yield.

Initial treatment is with broad spectrum antibiotics such as cefotaxime.

Norfloxacin is recommended for short term prophylaxis.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A
Done
Internet | Protected Mode: On
100%

Questions Set : REF3885 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF3885
Page
Safety
Tools

A 36-year-old man presented with a three day history of bloody diarrhoea.

He was apyrexial and mildly icteric.

Investigations revealed:

Haemoglobin	10.5 g/dL (13.0-18.0)
White cell count	19 $x10^9$/L (4-11 $x10^9$)
Platelets	70 $x10^9$/L (150-400 $x10^9$)
Serum urea	12.5 mmol/L (2.5-7.5)
Serum aspartate aminotransferase	90 U/L (1-31)
Prothrombin time	12s (11.5-15.5)
Blood film	Fragmented red cells

What is the most likely cause of his illness?

(Please select 1 option)

- *Escherichia coli* 0157 colitis
- Ischaemic colitis
- Leptospirosis
- *Salmonella* enterocolitis
- Ulcerative colitis

Done
Internet | Protected Mode: On
100%

Questions Set : REF3885 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF3885
Page
Safety
Tools

Blood film	Fragmented red cells

What is the most likely cause of his illness?

(Please select 1 option)

- ◉ *Escherichia coli* 0157 colitis ✓ Correct
- ○ Ischaemic colitis
- ○ Leptospirosis
- ○ *Salmonella* enterocolitis
- ○ Ulcerative colitis

The combination of

- Bloody diarrhoea
- Haemolytic anaemia
- Thrombocytopenia but normal clotting and
- Renal impairment

suggests haemolytic-uraemic syndrome.

This is associated with *E coli* 0157 toxin most commonly.

Next question

Tag Question

Remove question

Done
Internet | Protected Mode: On
100%

Questions Set : REF3884 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF3884
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 4 hrs 57 mins 33 secs

Question: 81 of 100

A 52-year-old man with a diagnosis as a child of coeliac disease had been asymptomatic despite poor dietary compliance.

He presents with a one month history of intermittent, colicky, central abdominal pain and 3 kilogram weight loss and positive faecal occult bloods.

What is the most appropriate investigation?

(Please select 1 option)

- Anti-endomysial antibody.
- Colonoscopy.
- CT scan of abdomen.
- Distal duodenal biopsy.
- Small bowel enema.

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
100%

Questions Set : REF3884 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF3884
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 4 hrs 58 mins 39 secs

Question: 81 of 100

A 52-year-old man with a diagnosis as a child of coeliac disease had been asymptomatic despite poor dietary compliance.

He presents with a one month history of intermittent, colicky, central abdominal pain and 3 kilogram weight loss and positive faecal occult bloods.

What is the most appropriate investigation?

(Please select 1 option)

○	Anti-endomysial antibody.
◉	Colonoscopy. ✓ Correct
○	CT scan of abdomen.
○	Distal duodenal biopsy.
○	Small bowel enema.

New-onset weight loss with positive faecal occult bloods and central abdominal pain in a 52-year-old man must be assumed to be colonic carcinoma until proven otherwise.

Colonoscopy is the best way to check for this and would also demonstrate inflammatory bowel disease if present.

If the colonoscopy were negative, then an OGD would be needed to check for upper gastrointestinal malignancy.

Next question | Tag Question | Remove question

Show to
© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A
Done
Internet | Protected Mode: On
100%

Questions Set : REF3883 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF3883
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 4 hrs 58 mins 39 secs

Question: 82 of 100

A 45-year-old woman is diagnosed with a duodenal ulcer.

Which one of the following is the most sensitive test for detecting current infection with *Helicobacter pylori*?

(Please select 1 option)

- Culture of a gastric biopsy
- Gastric fundal biopsy
- Presence of *Helicobacter pylori* serum antibodies
- The (^{13}C) urea breath test
- Urease test on gastric biopsy

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
100%

Questions Set : REF3883 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF3883
Page Safety Tools

Question: 82 of 100

A 45-year-old woman is diagnosed with a duodenal ulcer.

Which one of the following is the most sensitive test for detecting current infection with *Helicobacter pylori*?

(Please select 1 option)

- Culture of a gastric biopsy
- Gastric fundal biopsy
- Presence of *Helicobacter pylori* serum antibodies
- The (^{13}C) urea breath test ✓ Correct
- Urease test on gastric biopsy

The gold standard for diagnosis of *H. pylori* remains culture of a gastric biopsy. Yet this test is only 72% sensitive.

The rapid urease test on a biopsy is 80-95% sensitive and 95-100% specific. Histology is 80-90% sensitive and 95% specific.

The urease breath test is approximately 95% sensitive and 98-100% specific. Therefore the most specific and clinically applicable would be the urease breath test.

The presence of IgG antibodies to *H. pylori* could indicate previous infection.

A gastric antral biopsy can give false negative results following proton pump inhibitor (PPI) treatment.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
100%

Questions Set : REF3881 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF3881
Page Safety Tools

Work Smart Session - MRCP Part 1

Time taken: 4 hrs 59 mins 46 secs

Question: 83 of 100

A 24-year-old woman was referred with tiredness and intermittent bloody diarrhoea and a past history of cerebral venous thrombosis.

On examination the sclera of the right eye was inflamed and multiple mouth ulcers were noted. At the colonoscopy, which confirmed colitis, two large vulval ulcers were noted.

Which is the most likely diagnosis?

(Please select 1 option)

- Behcet's disease.
- Crohn's disease.
- HIV infection
- Syphilis
- Ulcerative colitis.

Submit answer | Skip question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
100%

Questions Set : REF3881 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
File Edit View Favorites Tools Help
Favorites Suggested Sites Get More Add-ons
Questions Set : REF3881
Page Safety Tools

Dashboard
Questions
Scores
Community
Help
Shop

Work Smart Session - MRCP Part 1

Time taken: 5 hrs 1 mins 7 secs

Question: 83 of 100

A 24-year-old woman was referred with tiredness and intermittent bloody diarrhoea and a past history of cerebral venous thrombosis.

On examination the sclera of the right eye was inflamed and multiple mouth ulcers were noted. At the colonoscopy, which confirmed colitis, two large vulval ulcers were noted.

Which is the most likely diagnosis?

(Please select 1 option)

- (●) Behcet's disease. ✓ Correct
- ( ) Crohn's disease.
- ( ) HIV infection
- ( ) Syphilis
- ( ) Ulcerative colitis.

This is a classical description of the presentation of Behcet's, with oral and genital ulceration, colitis and scleritis.

Next question | Tag Question | Remove question

Show tools

Done
Internet | Protected Mode: On
100%

Questions Set : REF5326 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx?id=625427&ws=true
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF5326
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 5 hrs 1 mins 7 secs

Question: 83 of 100

With respect to liver cirrhosis, which of the following statements is correct?

(Please select 1 option)

- Endothelin causes dilatation of the sinusoids, thus decreasing portal hypertension
- In end-stage cirrhosis, liver transplantation is associated with 20% five year survival
- The final common pathway of hepatic fibrosis is mediated by the hepatic stellate cell
- Transforming growth factor is a potent promoter of the fibrogenic response by hepatocytes
- Tumour necrosis factor is an anti-inflammatory effector in fibrotic liver injury

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Internet | Protected Mode: On
100%

Questions Set : REF5326 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx?id=625427&ws=true
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF5326
Page
Safety
Tools

With respect to liver cirrhosis, which of the following statements is correct?

(Please select 1 option)

○	Endothelin causes dilatation of the sinusoids, thus decreasing portal hypertension
○	In end-stage cirrhosis, liver transplantation is associated with 20% five year survival
◉	The final common pathway of hepatic fibrosis is mediated by the hepatic stellate cell ✓ Correct
○	Transforming growth factor is a potent promoter of the fibrogenic response by hepatocytes
○	Tumour necrosis factor is an anti-inflammatory effector in fibrotic liver injury

The hepatic stellate cells, which reside in the space of Disse are central to the process of fibrosis within the liver.

Tumour necrosis factor-A is a pro-inflammatory effector in fibrotic liver injury, through activation of the stellate cells. These cells then secrete the fibrillar collagen, constituting the defining features of hepatic fibrosis.

Interleukin-10 is thought to exert anti-inflammatory effects on the stellate cell.

Endothelin is a vasoconstrictor in the hepatic sinusoids (similarly in the endothelium of the systemic circulation), and functions by causing contraction of the hepatic stellate cells, thus increasing intrahepatic sinusoidal resistance, and promoting portal hypertension.

Nitric oxide antagonises the effects of endothelin in the liver.

Five year survival after liver transplantation is now 75%.

For an update on liver cirrhosis refer to BMJ 2003;327:143-7.

Next question

Tag Question

Remove question

Done
Internet | Protected Mode: On
100%

Questions Set : REF3880 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx?id=625427&ws=true
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF3880
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 5 hrs 2 mins 30 secs

Question: 84 of 100

A 24-year-old woman had ulcerative colitis (UC) for seven years and was prescribed mesalazine 1.5 g per day.

She smoked 20 cigarettes per day and was 10 weeks pregnant. She complained of worsening symptoms with six bloody stools per day.

Which one of the following statements is correct?

(Please select 1 option)

- Azathioprine is relatively contraindicated.
- Initiation of an elemental diet risks fetal malnutrition.
- Oral corticosteroids are contraindicated.
- Oral mesalazine therapy should be withdrawn.
- Termination of the pregnancy is advisable.

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
100%

Questions Set : REF3880 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx?id=625427&ws=true
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF3880
Page
Safety
Tools

A 24-year-old woman had ulcerative colitis (UC) for seven years and was prescribed mesalazine 1.5 g per day.

She smoked 20 cigarettes per day and was 10 weeks pregnant. She complained of worsening symptoms with six bloody stools per day.

Which one of the following statements is correct?

(Please select 1 option)

- (●) Azathioprine is relatively contraindicated. ✓ Correct
- ( ) Initiation of an elemental diet risks fetal malnutrition.
- ( ) Oral corticosteroids are contraindicated.
- ( ) Oral mesalazine therapy should be withdrawn.
- ( ) Termination of the pregnancy is advisable.

The effect of pregnancy on UC is variable.

Oral corticosteroids and mesalazine are not contraindicated.

In general, the health of a mother with UC is the best predictor of the outcome of the pregnancy. Hence drug treatment is preferred to leaving active disease untreated.

The BNF states that azathioprine should not generally be started during pregnancy, but it is only relatively contraindicated. However, azathioprine is concentrated in breastfeeding.

In the context of pregnancy, an elemental diet does not risk maternal and/or fetal malnutrition.

Next question | Tag Question | Remove question

Done
Internet | Protected Mode: On
100%

Questions Set : REF3879 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF3879
Page Safety Tools

A 40-year-old man has a history of left-sided Crohn's colitis.

Though, previously treated with steroids and mesalazine, he has had several relapses in the past year. The last relapse, treated with high doses of steroids, was complicated by gastric bleeding.

Investigations show:

Haemoglobin	10.8 g/dL (13.0-18.0)
MCV	76 fL (80-96)
MCH	24 pg (28-32)
White cell count	10 $x10^9$/L (4-11 $x10^9$)
Platelets	400 $x10^9$/L (150-400 $x10^9$)
Serum total protein	70 g/L (61-76)
Serum albumin	30 g/L (37-49)
Serum CRP	30 mg/L (<10)

Abdominal X-ray is normal.

Which of the following is the most appropriate management?

(Please select 1 option)

- A trial of oral metronidazole for three months.
- Total colectomy with ileostomy construction.
- Total colectomy with pouch construction.

Done
Internet | Protected Mode: On
100%

Questions Set : REF3879 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF3879
Page
Safety
Tools

was complicated by gastric bleeding.

Investigations show:

Haemoglobin	10.8 g/dL (13.0-18.0)
MCV	76 fL (80-96)
MCH	24 pg (28-32)
White cell count	10 $x10^9$/L (4-11 $x10^9$)
Platelets	400 $x10^9$/L (150-400 $x10^9$)
Serum total protein	70 g/L (61-76)
Serum albumin	30 g/L (37-49)
Serum CRP	30 mg/L (<10)

Abdominal X-ray is normal.

Which of the following is the most appropriate management?

(Please select 1 option)

- A trial of oral metronidazole for three months.
- Total colectomy with ileostomy construction.
- Total colectomy with pouch construction.
- Treatment with azathioprine.
- Treatment with oral budesonide.

Done
Internet | Protected Mode: On
100%

Questions Set : REF3879 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF3879
Page
Safety
Tools

Serum CRP	30 mg/L (<10)

Abdominal X-ray is normal.

Which of the following is the most appropriate management?

(Please select 1 option)

- A trial of oral metronidazole for three months.
- Total colectomy with ileostomy construction.
- Total colectomy with pouch construction.
- **Treatment with azathioprine.** ✓ Correct
- Treatment with oral budesonide.

This patient has all the hallmarks of active Crohn's colitis that is failing to settle with first-line medical therapy.

The next step is a trial of azathioprine, which is used as a steroid-sparing agent. This is particularly relevent to this particular patient, as he has had a serious side-effect from previous steroid treatment.

Metronidazole is rarely effective in the treatment of active Crohn's colitis.

Given that Crohn's disease can recur following surgery, an operation should not be embarked upon without first a trial of the second-line medical therapies such as azathioprine, its metabolite 5-mercaptopurine, or infliximab.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Internet | Protected Mode: On
100%

Questions Set : REF3877 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF3877
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 5 hrs 6 mins 19 secs

Question: 86 of 100

A 32-year-old woman with Crohn's disease has a history of a right hemicolectomy for ileo-colonic disease.

Since the operation she has had frequent diarrhoea but no blood in the stools.

Investigations show:

ESR	10mm (0-20mm/1st hour)
Platelets	240 $x10^9$/L (150-400 $x10^9$)
Serum CRP	7 mg/L (<10)

Which is the best treatment?

(Please select 1 option)

- Cholestyramine
- Mesalazine
- Metronidazole
- Omeprazole
- Prednisolone

Done
Internet | Protected Mode: On
100%

Questions Set : REF3877 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF3877
Page Safety Tools

ESR	10mm (0-20mm/1st hour)
Platelets	240 x10^9/L (150-400 x10^9)
Serum CRP	7 mg/L (<10)

Which is the best treatment?

(Please select 1 option)

- ◉ Cholestyramine ✓ Correct
- ○ Mesalazine
- ○ Metronidazole
- ○ Omeprazole
- ○ Prednisolone

The ESR, CRP and platelet counts are not raised indicating that this patient's symptoms are not due to active Crohn's. Also the diarrhoea is not bloody which goes against active Crohn's colitis.

Hence mesalazine or prednisolone would not be effective here.

Metronidazole is typically given for peri-anal disease.

The history includes a previous right hemicolectomy for ileo-colonic disease.

Loss of the terminal ileum frequently leads to bile salt malabsorption and treatment with the bile salt chelator cholestyramine quickly relieves the problem.

Done
Internet | Protected Mode: On
100%

Questions Set : REF3876 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF3876
Page Safety Tools

A 55-year-old man on no current treatment for his quiescent ulcerative colitis is found to have an ESR of 95 mm/hr (0-20mm/1st hour).

Investigations show:

Haemoglobin	13.2g/dL (13.0-18.0)
WCC	4.5 $x10^9$/L (4-11 $x10^9$)
Platelets	160 $x10^9$/L (150-400 $x10^9$)
Corrected calcium	2.58 mmol/L (2.2-2.6)
IgG	25g/L (6-13)
IgA	1.8g/L (0.8-3.0)
IgM	1.6g/L (0.4-2.2)

What is the most appropriate next investigation?

(Please select 1 option)

- Bone marrow trephine and aspiration.
- Isotope bone scan.
- Plasma immunoelectrophoresis.
- Rectal biopsy.

Done
Internet | Protected Mode: On
100%

Questions Set : REF3876 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF3876
Page
Safety
Tools

Investigations show:

Haemoglobin	13.2g/dL (13.0-18.0)
WCC	4.5 $x10^9$/L (4-11 $x10^9$)
Platelets	160 $x10^9$/L (150-400 $x10^9$)
Corrected calcium	2.58 mmol/L (2.2-2.6)
IgG	25g/L (6-13)
IgA	1.8g/L (0.8-3.0)
IgM	1.6g/L (0.4-2.2)

What is the most appropriate next investigation?

(Please select 1 option)

- Bone marrow trephine and aspiration.
- Isotope bone scan.
- Plasma immunoelectrophoresis.
- Rectal biopsy.
- x Ray skeletal survey.

Done
Internet | Protected Mode: On
100%

Questions Set : REF3876 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF3876
Page Safety Tools

IgG	25g/L (6-13)
IgA	1.8g/L (0.8-3.0)
IgM	1.6g/L (0.4-2.2)

What is the most appropriate next investigation?

(Please select 1 option)

- Bone marrow trephine and aspiration.
- Isotope bone scan.
- Plasma immunoelectrophoresis. ✓ Correct
- Rectal biopsy.
- x Ray skeletal survey.

The ESR is not raised in quiescent UC. Hence there must be another reason in this case.

The only abnormal result given is a raised IgG. This suggests that myeloma is the diagnosis.

Plasma immunoelectrophoresis to look for an M band is the most appropriate next investigation.

A bone marrow trephine is the definitive investigation but is traumatic and painful to the patient and so is not the next investigation of choice.

Next question Tag Question Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done Internet | Protected Mode: On 100%

Questions Set : REF3779 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF3779
Page
Safety
Tools

A 35-year-old woman with a history of recurrent anaemia was noted to have target cells and Howell-Jolly bodies on a blood film examination.

Investigations revealed:

Haemoglobin	7.0 g/dL (11.5-16.5)
MCV	77 fL (80-96)
MCH	26.2 pg (28-32)
Serum B12	140 µg/L (160-760)
Red cell folate	95 µg/L (160-640)
Serum ferritin	10 µg/L (15-300)

What disease specific antibody is most likely to be present?

(Please select 1 option)

- Antiendomysial
- Antigastric parietal cell
- Antiglutamic acid decarboxylase
- Anti-intrinsic factor
- Antimitochondrial

Submit answer | Skip question | Tag Question | Remove question

Done
Internet | Protected Mode: On
100%

Questions Set : REF3779 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF3779
Page Safety Tools

Serum ferritin	10 µg/L (15-300)

What disease specific antibody is most likely to be present?

(Please select 1 option)

◉	Antiendomysial ✓ Correct
○	Antigastric parietal cell
○	Antiglutamic acid decarboxylase
○	Anti-intrinsic factor
○	Antimitochondrial

The patient has hyposplenism as suggested by the blood film and a mixed anaemia.

Coeliac disease could therefore fit the above picture with antiendomysial antibodies being the most appropriate selection from the above list.

- Antimitochonrial antibodies are seen in PBC
- Anti-gastric and anti intrinsic Abs are seen in pernicious anaemia
- Anti-GAD abs are found in auto-immune DM.

Screening for coeliac disease should include high-risk groups such as anaemia (iron or folate deficiency), hyposplenism, reduced bone density and infertility.

"Anti-endomysial IgA antibodies are extremely specific markers for CD and for dermatitis herpetiformis. These antibodies are directed to a component of the gut endomysium (connective tissue surrounding smooth muscle fibers of the gut)." (Further reading)

Done
Internet | Protected Mode: On
100%

Questions Set : REF2746 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF2746
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 5 hrs 13 mins 8 secs

Question: 89 of 100

A 52-year-old woman presented with history of worsening dysphagia over many years. Recently there had been episodes of ill-defined central chest discomfort and nocturnal cough.

What is the most likely diagnosis?

(Please select 1 option)

- Achalasia
- Barrett's oesophagus
- Motor neurone disease (MND)
- Oesophageal carcinoma
- Pharyngeal pouch

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
100%

Questions Set : REF2746 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF2746
Page
Safety
Tools

A 52-year-old woman presented with history of worsening dysphagia over many years. Recently there had been episodes of ill-defined central chest discomfort and nocturnal cough.

What is the most likely diagnosis?

(Please select 1 option)

◉	Achalasia ✓ Correct
○	Barrett's oesophagus
○	Motor neurone disease (MND)
○	Oesophageal carcinoma
○	Pharyngeal pouch

Achalasia presents most often in the third to fifth decade. Symptoms usually develop years before the patient presents. Vague chest discomfort is common. Thirty per cent have a nocturnal cough due to aspiration of oesophageal contents.

Barrett's oesophagus does not cause dysphagia.

MND causes dysphagia due to problems with chewing and initiating a swallow and would not cause chest discomfort.

Oesophageal carcinoma is very unlikely due to the duration of symptoms (years).

A pharyngeal pouch usually presents in the sixth to seventh decade with regurgitation and would not cause chest discomfort.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
100%

Questions Set : REF2663 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx?id=625427&ws=true
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF2663
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 5 hrs 14 mins 36 secs

Question: 90 of 100

Which of the following is the commonest cause of traveller's diarrhoea?

(Please select 1 option)

- *Escherichia coli*
- *Entamoeba histolytica*
- *Giardia lamblia*
- *Shigella flexneri*
- *Yersinia enterocolitica*

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
100%

Questions Set : REF2663 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx?id=625427&ws=true
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF2663
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 5 hrs 15 mins 16 secs

Question: 90 of 100

Which of the following is the commonest cause of traveller's diarrhoea?

(Please select 1 option)

- ◉ *Escherichia coli* ✓ Correct
- ○ *Entamoeba histolytica*
- ○ *Giardia lamblia*
- ○ *Shigella flexneri*
- ○ *Yersinia enterocolitica*

Enterotoxigenic *E coli* is the commonest cause of traveller's diarrhoea and is usually a self limiting condition.

Usually no treatment nor investigation is required for this brief diarrhoeal illness.

Other causes that may be associated with prolonged diarrhoea include *Giardia* and amoebiasis.

Chronic diarrhoea merits investigation.

Next question | Tag Question | Remove question

Internet | Protected Mode: On
100%

Questions Set : REF2374 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF2374
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 5 hrs 15 mins 16 secs

Question: 91 of 100

A 48-year-old woman complains of pruritis, steatorrhoea and bruising.

On examination, she is jaundiced, pigmented with spider naevi and hepatosplenomegaly.

What is the most likely underlying diagnosis?

(Please select 1 option)

- Alcoholic liver disease
- Alpha-1 antitrypsin deficiency
- Autoimmune hepatitis
- Primary biliary cirrhosis
- Wilson's disease

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
100%

Questions Set : REF2374 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF2374
Page Safety Tools

A 48-year-old woman complains of pruritis, steatorrhoea and bruising.

On examination, she is jaundiced, pigmented with spider naevi and hepatosplenomegaly.

What is the most likely underlying diagnosis?

(Please select 1 option)

- Alcoholic liver disease
- Alpha-1 antitrypsin deficiency
- Autoimmune hepatitis
- **Primary biliary cirrhosis** ✓ Correct
- Wilson's disease

She has clinical evidence of chronic liver disease and portal hypertension.

The two main conditions causing pigmentation and chronic liver disease are primary biliary cirrhosis (PBC) and haemochromatosis.

PBC is a chronic cholestatic inflammatory liver disease, the aetiology of which is probably autoimmune. It most commonly affects middle-aged women.

There is jaundice with skin pigmentation, risk of developing oesophageal varices and fat malabsorption, leading to deficiency of the vitamins A, D, E, K (hence osteomalacia and also bruising).

Serum antimitochondrial antibody is positive in 95-99% cases.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A
Done
Internet | Protected Mode: On
100%

Questions Set : REF2373 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF2373
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 5 hrs 16 mins 25 secs

Question: 92 of 100

A 58-year-old man complains of tiredness, fever, weight loss, arthralgia and diarrhoea.

Jejunal biopsy reveals flattened mucosa containing periodic acid-Schiff (PAS) positive macrophages.

What is the most likely diagnosis?

(Please select 1 option)

- Coeliac disease
- Parasitic infection
- Tropical sprue
- Tuberculosis
- Whipple's disease

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
100%

Questions Set : REF2373 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF2373
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 5 hrs 17 mins 8 secs

Question: 92 of 100

A 58-year-old man complains of tiredness, fever, weight loss, arthralgia and diarrhoea.

Jejunal biopsy reveals flattened mucosa containing periodic acid-Schiff (PAS) positive macrophages.

What is the most likely diagnosis?

(Please select 1 option)

- Coeliac disease
- Parasitic infection
- Tropical sprue
- Tuberculosis
- Whipple's disease ✓ Correct

Whipple's disease is rare and affects most commonly middle-aged males.

It can affect any organ, but dominated by involvement of small bowel, causing malabsorption.

The organism (*Tropheryma whippelii*) can be identified both between and within abnormal macrophages which stain magenta with PAS.

Treat with prolonged antibiotics, for example, parenteral penicillin and streptomycin for two weeks, followed by one year of doxycycline.

Next question | Tag Question | Remove question

Done
Internet | Protected Mode: On
100%

Questions Set : REF2354 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF2354
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 5 hrs 17 mins 8 secs

Question: 93 of 100

Do the following factors decrease large intestinal motility?

(Please select 1 option)

- Anticholinergic agents
- CCK-PZ
- Gastric distension
- Laxatives.
- Parasympathetic activity

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
100%

Questions Set : REF2354 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF2354
Page
Safety
Tools

Dashboard
Questions
Scores
Community
Help
Shop

Work Smart Session - MRCP Part 1

Time taken: 5 hrs 18 mins 11 secs

Question: 93 of 100

Do the following factors decrease large intestinal motility?

(Please select 1 option)

- (●) Anticholinergic agents ✓ Correct
- ( ) CCK-PZ
- ( ) Gastric distension
- ( ) Laxatives.
- ( ) Parasympathetic activity

The others and cholinergic agents increase large intestinal motility.

Next question | Tag Question | Remove question

Show tools

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
100%

Questions Set : REF1986 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF1986
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 5 hrs 18 mins 11 secs

Question: 94 of 100

A 43-year-old male presents with weight loss and watery diarrhoea.

Investigations reveal hypokalaemia with a pancreatic mass.

Which of the following would support the diagnosis of a VIPoma?

(Please select 1 option)

- Achlorhydria
- Hypoglycaemia
- Increased pancreatic polypeptide
- Migratory erythema
- Pellagra

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
100%

Questions Set : REF1986 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF1986
Page Safety Tools

Question: 94 of 100

A 43-year-old male presents with weight loss and watery diarrhoea.

Investigations reveal hypokalaemia with a pancreatic mass.

Which of the following would support the diagnosis of a VIPoma?

(Please select 1 option)

◉	Achlorhydria ✓ Correct
○	Hypoglycaemia
○	Increased pancreatic polypeptide
○	Migratory erythema
○	Pellagra

Achlorhydria is classically associated with VIPoma together with profuse diarrhoea, a hypokalaemic acidosis and hyperglycaemia.

Migratory erythema is associated with a glucagonoma.

Although raised pancreatic polypeptide is seen with a VIPoma it is unusual and is more commonly associated with its own syndrome.

Pellagra is associated with the carcinoid syndrome.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
100%

Questions Set : REF1947 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF1947
Page Safety Tools

Work Smart Session - MRCP Part 1

Time taken: 5 hrs 19 mins 6 secs

Question: 95 of 100

A 16-year-old boy with cystic fibrosis (CF) presents with abdominal pain.

Which of the following is most likely to be the cause?

(Please select 1 option)

- Irritable bowel syndrome
- Meconium ileus equivalent syndrome
- Pyelonephritis
- Renal calculi
- Ulcerative colitis

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
100%

Questions Set : REF1947 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF1947
Page
Safety
Tools

Shop

- Meconium ileus equivalent syndrome ✓ Correct
- Pyelonephritis
- Renal calculi
- Ulcerative colitis

Meconium ileus equivalent or distal intestinal obstruction syndrome occurs in older children and adults with CF and presents with colicky abdominal pain, distension, vomiting and failure to pass faeces.

The plain abdominal x-ray confirms small bowel obstruction.

Initial management includes rehydration with intravenous fluids and oral N-acetyl cysteine.

Other gastrointestinal complications of / associations with CF include:

- liver cirrhosis

- gall bladder disease

- pancreatitis

- peptic ulceration

- hiatus hernia

- coeliac disease and

- Crohn's disease.

Next question

Tag Question

Remove question

Done
Internet | Protected Mode: On
100%

Questions Set : REF1897 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF1897
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 5 hrs 19 mins 40 secs

Question: 96 of 100

Which of the following is not true of a patient with ascites due to liver cirrhosis?

(Please select 1 option)

- Cardiac output is often elevated
- Hepatic intrasinusoidal pressure is elevated
- Spontaneous bacterial peritonitis is a recognised feature
- The usual source of the ascitic fluid is mainly from the exudation from the surface of the liver
- Urinary sodium concentration is usually less than 10 mmol/l

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
100%

Questions Set : REF1897 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF1897
Page
Safety
Tools

Dashboard
Questions
Scores
Community
Help
Shop

Work Smart Session - MRCP Part 1

Time taken: 5 hrs 20 mins 57 secs

Question: 96 of 100

Which of the following is not true of a patient with ascites due to liver cirrhosis?

(Please select 1 option)

- Cardiac output is often elevated
- Hepatic intrasinusoidal pressure is elevated
- Spontaneous bacterial peritonitis is a recognised feature
- (●) The usual source of the ascitic fluid is mainly from the exudation from the surface of the liver ✓ Correct
- Urinary sodium concentration is usually less than 10 mmol/l

Hepatocellular failure is associated with hyperdynamic circulation and systemic vasodilatation with increased vascular capacitance.

Most patients have sodium and water retention.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
100%

Questions Set : REF1891 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF1891
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 5 hrs 20 mins 57 secs

Question: 97 of 100

Which of the following is correct regarding reflux oesophagitis of gastric contents?

(Please select 1 option)

- Can be excluded by a normal appearance at endoscopy
- Can be improved by *Helicobacter pylori* eradication
- Is a cause of asthma
- Is neutralised by bicarbonate secreted by the oesophageal mucosa
- Occurs during transient relaxation of the lower oesophageal sphincter

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
100%

Questions Set : REF1891 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF1891
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 5 hrs 21 mins 51 secs

Question: 97 of 100

Which of the following is correct regarding reflux oesophagitis of gastric contents?

(Please select 1 option)

- ○ Can be excluded by a normal appearance at endoscopy
- ○ Can be improved by *Helicobacter pylori* eradication
- ○ Is a cause of asthma
- ○ Is neutralised by bicarbonate secreted by the oesophageal mucosa
- ◉ Occurs during transient relaxation of the lower oesophageal sphincter ✓ Correct

Diagnosis is based predominantly on history, with a proportion of patients with reflux disease having a normal endoscopy.

H. pylori eradication is indicated in long term healing of gastric and duodenal ulceration, but not reflux disease.

Brunner's glands which secrete alkaline mucus are found in the duodenum .

Intra-oesophageal PH monitoring is used to exclude reflux as cause of bronchoconstriction.

Reflux oesophagitis of gastric contents is a cause of chronic cough and not asthma.

Done
Internet | Protected Mode: On
100%

Questions Set : REF1890 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF1890
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 5 hrs 21 mins 51 secs

Question: 98 of 100

A 32-year-old man develops profuse diarrhoea with mucus and blood.

Biopsies from the flexible sigmiodoscopy shows evidence of ulcerative colitis.

Which of the following is true of the condition?

(Please select 1 option)

- Colectomy may produce regression of gall bladder disease
- Goblet cells are unaffected in the mucosa
- Mesalazine therapy is associated with infertility in males
- Pseudopolyps on sigmoidoscopic examination have premalignant potential
- Topical 5-aminosalicylic acid is less effective than topical steroids in proctitis

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
100%

Questions Set : REF1890 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Questions Set : REF1890
Page Safety Tools

Question: 98 of 100

A 32-year-old man develops profuse diarrhoea with mucus and blood.

Biopsies from the flexible sigmiodoscopy shows evidence of ulcerative colitis.

Which of the following is true of the condition?

(Please select 1 option)

○	Colectomy may produce regression of gall bladder disease ← This is the correct answer
○	Goblet cells are unaffected in the mucosa
◉	Mesalazine therapy is associated with infertility in males ✕ Incorrect answer selected
○	Pseudopolyps on sigmoidoscopic examination have premalignant potential
○	Topical 5-aminosalicylic acid is less effective than topical steroids in proctitis

Mesalazine is 5-aminosalicylic acid.

Sulphasalazine is the combination of 5-ASA and sulphapyridine, the latter being a sulphonamide and causing oligospermia.

Pseudopolyps are not premalignant and may occasionally regress.

Topical 5-aminosalicylic acid is as effective as topical steroids in proctitis.

Goblet cells are depleted in the mucosa.

Next question Tag Question Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
100%

Questions Set : REF1864 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF1864
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 5 hrs 23 mins

Question: 99 of 100

Ten individuals are admitted to casualty with profuse vomiting after attending a retirement dinner in a Chinese restaurant.

They all ate at roughly 7 pm and became ill at roughly midnight. Nine ate a mixture of dishes except one female who ate vegetarian dishes with her rice.

What is the most likely infective organism?

(Please select 1 option)

- *Salmonella enteriditis*
- *Staphylococcus aureus*
- *E. Coli*
- *Clostridium perfringens*
- *Bacillus cereus*

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
100%

Questions Set : REF1864 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF1864
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 5 hrs 23 mins 47 secs

Question: 99 of 100

Ten individuals are admitted to casualty with profuse vomiting after attending a retirement dinner in a Chinese restaurant.

They all ate at roughly 7 pm and became ill at roughly midnight. Nine ate a mixture of dishes except one female who ate vegetarian dishes with her rice.

What is the most likely infective organism?

(Please select 1 option)

- *Salmonella enteriditis*
- *Staphylococcus aureus*
- *E. Coli*
- *Clostridium perfringens*
- *Bacillus cereus* ✓ Correct

This is a typical case of *Bacillus cereus*, with profuse vomiting which occurs approximately one to five hours after eating.

In this case it is likely that the rice itself had been infected.

Another possibility is *Staph. aureus* although this is less likely.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
100%

Questions Set : REF1765 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Google
Favorites
Suggested Sites
Get More Add-ons
Questions Set : REF1765
Page
Safety
Tools

Work Smart Session - MRCP Part 1

Time taken: 5 hrs 24 mins 43 secs

Question: 100 of 100

A 30-year-old Caucasian male presents with a six month history of weight loss, abdominal pain, and diarrhoea. On examination you note finger clubbing.

Which of the following diagnoses is least likely.?

(Please select 1 option)

○	Coeliac disease
○	Crohn's disease
○	Ileo-caecal TB ← This is the correct answer
○	Ulcerative colitis
◉	Whipple's disease ✕ Incorrect answer selected

Ileo-caecal TB is the only condition mentioned not associated with clubbing and would be very rare in a young Caucasian in the UK.

Finish | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Done
Internet | Protected Mode: On
100%

Clinical practice guideline

Irritable bowel syndrome in adults: Diagnosis and management of irritable bowel syndrome in primary care

National Collaborating Centre for Nursing and Supportive Care
commissioned by
National Institute for Health and Clinical Excellence

February 2008

National Collaborating Centre for Nursing and Supportive Care

This guideline was developed by the National Collaborating Centre for Nursing and Supportive Care (NCCNSC) on behalf of the National Institute for Health and Clinical Excellence (NICE). The guideline was commissioned and funded by NICE and developed in accordance with NICE processes and methodologies.

Based at the Royal College of Nursing, the NCCNSC is a partnership of organisations brought together for the purposes of supporting the development of NICE clinical practice guidelines. The partnership is comprised of representatives from the following organisations:

- Centre for Evidence-Based Medicine, University of York
- Clinical Effectiveness Forum for Allied Health Professions
- Healthcare Libraries, University of Oxford
- Health Economics Research Centre, University of Oxford
- Royal College of Nursing
- UK Cochrane Centre.

Disclaimer

As with any clinical practice guideline, the recommendations contained in this guideline may not be appropriate in all circumstances. A limitation of a guideline is that it simplifies clinical decision-making (Shiffman 1997). Decisions to adopt any particular recommendations must be made by practitioners in the context of:

- Available resources
- Local services, policies and protocols
- The circumstances and wishes of the patient
- Available personnel and devices
- Clinical experience of the practitioner
- Knowledge of more recent research findings

Contents

		Page
National collaborating centre for nursing and supportive care		2
Disclaimer		2
Guideline development group membership and acknowledgements		5
Terminology		8
Abbreviations		8
Glossary		10
1	EXECUTIVE SUMMARY	27
2	PRINCIPLES OF PRACTICE	32
2.1	Person-centred care	32
2.2	A collaborative interdisciplinary approach to care	32
2.3	Organisational issues	32
2.4	Background	33
2.5	Clinical need for the guideline	33
2.6	Management issues	35
3	SUMMARY OF GUIDELINE RECOMMENDATIONS	36
4	AIMS OF THE GUIDELINE	41
4.1	Who the guideline is for	41
4.2	Groups covered by the guideline	41
4.3	Groups not covered by the guideline	41
4.4	Healthcare setting	41
4.5	Diagnosis and management interventions covered by the guideline	42
4.6	Interventions not covered by the guideline	42
4.7	Guideline development group	42
5	METHODS USED TO DEVELOP THE GUIDELINE	44
5.1	Summary of development process	44
5.2	Clinical effectiveness review methods	45
5.3	Cost effectiveness review methods	59
5.4	Submission of evidence	73
5.5	Formulating recommendations	73
6	DIAGNOSIS	76
7	DIET AND LIFESTYLE	128
7.1	General dietary and lifestyle advice	135
7.2	Physical activity	136
7.3	Fibre	145
7.4	Probiotics and prebiotics	168
7.5	Aloe vera	191
7.6	Exclusion diets	199
8	PHARMACOLOGICAL INTERVENTIONS	212
8.1	Laxatives	214

8.2 Antimotility agents 260
8.3 Antispasmodics 291
8.4 Antidepressants 314
8.5 Adverse effects: pharmacological interventions 349
8.5.1 Adverse effects: antispasmodics, antimotility agents and laxatives 349
8.5.2 Adverse effects: tricyclics and selective serotonin re-uptake inhibitors 369
9 PSYCHOLOGICAL INTERVENTIONS 374
9.1 Relaxation 377
9.2 Biofeedback 381
9.3 Evidence to recommendation: relaxation and biofeedback 388
9.4 Psychotherapy 388
9.5 Cognitive behavioural therapy (CBT) 407
9.6 Hypnotherapy 441
9.7 Indirect comparison of psychological interventions 458
9.8 Evidence to recommendation: psychotherapy, CBT and hypnotherapy 463
10 COMPLEMENTARY AND ALTERNATIVE THERAPIES 465
10.1 Reflexology 467
10.2 Acupuncture 471
10.3 Herbal medicines 481
11 PSYCHOSOCIAL INTERVENTION: PATIENT INFORMATION AND SUPPORT GROUPS 507
11.1 Support groups and self help 509
11.2 Patient information 515
11.3 Evidence to recommendation: psychosocial and patient information 520
12 RECOMMENDATIONS FOR RESEARCH 521
13 IMPLEMENTATION OF THE GUIDELINE 524
14 RELATED NICE GUIDANCE 525
15 UPDATE OF THE GUIDELINE 525
16 REFERENCES 526
APPENDIX A Registered stakeholders
APPENDIX B Search strategies and searched databases
APPENDIX C Tables of included studies
APPENDIX D Quality assessment of studies
APPENDIX E Tables of excluded studies
APPENDIX F Grading the evidence
APPENDIX G Literature review of prognostic resource use and quality of life data
APPENDIX H PSA parameters
APPENDIX I Bristol Stool Form Scale
APPENDIX J General Practice Physical Activity Questionnaire
APPENDIX K Declarations of interests

Guideline development group membership and acknowledgements

Mr Jonathan Blanchard-Smith
Patient/carer representative
IBS Network

Dr Ian Bullock
Director
NCCNSC

Dr Jamie Dalrymple
Medical Practitioner, Drayton & St Faith's Medical Practice, Norwich
Primary Care Society for Gastroenterology

Ms Sarah Davis
Senior Health Economist
NCCNSC

Ms Jackie Eastwood
Specialist Pharmacist in Gastroenterology, St. Mark’s Hospital, Harrow
Royal Pharmaceutical Society of Great Britain

Dr Charles Foster
Senior Researcher, University of Oxford
British Heart Foundation, Health Promotion Research Group

Dr Jenny Gordon
Research and Development Fellow
NCCNSC

Mrs Jenny Gough
Nurse Consultant, Camden Primary Care Trust, London
Royal College of Nursing

Prof Elspeth Guthrie
Professor of Psychological Medicine & Medical Psychotherapy, Manchester Royal Infirmary
Royal College of Psychiatrists

Dr Miranda Lomer
Consultant Dietitian in Gastroenterology, King’s College London

British Dietetic Association

Ms Marion Saunders
Patient/carer representative

Ms Theresa Shaw (Chair)
Chief Executive
Foundation of Nursing Studies

Dr Richard Stevens
General Practitioner, East Oxford Health Centre
Royal College of General Practitioners

Dr Maggie Westby
Senior Research and Development Fellow
NCCNSC

Prof Peter Whorwell
Professor of Medicine and Gastroenterology, Wythenshawe Hospital, Manchester
British Society of Gastroenterology

Dr Mary Wilson
Nurse Specialist, Westwood Hospital, North Humberside
Royal College of Nursing

Staff at the NCCNSC who contributed to this guideline

Dr Anayo Akunne
Health Economist

Ms Nahara Martinez-Gonzales
Systematic Reviewer

Mr Paul Miller
Information Specialist

Ms Emma Nawrocki
Administrator

Mr Edward Weir
Centre Manager

The NCCNSC would like to thank the following people for their assistance with developing the guideline

Dr Yoon Loke

Dr Giok Ong

Dr Jacoby Patterson

Dr Joanne Lord

The NCCNSC also acknowledges the expert opinions of the following people

Kevin Whelan
Nutritional Sciences Division, King's College London

Professor E Quigley

Yvonne McKenzie, Liane Reeves, Annabel Drake, Anna Brian, Carolyn Johnstone, Adele Nichol, Kristina Zaremba
Gastroenterology Specialist Group of the British Dietetic Association

Scottish Nutrition & Diet Resources Initiative (SNDRI)

Terminology

Where the term ‘carer’ is used, this refers to unpaid carers as opposed to paid careworkers.

Abbreviations

ARR: Absolute Relative Risk

BNF: British National Formulary

CAM: Complementary and Alternative Medicine

CBT: Cognitive Behavioural Therapy

CEAC: Cost-effectiveness acceptability curve

CI: Confidence interval

CRP: C-reactive protein **-** is used mainly as a marker of inflammation

ESR: Erythrocyte Sedimentation Rate - is a non-specific measure of inflammation that is commonly used as a medical screening test.

EMA: Anti-endomysium antibodies, inflammatory markers used in the diagnosis of Coeliac disease

FBC: Full blood count

FOB: Faecal occult blood

GDG: Guideline development group

GI: Gastrointestinal

GP: General practitioner

GRADE: Guidelines Recommendations Assessment Development Evaluation

HRQoL: Health-related quality of life

IBD: Inflammatory Bowel Disease, A general term for any disease characterized by inflammation of the bowel. Examples include colitis and Crohn's disease. Symptoms include abdominal pain, diarrhea, fever, loss of appetite and weight loss.

IBS: Irritable Bowel Syndrome

IBS-A: Irritable Bowel Disease with alternating symptoms of diarrhoea and constipation

IBS-C: Irritable Bowel Disease with constipation as primary bowel dysfunction

IBS-D: Irritable Bowel Disease with diarrhoea as the primary bowel dysfunction

ICER: Incremental cost-effectiveness ratio

LY: Life-year

NHS: National Health Service

NICE: National Institute for Health and Clinical Excellence

NNT: Number needed to treat

OR: Odds ratio

PCT: Primary Care Trust

PEG: polyethylene glycol (macrogol)

PSA: Probabilistic sensitivity analysis

PSS: Personal Social Services

QALY: Quality-adjusted life-year

RCT: Randomised controlled trial

RR: Relative risk

SSRI: selective serotonin re-uptake inhibitors

TGTT: Total gut transit time.

TTG: Anti-transglutaminase antibodies, inflammatory markers used in the diagnosis of Coeliac disease

Organisations

DoH	Department of Health
NCCNSC	National Collaborating Centre for Nursing and Supportive Care
NICE	National Institute for Health and Clinical Excellence
RCN	Royal College of Nursing

General glossary

Absolute risk reduction (Risk difference): The difference in event rates between two groups (one subtracted from the other) in a comparative study.

Abstract: Summary of a study, which may be published alone or as an introduction to a full scientific paper.

Acupuncture: An ancient Chinese technique involving the insertion of fine needles just under the skin in specific locations in order to relieve pain and treat a wide variety of complaints. Historically, acupuncture is one component of an overall program of Chinese medicine that includes theory, practice, diagnosis, physiology, and the use of herbal preparations.

Adjustment: A statistical procedure in which the effects of differences in composition of the populations being compared (or treatment given at the same time) have been minimised by statistical methods.

Algorithm (in guidelines): A flow chart of the clinical decision pathway described in the guideline, where decision points are represented with boxes, linked with arrows.

Allocation concealment: The process used to prevent advance knowledge of group assignment in a RCT. The allocation process should be impervious to any influence by the individual making the allocation, by being administered by someone who is not responsible for recruiting participants.

Applicability: The degree to which the results of an observation, study or review are likely to hold true in a particular clinical practice setting.

Arm (of a clinical study): Subsection of individuals within a study who receive one particular intervention, for example placebo arm.

Association: Statistical relationship between two or more events, characteristics or other variables. The relationship may or may not be causal.

Baseline: The initial set of measurements at the beginning of a study (after run-in period where applicable), with which subsequent results are compared.

Behavioural therapy: A generic term to describe forms of psychological therapy based on the concept that the way we think about things affects how we feel and act. Behavioural therapy focuses on thinkingand behaviour and it aims to help people in the ways they act (behaviour).

Bias: Systematic (as opposed to random) deviation of the results of a study from the 'true' results that is caused by the way the study is designed or conducted.

Biofeedback: A technique in which an individual learns to consciously control involuntary responses such as heart rate, brain waves, and muscle contractions. Information about a normally unconscious physiologic process is relayed back to the patient as a visual, auditory, or tactile signal. These responses are electronically monitored and noted through beeps, graphs, or on a computer screen, which are seen and heard by the participant.

Blinding (masking): Keeping the study participants, caregivers, researchers and outcome assessors unaware about the interventions to which the participants have been allocated in a study

Bloating: Fullness or swelling in the abdomen that often occurs after meals

Borborygmus: The rumbling noise produced by the movement of gas through the intestines. The plural of this word is borborygmi.

Bristol Stool Form Scale: A validated, illustrated tool used to define stool type and consistency developed by Dr K W Heaton, Reader in Medicine at the University of Bristol. Copyright Norgine Ltd 2000.

Carer (caregiver): Someone other than a health professional who is involved in caring for a person with a medical condition.

Case-control study: A study in which the amount of exposure to a potentially causative factor in a group of patients (cases) who have a particular condition is compared with the exposure in a similar group of people who do not have the clinical condition (the latter is called the control group).

Clinical efficacy: The extent to which an intervention is active when studied under controlled research conditions.

Clinical effectiveness: The extent to which an intervention produces an overall health benefit in routine clinical practice.

Clinical impact: The effect that a guideline recommendation is likely to have on the treatment or treatment outcomes, of the target population.

Clinical question: In guideline development, this term refers to the questions about treatment and care that are formulated to guide the development of evidence-based recommendations.

Clinician: A healthcare professional providing healthcare, for example doctor, nurse or physiotherapist.

Cochrane Library: A regularly updated electronic collection of evidence-based medicine databases, including the Cochrane Database of Systematic Reviews.

Cochrane Review: A systematic review of the evidence from randomised controlled trials relating to a particular health problem or healthcare intervention, produced by the Cochrane Collaboration. Available electronically as part of the Cochrane Library.

Coeliac Disease: Coeliac disease (also called celiac disease, non-tropical sprue, c(o)eliac sprue and gluten intolerance) is an autoimmune disorder characterised by damage to all or part of the villi lining the small intestine. This damage is caused by exposure to gluten and related proteins found in wheat, rye, malt and barley, and to a lesser degree in oats.

Cognitive Behavioural Therapy, also called **Cognitive therapy:** A relatively short-term form of psychotherapy based on the concept that the way we think about things affects how we feel emotionally. Cognitive therapy focuses on present thinking, behaviour, and communication rather than on past experiences and is oriented toward problem solving. It aims to help people in the ways they think (cognition) and in the ways they act (behaviour).

Cohort study: A retrospective or prospective follow-up study. Groups of individuals to be followed up are defined on the basis of presence or absence of exposure to a suspected risk factor or intervention. A cohort study can be comparative, in which case two or more groups are selected on the basis of differences in their exposure to the agent of interest.

Co-morbidity: Coexistence of more than one disease or an additional disease (other than that being studied or treated) in an individual.

Comparability: Similarity of the groups in characteristics likely to affect the study results (such as health status or age).

Compliance: The extent to which a person adheres to the health advice agreed with healthcare professionals. May also be referred to as 'adherence'.

Concordance: An approach first used in the prescribing and taking of medicines but can be applied to many treatments in healthcare. It is an agreement reached after negotiation between a patient and a health care professional that respects the beliefs and wishes of the patient in determining whether, when and how medicines/treatments are to be taken. Although reciprocal, this is an alliance in which the health care professionals recognise the primacy of the patient's decisions about taking the recommended medications.

Confidence interval (CI): The range of numerical values within which we can be confident that the population value being estimated is found. Confidence intervals indicate the strength of evidence; where confidence intervals are wide they indicate less precise estimates of effects.

Confounding: In a study, confounding occurs when the effect of an intervention on an outcome is distorted as a result of an association between the population or intervention or outcome and another factor (the 'confounding variable') that can influence the outcome independently of the intervention under study.

Consensus methods: Techniques that aim to reach an agreement on a particular issue. Formal consensus methods include Delphi and nominal group techniques, and consensus development conferences. In the development of clinical guidelines, consensus methods may be used where there is a lack of strong research evidence on a particular topic. Expert consensus methods will aim to reach agreement between experts in a particular field.

Constipation: A condition in which bowel movements are infrequent, hard and dry, and elimination of faeces is difficult and infrequent.

Consultation: The process that allows stakeholders and individuals to comment on initial versions of NICE guidance and other documents so their views can be taken into account when the final version is being produced.

Cost-benefit analysis: A type of economic evaluation, which estimates the net benefit to society of an intervention as the incremental (difference in) benefit of the intervention minus the incremental (difference in) cost, with all benefits and costs measured in monetary units. If benefits exceed costs, the evaluation would be a basis for recommending the intervention.

Cost-consequences analysis: A type of economic evaluation, whereby both outcomes and costs of alternative interventions are described, without any attempt to combine the results.

Cost effectiveness: The cost per unit of benefit of an intervention. Benefits of different interventions are measured using a single outcome (for example, life-years gained, quality-adjusted life-years gained, deaths avoided, heart attacks avoided, cases detected).

Cost-effectiveness analysis: An economic study design in which alternative interventions are compared in terms of cost per unit of effectiveness.

Cost-effectiveness model: An explicit mathematical framework, which is used to represent clinical decision problems and incorporate evidence from a variety of sources in order to estimate the costs and health outcomes.

Cost-of-illness/economic burden studies: An analysis of the total costs incurred by a society due to a specific disease.

Cost impact: The total cost to the person, the NHS or to society.

Cost-minimisation analysis: A type of economic evaluation used to compare the difference in costs between programs that have the same health outcome.

Costing study: The simplest form of economic study, measuring only the costs of given interventions.

Cost-utility analysis: A form of cost-effectiveness analysis in which the units of effectiveness are quality-adjusted life-years (QALYs).

Counselling: The skilled use of the relationship (between the counsellor and patient) to help the patient develop self-knowledge, self-esteem and the ability to take control of his or her own life. (The British Association of Counselling and Psychotherapy).

Crohn's Disease: A chronic inflammatory disease of the digestive tract and it can involve any part of it - from the mouth to the anus. It typically affects the terminal ileum as well as demarcated areas of large bowel, with other areas of the bowel being relatively unaffected. It is often associated with auto-immune disorders outside the bowel, such as rheumatoid arthritis.

Cross sectional study: Examination of the relationship between disease and other variables of interest as they exist in a defined population assessed at a particular time.

Data extraction tables: Tabulated presentation of data collected from individual studies.

Decision problem: A clear specification of the interventions, patient populations and outcome measures and perspective adopted in an evaluation, with an explicit justification, relating these to the decision which the analysis is to inform.

Decision analytic techniques: A way of reaching decisions, based on evidence from research. This evidence is translated into probabilities, and then into diagrams or decision trees that direct the clinician through a succession of possible scenarios, actions and outcomes.

Delphi technique: A systematic interactive forecasting method based on independent inputs of a panel of selected experts over two or more rounds. Questions are usually formulated as hypotheses and experts are asked to comment. Each round of questioning is followed with the feedback on the preceding round of replies, usually presented anonymously. Thus the experts are encouraged to revise their earlier answers in light of the replies of other members of the group. It is believed that during this process the range of the answers will decrease and the group will converge towards the "correct" answer. After several rounds the process is complete and the median scores determine the final answer.

Deterministic analysis: A deterministic analysis is one in which the best estimate for each parameter has been used to give a single estimate of cost-effectiveness. It is the opposite of a probabilistic sensitivity analysis (See sensitivity analysis).

Diarrhoea: A condition in which the sufferer has frequent and watery or loose bowel movements (from the ancient Greek word διαρροή = leakage; lit. "to run through").

Differential Diagnosis: Distinguishing between two or more diseases and conditions with similar symptoms by systematically comparing and contrasting their clinical findings, including physical signs, symptoms, as well as the results of laboratory tests and other appropriate diagnostic procedures. See also Red Flags.

Discounting: Costs and perhaps benefits incurred today have a higher value than costs and benefits occurring in the future. Discounting health benefits reflects individual preference for benefits to be experienced in the present rather than the future. Discounting costs reflects individual preference for costs to be experienced in the future rather than the present.

Dominance: An intervention is said to be dominated if there is an alternative intervention that is both less costly and more effective.

Dosage: The prescribed amount of a drug to be taken, including the size and timing of the doses.

Drop-out: A participant who withdraws from a clinical trial before the end.

Economic evaluation: Comparative analysis of alternative courses of action in terms of both their costs and consequences.

Effect (as in effect measure, treatment effect, estimate of effect, effect size): The observed association between interventions and outcomes or a statistic to summarise the strength of the observed association.

Effectiveness: See “Clinical effectiveness”

Efficacy: See “Clinical efficacy”

Endoscopy: A procedure that uses an endoscope to diagnose or treat a condition. There are many types of endoscopy; examples include colonoscopy, sigmoidoscopy, gastroscopy, enteroscopy, and esophogealgastroduodenoscopy (EGD).

Epidemiological study: A study which looks at how a disease or clinical condition is distributed across populations, e.g. across geographical areas or over time, or between age groups.

Evidence: Information on which a decision or guidance is based. Evidence is obtained from a range of sources including randomised controlled trials, observational studies, expert opinion (of clinical professionals and/or patients).

Evidence table: A table summarising the results of a collection of studies which, taken together, represent the evidence supporting a particular recommendation or series of recommendations in a guideline.

Exclusion criteria (literature review): Explicit standards used to decide which studies should be excluded from consideration as potential sources of evidence.

Exclusion criteria (clinical study): Criteria that define who is not eligible to participate in a clinical study.

Expert consensus: See 'Consensus methods'.

Extra-colonic symptoms: IBS symptoms that are not directly associated with the GI tract but are not uncommon features of IBS e.g. low back pain, bladder symptoms, thigh pain, gynaecological symptoms

Extrapolation: In data analysis, predicting the value of a parameter outside the range of observed values.

False positive: Positive test diagnostic result in a subject who does not possess the attribute for which the test is conducted. The incorrect labelling of a healthy person following screening.

Flatus: Gas or wind produced in the intestines, mostly as a result of the normal activity of bacteria in the bowel.

Follow-up: Observation over a period of time of an individual, group or population whose relevant characteristics have been assessed in order to observe changes in health status or health-related variables.

Functional Bowel Disorder: In medicine, the term functional bowel disorder refers to a group of disorders which are characterised by chronic abdominal complaints without a structural or biochemical cause that could explain symptoms. Functional bowel disorders include: * Functional dyspepsia* Non-cardiac chest pain (NCCP)* Chronic abdominal pain* Functional constipation* Irritable bowel syndrome (IBS).

Generalisability: The extent to which the results of a study based on measurement in a particular patient population and/or a specific context hold true for another population and/or in a different context. In this instance, this is the degree to which the guideline recommendation is applicable across both geographical and contextual settings. For instance, guidelines that suggest substituting one form of labour for another should acknowledge that these costs might vary across the country.

Generic name: The general non-proprietary name of a drug or device.

Global Improvement: A research study outcome measuring an overall improvement in a group of defined IBS symptoms (e.g. pain, bowel habit, quality of life). Each symptom is given a score and the aggregate of the scores from each symptom forms the global improvement score.

Global improvement score: An aggregate score of groups of IBS symptoms used to measure changes in severity and frequency of symptoms before, during and after treatment interventions.

Gold standard: A method, procedure or measurement that is widely accepted as being the best available, to which a new method is compared.

Good Practice Points: Recommended good practice based on the clinical experience of the Guideline Development Group.

Grey literature: Reports that are unpublished or have limited distribution, and are not included in the common bibliographic retrieval systems.

Gut motility: A term referring to the contractions of the gastrointestinal tract (peristalsis). These contractions cause food to be pushed through the GI tract in a controlled fashion

Harms: Adverse effects of an intervention.

Health professional: Includes nurses, allied health professionals and doctors.

Health economics: The study of the allocation of scarce resources among alternative healthcare treatments. Health economists are concerned with both increasing the average level of health in the population and improving the distribution of health.

Health technology assessment: The process by which evidence on the clinical effectiveness and the costs and benefits of using a technology in clinical practice is systematically evaluated.

Health-related quality of life: A combination of an individual's physical, mental and social well-being; not merely the absence of disease.

Hydrogen Breath Test: Test for lactose intolerance that measures breath samples for too much hydrogen.

Hypnotherapy: A deep state of relaxation is achieved through focused attention. While in this trance-like state, the unconscious mind is highly receptive to new perspectives and ideas. The use of imagery and positive suggestions at this time can help a client imagine and actually experience

herself in the future, as she desires to be. This may make the desired changes happen much faster and with less resistance, as a result of the hypnosis experience.

Hypothesis: A supposition made as a starting point for further investigation.

Idiopathic Constipation: Constipation is termed idiopathic when it cannot be explained by any anatomical, physiological, radiological or histological abnormalities. The exact aetiology is not fully understood but it is generally accepted that a combination of factors may contribute to the condition.

Implementation: Introducing the use of the guidance recommendations in practice.

Incidence: The number of new cases of illness commencing, or of persons falling ill during a specified time period in a given population.

Inclusion criteria (literature review): Explicit criteria used to decide which studies should be considered as potential sources of evidence.

Incremental analysis: The analysis of additional costs and additional clinical outcomes with different interventions.

Incremental cost: The mean cost per patient associated with an intervention minus the mean cost per patient associated with a comparator intervention.

Incremental cost effectiveness ratio (ICER): The difference in the mean costs in the population of interest divided by the differences in the mean outcomes in the population of interest.

Incremental net benefit (INB): The value (usually in monetary terms) of an intervention net of its cost compared with a comparator intervention. The INB can be calculated for a given cost-effectiveness (willingness to pay) threshold. If the threshold is £20,000 per QALY gained then the INB is calculated as: (£20,000 x QALYs gained) – Incremental cost

Inflammatory Bowel Disease: General term for any disease characterized by inflammation of the bowel. Two of the most common Inflammatory Bowel Diseases are ulcerative colitis and Crohn's disease. Note: Not to be confused with Irritable Bowel Syndrome.

Intervention: Healthcare action intended to benefit the patient, for example, drug treatment, surgical procedure, psychological therapy.

Indication (specific): The defined use of a technology as licensed by the Medicines and Healthcare products Regulatory Agency (MHRA).

Intention-to-treat analysis (ITT analysis): An analysis of the results of a clinical study in which the data are analysed for all study participants as if they had remained in the group to which they were randomised, regardless of whether or not they remained in the study until the end, crossed over to another treatment or received an alternative intervention.

Internal validity: The degree to which the results of a study are likely to approximate the 'truth' for the participants recruited in a study (that is, are the results free of bias?). It refers to the integrity of the design and is a prerequisite for applicability (external validity) of a study's findings.

Intrinsic: Factors present within the individual.

Licence: An authorisation from the MHRA to market a medicinal product.

Life-years gained: Average years of life gained per person as a result of the intervention.

Logistic regression model: A data analysis technique to derive an equation to predict the probability of an event given one or more predictor variables. This model assumes that the natural logarithm of the odds for the event (the logit) is a linear sum of weighted values of the predictor variable. The weights are derived from data using the method of maximum likelihood.

Meta-analysis: A statistical technique for combining (pooling) the results of a number of studies that address the same question and report on the same outcomes to produce a summary result. The aim is to derive more precise and clear information from a large data pool. It is generally more reliably likely to confirm or refute a hypothesis than the individual trials.

Multivariate model: A statistical model for analysis of the relationship between two or more predictor (independent) variables and the outcome (dependent) variable.

Narrative summary: Summary of findings given as a written description.

Negative predictive value: The proportion of individuals with a negative test result who do NOT have the disease.

Nominal group technique: A methodology for achieving team consensus quickly when the team is ranking several options or alternatives or selecting the best choice among them. The method basically consists of having each team member come up with his or her personal ranking of the options or choices, and collation of everyone's rankings into the team consensus.

Number needed to treat: The number of patients that who on average must be treated to prevent a single occurrence of the outcome of interest.

Observational study: Retrospective or prospective study in which the investigator observes the natural course of events with or without control groups; for example, cohort studies and case–control studies.

Odds ratio: A measure of treatment effectiveness. The odds of an event happening in the treatment group, expressed as a proportion of the odds of it happening in the control group. The 'odds' is the ratio of non-events to events.

Off-label: A drug or device used treat a condition or disease for which it is not specifically licensed.

Opportunity cost: The opportunity cost of investing in a healthcare intervention is the other healthcare programmes that are displaced by its introduction. This may be best measured by the health benefits that could have been achieved had the money been spent on the next best alternative healthcare intervention.

Outcome: Measure of the possible results that may stem from exposure to a preventive or therapeutic intervention. Outcome measures may be intermediate endpoints or they can be final endpoints.

Pain score: A research study outcome measuring changes in pain using an aggregate score of pain type, duration, frequency and severity. Scales used vary.

p values: The probability that an observed difference could have occurred by chance, assuming that there is in fact no underlying difference between the means of the observations. If the probability is less than 1 in 20, the p value is less than 0.05; a result with a p value of less than 0.05 is conventionally considered to be ‘statistically significant’.

Peer review: A process where research is scrutinised by experts that have not been involved in the design or execution of the studies.

Peristalsis: Synchronized or coordinated contraction of the muscles that propel food content through the gastrointestinal (GI) tract to facilitate normal digestion and the absorption of nutrients. Peristalsis is dependent upon the coordination between the muscles, nerves, and hormones in the digestive tract.

Placebo: An inactive and physically identical medication or procedure used as a comparator in controlled clinical trials.

Positive predictive value: The proportion of individuals with a positive test result who actually have the disease.

Prevalence: The proportion of persons with a particular disease within a given population at a given time.

Prognosis: A probable course or outcome of a disease. Prognostic factors are patient or disease characteristics that influence the course. Good prognosis is associated with low rate of undesirable outcomes; poor prognosis is associated with a high rate of undesirable outcomes.

Proprietary name: The brand name given by the manufacturer to a drug or device it produces.

Psychotherapy: A set of techniques intended to cure or improve psychological and behavioural problems in humans. The commonest form of psychotherapy is direct personal contact between therapist and patient, mainly in the form of talking.

Psychological interventions: The treatment of any condition by psychological means. This may utilise insight, persuasion, suggestion, reassurance, and instruction so that patients may see themselves and their problems more realistically and have the desire to cope effectively with them. There are many different psychological interventions, these include psychotherapy, biofeedback, cognitive behavioural therapy, family therapy, hypnotherapy, interpersonal therapy and psychodynamic therapy.

Qualitative research: Research concerned with subjective outcomes relating to social, emotional and experiential phenomena in health and social care.

Quality of life: See “Health-related quality of life”

Quality adjusted life years (QALYs): An index of survival that is adjusted to account for the patient’s quality of life during this time. QALYs have the advantage of incorporating changes in both quantity (longevity/mortality) and quality (morbidity, psychological, functional, social and other factors) of life. Used to measure benefits in cost-utility analysis. The QALYs gained are the mean QALYs associated with one treatment minus the mean QALYs associated with an alternative treatment.

Quick reference guide (for a guideline): An abridged version of NICE guidance, which presents the key priorities for implementation and summarises the recommendations for the core clinical audience.

Randomisation: Allocation of participants in a research study to two or more alternative groups using a chance procedure, such as computer-generated random numbers. This approach is used in an attempt to ensure there is an even distribution of participants with different characteristics between groups and thus reduce sources of bias.

Randomised controlled trial (RCT): A comparative study in which participants are randomly allocated to intervention and control groups and followed up to examine differences in outcomes between the groups. The random allocation eliminates bias in the assignment of treatment to patients and establishes the basis for the statistical analysis.

Recurrent: A symptom and/or sign that resolves then returns at least once.

'Red Flag' symptoms: A warning term used to indicate further investigation of specific symptoms is warranted to identify potential differential diagnosis.

Reference standard (or gold standard): An agreed standard, for example for a test or treatment, against which other interventions can be compared.

Refractory IBS: people with IBS who do not respond to first line therapies after 12 months and who develop a continuing symptom profile.

Relative risk: The number of times more likely or less likely an event is to happen in one group compared with another (calculated as the risk of the event in group A/the risk of the event in group B).

Reliability/repeatability: The degree of agreement exhibited when a measurement is repeated under identical conditions. Reliability refers to the degree to which the results obtained by a measurement procedure can be replicated.

Remit: The brief given by the Department of Health and Welsh Assembly Government at the beginning of the guideline development process. This defines core areas of care that the guideline needs to address.

Resource implication: The likely impact in terms of finance, workforce or other NHS resources.

Retrospective cohort study: A study in which a defined group of persons with an exposure that occurred in the past and an appropriate comparison group who were not exposed are identified at

a time later than when they were exposed and followed from the time of exposure to the present, and in which the incidence of disease (or mortality) for the exposed and unexposed are assessed.

Review of the literature: An article that summarises the evidence contained in a number of different individual studies and draws conclusions about their findings. It may or may not be systematically researched and developed.

Secondary benefits: Benefits resulting from a treatment in addition to the primary, intended outcome.

Selection bias (also allocation bias): A systematic bias in selecting participants for study groups, so that the groups have differences in prognosis and/or therapeutic sensitivities at baseline. Randomisation (with concealed allocation) of patients protects against this bias.

Sensitivity (of a test): The proportion of individuals classified as positive by the gold (or reference) standard, who are correctly identified by the study test.

Sensitivity (of a search): The proportion of relevant studies identified by a search strategy expressed as a percentage of all relevant studies on a given topic. It describes the comprehensiveness of a search method (that is, its ability to identify all relevant studies on a given topic). Highly sensitive strategies tend to have low levels of specificity and vice versa.

Sensitivity analysis: A means of representing uncertainty in the results of economic evaluations. Uncertainty may arise from missing data, imprecise estimates or methodological controversy. Sensitivity analysis also allows for exploring the generalisability of results to other settings. The analysis is repeated using different assumptions to examine the effect on the results.

One-way simple sensitivity analysis (univariate analysis): each parameter is varied individually in order to isolate the consequences of each parameter on the results of the study.

Multi-way simple sensitivity analysis (scenario analysis): two or more parameters are varied at the same time and the overall effect on the results is evaluated.

Threshold sensitivity analysis: the critical value of parameters above or below which the conclusions of the study will change are identified.

Probabilistic sensitivity analysis: probability distributions are assigned to the uncertain parameters and are incorporated into evaluation models based on decision analytical techniques (For example, Monte Carlo simulation).

Specificity (of a test): The proportion of individuals classified as negative by the gold (or reference) standard, who are correctly identified by the study test.

Stakeholder: Those with an interest in the use of a technology under appraisal or a guideline under development. Stakeholders include manufacturers, sponsors, healthcare professionals, and patient and carer groups.

Statistical power: The ability to demonstrate an association when one exists. Power is related to sample size; the larger the sample size, the greater the power and the lower the risk that a possible association could be missed.

Stool: Solid waste that pass through the rectum as bowel movements. Stools are undigested foods, bacteria, mucus, and dead cells.

Stool score: A research study outcome measuring changes in bowel habit using an aggregate score of stool type, stool consistency, stool frequency, complete evacuation. Scales used vary.

Syndrome: A combination of signs and/or symptoms that forms a distinct clinical picture indicative of a particular disorder.

Synthesis of evidence: A generic term to describe methods used for summarising (comparing and contrasting) evidence into a clinically meaningful conclusion in order to answer a defined clinical question. This can include systematic review (with or without meta-analysis), qualitative and narrative summaries.

Systematic review: Research that summarises the evidence on a clearly formulated question according to a predefined protocol using systematic and explicit methods to identify, select and appraise relevant studies, and to extract, collate and report their findings. It may or may not use statistical meta-analysis.

Total gastrointestinal transit time (TGTT): The length of time food takes to pass through the gastrointestinal tract from ingestion to excretion. It is estimated using radio opaque markers and can define three types of delay: right colon (colonic inertial), left colon and recto sigmoid. The exact type of delay may be an important basis for treatment.

Time horizon: The time span used in the NICE appraisal which reflects the period over which the main differences between interventions in health effects and use of healthcare resources are expected to be experienced, and taking into account the limitations of supportive evidence.

Treatment allocation: Assigning a participant to a particular arm of the trial.

Treatment options: The choices of intervention available.

User: Any one using the guideline.

Utility: A measure of the strength of an individual's preference for a specific health state in relation to alternative health states. The utility scale assigns numerical values on a scale from 0 (death) to 1 (optimal or 'perfect' health). Health states can be considered worse than death and thus have a negative value.

Visceral hypersensitivity: Enhanced perception or enhanced responsiveness within the gut.

1 EXECUTIVE SUMMARY, KEY RECOMMENDATIONS and IBS ALGORITHM

The National Institute for Health and Clinical Excellence ('NICE' or 'the Institute') commissioned the National Collaborating Centre for Nursing and Supportive Care (NCC-NSC) to develop guidelines on irritable bowel syndrome (IBS). This follows referral of the topic by the Department of Health and Welsh Assembly Government. This document describes the methods for developing the guidelines and presents the evidence and consensus based recommendations. It is the source document for the NICE (abbreviated version for health professionals); Understanding NICE Guidance, and; Quick Reference Guide versions of the guidelines which will be published by NICE. The guidelines were produced by a multidisciplinary guideline development group and the development process was undertaken by the NCC-NSC.

The main areas examined by the guideline were during the:

- IBS Positive Diagnosis
- Red flags for suspected cancer and other morbidities
- IBS Management focussed on lifestyle advice relating to diet and physical activity, drug and psychological therapies.
- Referral and follow-up.

This guideline covers areas relevant to the diagnosis and management of IBS reflecting the complete patient journey, from the person presenting with IBS symptoms, positive diagnosis and management, targeted at symptom control. The guideline incorporates Cochrane reviews, published NICE clinical and public health guidance, Health Technology Assessment reports, systematic and health economic reviews produced by the National Collaborating Centre for Nursing and Supportive Care. Recommendations are based on clinical and cost effectiveness evidence, and where this is insufficient, the GDG used all available information sources and experience to make consensus recommendations using nominal group technique.

The care pathway reflects a logical sequencing to what is, in effect, tracking the progress of the patient from entry to primary care through to lifestyle adaptation and therapeutic intervention, enabling the person with IBS to learn to live with this chronic condition. The partnership that the person with IBS forms with their primary care clinician/team is key to this being a positive experience where shared decision making feature strongly in aiming for symptom control. This sequencing has enabled the Guideline Development Group (GDG), supported by the technical team, to look at the evidence reviews, understand the clinical context and consider the patient voice when shaping guidance. Patient experience is at the heart of development. Evidence published after June 2007 was not considered.

Healthcare professionals should use their clinical judgement and consult with patients when applying the recommendations. Recommendations aim to reduce variations in practice, thus improving patient outcomes related to both the diagnosis and continuous management of IBS. This guidance is intended to be the source document for primary care local policy development. Its success is dependent on the primary health care team and patients working in partnership in implementing key recommendations. The algorithm provides healthcare professionals, patients and carers to visualise the care pathway, summarising clinical and cost effective evidence and consensus decisions.

Key recommendations

The key recommendations were identified by the GDG as the recommendations that are the priorities for implementation. (The numbering corresponds to the abbreviated (NICE) version of the guideline).

1.1.1.1 Healthcare professionals should consider assessment for IBS if the person reports having had any of the following symptoms for at least 6 months:

- Abdominal pain or discomfort
- Bloating
- Change in bowel habit.

1.1.1.2 All people presenting with possible IBS symptoms should be asked if they have any of the following “red flag” indicators and should be referred to secondary care for further investigation if any are present (see ‘Referral guidelines for suspected cancer’, NICE clinical guideline 27, for detailed referral criteria where cancer is suspected):

- Unintentional and unexplained weight loss
- Rectal bleeding
- A family history of bowel or ovarian cancer
- A change in bowel habit to looser and / or more frequent stools persisting for more than 6 weeks in a person aged over 60 years.

1.1.1.3 All people presenting with possible IBS symptoms should be assessed and clinically examined for the following “red flag” indicators and should be referred to secondary care for further investigation if any are present (see ‘Referral guidelines for suspected cancer’, NICE clinical guideline 27, for detailed referral criteria where cancer is suspected).

- Anaemia
- Abdominal masses
- Rectal masses
- Inflammatory markers for inflammatory bowel disease.

If there is significant concern that symptoms may suggest ovarian cancer, a pelvic examination should also be considered.

1.1.1.4 A diagnosis of IBS should be considered only if the person has abdominal pain or discomfort that is either relieved by defaecation or associated with altered bowel frequency or stool form. This should be accompanied by at least two of the following four symptoms:

- Altered stool passage (straining, urgency, incomplete evacuation)
- Abdominal bloating (more common in women than men), distension, tension or hardness
- Symptoms made worse by eating
- Passage of mucus.

Other features such as lethargy, nausea, backache and bladder symptoms are common in people with IBS, and may be used to support the diagnosis.

1.1.2.1 In people who meet the IBS diagnostic criteria, the following tests should be undertaken to exclude other diagnoses:

- Full blood count (FBC)
- Erythrocyte sedimentation rate (ESR) or plasma viscosity
- C-reactive protein (CRP)
- Antibody testing for coeliac disease (endomysial antibodies [EMA] or tissue transglutaminase [TTG]).

1.1.2.2 The following tests are not necessary to confirm diagnosis in people who meet the IBS diagnostic criteria:

- Ultrasound
- Rigid/flexible sigmoidoscopy
- Colonoscopy; barium enema
- Thyroid function test
- Faecal ova and parasite test
- Faecal occult blood
- Hydrogen breath test (for lactose intolerance and bacterial overgrowth).

1.2.1.1 People with IBS should be given information that explains the importance of self-help in effectively managing their IBS. This should include information on general lifestyle, physical activity, diet and symptom-targeted medication.

1.2.1.5 Healthcare professionals should review the fibre intake of people with IBS, adjusting (usually reducing) it while monitoring the effect on symptoms. People with IBS should be discouraged from eating insoluble fibre (for example, bran). If an increase in dietary fibre is advised, it should be soluble fibre such as ispaghula powder or foods high in soluble fibre (for example, oats).

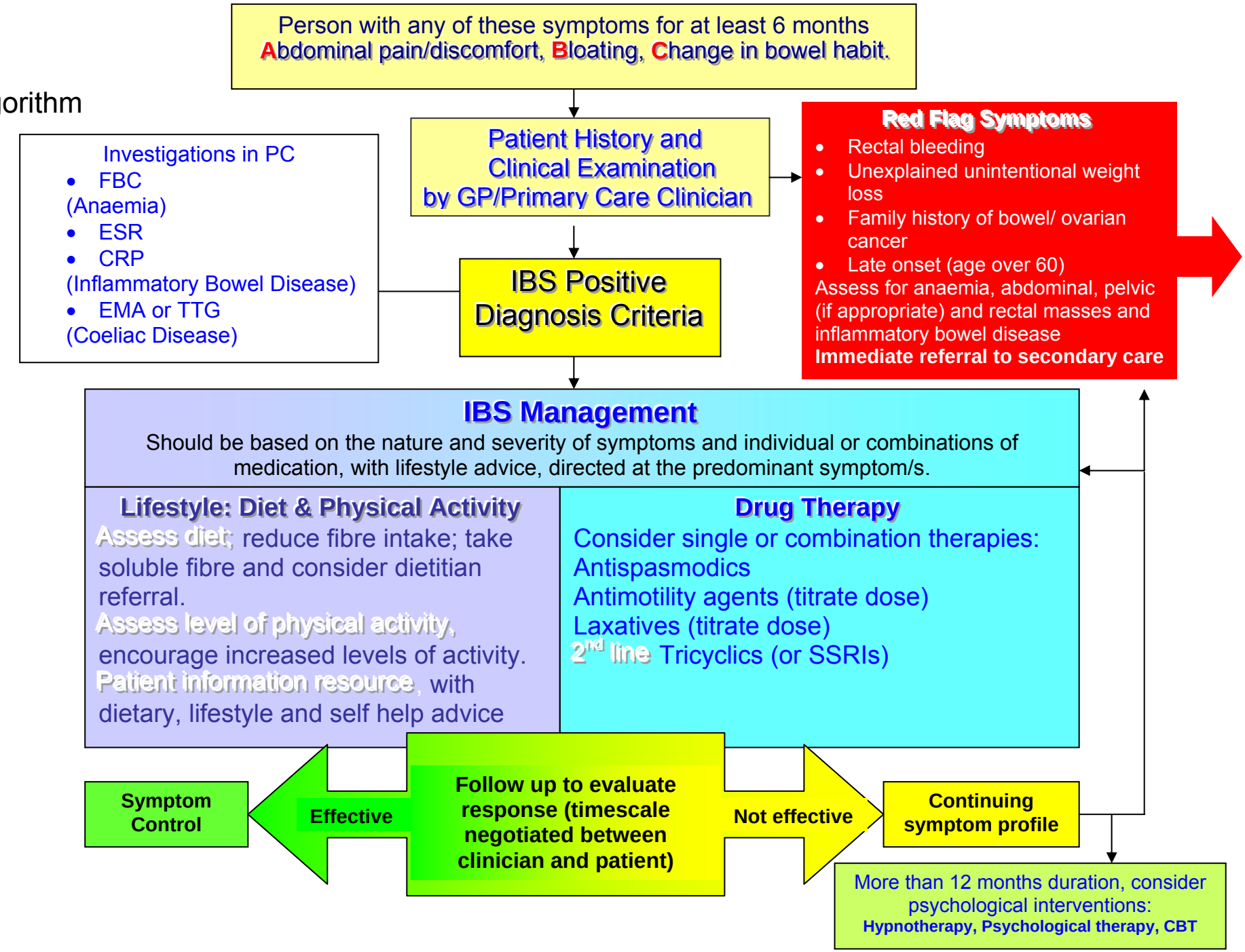
1.2.2.4 People with IBS should be advised how to adjust their doses of laxative or antimotility agent according to the clinical response. The dose should be titrated according to stool consistency, with the aim of achieving a soft, well-formed stool (corresponding to Bristol Stool Form Scale type 4).

1.2.2.5 Healthcare professionals should consider tricyclic antidepressants (TCAs)[**] as second-line treatment for people with IBS if laxatives, loperamide or antispasmodics have not helped. TCAs are primarily used for treatment of depression but are only recommended here for their analgesic effect. Treatment should be started at a low dose (5–10 mg equivalent of amitriptyline), which should be taken once at night and reviewed regularly. The dose may be increased, but does not usually need to exceed 30 mg.

The IBS algorithm demonstrates the importance of positive diagnosis in providing an effective platform for both the person presenting with IBS symptoms and primary care clinician to work towards symptom control. It importantly identifies red flag symptoms, meaning in practice that the person would leave this guideline and be referred to secondary/tertiary care for further investigation. The emergence of any of the 'red flags'during management and follow up should prompt referral for further investigation and/or referral into secondary care.

[**] At the time of publication (February 2008) TCAs did not have UK marketing authorisation for the indications described. Informed consent should be obtained and documented.

IBS Algorithm



2 PRINCIPLES OF PRACTICE

The principles outlined below describe the ideal context in which to implement the recommendations contained in this guideline.

These have been adapted from the NICE clinical practice guideline: *Assessment and prevention of falls in older people* (2004).

2.1 Person-centred care

- People who may have Irritable bowel syndrome (IBS) should be made aware of the guideline and its recommendations, and should be referred to the *Understanding NICE Guidance* version of the guideline.
- People who may have IBS should be involved in shared decision–making about individualised IBS management strategies.
- Healthcare professionals are advised to respect and incorporate the knowledge and experience of people who have been self managing this condition.
- People who may have IBS should be informed about any potential risks and/or associated complications with IBS.

2.2 Collaborative interdisciplinary approach to care

- All members of the interdisciplinary team should be aware of the guidelines and all care should be documented in the patient's health care records.
- A collaborative, multi-disciplinary approach should be provided by appropriately trained professionals.
- The roles of parents/carers and health professionals in implementing the guideline recommendations should be sensitively negotiated.

2.3 Organisational issues

- There should be an integrated approach to the diagnosis and management of IBS in Primary Care with a clear strategy and policy supported by management.
- Care should be delivered in a context of continuous quality improvement, where improvements to care following guideline implementation are the subject of regular feedback and audit.
- The health care team should have received appropriate training and have demonstrated their competence in the diagnosis and management of IBS.
- Commitment to and availability of education and training are required to ensure that all staff, regardless of their profession, are given the opportunity to update their knowledge, and are able to implement the guideline recommendations.

- People who have IBS should be cared for by personnel who have undergone appropriate training and who know how to initiate and maintain appropriate management of IBS. Staffing levels and skill mix should reflect the needs of patients.

2.4 Background to the current guideline

In January 2006, The National Collaborating Centre for Nursing and Supportive Care (NCC-NSC) was commissioned by NICE to develop a clinical guideline on the diagnosis and management of Irritable Bowel Syndrome (IBS) for use in Primary Care in England and Wales.

2.5 Clinical need for the guideline

Irritable bowel syndrome (IBS) is one of the most common functional gastrointestinal disorders. It is a chronic, relapsing and often life-long disorder, characterised by the presence of abdominal pain/discomfort associated with defaecation, a change in bowel habit together with disordered defaecation (constipation or diarrhoea or both), the sensation of abdominal distension, and may include associated non-colonic symptoms. These morbidities may cause dehydration, lack of sleep, anxiety and lethargy which may lead to time off work, avoidance of stressful or social situations and significant reduction in quality of life.

People may present with differing symptom profiles, most commonly 'diarrhoea predominant', 'constipation predominant', and alternating symptoms. Clinical management will inevitably be directed by the presenting symptoms, but different symptom types may have differing prognoses that assist in determining the type and urgency of investigations and subsequent management. Symptoms sometimes overlap with other gastrointestinal (GI) disorders such as non-ulcer dyspepsia, or with coeliac disease.

There are three possible diagnostic approaches which may be used; a diagnosis by excluding organic disease which may involve multiple investigative procedures; a diagnosis based on positive symptom criteria, resulting in a minimum of diagnostic tests; a diagnosis combining positive symptom based criteria with investigations to exclude 'red flag' symptoms. In practice diagnosis has been predominantly by exclusion of organic disease which has led to patients being subjected to investigations and tests which are not required to confirm IBS.

Diagnosis and management of IBS can be frustrating for patients and clinicians. Both parties need to have a clear understanding of the current state of knowledge of IBS and recognition of the chronic nature of the condition. The implication is that the management of this condition may involve a long-term therapeutic partnership between the person with IBS and the primary care clinician. There may be many contributing factors to be taken into consideration. Associated non-colonic problems include functional urinary and gynaecological problems, gallbladder and stomach symptoms, back pain, migraine and depression. It has previously been shown that if a non-colonic feature of IBS is especially severe (for example, a gynaecological symptom) the

patient may be referred to the wrong speciality. This may result in unnecessary and sometimes costly investigations and/or delayed treatment. IBS is associated with a disproportionately high prevalence of abdominal and pelvic surgery, although the cause of this has not been established.

IBS most commonly affects people between the ages of 20 and 30 years and is twice as common in women as in men. The prevalence of the condition in the general population is estimated to lie somewhere between 10 and 20%. Recent trends indicate that there is also a significant prevalence of IBS in older people; therefore, IBS diagnosis should be a consideration when an older person presents with unexplained abdominal symptoms. The true prevalence of IBS in the whole population may be higher than estimated, because it is thought that many people with IBS symptoms do not seek medical advice; NHS Direct online data suggest that 75% of people using this service rely on self-care. In England and Wales, the number of people consulting for IBS is extrapolated to between 1.6 and 3.9 million. Evidence suggests that age and race have no consistent effect on the incidence of symptoms. Healthcare professionals need to be sensitive to and take into consideration cultural, ethnic and communication needs of people for whom English is not a first language or who may have cognitive and/or behavioural disabilities. Appropriate action should be taken to facilitate effective consultation.

Causes of IBS have not been adequately defined, although gut hypersensitivity, disturbed colonic motility, post-infective bowel dysfunction or a defective antinociceptive (anti-pain) system are possible causes. Stress commonly aggravates the disorder and around half of IBS outpatients attribute the onset of symptoms to a stressful event. Lactose, gluten or other food intolerance is also identified as an antecedent. Colonic flora may be abnormal in IBS patients. People with IBS tend to alter their diet to alleviate symptoms of IBS, often this is self directed or guidance is sought from inadequately qualified nutritionists. Excluding individual foods or complete food groups without appropriate supervision can readily lead to inadequate nutrient intakes and ultimately malnutrition. In addition, symptoms often remain unresolved leading to further inappropriate dietary restriction.

Primary care investigations may include: routine blood tests such as full blood count, urea and electrolytes, and liver function tests; tests for thyroid function, tissue transglutaminase anti-endomysial antibodies (to exclude coeliac disease); inflammatory markers (to identify possible inflammatory bowel disease): stool microscopy; urinary screen for laxatives; and lactose tolerance testing. Other investigations such as gut transit studies (radiological tests to measure the time required for food to move through the digestive tract) and sigmoidoscopy (endoscopy of the lower part of the bowel) are routinely performed in secondary care.

Patients are likely to be referred to a secondary care specialist if symptoms are atypical (for example, patients over 40 years with change in bowel habit and/or rectal bleeding), if GI or

ovarian cancer is suspected on clinical examination, or if there is a family history of GI or ovarian cancer.

2.6 Management Issues

The aetiology of IBS has not yet been established and as a result management focuses on the relief of symptoms. The symptom profile, as previously described, may vary and may require a combination of different modalities to achieve effective relief. These include diet and lifestyle interventions, patient education and self help, pharmacological interventions, behavioural and psychological therapies, complementary and alternative therapies. No single drug will alleviate the multiple symptoms often present in people with IBS. Management should focus on the predominant symptom which may require concomitant use of medications and other therapeutic interventions. This guideline will review the different therapies commonly used in the management of IBS.

3 SUMMARY OF RECOMMENDATIONS

1. GUIDANCE

1.1 DIAGNOSIS OF IBS

Confirming a diagnosis of IBS is a crucial part of this guideline. The primary aim should be to establish the person's symptom profile, with abdominal pain or discomfort being a key symptom. It is also necessary to establish the quantity and quality of the pain or discomfort, identify its site (which can be anywhere in the abdomen) and whether this varies. This distinguishes IBS from cancer-related pain, which typically has a fixed site.

When establishing bowel habit, showing people the Bristol Stool Form Scale (see Appendix D of the NICE version and Appendix I of this document) may help them with description, particularly when determining quality and quantity of stool. People presenting with IBS symptoms commonly report incomplete evacuation/rectal hypersensitivity, as well as urgency, which is increased in diarrhoea-predominant IBS. About 20% of people experiencing faecal incontinence disclose this only if asked. People who present with symptoms of IBS should be asked open questions to establish the presence of such symptoms (for example, 'tell me about how your symptoms affect aspects of your daily life, such as leaving the house'). Healthcare professionals should be sensitive to the cultural, ethnic and communication needs of people for whom English is not a first language or who may have cognitive and/or behavioural problems or disabilities. These factors should be taken into consideration to facilitate effective consultation.

1.1.1 Initial assessment

1.1.1.1 Healthcare professionals should consider assessment for IBS if the person reports having had any of the following symptoms for at least 6 months:

- Abdominal pain or discomfort
- Bloating
- Change in bowel habit.

1.1.1.2 All people presenting with possible IBS symptoms should be asked if they have any of the following "red flag" indicators and should be referred to secondary care for further investigation if any are present (see 'Referral guidelines for suspected cancer', NICE clinical guideline 27, for detailed referral criteria where cancer is suspected).

- Unintentional and unexplained weight loss
- Rectal bleeding
- A family history of bowel or ovarian cancer
- A change in bowel habit to looser and / or more frequent stools persisting for more than 6 weeks in a person aged over 60 years.

1.1.1.3 All people presenting with possible IBS symptoms should be assessed and clinically examined for the following “red flag” indicators and should be referred to secondary care for further investigation if any are present (see ‘Referral guidelines for suspected cancer’, NICE clinical guideline 27, for detailed referral criteria where cancer is suspected).

- Anaemia
- Abdominal masses
- Rectal masses
- Inflammatory markers for inflammatory bowel disease.

If there is significant concern that symptoms may suggest ovarian cancer, a pelvic examination should also be considered.

1.1.1.4 A diagnosis of IBS should be considered only if the person has abdominal pain or discomfort that is either relieved by defaecation or associated with altered bowel frequency or stool form. This should be accompanied by at least two of the following four symptoms:

- Altered stool passage (straining, urgency, incomplete evacuation)
- Abdominal bloating (more common in women than men), distension, tension or hardness
- Symptoms made worse by eating
- Passage of mucus.

Other features such as lethargy, nausea, backache and bladder symptoms are common in people with IBS, and may be used to support the diagnosis.

1.1.2 Diagnostic tests

1.1.2.1 In people who meet the IBS diagnostic criteria, the following tests should be undertaken to exclude other diagnoses:

- Full blood count (FBC)
- Erythrocyte sedimentation rate (ESR) or plasma viscosity
- C-reactive protein (CRP)
- Antibody testing for coeliac disease (endomysial antibodies [EMA] or tissue transglutaminase [TTG]).

1.1.2.2 The following tests are not necessary to confirm diagnosis in people who meet the IBS diagnostic criteria:

- Ultrasound
- Rigid/flexible sigmoidoscopy
- Colonoscopy; barium enema
- Thyroid function test
- Faecal ova and parasite test
- Faecal occult blood
- Hydrogen breath test (for lactose intolerance and bacterial overgrowth).

1.2 CLINICAL MANAGEMENT OF IBS

1.2.1 Dietary and lifestyle advice

1.2.1.1 People with IBS should be given information that explains the importance of self-help in effectively managing their IBS. This should include information on general lifestyle, physical activity, diet and symptom-targeted medication.

1.2.1.2 Healthcare professionals should encourage people with IBS to identify and make the most of their available leisure time and to create relaxation time.

1.2.1.3 Healthcare professionals should assess the physical activity levels of people with IBS, ideally using the General Practice Physical Activity Questionnaire (GPPAQ; see Appendix J). People with low activity levels should be given brief advice and counselling to encourage them to increase their activity levels.

1.2.1.4 Diet and nutrition should be assessed for people with IBS and the following general advice given.

- Have regular meals and take time to eat.
- Avoid missing meals or leaving long gaps between eating.
- Drink at least eight cups of fluid per day, especially water or other non-caffeinated drinks, for example herbal teas.
- Restrict tea and coffee to three cups per day.
- Reduce intake of alcohol and fizzy drinks.
- It may be helpful to limit intake of high-fibre food (such as wholemeal or high-fibre flour and breads, cereals high in bran, and whole grains such as brown rice).
- Reduce intake of 'resistant starch' (starch that resists digestion in the small intestine and reaches the colon intact), which is often found in processed or re-cooked foods.
- Limit fresh fruit to three portions per day (a portion should be approximately 80g).
- People with diarrhoea should avoid sorbitol, an artificial sweetener found in sugar-free sweets (including chewing gum) and drinks, and in some diabetic and slimming products.
- People with wind and bloating may find it helpful to eat oats (such as oat-based breakfast cereal or porridge) and linseeds (up to one tablespoon per day).

1.2.1.5 Healthcare professionals should review the fibre intake of people with IBS, adjusting (usually reducing) it while monitoring the effect on symptoms. People with IBS should be discouraged from eating insoluble fibre (for example, bran). If an increase in dietary fibre is advised, it should be soluble fibre such as ispaghula powder or foods high in soluble fibre (for example, oats).

1.2.1.6 People with IBS who choose to try probiotics should be advised to take the product for at least 4 weeks while monitoring the effect. Probiotics should be taken at the dose recommended by the manufacturer.

1.2.1.7 Healthcare professionals should discourage the use of aloe vera in the treatment of IBS.

1.2.1.8 If diet continues to be considered a major factor in a person's symptoms and they are following general lifestyle/dietary advice, they should be referred to a dietitian for advice and treatment, including single food avoidance and exclusion diets. Such advice should only be given by a dietitian.

1.2.2 Pharmacological therapy

Decisions about pharmacological management should be based on the nature and severity of symptoms. The recommendations made below assume that the choice of single or combination medication is determined by the predominant symptom/s.

1.2.2.1 Healthcare professionals should consider prescribing antispasmodic agents for people with IBS. These should be taken as required, alongside dietary and lifestyle advice.

1.2.2.2 Laxatives should be considered for the treatment of constipation in people with IBS, but people should be discouraged from taking lactulose.

1.2.2.3 Loperamide should be the first choice of antimotility agent for diarrhoea in people with IBS[*].

1.2.2.4 People with IBS should be advised how to adjust their doses of laxative or antimotility agent according to the clinical response. The dose should be titrated according to stool consistency, with the aim of achieving a soft, well-formed stool (corresponding to Bristol Stool Form Scale type 4).

1.2.2.5 Healthcare professionals should consider tricyclic antidepressants (TCAs)[* *] as second-line treatment for people with IBS if laxatives, loperamide or antispasmodics have not helped. TCAs are primarily used for treatment of depression but are only recommended here for their analgesic effect. Treatment should be started at a low dose (5–10 mg equivalent of amitriptyline), which should be taken once at night and reviewed regularly. The dose may be increased, but does not usually need to exceed 30 mg.

---

[*] In certain situations the daily dose of loperamide required may exceed 16 mg, which at the time of publication (February 2008) was an out of licence dose. Informed consent should be obtained and documented.

[**] At the time of publication (February 2008) TCAs did not have UK marketing authorisation for the indications described. Informed consent should be obtained and documented.

1.2.2.6 Selective serotonin reuptake inhibitors (SSRIs)[***] should be considered for people with IBS only if TCAs have been shown to be ineffective.

1.2.2.7 Healthcare professionals should take into account the possible side effects when prescribing TCAs or SSRIs. After prescribing either of these drugs for the first time at low doses for the treatment of pain or discomfort in IBS, the person should be followed up after 4 weeks and then at 6–12 monthly intervals thereafter.

1.2.3 Psychological interventions

1.2.3.1 Referral for psychological interventions (cognitive behavioural therapy [CBT], hypnotherapy and/or psychological therapy) should be considered for people with IBS who do not respond to pharmacological treatments after 12 months and who develop a continuing symptom profile (described as refractory IBS).

1.2.4 Complementary and alternative medicine (CAM)

1.2.4.1 The use of acupuncture should not be encouraged for the treatment of IBS.

1.2.4.2 The use of reflexology should not be encouraged for the treatment of IBS.

1.2.5 Follow-up

1.2.5.1 Follow-up should be agreed between the healthcare professional and the person with IBS, based on the response of the person's symptoms to interventions. This should form part of the annual patient review. The emergence of any 'red flag' symptoms during management and follow-up should prompt further investigation and/or referral to secondary care.

[***] At the time of publication (February 2008) SSRIs did not have UK marketing authorisation for the indication described. Informed consent should be obtained and documented.

4 AIMS OF THE GUIDELINE

The aims of the guideline are:

- To evaluate and summarise the clinical and cost evidence relating to all aspects of the diagnosis and treatment of Irritable Bowel Syndrome (IBS).
- To highlight gaps in the research evidence.
- To formulate evidence-based cost effective clinical practice recommendations relating to the diagnosis and treatment of IBS.
- To formulate consensus recommendations shaped around available evidence and expert GDG opinion in those areas of diagnosis and treatment of IBS where there is no clear clinical and cost effective evidence base.

4.1 Who the guideline is for

The guideline is of relevance to all people with IBS, carers for those people with IBS, primary healthcare professionals and social care staff that are involved in the care and/or support of those people diagnosed with IBS.

4.2 Groups covered by the guideline

Adults (18 years and older) who present to primary care with symptoms suggestive of IBS are covered by the guideline.

4.3 Groups not covered by the guideline

The following groups are not covered by the guideline:

a) Patients with other gastrointestinal disorders such as non-ulcer dyspepsia or coeliac disease will not be covered, except when a co-morbidity has specific relevance to the management of IBS.
b) Children and young people under 18 years of age.

4.4 Healthcare setting

It is recognised that the NHS is rapidly developing patterns of service delivery, with primary and secondary care borders blurring. The guideline will cover the care that is provided by primary healthcare professionals and it will indicate where secondary care referral is appropriate. The guideline is sensitive to the variations in commissioning of services relating to the diagnosis and treatment of IBS. The guideline recognises that there is current variation to service availability in both primary and secondary care across England and Wales, and at times will not state where care is accessed.

4.5 Diagnosis and management interventions covered by the guideline

The following diagnostic and treatment interventions will be covered. They have been classified into logical coherent areas of the guideline, supported by clinical and cost effectiveness reviews, and are consistent with the patient algorithm which typically reflects the patient pathway.

Diagnosis

Positive Diagnosis utilises criterion based reference tools. Negative diagnosis uses exclusion diagnosis through negative test results. This is typically characterised by primary care clinicians requesting a raft of investigations to rule out other co-morbidities. Diagnosis also addresses the identification of red flags that may lead to an alternative diagnosis such as bowel cancer. This guideline is cross referenced to NICE clinical guideline 27 (Suspected Cancer Referral).

Lifestyle: diet and exercise

This section of the guideline reviews clinical and cost effectiveness evidence relating to patient lifestyle. It is focussed on shared care decision making between the primary care clinician and the person with IBS. This develops coping behaviours and modifies lifestyle relating to dietary input/changes and levels of exercise that work towards alleviating symptom based IBS profiles.

Drug therapy

This section of the guideline reviews clinical and cost effectiveness evidence relating to different pharmacological treatments options that are prescribed to alleviate symptom based IBS profiles.

Referral and follow-up

This section provides consensus based recommendations and narrative on the importance of referral and follow up once diagnosis has been made. This also incorporates clinical and cost effective reviews and recommendations on referral for people with intractable IBS, defined as a continuing symptom profile and lack of response to first line treatment interventions.

4.6 Interventions not covered by the guideline

If during the process of diagnosis for IBS another disease is suspected, further diagnosis and treatment of this disease will not be covered. Management and diagnosis of co-morbidity will not be covered. New drugs in development are not covered as they are not licensed for use.

4.7 Guideline Development Group

The guideline recommendations were developed by a Guideline Development Group (GDG) convened by the NICE-funded National Collaborating Centre for Nursing and Supportive Care (NCC-NSC) with membership approved by NICE. Members included representatives from patient groups; nursing; general practice and gastroenterology medicine; pharmacy; dietetics; public health; technical team from the NCC-NSC.

The GDG met 13 times between May 2006 and July 2007. All members of the GDG were required to make formal declarations of interest at the outset, and these were updated at every subsequent meeting throughout the development process. This information is recorded in the meeting minutes and kept on file at the NCC-NSC. The GDG declarations are recorded in Appendix K.

5 METHODS USED TO DEVELOP THE GUIDELINE

5.1 Summary of development process

The methods used to develop this guideline are based on those outlined by Eccles and Mason (2001). The structure of the recommendations sections (sections 6 to 11) (i.e. recommendations; evidence statements, evidence narrative and guideline development group commentary) came from McIntosh et al. (2001).

The stages used in the development of this guideline were as follows:

- Guideline scope development following referral from the department of health
- NICE stakeholder review and feedback
- Multidisciplinary guideline development group convened with formal appointment of the clinical lead and chair of the group by competitive interview
- Establish key clinical questions
- Identify sources of evidence
- Retrieve potential evidence
- Evaluate potential evidence relating to clinical and cost effectiveness, quality of life, for eligibility, quality and relevance
- Extract relevant data from studies meeting methodological and clinical criteria
- Interpret each paper, taking into account the results (including, where reported, beneficial and adverse effects of the interventions, cost, comfort and acceptability to patients), the level of evidence, the quality of the studies, the size and precision of the effect, and the relevance and generalisability of the included studies to the scope of the guideline
- Analyse, where appropriate using statistical synthesis, the results reported in the studies
- Prepare evidence reviews and tables which summarize and grade the body of evidence
- Formulate conclusions about the body of available evidence based on the evidence reviews by taking into account the above factors
- Agree final recommendations
- Submit drafts (short version and full version) of guideline for feedback from NICE registered stakeholders
- Consider stakeholders comments (GDG)
- Submit final version of the guideline to NICE.

NCC-NSC technical team members searched bibliographic databases for evidence, examined and quality assessed the evidence. The technical team compose successive drafts of the recommendations and guideline documents (including the full version of guideline; the NICE version and the quick reference guide), based on the evidence reviews and GDG input and deliberations. The GDG having interpreted the evidence formulated the recommendations. The NICE patient and public involvement programme produced the information for the public version,

using the NICE version of the guideline, in collaboration with the NCC-NSC. The general methods for the evidence reviews are reported in sections 5.2 and 5.3. This relationship between the clinical and cost effectiveness results, evidence statements and resulting recommendations, is reported for each review in sections 6 to 11.

The search strategies for the reviews are presented in Appendix B. The included studies for each review are reported in Appendix C; the methodological assessments of the included studies are in Appendix D and the studies excluded from each review are listed in Appendix E.

5.2 Clinical effectiveness review methods

This section describes the methods of systematic reviewing that are common to all clinical effectiveness reviews of intervention studies. At the start of the guideline development process, a general protocol was discussed with the GDG which resulted in the selection criteria and approaches to analysis described below. Further details specific to the reviews are given for each review.

Selection criteria

The following selection criteria were to be applied to studies to determine their suitability for inclusion in the reviews

Types of studies

For intervention studies, the randomised trial (RCT) is the primary trial design. Quasi randomised studies could also be included (e.g. allocation by alternation, date of birth, etc). Where there is insufficient evidence from RCTs or quasi RCTs, cohort studies could be considered.

Both parallel and crossover trial designs could be included in the guideline: in the former, patients are randomised to one of two (or more) interventions; in the latter, patients receive interventions in a randomised order, crossing over to the second (and third) interventions after a specified period (‘washout period’).

Crossover trials are common in chronic conditions: they have the advantage that the patient acts as their own control, so there are no differences in baseline patient characteristics for each intervention, unlike parallel trials in which different patient groups receive the interventions. The crossover design is only appropriate when the condition is truly chronic (i.e. no progression or regression) and when the interventions make no permanent or slow decaying changes to the patient’s condition. Crossover trials have the disadvantage that effects of the second intervention may be influenced by those in the first period (carryover effects). To avoid errors of this type, better designed crossover trials have a washout period between interventions, in which the patient characteristics are allowed to return to the levels present before the first

intervention. Ideally, the characteristics are measured at intervals following the first intervention period, and the second intervention is delayed until the baseline values are retrieved, but, especially in older studies, this is usually approximated by the trialists using a 'washout period' they believe to be appropriate.

Some studies do not have a washout period, and the GDG's view was that crossover trials without washout periods should not be included, unless first period data are available – although, even this should be treated with caution, unless individual patient data are reported. For each review, the GDG decided if crossover trials were allowable, and, if so, defined the washout period. Factors taken into consideration included the lifetime of the intervention (especially for drugs). The washout period for each review is given in the methods section for that review. Trials with washout periods shorter than the pre-determined value should be excluded. Studies that do not state a washout period should be assumed to have none, and therefore should be excluded.

Studies should be restricted to the English language, with the exception of studies translated for Cochrane reviews, but the date should not be restricted.

Types of participants

Participants should be adults (18 years and older). However, studies could be included if they had some participants slightly below 18 years, provided that the mean age indicated that the majority were adults.

Participants should have a diagnosis of IBS. Suitable definitions included Rome I, Rome II or Manning criteria. Studies could also be included if the authors stated the patients had IBS, or if they described patients who had a set of symptoms suggestive of IBS. Studies reporting patients with single symptoms such as chronic constipation/diarrhoea in isolation should not usually be included. Studies could be included if a proportion of the patients had IBS, provided the IBS subgroup was reported separately, but such studies should be treated with caution unless the IBS subgroup members were separately randomised to treatments.

All settings could be included, but those in secondary/tertiary care should be distinguished from those in primary care only. This decision was taken regardless of the date of the study (people who were outpatients 20 years ago would now be treated in primary care).

Indirect evidence may be considered for some reviews, where direct evidence is not available, or is insufficient (for example, the use of laxatives in the treatment of constipation in non-IBS patients). In all cases, indirect evidence should be used to provide additional information, and its quality should be downgraded accordingly. Indirect evidence should not be combined in a meta-

analysis with direct evidence. The indirect evidence permitted is given in the methods section for each review.

Types of intervention

The interventions varied across reviews and are detailed at the beginning of each review.

Interventions could be given in three different ways:

- As short-term rescue medication (e.g. antimotility agents for acute diarrhoea episodes)
- As a longer-term maintenance treatment (e.g. antispasmodics)
- As a 'one-off' intervention or series of treatments at the start of the management period (e.g. psychotherapy).

For the longer-term, maintenance interventions, the GDG specified a minimum acceptable period for the intervention. This was set at four weeks, and the reason for this was partly to take into account women's menstrual cycles. Maintenance studies with intervention durations of less than four weeks should not be included.

Types of outcome measures

The GDG decided on a number of outcomes related to symptom control. These would either be measured as the number of patients with a particular feature (dichotomous outcomes) or as a mean measurement, preferably on a validated scale (continuous outcomes). The following outcomes were considered to be primary:

- Global improvement of symptoms
- Global symptom scores.

Other outcomes were also considered important:

- Abdominal pain
- Bloating
- Stool score/general improved bowel habit
- Quality of life, using a validated scale
- Adverse effects.

The time of measurement and duration of follow-up should be recorded, together with information on whether the studies reported a change in symptoms from baseline, final values following treatment, or a mean value based on diary records.

'Global' meant a measure that took into consideration a combination of the following IBS symptoms: pain, bloating and stool properties (e.g. frequency, consistency, ease of passage). Alternatively, the participants could have assessed their overall symptoms as improved/same/worse; provided this did not obviously refer to just one component of IBS, these

measurements could also be included in the ‘global’ category. Studies in which the authors labelled their outcomes as ‘global’ but in fact only measured one component should be analysed as single components.

The GDG decided that different definitions of improvement should not be distinguished (e.g. 100%, 75% improvement, slight, much), and that categorical outcomes should be dichotomised, e.g. grouping together ‘much improvement’ with ‘slight improvement’.

For the individual symptom components, studies could record the number of people with that symptom at the end of the study or during the study, or they could record changes in symptoms over time, or a final symptom score at a particular time. For a positive outcome, the number of people with fewer symptoms (e.g. less pain) or the number with no symptoms should be recorded. For a negative outcome, the number with more symptoms (e.g. increased bloating), and the number of people with that symptom should be used. These two types of outcomes (absolute and increase/decrease) could be recorded on the same forest plot, but should not be combined in a meta-analysis.

For continuous outcomes, we recorded the severity score of the symptom (negative outcome) or the improvement in the symptom score (positive outcome).

Stool scores can have various formats: sometimes the raw values are recorded (e.g. stool frequency or consistency) or the severity may be assessed on a visual analogue scale. In the former, this measurement is only meaningful when the results are given separately for the different types of IBS - whether this is a positive or negative outcome depends on what type of IBS the person had. Therefore, if a study has people with a range of types of IBS, this type of raw value measurement should be disregarded. The severity score may be included as an acceptable outcome measure, as may the patient’s assessment of improved bowel habits.

We note that the majority of these outcome measures are subjective and therefore, have potential for bias.

SEARCH STRATEGY

The search strategies and the databases searched are presented in detail in Appendix B. All searches were carried out on the following core databases: Medline, Embase, Cinahl (all using the OVID interface) and The Cochrane Library. Additional databases were searched for individual reviews where appropriate.

For this guideline, a general set of terms was produced relating to IBS. The relevance of the terms diarrhoea and constipation was explored before they were included in the IBS filter. For each review, terms related to the intervention were combined with the set of IBS terms. Where

appropriate, study design filters (RCT and systematic review) were applied. Results were limited to papers published in English where possible. All searches were updated to June 2007.

Hand-searching was not undertaken following NICE advice that exhaustive searching on every guideline review topic is not practical or efficient (Mason 2002). Reference lists of articles were checked for studies of potential relevance.

METHODS OF THE REVIEW

Sifting process

Once the search had been completed, the following sifting process took place:

- 1st sift: one reviewer sifted the title/abstract for articles that potentially met the eligibility criteria
- 2nd sift: full papers were ordered that appeared relevant and eligible or where relevance/eligibility was not clear from the abstract
- 3rd sift: full papers were appraised, generally by one reviewer using an inclusion criteria form, and this was checked where necessary by a second reviewer.

Quality assessment and validity

Once individual papers were retrieved, the articles were checked for methodological rigour (using quality checklists appropriate for each study design), applicability to the UK and clinical significance. Assessment of study quality concentrated on dimensions of internal validity and external validity. At this stage, some studies were excluded if the interventions were not licensed for use in the UK or they were not regularly used in the UK. Studies in which the interventions were obsolete were also excluded.

Studies for which the methodological quality indicated a high potential for bias were included in the review, but were not included in the analysis.

Data abstraction

Data from the included studies were extracted by one reviewer for each review, with random checking by a second reviewer, and entered into a Microsoft Access relational database that had been especially designed for the guideline. The use of the database provided a more structured extraction, for example, only certain choices could be made for some items, although free text fields were also used. The main advantage of using a database for this purpose is that a large amount of detail can be input, and then an overview obtained using database sorting procedures. The following data were extracted from each study:

- Review being addressed
- Study details: study design (RCT, quasi-randomised, cohort study, etc); parallel/crossover, washout period; country where trial conducted; setting; funding
- Study quality

- Participants: age (mean and range), gender (ratio male:female), co-morbidities, inclusion/exclusion criteria, IBS diagnosis method, type of IBS, presence of bloating, presence of pain, measure of severity of IBS, symptom status at trial entry, length of time since diagnosis, duration of symptoms, ethnicity, socio-economic group, weight, post-infective/non post-infective initiated IBS
- Interventions: class (e.g. insoluble fibre) and sub-class (e.g. wheat bran), total amount per day, frequency/time of consumption, means of delivery (oral capsule, taken as a food, drink, etc), duration of treatment; concurrent treatment in both arms
- Comparator: placebo (details of what it is), other control group, other intervention
- Outcome: including follow-up period, scales used, definition of success (if using "improved", "complete response", etc)
- Results for each outcome.

If studies were published more than once, data were extracted from the most recent report where there were differences; otherwise all papers were used for data extraction.
Masked assessment, whereby data extractors are blind to the details of journal, authors etc, was not undertaken.

Appraisal of methodological quality

The methodological quality of each trial was assessed by one reviewer and randomly checked by a second. The following quality items were assessed:

- *A priori* sample size calculation:
    - Whether or not this was carried out
- Method of generation of the randomisation sequence:
    - The means by which interventions are distributed amongst the participants
    - Whether the method was reported or unclear (i.e. no details given)
    - Whether the reported method was adequate, inadequate or partial (Table 1)
- Allocation concealment at randomisation:
    - The means of preventing the treatment assignment being known *before* the time of allocation
    - Whether the method was reported or unclear (no details)
    - Whether the reported method was adequate, inadequate or partial (Table 1)
- Baseline comparability of treatment groups:
    - For relevant risk factors
- Patients stated to be blinded, especially for comparisons with placebo:
    - Blinding involves hiding the nature of the intervention from participants, clinicians and treatment evaluators *after* allocation has taken place

    - Blinding may be not be possible depending on the nature of the interventions
    - Blinding may be more important for some outcomes than others (this is noted in the reviews)
- Outcome assessor stated to be blinded
- No loss to follow-up for each outcome:
    - Studies with at least 20% of data missing from any group were considered to be potentially biased
    - Those with moderate loss to follow up (20 to 50%) were considered in sensitivity analyses
    - Those with 50% or more patients missing from any one group were regarded as flawed and not analysed further
- Intention to treat analysis:
    - Trial participants should be analysed in the groups to which they were randomised regardless of which (or how much) treatment they actually received, and regardless of other protocol irregularities
    - All participants should be included regardless of whether their outcomes were actually collected
- For crossover trials, the washout period relative to the minimum for the review:
    - Studies in which the washout period was shorter than the minimum were not included, as were studies with no washout or none stated
    - Studies reporting first period only data as individual patient data were included
- The intervention time relative to a minimum of 4 weeks or as defined for the particular review:
    - Studies in which the intervention time was shorter than 4 weeks were usually excluded, but slightly shorter durations could be included in the absence of other data.

Table 1:

Adequate Sequence Generation

- Coin toss, throwing a dice, shuffling, drawing lots (from a container).
  Partial: drawing a card from a pack.
- Computer- or calculator- generated sequence (including minimisation and biased-coin/urn design). **Partial**: "random permuted blocks".
- Random number table or statistical tables. **Partial**: random numbers, randomisation table.
- Randomised Latin square design.

Inadequate Sequence Generation

- Randomised Latin square. For example, allocation by alternation, birthdate, day of week.

Adequate Allocation Concealment

- Central randomisation: with contacting details and/or statement that central office retained schedule; must apply to all patients. **Partial**: vague statement of central randomisation.
- Independent 3rd party: allocates interventions *and* retains schedule, or statement that *allocator* has no knowledge of patients. **Partial**: 3rd party, but unclear treatment allocation.
- 3rd party cluster randomisation: 3rd party has no knowledge of clusters.
  Partial: unclear what 3rd party knew.
- Different parties (including one of authors): should have no knowledge of the patients *and* retain the schedule.
- Secure computer assisted method, e.g. locked file. **Partial**: as adequate, but unclear access.
- Sequentially numbered, opaque, sealed envelopes - all required, else **partial**.
- Serially numbered, identical containers, allocated sequentially - all required, else **partial**.

Inadequate allocation concealment

- For example, schedule known in advance, birthdate, case record number.

Data synthesis

Meta-analysis of similar trials, where appropriate, was carried out using *The Cochrane Collaboration's* analysis software, Review Manager (Version 4.2). Trials were pooled using a fixed effects model and plotted on forest plots. Where there was significant heterogeneity, a random effects model was used as a sensitivity analysis.

For dichotomous studies, we used the analyses reported by the authors, which was usually those reporting an outcome. Where there were incomplete data reported (more than 20% missing in any one group), we carried out sensitivity analyses, excluding these studies.

Where it was possible to combine studies, outcomes were summarised for dichotomous data using odds ratios (as default), relative risks (where the event rate in either arm was greater than 20%), or Peto odds ratios (where there were studies with no events in one arm). Numbers needed to treat (with the control group rate to which they apply) were calculated from the risk difference, where appropriate. The number needed to treat (NNT) is the number of people who would have to be treated for one to have an improved outcome.

For continuous data, weighted mean differences were used and where the studies reported measurements on different scales, standardised mean differences were used. Studies reporting final values and studies reporting change scores were combined if the scales used were the same, otherwise they were reported separately. Summary statistics and their 95% confidence intervals (95% CI) were reported where sufficient detail allowed their calculation.

In some studies, the mean difference was given with a p-value for the difference; this allowed calculation of the standard error. Results from such studies could then be combined in a meta-analysis with other studies reporting means and standard deviations: the standard error and mean difference were calculated for each study and then the studies pooled using the fixed effects generic inverse variance method in RevMan to give a weighted mean difference and 95% confidence intervals. This procedure is only appropriate when the same scales are used or transformation between scales is possible.

Crossover and parallel studies were analysed separately because there were insufficient data to calculate correlation factors. Trials were analysed by the conventional approach of treating the two arms of the crossover as if they were from a parallel trial with separate groups. Alternatively, if first period data were available, these were used in the analysis and the parallel and first period (pseudo-parallel) trials combined.

Stratifications

We planned *a-priori* to separate studies by the type of IBS, into patients with constipation predominant, diarrhoea predominant and alternating types. Studies that did not say or that considered all types of IBS together were treated as a separate group. Other stratifications were planned depending on the review.

Subgroup analyses

Randomised trials generally report four different types of subgroup analysis:

- Between-trial, in which the *studies* are separated according to the particular variable considered (e.g. dose)
- Within-trial subgroup analyses, with stratification of the *participants* by the particular characteristic (e.g. post-infective or not) followed by randomisation

- *A-priori* defined within-trial subgroup analyses, in which the *participants* were not stratified, but later separated according to pre-specified characteristics – these analyses should be included cautiously, because the interventions are not randomised to the subgroups
- Post-hoc within-trial subgroup analyses, in which the *participants* were separated afterwards without pre-specification.

All subgroup analyses are non-randomised comparisons between the different subgroups, however, types 1 and 2 are more reliable. Type 3 analyses can be included in meta-analyses with caution, but post-hoc within trial subgroup analyses were considered to be data-driven and were included only under exceptional circumstances. Most commonly in the guideline, the term 'subgroup analysis' refers to between-study comparisons.

Subgroup analyses were carried out in order to investigate heterogeneity or to investigate pre-specified features. We assessed heterogeneity between trials by visual inspection of forest plots, noting where there was poor overlap of horizontal lines, and by using statistical measures: the χ^2 test for heterogeneity and the level of inconsistency, I^2 ($I^2 = [(\chi^2 - df)/ \chi^2] \times 100\%$, where df is the degrees of freedom). We considered that there was heterogeneity if the p-value (for heterogeneity) was less than 0.1 and I^2 was greater than 50%. Any heterogeneity was explored further and unexplained heterogeneous results were not used as the basis for recommendations.

The following pre-specified factors were proposed for subgroup analyses:

- Type of intervention (e.g. soluble fibre/insoluble/both)
- Dose (defined for the particular review)
- Duration of intervention
- Post-infective/Non-post-infective
- Symptom severity.

Subgroup analyses specific to each review were also carried out, as appropriate.

Sensitivity analyses

Sensitivity analyses were carried out to investigate assumptions within the analyses. These included the following:

- Methodological quality
- Setting.

For methodological quality, we paid particular attention to allocation concealment, loss to follow-up and blinding of patients. We did not include studies with more than 50% loss to follow-up for a particular outcome in the analyses. Otherwise we carried out sensitivity analyses on studies

that had between 20 and 50% withdrawals from any group (or protocol deviations that were eliminated from the study's analyses).

Sensitivity analyses were also carried out where there were quasi-randomised studies (e.g. sequence generation by alternate allocation or date of birth) or inadequate allocation concealment. If these represented the only evidence, their quality was downgraded accordingly.

Significance

Sometimes the results were statistically significant, but small in size. In this case, the GDG decided on what was a clinically important difference in the summary statistics for a particular outcome. Some meta-analyses gave pooled summary statistics close to the null value. Where the confidence interval was narrow, we considered this to be 'evidence for no significant difference' between interventions and the approach became similar to that of an equivalence trial (Alderson 2004). Where the confidence interval was wide, there was considered to be insufficient information to determine if there was a difference between interventions. For most outcomes, the GDG judged what constituted a wide confidence interval; if there was any doubt, they decided there was uncertainty.

General approach to reviewing

The clinical effectiveness reviews seek to determine answers to a number of questions, which were investigated using the following comparisons:

- Does the intervention work? (and is it harmful?):
    - Direct comparisons of intervention with placebo/none
- Is there a dose effect?
    - Direct dose comparisons
    - Subgroup analyses (across trials) of intervention versus placebo, by dose
- Is the duration of treatment important?
    - Direct comparisons of different durations
    - Subgroup analyses of intervention versus placebo, by duration
- Is the intervention better than another treatment?
    - Direct comparisons
    - Subgroup analyses of interventions versus placebo, by type of intervention
- Is the intervention useful as an adjunct to another treatment?
    - Direct comparisons (A + B versus B alone)
- Are there (pre-specified) subgroups of patients for whom the intervention is more effective?
    - E.g. type of IBS (constipation, diarrhoea, alternating); severity of IBS
    - Subgroup analyses: preferably within trials (stratification then randomisation for each subgroup) or across trials; less acceptably, within trials.

We note that the best type of information is from direct comparisons in which two values of the variable considered (e.g. dose 1 and dose 2) are randomised to different groups of people. However, some useful information can be obtained from between-study subgroup analyses.

Grading evidence

For some reviews, we used the GRADE[‡] scheme (GRADE working group 2004) to assess the quality of the evidence for each outcome using the approach described below, and evidence summaries across all outcomes were produced.

According to the GRADE scheme, evidence is classified as high, moderate, low or very low:

- High - further research is very unlikely to change our confidence in the estimate of effect
- Moderate - further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
- Low - further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
- Very low - any estimate of effect is very uncertain.

The procedure adopted when using GRADE was:

1. A quality rating was assigned, based on the study design – for example, RCTs started as high and observational studies as low.
2. This rating was up or downgraded according to specified criteria: study quality, consistency, directness, preciseness and reporting bias. These criteria are detailed below. Criteria were given a downgrade mark of -1 or -2 depending on the severity of the limitations.
3. The downgrade/upgrade marks were then summed and the quality rating revised. For example, a decrease of -2 points for an RCT would result in a rating of 'low'.
4. Wherever possible, reasoning was explained for the downgrade marks.

Study quality

Study quality is assessed against standard criteria, depending on the study design. For randomised trials, we took into account: the adequacy of allocation concealment; blinding of participants for comparisons and outcomes susceptible to bias; loss to follow-up and deviations from intention to treat. The GDG regarded blinding of participants to be important for the comparisons with placebo, but did not necessarily consider blinding of different active interventions to be critical. They did not consider blinding to be important for the psychological interventions, mainly because this was not possible to achieve. The majority of outcomes in the IBS guideline are subjective and therefore susceptible to bias. A downgrade mark of -1 was given for inadequate allocation concealment and for a loss to follow-up of more than 20% in any one arm or overall. A loss to follow-up of 50% or more was given a downgrade of -2 (but was more usually excluded from the analysis). If the evidence was a meta-analysis of several

[‡] GRADE – Grading of Recommendations Assessment, Development and Evaluation

studies, we took into consideration the proportion and weighting of poor quality studies, and in some instances carried out sensitivity analyses disregarding these studies and giving a separate rating for the new meta-analysis.

Consistency

When several RCTs have widely differing estimates of treatment effect (heterogeneity or variability in results) the results are regarded as inconsistent. We defined this as a p-value for heterogeneity less than 0.1 and an I^2 value greater than 50%. Where this was the case, we gave a downgrade mark of -1. Where possible, we carried out pre-defined subgroup analyses to investigate heterogeneity and reported these results separately. Generally, we did not regard single trials (especially smaller ones) as having inconsistency unless there were *a-priori* defined subgroups showing widely different effects.

Directness

Directness refers to the extent to which the population, interventions, comparisons and outcome measures are similar to those defined in the inclusion criteria for the reviews. Indirectness is only relevant if there is a compelling reason to expect important differences in the size of the effect. For example, many interventions have more or less the same relative effects across patient groups, so extrapolation is possible and reasonable. There are various types of indirectness found in studies:

- When the guideline-defined drugs differ from those in the studies, but are within the same class. Similar issues arise for other types of interventions, for example, different types of psychotherapy.
- When there are no direct comparisons of interventions, investigators must make comparisons across studies. For example, we want to know the difference in effectiveness between interventions A and B, but we only have information on A versus placebo and B versus placebo.
- Specifically for IBS, the GDG decided that a difference in setting – secondary care in the studies rather than primary care in the guideline – was a relevant indirectness factor. Their reasoning was supported by differences found in surveys of IBS in primary and secondary care (Miller 2006).

Preciseness

This is a rather subjective, but nevertheless important category. Evidence is considered to be imprecise if:

- The sample size is small. This is a subjective measure and is more important in a single study. If there was a power calculation for that outcome and comparison, it was used to decide if a study was 'small'. Otherwise we used the rule of thumb that if the study had less than 25 patients in any one arm, this was too small. The rationale for this was that below this size, assumptions about normal distributions become much less valid. However, if these

small studies were combined in a meta-analysis, we regarded their use as much more acceptable.

- There are sparse data (only a few events and they are uninformative).
- If confidence intervals are sufficiently wide that the effect estimate is consistent with both important harms and important benefits, and would lead to conflicting recommendations. This category requires the GDG to decide what are important harms and benefits for that outcome measure. Where the confidence intervals were very wide, we gave a downgrade mark of -2.

Reporting bias

Reporting bias occurs in two main ways:

- Publication bias, in which papers are more likely to be published if their results are statistically significant. The existence of publication bias in the studies in a meta-analysis can be investigated in a limited way using funnel plots, in which the standard error is plotted against the log odds ratio, the log relative risk or the mean difference. Asymmetry is indicative of reporting bias. This method is usually only useful when there are at least five studies. Industry sponsored studies are also regarded as potentially biased.
- Outcome bias, in which authors do not report some outcomes (probably because they have non-significant results), even though they say in the methods section that they have measured them.

We note that the GRADE approach, although rigorous, still requires judgements to be made, for example, what is a 'wide' confidence interval; what is a 'small' study; how important is blinding of patients for a particular outcome; how serious is it that the study population is treated in secondary care rather than primary? We have indicated how we considered these difficulties in the bullet points above, and the GDG made judgements as appropriate.

Evidence Statements

The GRADE summary (where used) was condensed into evidence statements, which are based on the quantity and quality of the evidence as shown in Table 2. Sometimes the evidence statements summarised more than one outcome measure. Where there were no GRADE summaries, evidence statements were made based on the analyses.

Table 2: Evidence statements

Description	Quality	Quantity
Strong evidence	Good quality	Large amount of data / meta analysis
Good evidence	Good quality	
Moderate evidence		Reasonable amount
Fair evidence	Acceptable quality	
Limited evidence		Not much evidence: trial < 50 people
Weak evidence	Poor quality	
Insufficient evidence		Not enough evidence to judge: trial size < 20 people or wide confidence interval

Generally, for randomised trials, a GRADE rating of 'good' equated with the wording 'good' or 'strong' evidence; a rating of 'moderate' with 'fair' evidence; a rating of 'low' was given the wording 'weak' evidence and a rating of 'very low' was described as 'insufficient' evidence.

5.3 Cost effectiveness review methods

Health economic evidence is useful in guideline development as it assesses the costs and benefits of alternative courses of action which could be recommended within the guideline. Cost-effectiveness evidence can be used to determine whether a particular recommendation would result in the efficient use of NHS resources by considering whether it achieves additional health gain at an acceptable level of cost. Whilst cost-effectiveness is an important consideration for all recommendations made within the guideline, two areas were identified as being priority areas for which cost-effectiveness evidence would have particular importance for informing recommendations. These were identified by the health economist in conjunction with the GDG after consideration of the importance of each clinical question in terms of the number of patients likely to be affected and the impact on costs and health outcomes for those patients.

The use of tests to exclude alternative diagnoses in people with IBS-like symptoms was considered to be a high priority area for economic evaluation for the following reasons: diagnostic testing has the potential to result in earlier diagnosis of organic disease which may improve health outcomes; the widespread use of tests may have significant cost implications; the use of tests may result in unnecessary anxiety for patients, particularly if the rate of false positive results is high; invasive tests may have adverse consequences for patients in terms of complications.

The use of pharmacological and behavioural interventions in the management of IBS was also identified as a high priority area for economic evaluation. Pharmacological interventions were identified as an area of high priority because the ongoing use of these interventions in a large number of IBS patients would have significant implications for the use of NHS resources. Behavioural interventions were identified as an area of high priority because these are not widely used at present in the management of IBS and therefore significant additional resources may be required if these are recommended for widespread use.

Two approaches were employed to provide cost-effectiveness evidence for the GDG to consider when making recommendations. Firstly, a review of the health economic literature was carried out and relevant health economic evidence was presented to the GDG. Secondly, further economic analysis was carried out in the priority areas where there was insufficient evidence available from the published literature to inform recommendations and where there was sufficient evidence to demonstrate the clinical effectiveness for the intervention or diagnostic strategy. This further economic analysis was conducted in the form of a cost-effectiveness analysis where the additional benefits were measured in terms of quality-adjusted life-years (QALYs) and the additional costs were assessed from an NHS and personal social services perspective. The GDG considered the incremental cost per QALY for alternative management and diagnostic strategies alongside the clinical effectiveness evidence when formulating recommendations. Where one clinical strategy was clearly more effective and less costly than another it was considered cost-effective. Where one strategy was more effective but also more costly, the incremental cost per QALY was estimated and this was compared to a cost-effectiveness threshold of £20,000 to £30,000 per QALY in line with the principals laid out in the NICE Guidelines Manual (NICE 2007). For those clinical questions not prioritised for economic analysis, the GDG considered the likely cost-effectiveness of associated recommendations by making a qualitative judgement on the likely balance of costs, health benefits and any potential harms.

5.3.1 Economic literature review methods

Background

The diagnostic review described in chapter 6 provides evidence on several criterion based reference tools that are useful in the diagnosis of IBS in patients who do not have “red-flag” symptoms. However, some patients meeting the diagnostic criteria for IBS, following the application of a criterion based reference tool, may have another disease which has similar symptoms to IBS, such as inflammatory bowel disease (Crohn’s disease and ulcerative colitis), coeliac disease or lactose intolerance. In some patients these conditions may be mistakenly diagnosed as IBS and sometimes they may be present alongside IBS. The health economic review aimed to assess whether further diagnostic testing to identify patients with alternative diagnoses is cost-effective in patients meeting the diagnostic criteria for IBS who do not have any “red-flag” symptoms.

The clinical effectiveness reviews presented in Chapters 7 to 10 assess the effectiveness of various interventions which may be useful in the management of IBS. The economic review aimed to assesses the cost-effectiveness of these interventions to manage IBS based on the published literature. Whilst pharmacological interventions and behavioural interventions were identified by the GDG as being priority areas for which cost-effectiveness evidence would have particular importance for informing recommendations, this review was not restricted to these interventions and evidence was included on any of the management interventions covered by this guideline.

OBJECTIVES

- To determine the cost-effectiveness of tests to identify alternative diagnoses in patients meeting the diagnostic criteria for IBS who do not have any “red-flag” symptoms.
- To assess the cost-effectiveness of interventions used in the management of IBS.

SELECTION CRITERIA

Types of studies

The types of studies included in the review were trial or model based economic evaluations including cost-effectiveness analyses, cost-utility analyses and cost-benefit analyses. Cost-minimisation studies were excluded except where therapeutic equivalence had been demonstrated.

Population

The population considered was patients meeting the diagnostic criteria for IBS who do not have any “red-flag” symptoms.

Types of intervention

The following interventions were considered: diagnostic tests for inflammatory bowel disease; coeliac disease; lactose intolerance; all interventions used in the management of IBS.

Outcomes

The outcomes assessed by the review were: cost per QALY; cost per LY; cost per correct diagnosis; cost per unit of clinical effect; cost-benefit ratio; net benefit.

SEARCH STRATEGY FOR IDENTIFICATION OF STUDIES

Searches were performed on the MEDLINE database for objective 1 using the strategy given in appendix B. Specific searches were also performed on the NHS EED database using the MeSH terms for inflammatory bowel disease (exploded to include Crohn's disease and ulcerative colitis), lactose intolerance and coeliac disease. Free-text searching on the NHS EED database was explored but did not yield any further relevant papers.

Searches were performed on the MEDLINE database for objective 2 using the strategy in Appendix B. Specific searches were also performed on the NHS EED database using the MeSH term for irritable bowel syndrome which yielded two further papers. Free-text searching on the NHS EED database was explored but did not yield any further relevant papers.

Included papers

The search results for both objectives were sifted together to allow identification of any cross-relevant information. Twenty-five papers were retrieved in full, of which 10 addressed the cost-effectiveness of management strategies (objective 2), with 4 included in the review, and 15 addressed the cost-effectiveness of tests to identify alternative diagnoses (objective 1), with 4 included in the review. Excluded papers and the reasons for exclusion are detailed in Appendix E. The most common reasons for exclusion were that the paper was not an economic evaluation or that it considered an inappropriate population. Included studies were reviewed by the health economist and the quality of each study was critically appraised using a validated check-list for economic analyses (Drummond 1997). Each study is discussed under the clinical question it addresses within chapters 6 to 10 of the guideline. The characteristics of the included studies are given in Appendix C and the details of the quality assessment are provided in of Appendix D.

5.3.2 Cost-effectiveness modelling methods

Having considered the published clinical and cost-effectiveness evidence on the use of diagnostic tests in people with IBS, the GDG decided that further economic analysis was needed to determine the cost-effectiveness of serological tests for coeliac disease in people meeting the IBS diagnostic criteria compared to initiating IBS management without testing for coeliac disease. This was done by adapting one of the published economic analyses to make it

more applicable to the NHS in England and Wales. Further details on the cost-effectiveness analysis carried out for this area of the guideline is provided in Chapter 6.

There was insufficient cost-effectiveness data identified from the published literature to allow the GDG to determine whether each of the various management interventions were cost-effective. An economic analysis was carried out to estimate the cost-effectiveness of pharmacological interventions and behavioural interventions in the management of IBS as these had been identified by the GDG as areas where cost-effectiveness evidence would be particularly important in informing recommendations. The remainder of this chapter describes the methods used in this economic analysis. The results are presented in the relevant chapter subsection for each pharmacological intervention and behavioural therapy.

The general approach

- Two models were developed to estimate the cost-effectiveness for different types of IBS management interventions:
  - A long-term maintenance therapy model for pharmacological interventions which are taken on a regular basis such as laxatives, anti-motility agents, antispasmodics, tricyclics and SSRIs.
  - A “one-off” intervention model for behavioural interventions (CBT, psychotherapy and hypnotherapy) which are given over a defined period with the expectation that benefit continues beyond the intervention period.
- Modelling was carried out using the best available evidence
- Assumptions made in the model have been described explicitly. The validity of these assumptions was discussed with the GDG during the development of the model and the interpretation of the cost-effectiveness results
- The importance of model assumptions was examined through univariate sensitivity analysis
- Parameter uncertainty was explored by carrying out a probabilistic sensitivity analysis (PSA)
- Limitations of the analysis are explicitly discussed alongside the cost-effectiveness results.

Identifying evidence on prognosis, resource use and quality of life

A rapid literature review was carried out to identify data which could be used to inform the health economic modelling. This review had three objectives:

- To identify cohort studies providing prognostic data which could be used to inform the health economic model by determining health states which could be used to describe the natural history of IBS
- To identify quality of life data measured in people with IBS and determine what factors influence quality of life in IBS and how estimates of quality of life could be incorporated to reflect the natural history of IBS or the impact of interventions on quality of life in the economic model

- To identify estimates of health care resource use and costs for people with IBS and determine what factors influence resource use in IBS and how estimates of resource use could be incorporated to reflect the natural history of IBS or the impact of interventions on resource use in the economic model.

The methods and results of this review are described in Appendix F. Where the data from this review has been used to inform the economic model it has been discussed in the relevant methods section below.

Key assumptions

- The model used estimates of clinical effectiveness that were obtained from the systematic reviews of RCTs. These clinical effectiveness reviews combined the results from studies across the whole class (e.g. all antispasmodics), but also examined subgroups of that class (e.g. antimuscarics and direct-action smooth muscle relaxants). The model used a combined estimate of clinical effectiveness across the whole class unless there was evidence to demonstrate a significant difference in effectiveness between sub-groups or between interventions (e.g. individual drugs).
- Clinical effectiveness was estimated in the model by considering the proportion of patients who experienced a global improvement of symptoms. This was the primary outcome of the clinical effectiveness review and was also considered by the GDG to be closely related to an improvement in quality of life across the many different interventions considered by the economic model. Where evidence on global improvement of symptoms was unavailable, a symptom specific response rate was used after discussion with the GDG as to which of the available outcomes was most relevant. The efficacy data used for each individual class of interventions is discussed within the relevant chapter sub-section for that intervention.
- Cost-effectiveness was estimated for each IBS subtype (e.g. IBS-D/C/A) for which there was evidence of clinical effectiveness or for the population as a whole if trials did not show a difference in effectiveness between subgroups or did not provide effectiveness evidence by subgroup. The GDG considered whether the estimated cost-effectiveness was likely to apply equally to all IBS subtypes when formulating recommendations.
- Interventions which did not have sufficient evidence to demonstrate clinical effectiveness were excluded from the cost-effectiveness analysis. This judgement was made by the GDG after considering the clinical effectiveness evidence for each intervention.
- The model for long-term maintenance therapies estimated the cost-effectiveness of initiating therapy with interventions from within a particular class using a defined patient pathway. This management strategy was compared to a “no treatment” alternative in which patients were not given any specific intervention and were not advised to return for follow-up. The “no treatment” alternative provided a common baseline, against which the costs and benefits of interventions from different classes could be assessed.

- The model for “one-off” interventions considered the addition of psychological interventions to usual care compared to usual care alone in patients with refractory IBS. The population and comparator were selected to reflect the available RCT evidence on the clinical effectiveness of psychological interventions. The RCTs for these behavioural interventions were considered by the GDG to be representative of patients with refractory IBS. In the majority of these trials ongoing IBS drug therapy was continued in both arms of the trial. The GDG interpreted these RCTs as reflecting the clinical effectiveness of adding behavioural therapy to usual care rather than replacing usual care with behavioural therapy.
- The cost-effectiveness of initiating therapy with *either* interventions from class A *or* interventions from class B was assessed where these represented mutually exclusive alternatives. Direct evidence comparing interventions from different classes was used where available. Otherwise, an indirect comparison was made using “no treatment” as the common comparator. However, these indirect comparisons should be treated with caution as they were not based on randomised comparisons and may be subject to bias.
- The majority of the pharmacological interventions are used to treat a specific aspect of the individual’s symptom profile and can therefore be used in combination if more than one symptom is problematic. In this case they are not mutually exclusive alternatives and the incremental cost-effectiveness of one compared to the other has not been estimated.

Cost-effectiveness of intermittent use of maintenance treatments

- The intermittent use of maintenance treatments was considered by scaling drug costs and benefits by the proportion of days on which the treatment is used.
- If two interventions are used intermittently but not concurrently, for example laxatives and anti-motility agents in patients with IBS-A, the costs and benefits of each intervention were scaled according to the proportion of days on which they were used and the total costs and benefits have been summed across both interventions. The assumption here was that the benefit gained from treating a particular IBS symptom which was present on some days was independent of the benefit gained from treating another IBS symptom which was present on other days.

Cost-effectiveness of combined use of maintenance treatments

- The combined use of two interventions from different classes concurrently was not explicitly modelled as there was no direct evidence on the use of combined versus single interventions in the management of IBS. The cost-effectiveness of using maintenance treatments in combination was considered qualitatively by the GDG based on the cost-effectiveness evidence for individual treatments and the likely additive effects of the interventions on costs and benefits.

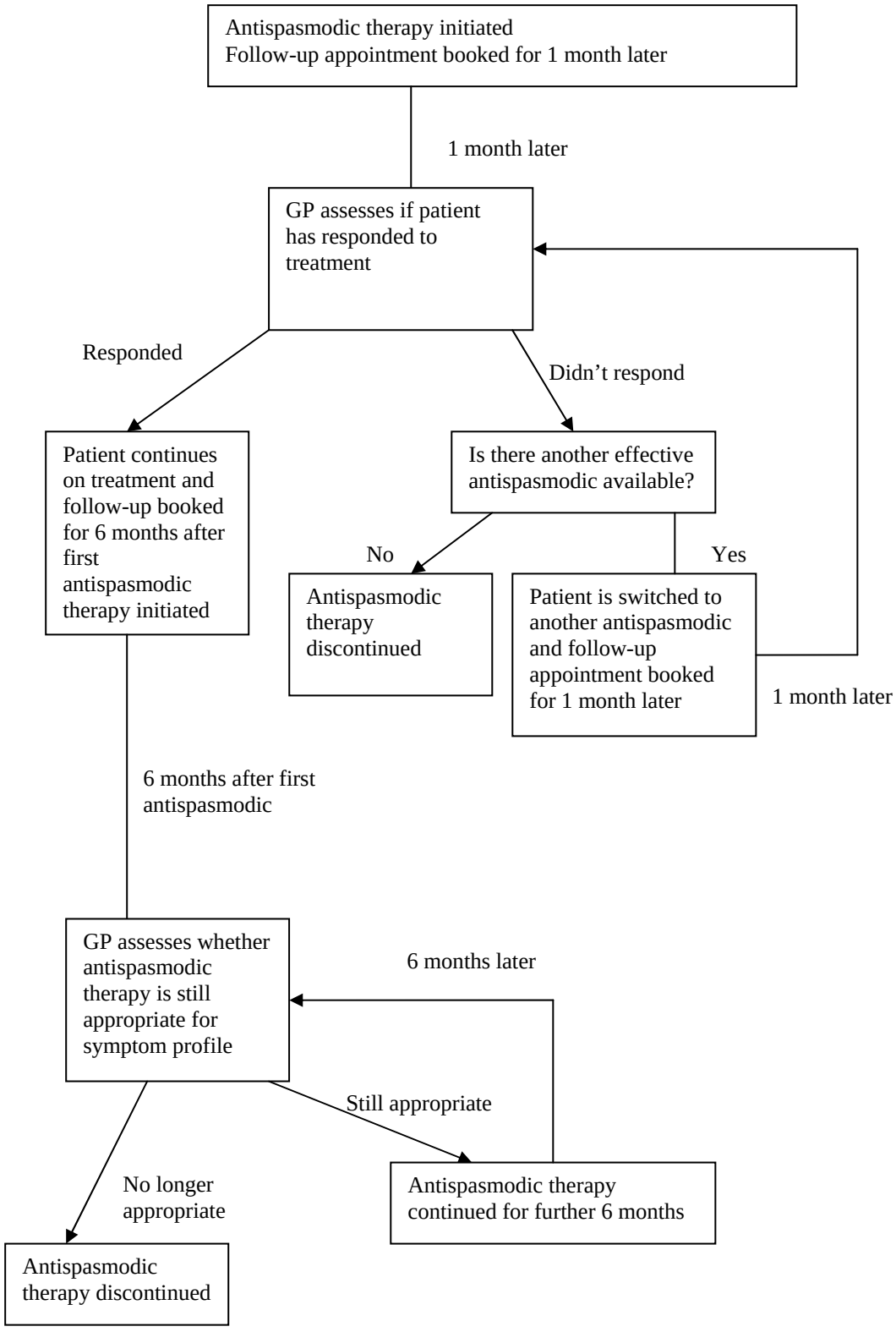
Determining the clinical pathway for maintenance interventions

In order to estimate the cost-effectiveness of maintenance interventions it was necessary to quantify the costs associated with prescribing and monitoring interventions and an appropriate time-frame for the analysis in terms of the duration over which costs and benefits were expected to differ as a result of a decision by a health care professional to initiate a particular a intervention.

There was evidence from the prognostic data reviewed in Appendix G that a patient's predominant symptom may change over medium term intervals (1-3 months) resulting in them switching between IBS subtype classifications. Evidence from Drossman (2005) showed that only 24.2% of patients remained in their baseline subtype over the study duration of 15 months. This suggests that any long-term maintenance therapy should be regularly reviewed to assess its continued relevance to the patient's evolving symptom profile. On the basis of this evidence the model was developed to consider periods of 6 months. In the first 6 months we estimated the cost-effectiveness of initiating a long-term maintenance therapy. We then estimated the cost-effectiveness of continuing the intervention for another 6 months in individuals who continue to experience a therapeutic benefit from the intervention.

The clinical pathway modelled is described in detail below and summarised in Figure 1 using antispasmodic therapy as an example. A slightly modified patient pathway has been used for tricyclics and SSRIs as these interventions require more frequent follow-up. This is described in detail in the tricyclics and SSRI section of Chapter 8.

Figure 1. Patient pathway for maintenance therapies illustrated for antispasmodics



Clinical pathway for maintenance model (See Figure 1 above)

- Patients initially receive the lowest cost intervention from within a class if there is no difference in effectiveness within the class (if there is a difference, each of the alternative interventions has been considered to estimate which is the most cost-effective to use first).
- Patients who demonstrate a successful response after 1 month continue on therapy until 6 months after treatment was initiated.
- Patients who do not respond switch to the next lowest cost therapy and response is assessed again after 1 month.
- The number of switches is limited by the number of effective interventions available.
- All patients receiving pharmacological maintenance interventions are reviewed after 6 months to assess whether the class of intervention is still relevant to the symptom profile.
- The above treatment pathway was compared to a “no treatment” alternative in which patients are not given any specific intervention and are not advised to return for follow-up.
- An analysis was undertaken to assess the maximum number of switches that are cost-effective by considering the additional cost and benefit of each additional switch of therapy.
- Probability of response to each subsequent intervention within a class was assumed to be independent of the response to previous interventions. A sensitivity analysis using lower response rates of 50% and 0% was carried out to test the impact of this assumption on cost-effectiveness.
- It was assumed that there is no fall off in treatment effect during the six month period for patients who have responded during the first month. This is an approximation, as some patients may experience a reduction in efficacy over time and may withdraw from treatment but the impact of this on cost-effectiveness is likely to be small given that treatment is reviewed every 6 months and patients are likely to discontinue therapy if it is no longer effective.
- It was assumed that the treatment effects do not persist after an intervention has been discontinued. This means that patients who stop therapy are assumed to return to their previous health state and patients who switch therapy do not experience the combined effects of both therapies in the cross-over period.

Clinical pathway for one-off interventions

- One-off interventions are given over a defined period with the expectation that benefit continues beyond that period.
- Follow-up data from trials were used to estimate the rate of fall-off in effectiveness and the time until no further benefit is expected. This determined the duration of the cost-effectiveness analysis.
- The number of patients responding over the duration of intervention and follow-up was fitted to the data available from the RCTs. Between the time points for which data is available we have assumed that the rate of change in effect is constant.

- Where the evidence was equivocal, such that alternative assumptions on the rate of fall-off in effectiveness could be justified, these alternative assumptions were considered in sensitivity analysis to assess how they alter the cost-effectiveness.
- Where the duration of continued effectiveness is over 1 year, discounting at 3.5% was applied to estimate the net present value of future costs and benefits.

Estimating the benefits associated with response to treatment

- In order to estimate cost-effectiveness it was necessary to estimate the benefits associated with treatment. In general these may be a gain in duration or quality of life, or a reduction in NHS resource use (such as fewer GP consultations).
- There was evidence from the literature review detailed in Appendix G to show that HRQoL is lower in patients with IBS than in matched controls (Akehurst 2002) and that HRQoL varies significantly by symptom frequency and severity but not by IBS subtype (El-Serag 2002). Akehurst (2002) found that resource use was significantly higher in patients with IBS than matched controls, but the evidence on resource use by symptom frequency, severity or IBS subtype was inconsistent (see Appendix G). We assumed in the model that patients responding to treatment experience a gain in health related quality of life but no reduction in resource use unless there was direct evidence from RCTs to demonstrate reduced resource use. We did not consider survival gains as IBS management interventions are not expected to affect survival.
- Utility is a measure of health related quality of life where a score of 1 represents full health and a score of 0 is a health state equivalent to death. Using the data presented in Mearin (2004) we estimated health state utility scores for high and low severity symptoms by aggregating scores across the IBS subtypes for patients with high frequency symptoms (present >50% of the time). This gave an estimated mean health state utility of 0.704 for patients with high severity symptoms and 0.775 for patients with low severity symptoms. We assumed that the utility gain associated with response to treatment was equivalent to an improvement in symptom severity (high to low severity). This was equivalent to an additional 0.071 QALYs per year of continued response (Mearin 2005). For comparison, an additional 0.135 QALYs would represent a complete resolution of IBS symptoms (Akehurst 2002). Our method for estimating QALY gain is quite crude as it assumes that all patients who experience a therapeutic response have the same increase in HRQoL and it does not distinguish between varying degrees of improvement in HRQoL. Where possible, we have used an improvement in global symptoms to determine whether there has been a therapeutic response to treatment in order to prevent bias being introduced by the use of different outcomes for different interventions.
- Given the limitations of the approach used to estimate QALY gains, a threshold analysis was also carried out to estimate the minimum treatment associated QALY gain for which treatment is still cost-effective.

- Adverse effects were not explicitly included in the model. Many of the adverse outcomes of interest considered in the adverse effects review (see section 8.5) were very similar to the symptoms of the IBS itself and were also considered within the effectiveness outcomes. It is likely that these adverse effects would have been captured by the clinical effectiveness estimate as this was based on global symptom score improvement. Therefore, patients who experienced a worsening of their IBS symptoms as a result of a specific intervention would be considered to have not responded to that intervention in the model and would discontinue that treatment. No other adverse effects were identified by the GDG as having the potential to significantly impact on costs and quality of life for the interventions considered by the economic model.

Estimating the costs of the patient pathway

- Costs were considered from an NHS and PSS (Personal Social Services) perspective and included: drug costs for prescribed medications, consultation costs for the behavioural therapies and consultation costs for initiating and monitoring pharmacological interventions.
- Drug costs were based on the doses used in clinical trials and it was assumed that the lowest cost preparation would be prescribed regardless of whether this is proprietary or generic. Drug costs were based on the published costs given in the British National Formulary (Joint Formulary Committee 2007).
- Sensitivity analysis was carried out to consider whether the cost-effectiveness would be significantly different if the most costly preparation were to be used.
- Sensitivity analysis was carried out on alternative doses to those used in the trials where the GDG advised that these alternative doses were likely to be equally efficacious and more relevant to clinical practice.
- The cost of non-pharmacological interventions was estimated using the duration of clinical contact time required to deliver the intervention and the reference costs (Netten 2006) for face-to-face time with the relevant healthcare professional.

Estimating the probability of an improvement in global symptoms

- The probability of response was taken from the clinical effectiveness review using the probability of an improvement in global symptoms, unless this was unavailable. In that case an alternative symptom specific response rate was used after discussion with the GDG as to which of the available outcomes was most relevant. The efficacy data used for each individual class of interventions is discussed within the relevant chapter sub-section for that intervention.
- In the management intervention model, the cost-effectiveness was dependent on (i) the number of additional patients who respond in the treatment arm compared to the control arm, and (ii) the number failing to respond to treatment as these patients incur one month of treatment cost without benefit. In the one-off intervention model, the cost-effectiveness was

also dependent on the probability of response in the comparator arm as this determines the absolute difference in response rates and therefore the clinical benefit.

- There was evidence from cohort studies that some patients experience an initial improvement in symptoms without any specific intervention. This may be a non-specific treatment effect following diagnosis and reassurance or it may be that symptoms fluctuate naturally and patients consult when their symptoms are particularly bad but symptoms then improve without any intervention. There was also evidence from randomised controlled trials that some patients in the placebo arms of controlled trials experienced an improvement in symptoms.
- Therefore we assumed a non-zero response rate in the no treatment arm of the model.
- The probability of moving from a high to low symptom severity state estimated from the Mearin (2004) cohort study (45%) was used to estimate the response rate in the no treatment arm in the base case analysis, except where the population was deemed to be refractory.
- The RCTs for behavioural interventions (CBT, psychotherapy and hypnotherapy) were considered to be representative of patients with refractory IBS. In the majority of these trials ongoing IBS drug therapy was continued in both arms of the trial. The mean response rate from the comparator arms of these trials (25%) was used to estimate the proportion of patients with refractory IBS that experienced an improvement in global symptoms under usual care which included the continuation of any ongoing drug therapy.
- A sensitivity analysis was carried out using the average response rate in the placebo arm of the RCTs. The response rate in the comparator arm of the RCTs varied from 0% to 71% over the studies used to estimate efficacy for the economic model with a mean value of 47.5%. The studies from the laxative review could not be used to estimate the placebo arm response rate as a different outcome was used to determine response for this intervention. However, the response rate using the alternative outcome was similar to that found in the other studies for the standard outcome.
- For refractory patients, the mean response rate from the control arms of the CBT trials (9%) was used in a sensitivity analysis to examine the impact of assuming a lower response rate in refractory patients continuing usual care.
- A sensitivity analysis was carried out assuming zero response in the no treatment arm but maintaining the absolute difference in response between treatment and no treatment from the basecase analysis.

Probabilistic sensitivity analysis (PSA) is used to provide an estimate of the uncertainty in the cost per QALY estimate due to uncertainty in the model parameters used to estimate the cost-effectiveness. The most obvious example of parameter uncertainty in the model was the confidence intervals surrounding the clinical effectiveness estimates, but other parameters used in the model which were based on empirical measurement also had some uncertainty associated with them. We carried out a PSA which considered the parameter uncertainty around

the clinical effectiveness estimates, the response rate in the comparator arm, the utility gain associated with a response to treatment and the costs of psychological interventions due to variation in the number and duration of sessions used in the RCTs. Where direct evidence from the RCTs on resource use reduction was applied in the model, the parameter uncertainty around this was also estimated in the PSA. The reference costs for pharmaceutical interventions and clinical contact time with health care professionals were assumed to be fixed in the model, as was the discounting rate which was fixed by the NICE "reference-case" for economic evaluations (NICE 2007). In the PSA we characterised the parameter uncertainty by using a probability distribution to describe each of the parameters, details of which can be found in Appendix H. We then sampled from each distribution independently under the assumption that there was no correlation between the different input parameters. However, the same random number set was used to sample common parameters across the different cost-effectiveness comparisons to prevent sample bias being introduced when comparing the incremental cost-effectiveness of two interventions. We then calculated the model outcomes (incremental costs, incremental QALY gains) for each set of sampled parameters and used these to estimate the uncertainty surrounding the cost per QALY estimate.

We based our PSA on 1000 samples of the parameter distributions. The results are presented as cost-effectiveness acceptability curves which show the proportion of samples that resulted in a cost per QALY value below various thresholds. It should be noted that the PSA did not account for uncertainty around the model assumptions and these were explored separately using univariate sensitivity analysis. Table 1 gives the basecase parameters that were used in estimating the cost-effectiveness of all of the pharmacological and behavioural interventions. Parameters that were specific to each intervention, such as efficacy estimates and intervention costs, are tabled in the relevant section of Chapters 8 and 9.

Table 1: Base case parameters applied in the economic model for all interventions

Description	Mean (95%CI)	Evidence
Utility gain associated with a response to treatment	0.071 (0.02 -0.147)	Mearin (2004), difference between high and low intensity symptoms
Response rate for no treatment arm	45% (33% - 57%)	Mearin (2004), 1 month probability of transition from high to low intensity symptoms
Response rate for usual care in people with refractory IBS	25% (19% - 32%)	Comparator arms of RCTs in psychological interventions*
Discounting rate for costs and benefits	3.5%	NICE (2007), NICE reference case value
Cost for GP appointment to initiate intervention / review medication	£18	Netten (2006), GP cost per surgery consultation (excluding qualification and direct care staff costs)

* Psychological interventions includes CBT, psychotherapy and hypnotherapy

5.4 Submission of evidence

No formal request was made for submission of evidence.

5.5 Formulating recommendations and determining key recommendations

EVIDENCE TO RECOMMENDATIONS

Each review summarises the evidence, and the GDG are asked to interpret the evidence before drafting recommendations. In each case, this includes a consideration of the clinical and cost effectiveness evidence; an indication of the factors the GDG took into account, including the balance between benefits and harms; the GDG's reasoning and conclusions, and, where relevant, the level of agreement amongst the group.

This is reported in each individual review section, illustrating the relationship between published clinical and cost effective evidence and recommendations for clinical practice.

KEY RECOMMENDATIONS

Methodology

There are generally three main methods reported for developing consensus. These are Delphi, consensus development panels and nominal group processes (Bowling 2002). The nominal group technique (NGT) was originally developed by Delbecq et al (1971) as an organisational planning tool. The methodology allows individuals to work in the presence of others, but verbally interaction is prevented, enabling consensus to be developed without the social pressures normally exerted through open dialogue (Zastrow and Navarre 1977). Individual ideas are shared within the group, with facilitated discussion enabling the group to see how individuals are expressing their ideas. Normal practice is for the facilitator to then ask the group to prioritise, with aggregated rankings recorded. This methodology works extremely well towards the end of guideline development, particularly in relation to developing consensus agreement.

The GDG having worked together for the previous 12 meetings had become a mature working group; individuals within the group were able to express their views relating to key recommendations within a social setting (the last GDG meeting). This was important for the group, who were able to use this experience and the content of discussion to then go into a round of voting to move agreed recommendation into a potential top 10 list, which reflected the key priorities for the guideline. Iteration is usual within consensus methodology, and a second round of voting was necessary in order to gain full consensus within the group.

Process

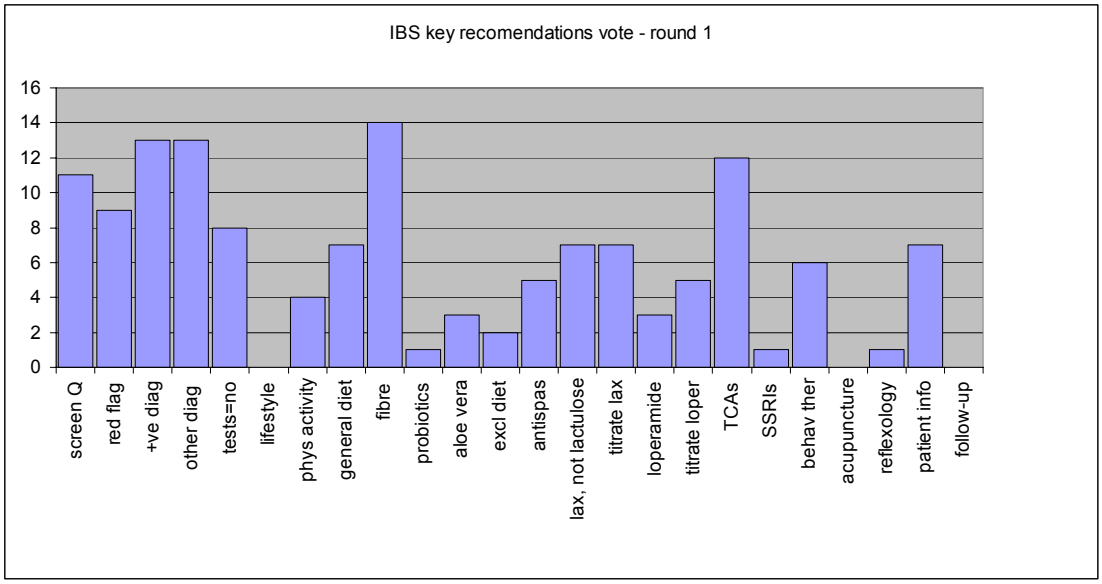
The GDG was asked to vote on key recommendations by secret email ballot using an Excel spreadsheet. This incorporated the full list of recommendations and votes were allocated to the group, in order to try and determine the key priorities for the guideline. Developing consensus through validated instruments is key to ensure that the final list of up to ten key

recommendations fully reflect the group as a whole. This enables all constituent members of the group to have equal weighting of opinion as their opinion moves towards a consensus group position. Typically, NGT works well for small groups, with 12 to 15 people widely acknowledged in the literature as the maximum number of people involved in this process.

Results in round 1: 15 GDG members voted (100%), but one voting paper was spoiled and we were unable to obtain clarification from this member. Therefore results were based on a 93% representive opinion of the GDG relating to Round 1 voting.

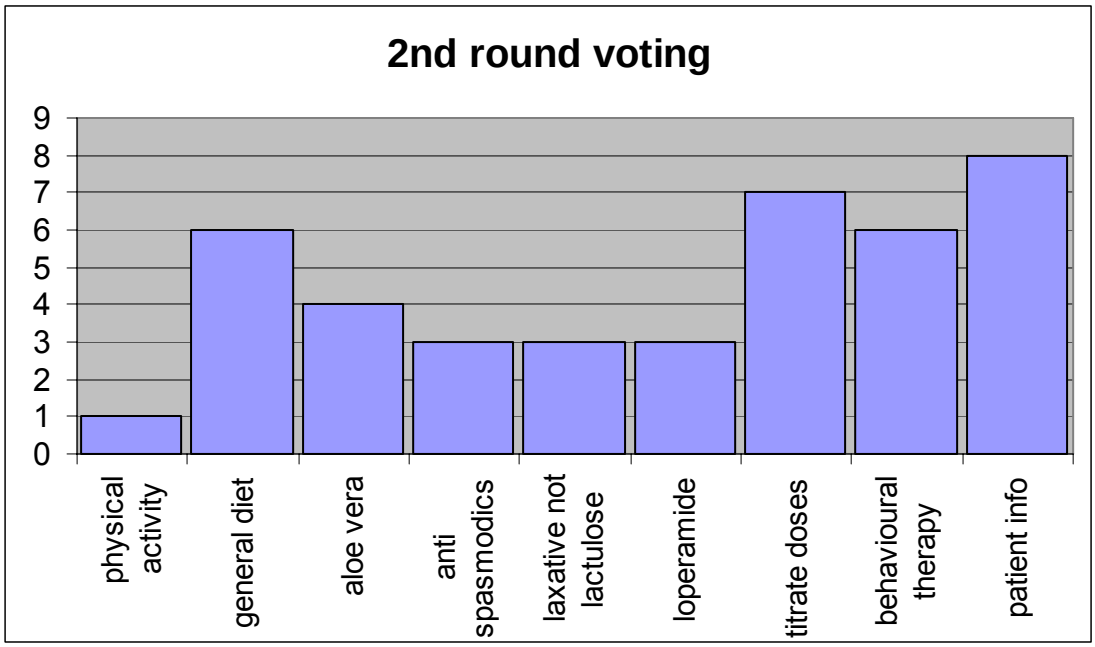
The results for this round of voting are seen below in table 1.

Table 1.



All recommendations with more than 50% of the vote were selected automatically as key recommendations; i.e. screening question, red flags, positive diagnosis, other diagnostic tests, tests that should not be done, fibre, and tricyclics. This gave seven recommendations, but the next highest results gave four recommendations with 7 votes. This determined the need for a second round of voting. Those recommendations with 2 or fewer votes were excluded, and the GDG were asked to choose three of nine recommendations. Between the two rounds, two recommendations were combined (the two relating to titration of medication doses) and the patient information recommendation was revised.

Results in round 2: 14 of 15 GDG members voted and one member only voted for two recommendations. Results are based on 93% group representive opinion of the GDG.



In analysing the voting for round 2, two further recommendations were selected: patient information and titrating doses of laxatives and antimotility agents. Two other recommendations had six votes each, general diet and psychological interventions and it was decided to exclude both of them, leaving the following nine key recommendations.

Summary

The NGT worked well in developing consensus opinion, reflected by the key recommendations emergent from the process. The nine key recommendations represent the heart of the full guideline and full guideline recommendations. They articulate the evidence supporting the key areas of healthcare practice that will be shaped by the guideline, providing the possibility with effective implementation for people with IBS symptoms being properly diagnosed and managed within primary care.

6 DIAGNOSIS

INTRODUCTION AND BACKGROUND

Irritable bowel syndrome (IBS) is a chronic, relapsing and often life-long disorder. It is characterised by the presence of abdominal pain associated with defaecation, or a change in bowel habit together with disordered defaecation (constipation or diarrhoea or both), and the sensation of abdominal distension. Symptoms sometimes overlap with other gastrointestinal disorders such as non-ulcer dyspepsia, or with coeliac disease. Diagnosis of IBS has proven difficult historically for many reasons, not least that traditionally an exclusion diagnostic approach has been selected by clinicians. Each year, typically approximately 10% of the population will experience IBS symptoms, with up to half of these presenting to primary care clinicians. In reviewing the literature, it is clear that in the absence of gold standard diagnostic criteria, several criterion referenced diagnostic tools have emerged over the last two decades. These have been used in both prevalence and incidence studies, and have proven to be useful for clinicians in enabling them to provide a diagnosis for those patients presenting with IBS symptoms. These criteria have also allowed for standardisation of IBS diagnosis in research.

Definition

For the purpose of this guideline, IBS is defined using the Rome II criteria, used mainly in the context of research. The Rome group is a pan-European clinician group that have met for the last decade, seeking to provide both clarity and direction for clinicians and patients alike.

The Rome II criteria characterises IBS as:

- At least 12 weeks (which need not be consecutive), in the preceding 12 months, of abdominal discomfort or pain with two of the following three features:
    - Relief by defaecation
    - Onset associated with a change in frequency of stool
    - Onset associated with a change in stool appearance.

The IBS population

IBS most commonly affects people between the ages of 20 and 30 years and is twice as common in women as in men. The prevalence of the condition in the general population in the UK is estimated to lie somewhere between 10 and 20%. Recent trends indicate that there is also a significant prevalence of IBS in older people; therefore, IBS diagnosis should be a consideration when an older person presents with unexplained abdominal symptoms. Because incidences of other conditions with similar symptoms are higher in the elderly population, use of certain diagnostic tests is warranted. Co-morbid conditions and poly-pharmacy are common in this patient population. The true prevalence of IBS in the whole population may be higher than estimated, because it is thought that many people with IBS symptoms do not seek medical advice; NHS Direct online data suggest that 75% of people using this service rely on self-care. In England and Wales, the number of people consulting for IBS is extrapolated to between 1.6

and 3.9 million. Evidence suggests that age and race have no consistent effect on the incidence of symptoms. Healthcare professionals need to be sensitive to and take into consideration cultural, ethnic and communication needs of people for whom English is not a first language or who may have cognitive and/or behavioural disabilities. Appropriate action should be taken to facilitate effective consultation.

Investigations commonly requested by clinicians

Primary care investigations are likely to include: routine blood tests such as full blood count, urea and electrolytes, liver function tests; tests for thyroid function, tissue transglutaminase anti-endomysial antibodies (test for coeliac disease); inflammatory markers, stool microscopy; urinary screen for laxatives; and lactose tolerance testing. Other investigations such as gut transit studies (radiological tests to measure the time required for food to move through the digestive tract) and sigmoidoscopy (endoscopy of the lower part of the bowel) are routinely performed in secondary care. Determining the criteria for such requests and appropriate referral into secondary care will be addressed in the guideline.

The need for effective diagnosis – clarifying concepts

IBS is associated with a disproportionately high prevalence of abdominal and pelvic surgery, although the cause of this has not been established. Diagnostic test methodology has traditionally been applied when comparing a new or alternative test with the acknowledged gold standard reference.

Gold standard reference points aim to represent the 'truth', and when a test is carried out there are four possible outcomes. These are:

1. True positive (detects disease when present)
2. False positive (detects disease when it is absent)
3. True negative (can identify absence of disease)
4. False negative (can identify someone as being disease free when they have it).

It is widely acknowledged within the literature that there is no gold standard reference for the diagnosis of IBS, which means that comparison of definitive diagnostic tests remains difficult. Diagnostic criteria in themselves can be seen as having enormous value, and these could be directly compared in other disease areas to the gold standard reference. In this narrative review of 170 studies/papers, comparisons of criteria are made against a definitive diagnosis of IBS through clinician expertise, augmented by a whole battery in many cases of diagnostic investigations.

In measuring accuracy of diagnostic test/criteria, two measures are used. These are sensitivity and specificity.

Sensitivity

This is a measure (usually expressed as a % of the total population that the test is applied to) that indicates how good the test is in identifying people with the disease.

Specificity

This is a measure (usually expressed as a % of the total population that the test is applied to) that indicates how good the test is in identifying people without the disease.

Problems associated with using these as single measures are acknowledged, as they are difficult to interpret for individual patients. For example, if a test has a sensitivity of 85%, what if I am one of the 15% that the test has failed to identify. In real world situations, what patients and clinicians generally want to know is *'If this test is positive, does it mean that I have a positive diagnosis?'* or; *'If this test is negative, does this mean that I do not have the disease?'*

What may be more useful is for these single measures to be expressed as a probability; a likelihood of accuracy. Again this is expressed as a %, with positive tests measured against a whole study population who had the test. For example, 37 positive results out of 100 would be a 37% prediction, expressed as a positive predictive value (PPV) of 37% (Dawes et al, 2005). This can be viewed from the reverse perspective; how many negative tests were recorded out of the total study population who had the test. For example 63 negative results out of 100 would be a 63% prediction, expressed as negative predictive value (NPV) of 63%. Using real data (Steurer 2002), of 1000 women who received a positive mammogram result, 90 actually had breast cancer, meaning that the PPV for mammography is 9%. Converted to probability, this means that women have a 1 in 11 chance of having breast cancer if they have a positive mammogram result. Of the 12,102 negative mammogram results, 12,090 did not have breast cancer (meaning that 12 did have breast cancer). This means that the NPV for mammography is 99.9%. Converted to a probability, this means that women have a 1 in 1000 chance of having breast cancer if they receive a negative mammogram result. This is extremely useful to clinicians in trying to establish risk and/or probability of a disease in a particular individual, enabling them to articulate this to the person seeking consultation.

Odds ratios

This is another way of measuring test accuracy (see Appendix 2 of this chapter). Its real value is in estimating test accuracy. This is calculated using test Likelihood Ratio's (LR) by taking the positive LR and dividing this by the negative LR. Likelihood ratios are useful in estimating the value of diagnostic tests, and as a general principle, the higher the likelihood ratio the more useful that test will be. A high odds ratio is an indicator of a good diagnostic test.

A main aim of the guideline

One of the main aims of this guideline is to identify diagnostic criteria for people presenting with symptoms suggestive of IBS and to ensure that primary care clinicians and people who may have IBS have a reference tool that is both sensitive and specific, with high predictive value of the syndrome. This is an area of healthcare practice which is currently absent, and creates great uncertainty for both clinicians and people who may have IBS.

OBJECTIVES

1. To determine the effectiveness of diagnostic criteria for people with IBS.
2. To determine the clinical utility of diagnostic tests to exclude alternative diagnoses in people meeting the diagnostic criteria for IBS.

SELECTION CRITERIA

The selection criteria for this systematic narrative review was to analyse all relevant literature related to diagnosis of IBS. Due to the absence of a gold standard reference for this disease, diagnostic review methodology was not applicable. On this basis, the GDG accepted that a systematic narrative review was the best way of measuring current practice against peer reviewed literature. This review formed the basis for GDG consensus discussions and recommendations for diagnosis of IBS. Studies identified were then quality assessed. Studies included in the review importantly had to have used a criterion referenced diagnostic tool, studies that failed to do so were excluded from the review. This ensured that all relevant studies provided the evidence base in validating a diagnostic tool, enabling primary care clinicians to make a positive IBS diagnosis around symptom recognition.

Types of studies

All published literature on IBS diagnosis was included. This resulted in a large search and, post-sifting, a large number papers being reviewed for potential inclusion in the review.

SEARCH STRATEGY FOR IDENTIFICATION OF THE LITERATURE

Searches were performed on the following core databases: MEDLINE, EMBASE, CINAHL and *The Cochrane Library* (1966 to current day with guidance from the GDG). Additional databases were not searched for this review. A sensitive search strategy was employed, as recommended by Haynes and Wilczynski (2004) in determining optimal search strategies for retrieving scientifically strong studies of diagnosis. The search strategies are listed in Appendix B.

METHODOLOGY

The benefits of a systematic narrative review of the clinical evidence in the absence of diagnostic test studies are highlighted by Oxman and colleagues. Applying the quality assurance principles advocated by Oxman (1994), a valid review article can provide the best possible source of information that can lay a foundation for clinical decisions to be made. There is

argument that focused narrative reviews for individual outcomes, in this case, IBS diagnosis, are more likely to provide valid results that are useful for clinicians.

STRUCTURE OF THE REVIEW

Having provided the background and context for this review, diagnostic criteria are presented that emerge from the systematic narrative review of the literature. Data is presented in three main sections of the review.

In the first section, the evidence relating to the use of criterion based tools in the diagnosis of IBS is presented and discussed. The effectiveness data for each tool is summarized in Table 1 and specificity, sensitivity and positive predictive value of the criteria are reported where available. Studies included in the table illustrate how research has validated the use of these tools, where the criteria used is matched against a clinical reference standard (in all studies this was an expert gastroenterologist) by using specificity, sensitivity and positive predictive value data. The excluded studies are listed in Appendix E and are excluded on the basis that no criterion reference tool was used. This systematic narrative review is followed by a description of an interactive exercise used by the GDG to assess the strengths and weaknesses of each of the identified tools.

In the second section, the evidence relating to the utility of tests to exclude alternative diagnoses is presented and discussed. This is followed by a review of the economic literature for diagnostic testing and an adaptation of one of the cost-effectiveness models identified in the economic literature review.

IBS DIAGNOSTIC CRITERIA

The use of diagnostic criteria has merged over the last three decades, with leading GI specialists such as Manning and Kruis leading the way. Such diagnostic criteria were forerunners to a consensus process amongst leading clinicians which became known as the Rome process. Rome III is the latest iteration and builds on the validated work from authors, in particular the Manning criteria.

Pre-Rome

The first paper to address diagnostic criteria for IBS was a working team report published in 1989 for the 1988 International Congress of Gastroenterology in Rome, Italy. This is acknowledged as the Rome criteria.

Establishment of Rome Committee Process

Following the 1989 publication, a committee was set up the same year to develop for the first time a classification system for all the 21 functional gastro intestinal disorders (FGID). This report was published in 1990 heralding the beginning of the Rome Criteria process. The criteria

for IBS in 1989 did not feature pain as a symptom, which is now a current ROME criteria requirement for the diagnosis of IBS.

Rome I

From 1990-1995, seven committees formed to elaborate on the 1990 classification system. Knowledge of this classification system was quite limited, since the journal had a small circulation and was not listed in MEDLINE. The committee however were able to publish a book which featured the updated Rome I criteria in 1992 and it was the first time that pain was required for the diagnosis.

Rome II

By 1995, interest had grown from both clinicians and the pharma industry. Funding was secured from industry to support the development of Rome II. The number of committees was expanded, with wider international contributions forming the basis of this updated set of criteria. Emerging from this process, the criteria were available from 1999 and first published in 2000.

Rome III

Because of the success of the Rome II process, funding support from industry was forthcoming to maintain this consensus process. A co-ordinating committee was formed in 2001 for Rome III (Drossman, Corazziari, Delvaux, Spiller, Talley, Thompson and Whitehead). Work began in May 2003, leading to publication of new criteria in 2007.

Kruis criteria

The aim of the original study was to create a scoring system for IBS diagnosis incorporating history, physical examination and some basic investigations (ESR and blood count).

[1]Validated criterion reference tool reviewed and acknowledged as used within practice over the last 3 decades.

Kruis patient questionnaire

1. Did you come because of abdominal pain? No Yes
   Do you suffer from flatulence? No Yes
   Do you suffer irregular bowel movements? No Yes

2. Have you experienced this for > 2years? No Yes

3. How can your abdominal pain be described: burning, cutting, very strong, terrible, feeling of pressure, dull, boring, not so bad?

[1] In the absence of a gold standard, the reference standard was expert gastroenterologist diagnosis.

4. Have you alternating diarrhoea/constipation? No Yes

5. Have your stools any of the following properties? Pencil-like; rabbit pellets; hard in the first portion and looser in the second portion; mucus?

If the patient answers yes in any of sections of each question, a scoring system is allocated as follows:

Question 1	34 points
Question 2	16
Question 3	23
Question 4	14

Question 5 carries no score.

Total score possible 87 points.

The patient questionnaire is then validated by the clinician who can subtract from the original total if they identify markers or indicators of disease, potential red flags.

Kruis clinician questionnaire

1.	Abnormal physical findings, and/or history for alternative diagnosis of IBS	No	Yes
2.	ESR > 20mm/2hr	No	Yes
3.	Leucocytosis > 10.000/ccm	No	Yes
4.	Haemoglobin F < 12g/ M < 14g	No	Yes
5.	History of blood in stool	No	Yes
6.	Fever (> 38.5) in the last week	No	Yes
7.	Underweight	No	Yes
8.	Loss of weight > 5kg in last 6 months	No	Yes

If the clinician answers yes to questions 1 – 5, a scoring system is allocated as follows:

Question 1	- 47 points
Question 2	- 13
Question 3	- 50
Question 4	- 98
Question 5	- 98

Questions 6 – 8 carry no score. This is then subtracted from the original patient score.

Manning criteria

The patient should present with at least 2 of the following symptoms for an IBS diagnosis to be made:

- Onset of pain associated with more frequent bowel movements
- Onset of pain associated with more loose bowel movements
- Relief of pain with defaecation
- Abdominal distension
- Sensation of incomplete evacuation with defaecation
- Passage of mucus.

Rome Criteria

At the 13th International Congress of Gastroenterology in Rome in 1988 a group of physicians defined criteria to more accurately diagnose IBS. The Rome criteria are:

The patient should present with 3 months of continuous or recurring symptoms of abdominal pain or irritation that:

- May be relieved with a bowel movement
- May be coupled with a change in frequency, or
- May be related to a change in the consistency of stools.

Two or more of the following are present at least 25 percent (one quarter) of the time:

- A change in stool frequency (more than 3 bowel movement per day or fewer than 3 bowel movements per week)
- Noticeable difference in stool form (hard, loose and watery stools or poorly formed stools)
- Passage of mucous in stools
- Bloating or feeling of abdominal distention
- Altered stool passage (e.g. sensations of incomplete evacuation, straining, or urgency).

Rome I criteria (1992)

The patient should present with at least 3 months of continuous or recurrent symptoms for an IBS diagnosis to be made:

Abdominal pain or discomfort, which is:

- Relieved with defaecation
- and/or associated with altered bowel frequency
- and/or associated with altered stool consistency
- and/or two or more of the following, on at least 1/4 of days:
- Altered stool frequency
- Altered stool form
- Altered stool passage (straining, urgency or tenesmus)

- Passage of mucus
- Usually with bloating or a feeling of abdominal distension.

Rome II criteria

The Rome II Criteria, published in 2000, were developed by 10 multinational working teams that collaborated over 4 years to arrive at a consensus for symptom-based diagnostic standards.

Twelve weeks* or more in the past 12 months of abdominal discomfort or pain that has 2 out of 3 features:

- Relieved with defaecation
- Associated with a change in frequency of stool
- Associated with a change in consistency of stool.

*The twelve weeks need not be consecutive

The following are supportive, but not essential to the diagnosis. One or more are usually present. They add to the clinician's confidence that the intestine is the origin of the abdominal pain. The more of these symptoms that are present, the greater the confidence with an IBS diagnosis:

- Abnormal stool frequency (> 3/day or < 3/week)
- Abnormal stool form (lumpy/hard or loose/watery) > 1/4 of defaecations
- Abnormal stool passage (straining, urgency or feeling of
- incomplete evacuation) > 1/4 of defaecations
- Passage of mucus > 1/4 of defaecations
- Bloating or feeling of abdominal distension > 1/4 of days.

ROME III Diagnostic Criteria*

Recurrent abdominal pain or discomfort** at least 3 days/month in last 3 months associated with two or more of criteria #1 - #3 below:

Pain or discomfort at least 2-3 days/month (question 1>2)

For women, does pain occur only during menstrual bleeding? (question 2=0 or 2)

1. Improvement with defaecation

   Pain or discomfort gets better after BM at least sometimes (question 4>0)
2. Onset associated with a change in frequency of stool

   Onset of pain or discomfort associated with more stools at least sometimes (question 5>0), OR Onset of pain or discomfort associated with fewer stools at least sometimes (question 6>0)
3. Onset associated with a change in form (appearance) of stool

Onset of pain or discomfort associated with looser stools at least sometimes (question 7>0), OR Onset of pain or discomfort associated wit harder stools at least sometimes (question 8>0)

* Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis

Yes. (question 3=1)

**"*Discomfort" means an uncomfortable sensation not described as pain*.

In pathophysiology research and clinical trials, a pain/discomfort frequency of at least two days a week is recommended for subject eligibility.

Pain or discomfort more than one day per week (question 1>4)

How to use the questionnaire?

Criteria for IBS-C

(question 9>0) and (question 10=0)

Criteria for IBS-D

(question 9=0) and (question 10>0)

Criteria for IBS-M

(question 9>0) and (question 10>0)

Criteria for IBS-U

(question 9=0) and (question 10=0)

The timely publication of ROME III is beneficial to this guideline, it brings together many studies that have incorporated ROME criteria, and this latest iteration closely aligns the thinking of the GDG, in particular in relation to the implementation of diagnostic criteria for primary care clinicians to use.

ROME III Criteria - Questionnaire

1. In the last 3 months, how often did you have discomfort or pain anywhere in your abdomen?	0 Never → 1 Less than one day a month 2 One day a month 3 Two to three days a month 4 One day a week 5 More than one day a week 6 Every day	***Skip remaining questions***
2. For women: Did this discomfort or pain occur only during your menstrual bleeding and not at other times?	0 No 1 Yes 2 Does not apply because I have had the change in life (menopause) or I am a male	
3. Have you had this discomfort or pain 6 months or longer?	0 No 1 Yes	
4. How often did this discomfort or pain get better or stop after you had a bowel movement?	0 Never or rarely 1 Sometimes 2 Often 3 Most of the time 4 Always	
5. When this discomfort or pain started, did you have more frequent bowel movements?	0 Never or rarely 1 Sometimes 2 Often 3 Most of the time 4 Always	
6. When this discomfort or pain started, did you have less frequent bowel movements?	0 Never or rarely 1 Sometimes 2 Often 3 Most of the time 4 Always	
7. When this discomfort or pain started, were your stools (bowel movements) looser?	0 Never or rarely 1 Sometimes 2 Often 3 Most of the time 4 Always	
8. When this discomfort or pain started, how often did you have harder stools?	0 Never or rarely 1 Sometimes 2 Often 3 Most of the time 4 Always	
9. In the last 3 months, how often did you have hard or lumpy stools?	0 Never or rarely 1 Sometimes 2 Often 3 Most of the time 4 Always	Alternative scale: 0 Never or rarely 1 About 25% of the time 2 About 50% of the time 3 About 75% of the time 4 Always, 100% time
10. In the last 3 months, how often did you have loose, mushy or watery stools?	0 Never or rarely 1 Sometimes 2 Often 3 Most of the time 4 Always	Alternative scale: 0 Never or rarely 1 About 25% of the time 2 About 50% of the time 3 About 75% of the time 4 Always 100% time

Table 1: Summary Table of Diagnostic Papers with diagnostic data provided (reference standard was expert gastroenterologist diagnosis)

Criteria used in study	Study authors/Name of study	N= (if appropriate)	Sensitivity/Specificity Se= Sp=	Predictive value (PPV)
Kruis	Kruis et al 1984	N=108	Se= 83% Sp = 97% Accuracy if score ≥ 44 is 99%	Based on IBS prevalence if score is ≥ 44 10% 87.1% 30% 96.4% 50% 98.4%
	Dogan and Unal 1996a,Turkey	N=347	Se= 81% Sp= 91% if score of 44 points was positive	PPV= 90%
	Frigerio et al 1992 Italy	N=1257	Se= 47% in men, 60% in women Sp= 94% men, 95% women	PPV= 54% men, 82% women Negative Predictive value 91.6% men -87.3% women
	Osset et al 1991 Italy	Quoting from Kruis 1984	Se= 83% Sp= 97% 99% accurate if score is > 44 points	
	Dogan and Unal 1996b,Turkey : Manning discriminated IBS from OGD	N=347	Se= 90% Sp= 87% if > 3 positive.	PPV=87%
	Rao et al 1993	N=123	Se=67% Sp=93%	PPV=93.4%
	Talley et al 1990	N=361	Se= 42% Sp= 85%	
Manning + Kruis	Dogan and Unal 1996c,Turkey: Correlation significant in IBS r=0.714 p=<0.05 but not in OGD r = 0.190 p=>0.05	N=347	Se= 80% Sp= 97%	PPV=96%
Manning (3/6)	Jeong et al 1990	N=172	Se= 67% Sp= 70%	
	Smith 1992 Manning ≥ ¾	N=109	Se= 63% Sp= 85%	
Manning (>3/6)	Talley et al 1990	N= ??	Se= 84% Sp= 76%	
	Kruis et al 1984	N=479	Se= 64% Sp= 99%	94%
Rome	Saito et al 2003a, USA	Prevalence Cohort study	Prevalence rates by criteria:	

		1st survey 1987n=1121 2nd survey 1989 3rd survey 1992 n=892 response n=643 (72%)	Rome (1989) 27.6 per 100 (95%CI:23.6-31.5) Rome (1990) 5.1 per 100 (95%CI:3.2-7.1)	
	Vanner et al 1999	N=384 (retrospective) N=95	Se= 63% Sp= 100%	98%
Rome I	Saito et al 2003b, USA Chey et al 2002a, USA Mearin et al 2001a Spain Patients diagnosed with Manning, Rome I and Rome II. > 2/3 of subjects fulfilling Manning or Rome I would not be diagnosed as having IBS if using RomeII.	 N= 1014 women N=281	Rome I (1992) 6.8 per100 (95%CI 4.7-8.9) Se=83% Sp= not given Se/Sp = not given	Good agreement between Rome I and II (>95% Kappa >0.68)
Rome II	Saito et al 2003c, USA Chey et al 2002b, USA Difference in sensitivity seemed to be attributable to more restrictive time requirement for pain with Rome II Boyce et al 2000, Australia (prevalence study)	 N=1014 women N=2910	Rome II (1999) 5.1 per 100 (95% CI:3.1-7.0) Se= 47% Sp=not given See table 2 in paper	Rome II and Rome (79% kappa 0.29) Rome II more restrictive. Results similar for other studies Mearin *et al*, Thompson *et al* Chey *et al* If different thresholds are used subjects identified are not the same. Manning identified less severe symptoms. Treatment would be no different using any criteria.
BDQ (Talley et al) Validated q'aire for	Bijkerk et al 2003, Netherlands	N= 99	All patients had diagnosis of IBS but only18% (n=14) met Rome II	

identifying IBS			GP diagnosis based on Bloating (87%) and absence of alarm features (87%) rather than diagnostic criteria. GP diagnosis correlated most closely with Manning. GP's reported tests to exclude organic disease in pts over 50.	

RESULTS OF THE REVIEW AND DISCUSSION

Of the 170 papers reviewed, 45 were excluded as no diagnostic criteria were used in the study population, or they were discussion/professional papers highlighting aspects of care relating to IBS, of which diagnosis was mentioned. Of the remaining 125 papers, 18 studies provided useful data which has been extracted and presented in Table 1. The remaining papers all provided useful background information on the use of diagnostic criteria; many studies used the reference criteria as a way of measuring prevalence and incidence of IBS in general populations. Literature was drawn from a wide international base, with Europe, North America and South East Asia providing the main source of data.

Issues to consider

From this extensive review of the literature, a number of key observations have emerged which the GDG will need to consider in moving towards consensus opinion as to how IBS is diagnosed; which criteria to use in diagnosing IBS and how this potentially will move clinicians away from an exclusion diagnostic approach towards positive diagnosis of IBS, management and patient follow-up. Of significance is the potential cost saving to the NHS of tests that are routinely requested but prove to be of little added value.

Diagnostic thresholds

Clinicians need to be able to determine whether a person has IBS (or not). Balance between missing the diagnosis and over diagnosing is a possibility because criteria may be too vague. Thresholds can be set across different parameters. These include:

- Severity of bowel symptoms
- Symptom count – either all symptoms given equal weight (e.g. Manning – 2 or more symptoms being given equal weight) or identified symptoms being considered as essential with others considered as accessory symptoms (Rome I)
- Duration threshold in combination with symptom count (Rome II) and symptom frequency appears to be highly relevant (Mearin 2003)
- Rome II requires the presence of both abdominal pain and changes in bowel habit and duration of symptoms (at least 12 weeks in last 12 months)
- Rome considers abdominal pain and changes in bowel habit independently and no minimum duration of symptoms
- Kruis developed according to symptoms and evaluation of lab tests
- Following a positive diagnosis of IBS based on clinical criteria clinicians can be reassured that the diagnosis is durable. (Adeniji 2004, follow-up of 196 patients with a diagnosis of IBS between 1989-92 35/86 pts had had further diagnostic investigations without diagnosis changing)
- Prevalence of IBS measured across a New Zealand population cohort (N=980) using 2 of the manning criteria emerged as 18.1%. This decreased to 10.3% if 3 or more of the

Manning criteria were used to identify an IBS diagnosis. This then fell to 3.3% when 4 or more of the criteria were used (Barbezat 2002).

A key question for the GDG was "Should a positive diagnostic approach include severity threshold or disabling threshold?"

What happens to patients who do not meet Rome II?

- How important is diagnostic precision for clinicians (this is a different priority for research)? Is the priority to exclude structural cause and/or red flags for symptoms?
- Would treatment be different if patients were diagnosed using Manning or Rome? Does this matter?
- Do they have alternative diagnosis (eg FBD) and/or go for lots of investigations and then turn out to be IBS?
- Manning: discriminates upper GI disease from IBS but not IBD (3 or more Manning criteria were frequent in patients with ulcerative colitis in remission (Isgar 1983).
- Kruis: was not able to discriminate IBS from organic GI Disease (Frigerio 1992).

Clinician ignorance of IBS diagnostic criteria

- An Italian study (Bellini 2005) of 28 generalist GPs – 17 judged knowledge of IBS to be insufficient but only three thought that further education might be useful. Ten GPs were familiar with Rome II prior to the study; 19 agreed with Rome II criteria when they used them as part of the study. They reported satisfactory management in approximately 60% of patients.
- Important symptoms for this group – Primary symptoms: changes in bowel habit, abdominal pain relieved by evacuation, bloating. Secondary symptoms: difficult or incomplete evacuation, passing mucous with BM.
- Following clinical evaluation GPs ordered further investigations in large numbers of patients. GPs with more than 20yrs experience requested less investigations than younger colleagues (p= 0.001). 168/229 patients had routine bloods, 30 – abdominal ultrasound, 87 FOB, 83 faecal analyses, 81 – Thyroid Function, 70 – lower GI endoscopy.
- All agreed that counselling, reassurance, information about natural course of condition and suggestions for coping strategies were first step in management. Patients with diarrhoea were prescribed wider ranging therapeutic interventions and perceived to be in more need of further investigations than those with constipation.
- In 145/229 cases referral to at least one specialist was made (GI specialist most common but gynaecological referral for 19% of women). Referral did not vary with clinical presentation and the most common reasons for referral were diagnostic confirmation, patient need for reassurance and patient request.

- Patients frequently attribute food intolerance (37%) and stress (43%) as the causes of IBS. GPs consider stress (71%), fibre deficiency (83%) and disturbed motility (62%) as most important factors (Bijkerk 2003).
- Helpful clues to aid diagnosis: symptoms chronic or recurrent; pain is variable in location and timing; D and C may alternate; onset sometimes follows GI tract infection; findings on physical examination are usually normal except for abdominal tenderness (Paterson 1999, Canadian IBS position statement).
- USA Primary Care practice based diagnostic evaluations differ significantly from speciality expert opinion based guidelines. Implementation of speciality guidelines in Primary Care would increase utilisation but with limited improvement of diagnostic outcomes (Yawn 2001).
- Patients under 50 yrs of age who meet Manning and have no red flags require no investigations (Paterson et al 1999 Canadian IBS position statement).
- Patient expectations: reassurance, counselling, pharmacotherapy, diagnostic tests and referral to specialist. Dietary interventions were considered less important. Most people with IBS in this study stated that improvement in worst symptom should be target of treatment. Global improvement and QoL were considered much less important as treatment goal.
- A British study in general practice (n=400) Gladman and Gorard (2003) Sent a questionnaire to a random selection of 200 GPs and 200 clinician members of British Society of Gastroenterologists asking about their knowledge of functional GI disorders and their knowledge and use of Manning and Rome criteria for diagnosis. 68/137 GPs believed functional GI disorders were psychosomatic compared to 36/167 of consultants (p=<0.001). Consultants believed that understanding had increased over last 20 years; 50%GPs believed it had not changed. Both believed diagnosis and management had not improved in past 20 years. Only 29/137 GPs had heard of Manning; 16/137 of Rome compared to 134/166 and 139/167 Consultants respectively (p=0.0001). Only 18 GPs used either Manning or Rome in practice and despite increased awareness only 40% consultants used one or other diagnostic criteria in their practice.

Many studies of IBS and developed guidelines to date have been produced by specialists who had seen patients with particularly severe or intractable symptoms. This clinical guideline was developed from a different starting point, with the essential focus being in primary care. All development and implementation must be framed with questions of applicability to General Practice.

The GDG noted that GPs consider Rome II too complicated and more suited for use in secondary care or for research purposes (Thompson 1997; Bellini 2005). The need for a pragmatic useful diagnostic tool was felt to be the most important aspect to the review. As the majority of IBS patients are treated by GPs, any recommendations for the use of diagnostic criteria should ensure that their ease of use by GPs in their practice is established, rather than

expecting GPs to use criteria that do not apply in the reality of day-to-day practice (Corsetti and Tack 2004).

What is the role of red flag symptoms alongside diagnostic criteria IBS diagnosis?

- The Manning criteria do not consider red flag symptoms. The addition of red flag symptoms seems to enhance diagnostic accuracy (Paterson 1999, Canadian IBS position statement). The GDG considered this aspect of the review at length, recognising the need for recommendations supporting the IBS algorithm to ensure that red flag symptoms take the patient out of this guideline and into other related NICE guidance.
- The addition of red flags to the Manning criteria increases the PPV of Manning and Rome I and II (Vanner 1999; Hammer 2004).
- Red flag symptoms – these seem to enhance original criteria and importantly relate this guidance to other relevant NICE guidelines, in particular NICE Clinical Guideline 27 'Suspected Cancer Referral' published in 2005.

Discussion

The need for clinicians to be guided in the diagnosis of IBS has emerged as a strong recurrent theme in this systematic narrative review. The seminal work of Manning laid a foundation to enable clinicians to be guided by such criteria in attempting to provide direct answers to patients presenting with a range of symptoms. This work has undoubtedly influenced the development of thinking within the Rome group, and the Rome criteria recently published as Rome III reflects the benefit of validation of the key aspects of the criteria and pragmatic decisions relating to the length of presenting symptom such as pain (6 months). The use of available diagnostic criteria summarised in this review (Table 1) have typically been augmented by further diagnostic investigations that have limited or no benefit and these add considerable costs to the NHS.

The use of consensus agreement regarding the recommendation of single diagnostic criteria serves three main purposes:

- Increased patient confidence through positive diagnosis
- Increased clinician confidence
- Potential for considerable NHS disinvestment in avoiding unnecessary investigations and referrals to multiple specialities.

When looking at combinations of possible criteria used in the available diagnostic tools reviewed, the emergence of Rome III has proven to be timely in relation to guideline development. It features strengths of previous diagnostic criteria, while minimising weaknesses of reviewed tools.

Key questions that emerge from the literature aim at identifying a gold standard or best reference tool. The challenge is that when thresholds differ, results are inconsistent. For

clinicians, diagnostic precision of IBS is often of low priority when compared to excluding other structural cause. This is a conceptual misinterpretation which can be explained as under-confident application of clinical examination and clinical history interpretation. Perhaps of significant note, regardless of which criteria were used in included studies in the review, treatment rarely differed against symptom profiles.

Over a decade ago, Jeong and colleagues having identified that Manning had reasonable specificity, called for better diagnostic criteria with improved accuracy to be developed. The road to Rome and the subsequent development of international consensus over the last 15 years has been useful in predetermining consistency in research application. It however, may have distracted from refinement of a tool that is easy and straightforward to use for primary care clinicians.

What clearly emerges from the literature is that with careful history and physical examination, positive diagnosis of IBS is possible. This, augmented by simple laboratory investigations to rule out more serious underlying pathology in the absence of red flag symptoms, would seem to be a step forward for both clinicians in diagnostic practice and patients in receiving timely interventions.

Perhaps it is fitting to highlight within this review that clinicians have been seeking to change the way that they think about diagnostic approaches in relation to this chronic syndrome. The Manning (1978) paper titled “Towards a positive diagnosis of Irritable Bowel Syndrome’ clearly indicates a diagnostic aim, this over the last three decades has been lost, with negative diagnosis by ruling out other conditions being the predominant clinician approach. Returning to the original aim of Manning and colleagues by seeking to influence the behaviour of primary care clinicians in the way that they think and approach diagnosis of people presenting with IBS symptoms is an important objective of this guideline.

GDG interpretation of the review and application of the guideline

General practitioner (GP) training has focussed on the importance of what happens within a typical patient consultation. This is usually recorded and analysed to enable new GPs to reflect on the detail within the consultation, in particular the quality of verbal and non-verbal behaviour, the sequencing of questions and information gathered to enable diagnosis. This is based around simulation and objective structured clinical examination methodology and has effectively enabled GP trainees to experience and develop understanding related to the importance of clinical history prior to physical examination. Using this approach, the NCC-NSC planned an interactive session for the GDG to fully engage with relevant issues. This was felt to be important in demonstrating that in guideline development, the GDG had explored the utility of different criteria that would then inform any consensus recommendations and lay the foundation for a positive implementation experience.

In order to test the utility of different criteria, NCC-NSC staff ran an interactive diagnostic simulation with members of the GDG. A number of typical IBS patient profiles were written by the technical team, which were then shared with four subgroups of the GDG. Details of the patient profiles are listed in Appendix 3 to this chapter.

Sub group constituency:

- Primary or secondary care doctor and/or
- Primary or secondary care nurse and/or
- Allied health professional (eg. Dietician or pharmacist) and/or
- Patient representation allocated to comment and input across the four groups.

One patient profile randomly selected from the total number of prepared patient profiles were randomly allocated to each of the GDG subgroups. Each group then had to discuss the use of allocated diagnostic criteria and elect one member of the group to role-play a GP consultation, responding to the simulated patient profile. Group A were asked to use Kruis Criteria; Group B were asked to use Manning criteria; Group C were asked to use Rome criteria;Group D were asked to use Rome II criteria.

Each group selected a physician to role-play the consultation, timed at a typical 8 minute general practitioner consultation. Two groups selected their GP member, with the other group selecting the GDG clinical lead who is a Gastroenterologist. Members of the NCC-NSC team role-played the four different patients. ROME III at the time of the patient simulation was unpublished, and therefore was unable to be used in this exercise. During each of the four role-plays, GDG members were asked to observe the consultation and record their observations. These typically related to the ease and logical progression of the consultation, shaped by the diagnostic criteria. This simulation enabled the GDG to both interpret the evidence and evaluate how easily the criterion reference based tool could work within a busy primary care environment.

The NCC-NSC technical team transcribed the detail within each of the GP consultations and recorded the information gathered from the patient using each of the three criteria referenced tools. The content was analysed and grouped in emerging themes (see Table 1) to enable the group to fully understand what was possible in recreating the primary care consultation. Typically patients are reticent to come and see a primary care clinician with issues relating to bowel habit/function, and this reticence was simulated with behaviours that demonstrated both hesitancy and embarrassment.

Observations were recorded from three main areas for feedback:

1. How the GDG clinician felt using the diagnostic criteria allocated to them.
2. How GDG members felt each of the diagnostic criteria worked in this simulated patient consultation.

3. How the NCC team member felt when role playing the IBS patient, in relation to the sequencing of ideas and extracting of important patient information, facilitating an effective diagnosis.

This was a powerful exercise in embedding the evidence review into a simulated patient-clinician exchange. The importance of ensuring that the guideline recommendations are able to be effectively implemented into routine primary care is clearly important in ensuring that current variations in diagnosing IBS are addressed.

Outcomes from the evidence review and diagnostic criteria simulated exercise were:

- A strong evidence base for the use of diagnostic criteria with good predictive value.
- Expert (GDG) evaluation of how potential tools could enable primary care clinicians to make a positive diagnosis of IBS, supported by a limited number of investigations that may augment an IBS positive diagnosis.
- Agreement of evidence based positive diagnostic criteria for use in primary care which reflects current evidence.
- A contemporised Manning criteria which are consistent with ROME III criteria.
- The decision to refer to agreed criteria as 'Positive Diagnostic Criteria'.

KRUIS (A SCORE OF >44 = IBS)

STRENGTHS	WEAKNESSES
VERY SPECIFIC	**NEEDS OTHER TESTS – TIME AND COST IMPLICATIONS**
	TOO MANY QUESTIONS
	SCORING CONFUSING
	COUNTER INTUITIVE – CLOSED QUESTIONS
	OMISSION – RELIEF OF PAIN BY DEFAECATION
	PATIENT NOT REASSURED – NO DIAGNOSIS
	NO WAY TO EXPLORE EXTRA COLONIC SYMPTOMS

MANNING (> 3 CRITERIA = IBS)

STRENGTHS	WEAKNESSES
SIMPLICITY	**VERY 'PAIN' FOCUSSED – NO MENTION OF DISCOMFORT**
CLEAR QUESTIONS	**NO RED FLAGS**
INSPIRED CONFIDENCE	**DOESN'T MENTION CONSTIPATION SPECIFICALLY**
EASIEST TO USE IN WORKING PRACTICE	**LANGUAGE OLD FASHIONED**
TIMESCALES	**OMISSION – FLATUS**
	NOT NATURAL FLOW
	? VALIDITY OF DIAGNOSIS FROM 2 SYMPTOMS

ROME I

STRENGTHS	WEAKNESSES
SIMILAR TO MANNING	**APPLICATION – TIME TAKEN**
ENABLED DIAGNOSIS	**COMPLEXITY**
	COUNTER INTUITIVE – CLOSED QUESTIONS

ROME II

STRENGTHS	WEAKNESSES
THOROUGH CONSULTATION	**APPLICATION – TIME TAKEN**
REASSURING FOR PATIENT	**COMPLEXITY**
	MISSED DIAGNOSIS
	DID NOT INFLUENCE FINAL DIAGNOSIS – USED CLINICAL JUDGEMENT
	COUNTER INTUITIVE – CLOSED QUESTIONS

GDG DISCUSSION

Following the simulated consultation, members of the GDG discussed the high importance of good communication in establishing the clinician-patient relationship. Typically, the evidence demonstrates that diagnostic tendency within primary care is for an exclusion diagnostic approach which is experienced as a negative diagnosis by people with IBS. This can be time consuming, sub-optimal and cost inefficient in relation to unnecessary investigations that are likely to add little or no benefit to predictive value, and can mean that patients are subject to inappropriate referrals to other specialities such as gynaecology. The GDG reflected the importance of language used in the first meeting between people with IBS symptoms and primary care clinicians, supporting the positive diagnostic approach of *'you have IBS'* as opposed to '*all investigations are negative and you have nothing else wrong with you, it must be*

IBS'. This exclusion diagnosis approach is widely reported as typical in the patient population, supported by both patient representatives on the GDG.

Themes emerging from the exercise and focussed GDG discussion

- IBS is a lifelong condition that needs to be managed effectively.
- Symptoms that are most crucial in diagnosis are pain/discomfort relieved by bowel movement, bloating (more common in women; men describe it as abdominal tension) and disordered bowel habit. It was noted that language in the Manning criteria needed to be contemporised; this was discussed and agreed, e.g. pain was contemporised to pain/discomfort.
- Pain/discomfort induced by eating is also common symptom.
- Extra-colonic symptoms were commonly reported in secondary care – with good discussion around their prevalence in primary care.
- The severity of the condition may or may not be useful as a threshold. Whilst high sensitivity maybe attractive, it is important not to miss patients by having too high an exclusion criteria, as reported in the evidence for Rome II, and supported by the simulated consultation feedback and analysis.
- IBS co-exists with other conditions. The possibility of missing inflammatory bowel disease initially would not be perceived by the GDG as problematic
- There is clear evidence supporting diagnostic criterion based reference tools, but their use in practical clinical settings has been reported to be difficult, this was noted by the group and it was felt that published criteria in this guideline should reflect the validated tools, but ordered in such a way that ensures that the tool is intuitive for clinicians to use. It should also facilitate the type of discussion that enables a full history to emerge.
- The individual patient story is very important, emphasising the need for the primary care clinician to focus on the most severe symptom while also establishing other related symptoms.

Published evidence from the diagnostic tools has shaped recent diagnostic approaches for IBS. Whorwell (2006) refers to this as a diagnostic triad, seen below:

- **Pain/discomfort – quality and quantity**
  Site of pain: in IBS it can be anywhere in the gut. If the site of pain varies it is unlikely to be cancer (tumour fixed). Need to distinguish this IBS pain discomfort from that caused by gall bladder disease. IBS patients do not tolerate abdominal surgery well.

- **Bowel habit – quality and quantity**
  Giving patients' descriptive examples (e.g. like porridge, rabbit pellets) and using the Bristol Stool Form Scale helps. Incomplete evacuation is reported, creating rectal hypersensitivity. Urgency is increased in Diarrhoea; prevalence for those incontinent is 20% (patients often do not disclose unless asked directly).

- **Bloating in women**
  (Absence of bloating in women = red flag) Less common in men, although they may report that the abdomen is tight/hard.

The diagnostic triad clearly reflects the valuable work published by Manning and the Rome group. It also highlights the importance of the extra-colonic features that maybe reported by people presenting with IBS symptoms, typically these include nausea, low back pain, bladder symptoms and thigh pain.

The GDG agreed that primary care clinicians should ask open questions to establish the multiple features of the syndrome, recognising that a potential conflict may exist within Primary Care in terms of the time available to the clinician in exploring the whole range of presenting symptoms.

Diagnostic certainty

In establishing the sensitivity and specificity of different diagnostic criteria by using a clinical reference standard (expert gastroenterologist diagnosis), looking at a pragmatic diagnostic reference tool appears to be of great value to the primary care clinician. The advent of ROME III during the development of this guideline was both timely and beneficial in shaping the and further strengthening the diagnostic criteria agreed within final recommendations. Of equal value, is the provision of clear economic evidence relating to supplementary diagnostic tests.

UTILITY OF TESTS TO EXCLUDE ALTERNATIVE DIAGNOSES

In order to determine the utility of diagnostic tests used to exclude alternative diagnoses in people meeting symptom based criteria for IBS, we needed evidence on the pre-test probability of organic GI disease in people meeting IBS diagnostic criteria and the accuracy of diagnostic tests in identifying organic GI disease. A published systematic review by Cash (2002) was identified which considered the utility of diagnostic tests by evaluating the evidence in these two areas. The selection criteria for the review were:

- Use of a cohort of IBS patients explicitly diagnosed via symptom based criteria (a priori).
- Performance of common diagnostic tests with either blinded comparison with gold standard.
- Results quantified as normal or abnormal with abnormal test resulting in alternative diagnosis of organic disease.

Six studies were included in the Cash (2002) systematic review and these were quality assessed using eight quality criteria (Hamm 1999; Tolliver 1994; Pimental 2000; Sanders 2001; Francis 1996; MacIntosh 1992). All were prospective cohorts of consecutive patients. All were in secondary care, except Hamm (1999) which did not state whether the participants were in primary or secondary care. The patients in Hamm (1999) were all enrolled in a treatment trial. One study had a control group of healthy volunteers (Sanders 2001). In addition to these six

studies our search identified two further studies which had been published since the systematic review and which met the inclusion criteria (Sanders 2003; Pimentel 2003). Each study used different criteria for recruiting patients. These are summarised as follows:

- Referral for abdominal pain not previously evaluated (Tolliver 1994)
- Diagnosis of IBS made at first attendance and evaluated within 6 months (Francis 1996)
- Enrolment in treatment trial i.e. not all recent diagnosis (Hamm 1999)
- Referral for altered bowel habit or requesting investigation to reassure following clinical diagnosis of IBS (Sanders 2001)
- Referral for breath testing (Pimentel 2000)
- All patients attending gastroenterology practice (MacIntosh 1992)
- Primary care attendees, including people entering GP surgery for any reason (Sanders 2003)
- Advertisement within community and IBS support groups (Pimentel 2003).

The study characteristics and results are summarised in Tables 3 to 10 below for each class of diagnostic test. The number of abnormal test results is reported alongside the alternative diagnoses resulting from these tests. Where the tests were not given to the whole study cohort this has been noted. For lactose intolerance and bacterial overgrowth we have noted in Table 4 10 whether the diagnosis was confirmed by an improvement in symptoms following treatment, as an abnormal hydrogen breath test result does not provide a definitive diagnosis of either condition.

Table 2 is reproduced from Cash (2002) and summarises the evidence on the pre-test probability of organic GI disease from the 6 studies included in the systematic review. This is compared to general population data presented by Cash (2002), although it was not clear how the general population sample was defined. In addition to the data presented by Cash, Sanders (2003) reported a general population prevalence of 1% for coeliac disease in people recruited from a UK primary care setting and a prevalence of 3.3% in people meeting IBS diagnostic criteria.

Table 2: Pre-test probability of organic GI disease in people meeting symptom based criteria for IBS and in the general population

Organic GI disease	IBS patients (%)	General population (%)
Colitis/IBD	0.51-0.98	0.3-1.2
Colorectal cancer	0 – 0.51	4-6
Celiac disease	4.67	0.25-0.5
Gastrointestinal infection	0-1.7	N/A
Thyroid dysfunction	6	5-9
Lactose malabsorption	22-26	25

The evidence on the clinical utility of tests for alternative diagnoses in patients meeting IBS diagnostic criteria can be summarised as follows:

- The pre-test probability of organic disorders, including colon cancer, inflammatory bowel disease, thyroid disease and lactose malabsorption was no different in IBS populations when compared to the general population.
- One exception was coeliac disease which did appear to higher incidence amongst the IBS population.
- In the IBS population, common investigations including endoscopy of the colon, ultrasound, stool ova and parasite testing, faecal occult blood, thyroid function testing and hydrogen breath testing for lactose intolerance and bacterial overgrowth were unlikely to lead to the diagnosis of organic disease. Rectal biopsy was also demonstrated to be ineffective.

“It is amazing to see the expensive, dangerous and extensive workups to which healthy patients are subjected by physicians searching for an organic cause in patients who obviously suffer from IBS.” Jeong et al (1993). Repeated testing can also undermine patient confidence in a positive IBS diagnosis.

Table 3: Colonic evaluation

Study	Population tested	Tests used	Gold standard	Abnormal tests	Alternative diagnosis
Hamm (1999)	Rome criteria met for at least 6 months, and no colonic endoscopic exam in previous 2 years. i.e. not all recent diagnosis	Age <50: Flexible sigmoidoscopy Age >50: Colonoscopy or flexible sigmoidoscopy plus barium enema	None	7/306 (2%) 1146 patients not tested	3 IBD 1 colonic obstruction 3 colonic polyps without malignancy
Tolliver (1994)	International Congress of Gastroenterology Symptom Criteria for IBS. Referred to secondary care without prior diagnosis	Air contrast barium enema, flexible sigmoidoscopy and / or colonoscopy.	None	43 abnormalities in 23 patients (all 196 tested)	2 which could be cause of IBS symptoms 1 IBD 1 cancer
MacIntosh (1992)	IBS patients referred to secondary care, (89% fulfilled Manning 3 or more and 84% fulfilled Rome criteria)	Sigmoidoscopy, colonoscopy, phosphate enema, rectal biopsy	None	0/89 (all patients tested)	None
Francis (1996)	Patients evaluated within 6 months of diagnosis, met Rome criteria and normal stool exam, haematological and biochemical indices including ESR.	Sigmoidoscopy in all, plus barium enema or colonoscopy in over 45 year olds.	None	0/125 (all patients tested)	None except diverticular disease

Table 4: Lactose intolerance

Study	Population tested	Tests used	Gold standard	Abnormal tests	Alternative diagnosis
Hamm (1999)	Rome criteria met for at least 6 months. Not all recent diagnosis	Hydrogen breath test	None – ideally should report response to lactose restricted diet	23% of 1122 patients 330 not tested	Unconfirmed lactose intolerance as no response to treatment recorded
Tolliver (1994)	International Congress of Gastroenterology Symptom Criteria for IBS. Referred to secondary care without prior diagnosis	Hydrogen breath test	3 year follow-up to assess symptoms	48/186 (10 not tested, doesn't state why)	Possible lactose malabsorption but no difference in symptoms at 3 years compared to those without diagnosis

Table 5: Thyroid function

Study	Population tested	Tests used	Gold standard	Abnormal tests	Alternative diagnosis
Hamm (1999)	Rome criteria met for at least 6 months and without test in previous 12 months. Not all recent diagnosis	TSH and thyroxine	None – ideally should report resolution of symptoms following treatment	67/1209 (6%) 3% hypo and 3% hyper	Hypo or hyperthyroidism
Tolliver (1994)	International Congress of Gastroenterology Symptom Criteria for IBS. Referred to secondary care without prior diagnosis	T3 T4 TSH	None – ideally should report resolution of symptoms following treatment	1/171, author states this provided no useful clinical information 25 not tested	Not clear

Table 6: Stool tests

Study	**Population tested**	**Tests used**	**Gold standard**	**Abnormal tests**	**Alternative diagnosis**
Hamm (1999)	Rome criteria met for at least 6 months and without test in previous 3 months. Not all recent diagnosis	Faecal ova and parasite test	None – ideally should report resolution of symptoms following treatment	19/1154 (2%) 298 not tested	Enteric infection of unconfirmed clinical significance
Tolliver (1994)	International Congress of Gastroenterology Symptom Criteria for IBS. Referred to secondary care without prior diagnosis	Occult blood and parasites	Occult blood - structural evaluation Parasites – none, should report resolution of symptoms following treatment	Occult blood 15/183 (13 not tested) Parasites 0 /170 (26 not tested)	1 Hemorrhoids, 2 annal fissures, 1 melanosis coli

Table 7: Other laboratory tests

Study	Population tested	Tests used	Gold standard	Abnormal tests	Alternative diagnosis
Tolliver (1994)	International Congress of Gastroenterology Symptom Criteria for IBS. Referred to secondary care without prior diagnosis	FBC, HgB, ESR, Chemistry panel, urine analysis	None	FBCand HgB; 0/196 Chemistry: 2/196 Urine: 4/157 (39 not tested_	No useful clinical information
Sanders (2001)	Rome II without "sinister symptoms" of weight loss, rectal bleeding, nocturnal diarrhoea or anaemia (2ndary care)	FBC, ESR, blood urea nitrogen, serum electrolyte conc, thyroid function, CRP, blood glucose.		CRP: 2/300 ESR: 1/300 Liver function: 2/300 Anaemia: 1/300 All patients tested	3 IBD (abnormal CRP / ESR) 2 excess alcohol (IBS symptom response to reduced intake not reported) Anaemia was secondary to coeliac disease

Table 8: Coeliac screening

Study	Population tested	Tests used	Gold standard	Abnormal tests	Alternative diagnosis
Sanders (2001)	Rome II without "sinister symptoms" of weight loss, rectal bleeding, nocturnal diarrhoea or anaemia (2ndary care)	IgA and IgG antiglandin, endomysial antibody	Duodenal biopsy	66/300 All patients tested	14 Coeliac disease confirmed by biopsy, 1 positive serology but refused biopsy Response to diet not reported
Sanders (2003)	Primary care cross-sectional study, IBS diagnosis from Rom II (subgroup of whole cross-sectional cohort)	IgG/IgA antiglandin and EMA	Small bowel biopsy, and follow-up after diet	Positive tests not reported for IBS subgroup All patients tested	4/123 IBS patients had coeliac disease, all responded to diet

Table 9: Ultrasound

Study	Population tested	Tests used	Gold standard	Abnormal tests	Alternative diagnosis
Francis (1996)	Patients evaluated within 6 months of diagnosis, met Rome criteria and normal stool exam, haematological and biochemical indices including ESR.	Ultrasound of abdomen and pelvis	None	22/125 (18%) All patients tested	No change to IBS diagnosis

Table 10: Bacterial overgrowth

Study	Population tested	Tests used	Gold standard	Abnormal tests	Alternative diagnosis
Pimentel (2000)	Referred for lactulose hydrogen breath test Rome I criteria. Excluded if evidence of rapid transit	Hydrogen breath test	Reported symptom resolution and repeat test result but only in minority of treated patients	157 of 202 (78%)	Only 47 had repeat test to confirm response to therapy 25 achieved eradiation and 45% of these no longer met Rome criteria
Pimentel (2003)	Community and IBS support group advertisement, Rome criteria	Hydrogen breath test	Reported symptom response and repeat test results	84% of 111 had positive first test	20% of those with positive test and antibiotic treatment achieved normal second test, symptom improvement associated with treatment and normal second test

ECONOMIC EVIDENCE ON DIAGNOSTIC TESTS TO IDENTIFY ALTERNATIVE DIAGNOSES

Of the four included studies, two consider the cost-effectiveness of screening for coeliac disease in the IBS population, one considers the cost-effectiveness of endoscopy in the IBS population and one considers the cost-effectiveness of diagnostic strategies for IBD in patients who do not meet the Rome criteria for IBS. The characteristics of the included studies are given in Appendix C. All four were model based economic evaluations with two considering the short-term diagnostic period (Suleiman 2001; Dubinsky 2002) and two considering patient outcomes over longer time-frames of 10 years or more (Spiegel 2004; Mein 2004). The quality of each study has been critically appraised using a validated check-list for economic analyses and details are provided in Appendix D. Due to variation in the interventions and populations considered, each study will be discussed separately.

Mein (2004)

The primary aim of this study was to assess the cost-effectiveness of coeliac disease testing in patients with suspected irritable bowel syndrome in the US health care system. This was done by using a decision tree to estimate the number of coeliac disease cases detected, QALYs gained and costs resulting from three testing strategies and comparing these to no testing. The three strategies were; tissue transglutaminase antibody (TTG), antibody panel, or upfront endoscopy with biopsy. All positive serological tests were followed by endoscopy with small bowel biopsy and the potential complications of this procedure were accounted for. All positive upfront endoscopies were assumed to be confirmed by an antibody panel. Long-term treatment costs were assumed similar between patients with IBS and those diagnosed with coeliac disease. The increase in health-related quality of life associated with correctly diagnosing coeliac disease in patients with suspected IBS and initiating a gluten-free diet was estimated indirectly by comparing utility estimates for treated and untreated coeliac disease and IBS measured in different populations. This is less reliable than direct utility measurement as it combines estimates from different populations. However, the uncertainty surrounding this parameter has been adequately examined in a sensitivity analysis. The authors stated that they used conservative assumptions to deliberately bias the model against testing for coeliac disease. These included assuming no reduction in resource use or increase in life-expectancy following correct diagnosis of coeliac disease and initiation of treatment. The base case prevalence for coeliac disease in patients with suspected IBS was 3% and was varied from 1 to 5% in a sensitivity analysis.

The probabilistic model estimated that testing with TTG would detect 28 out of 30 cases present in a population of 1000 individuals but testing with a full antibody panel would only detect one further case. The median incremental cost per case detected was $6,700 (interquartile range $4,800 - $9,700) for TTG vs no testing and $12,300 ($8,900 - $17,700) for antibody panel vs no testing. The incremental cost per case detected for antibody panel vs TTG was $167,000

($110,000 - $279,000). The incremental cost per QALY was $11,200 ($7,200 - $17,900) for TTG vs no testing and $20,900 ($13,500 – $34,300) for antibody panel vs no testing. The incremental cost per QALY for antibody panel vs TTG was $287,000 ($99,400 - $675,000). The upfront biopsy strategy resulted in a lower QALY gain and higher costs than TTG testing and was therefore dominated by TTG testing. In the one-way deterministic sensitivity analysis, reducing the prevalence to 1% increased the cost per QALY of TTG vs no testing from $7,400 to $19,900 and decreasing the utility gain associated with treatment from 0.024 to 0.01 increased the cost per QALY to $17,900. This demonstrates that whilst the cost-effectiveness results are sensitive to changes in these parameters, the TTG testing strategy is still cost-effective compared to no testing at the thresholds considered ($50,000 to $100,000 per QALY).

This study provided evidence that TTG testing followed by confirmatory endoscopy with biopsy would be cost-effective in patients with suspected IBS in the US health-care system. We converted the cost per QALY directly from 2003 US$ to 2006 UK£ using Health Care Purchasing Power Parity rates (2003 PPP rates UK/US = 2317/5711, OECD 2006) and Hospital and Community Health Services Pay and Pricing Index (2006/2003 = 241.3/224.8 (Netten 2006) and this gave a cost per QALY for TTG vs no testing of £4,900. This is a crude estimate as it assumes that each component of the total cost has an equal weighting in both counties, which may not be true due to differences in the health care systems between the US and UK. However, the relatively low value of this estimate compared to typical UK thresholds of £20,000 to £30,000 per QALY, suggests that this intervention may also be cost-effective from a UK NHS and PSS perspective.

Spiegel (2004)

This aim of this study was to assess the cost-effectiveness of screening for coeliac disease in patients fulfilling the Rome II criteria for diarrhoea predominant IBS (IBS-D) in the US health care system. A strategy of screening for coeliac disease using serological tests followed by confirmatory endoscopy with biopsy was compared with a strategy of initiating IBS therapy without screening for coeliac disease. This was done using a decision tree to estimate the number of patients receiving appropriate therapy for either IBS or coeliac disease, the number of missed coeliac disease diagnoses and the number of patients for whom IBS treatment was delayed due to coeliac disease testing. It was assumed that 1 in 4 clinicians eventually test for coeliac disease in patients who do not respond to empiric IBS treatment, resulting in an average diagnostic delay of 6 months. A Markov model was then used to estimate transitions between states of symptomatic improvement and remission once patients have begun treatment for either IBS or coeliac disease. The analysis was based on a generic serological test using data which reflected the range of serological tests available (anti-EMA and anti-TTG IgA antibodies). The results are presented in terms of the cost per additional patient with symptomatic improvement after 10 years. The authors state that the model was deliberately biased in favour of IBS treatment without testing for coeliac disease in order to place the burden of proof for cost-

effectiveness on coeliac testing. This was done by using estimates from the unfavourable end of the range presented in the literature for the following parameters; coeliac disease prevalence, sensitivity and specificity of tests for coeliac disease, rate of coeliac disease testing in patients not responding to empiric IBS therapy, IBS treatment effectiveness and cost. For example, IBS treatment was assumed to be effective in 75% of patients based on the effectiveness of alosetron but the cost of therapy was assumed to be $45 per month which is similar to the cost of loperamide. The model also assumed that 30% of the population with coeliac disease had "latent" or "potential" coeliac disease which would not be detected by small bowel biopsy but would have the potential to benefit from a gluten free diet. It also assumed that 5% of the population with coeliac disease would have concurrent IgA deficiency which would render serological screening for IgA antibodies ineffective. These assumptions were based on limited data but were included to bias the model against testing for coeliac disease and their impact was explored through sensitivity analyses.

The deterministic base case model estimated that testing for coeliac disease resulted in 51.6% of the cohort achieving symptomatic improvement at 10 years, whilst initiating IBS therapy without testing for coeliac disease resulted in 50.9% of the population achieving symptomatic improvement. The incremental cost was $77 per patient resulting in a cost per additional symptomatic improvement after 10 years of $11,000. The probabilistic model resulted in a median cost per symptomatic improvement of $12,983 (95% CI: Dominating to $41,031). The results were sensitive to the prevalence of coeliac disease in the population considered. The cost-effectiveness ratio was under $50,000 when the prevalence was >1% and screening dominated no screening (resulted in more health gain at reduced cost) when the prevalence was over 8%.

These results were difficult to interpret as they were presented for the US health care system and did not provide benefits measured in QALYs. The aim of a Markov model is usually to determine the proportion of time a patient spends in each health state over the duration of the model and to use this to estimate their aggregate health gain over the time-horizon considered. This analysis did not present results in terms of the time spent in the symptom remission state, but instead presented the results in terms of the number of patients in this state at the end of the model, which may not accurately reflect the amount of health benefit accrued over the duration of the model. It was therefore less useful in determining whether testing for coeliac disease is cost-effective compared to no testing than the evidence provided by Mein (2004).

Dubinsky (2002)

This study examined the cost-effectiveness of initial serodiagnostic screening followed by standard invasive testing, compared to standard testing alone in patients presenting with symptoms suggestive of IBD from a third-party payer perspective in the US health care system. The authors state that the population considered by this analysis was patients presenting with

symptoms which did not meet the Rome I criteria for IBS. As the aim of this review is to consider the cost-effectiveness of testing for alternative diagnoses in patients meeting the diagnostic criteria for IBS, following the application of a criterion based reference tool, this study was not directly relevant to the target population. We would expect the patient population meeting the diagnostic criterion for IBS to have a lower prevalence of IBD. As the analysis considered a wide range of prevalence values (5% to 75%) in a sensitivity analysis, the results for the lower end of this prevalence range were considered to have some relevance to the target population.

The decision analytic model considered six alternative diagnostic strategies. Two levels of serodiagnostic screening were evaluated. In the primary screening strategy (PR 1) patients received a primary assay followed by a gold standard invasive diagnostic test if the primary screen was positive or if a negative primary screen was followed by persistent symptoms. In the sequential screening strategy (SS 1) a positive primary assay was followed by a confirmatory assay and if this was positive it was followed by a gold standard test. Negative results followed by persistent symptoms were investigated using the gold standard test as in the primary screen. These were compared to gold standard testing upfront (GS 1) which consisted of colonoscopy with biopsies and histological examination as well as a barium upper GI series and small bowel follow-through. Three additional strategies were also considered in which the first three strategies were extended to include a second gold standard test in patients with persistent symptoms following the first gold standard test (PS 2, SS 2 and GS 2). The proportion of patients returning with persistent symptoms due to IBS not meeting the Rome I criteria or other causes of symptoms was assumed to be 50% based on expert opinion and varied from 0 to 100% in a sensitivity analysis. A decision tree model was used to estimate the accuracy and cost of each of the six strategies. No costs or health benefits following diagnosis were estimated. An incremental cost-effectiveness analysis was also presented which compared the relative cost-effectiveness of the six competing strategies.

In the basecase model all of the serodiagnostic strategies had lower costs and higher diagnostic accuracy than the gold standard strategies. The SS 1 strategy had the lowest cost and a diagnostic accuracy of 96.95%. The SS 2 strategy cost $20.30 more per patient but had a slightly higher diagnostic accuracy of 97.90% resulting in a cost per % increase in accuracy of $2,137. The SS 1 strategy dominated all other strategies by having higher accuracy and lower cost and also resulted in the lowest number of invasive procedures out of all six strategies (610 for SS 1 vs 1000 for GS 1 and 1010 for GS 2). In the cost sensitivity analysis, standard invasive testing was more cost-effective when the costs of testing were varied outside of the plausible range considered by the sensitivity analysis.

Standard invasive testing was more cost-effective when the prevalence of IBD was varied to >76%, or when the proportion of patients with persistent symptoms was varied to over 89%.

These results suggest that serodiagnostic screening for IBD in patients with “atypical” IBS symptoms would be less costly and more effective than immediate gold standard invasive testing. These results are based on cost data from the US and the conclusions may be different in a UK analysis if the relative costs of invasive and non-invasive testing are significantly different. Whilst these results apply to patients with “atypical” IBS who do not meet the Rome I criteria, the sensitivity analyses carried out demonstrate that they will apply equally to groups with lower prevalence rates of IBD, provided that less than 89% of patients are given the gold standard test after returning with persistent symptoms following a negative serodiagnostic test. This study does not address whether further testing in patients returning with persistent symptoms is beneficial but assumes that this occurs in practice regardless. This number may be higher or lower in the group meeting the diagnostic criteria for IBS depending on the confidence placed on the positive diagnosis. This study did not address whether these strategies for diagnosing IBD are cost-effective compared to a strategy of initiating IBS treatment, following a positive IBS diagnosis, without excluding IBD. It therefore did not demonstrate the cost-effectiveness of serological testing for IBD in patients meeting diagnostic criteria for IBS.

Suleiman (2001)

The aim of this study was to assess the incremental cost-effectiveness of endoscopic procedures in the work-up for IBS. It did not consider the incremental cost-effectiveness of a specific test for an alternative diagnosis in patients with IBS, but considered the increase in diagnostic probability achieved by using various sequences of tests to exclude alternative diagnoses. These tests included; hydrogen breath test to exclude lactase deficiency or bacterial overgrowth, flexible sigmoidoscopy and colonoscopy to exclude inflammatory colitis, diverticular disease and colon cancer, and small bowel follow-through to exclude small bowel cancer. A decision tree was used to estimate the probability of IBS in the remaining population following each diagnostic test. Various sequences of tests were considered but each began with a clinical history, physical examination and laboratory tests. The costs of further testing following false positive tests and the costs and health impact of delayed diagnosis of IBS or alternative diagnoses were not considered. The authors presented incremental cost-effectiveness ratios (ICERs) for flexible sigmoidoscopy and colonoscopy in terms of the incremental cost per 1% increase in IBS probability, but these figures considered the cost in the individual and did not take into account the number of patients who would be tested at each stage of the diagnostic sequence. The authors also presented average cost-effectiveness ratios, “ACERs” which gave the cost of the whole diagnostic sequence in a cohort of patients divided by the number of correct diagnoses.

The model demonstrated that lower ACERs are achieved by using flexible sigmoidoscopy after rather than before hydrogen breath testing and small bowel follow-through. The same was found for colonoscopy in the absence of a previous flexible sigmoidoscopy. The results demonstrated that carrying out colonoscopoy without flexible sigmoidoscopy at the end of the diagnostic

sequence would result in a lower ACER than carrying out colonosocopy following flexible sigmoidoscopy at the end of the diagnostic sequence.

The relevance of these results to this review was limited as the study did not consider the incremental cost-effectiveness of testing for a specific alternative diagnosis in patients meeting IBS diagnostic criterion. However, it did demonstrate that the cost of diagnostic testing can be reduced by using more costly interventions at the end of a diagnostic sequence without changing the number of correct diagnoses. The clinical outcomes did not vary when the ordering of tests was varied due to the assumption that each test is independent of the next. In practice this may not be strictly true and there may be some dependence resulting in slightly different clinical outcomes depending on the test sequencing. However, it is still likely that lower costs would be achieved in practice by using more costly invasive investigations at the end of the diagnostic sequence as this would reduce the number of people who require these invasive tests. This would also minimise adverse health outcomes due to complications.

Summary

There was some relevant published literature concerning the cost-effectiveness of screening for coeliac disease in patients with suspected IBS. The study by Mein (2004) provided a cost per QALY for coeliac testing vs no testing from a US perspective. Whilst this could not be applied directly to the population under consideration, due to differences in the health care systems between the US and the UK, the low cost per QALY suggested that this intervention may also be cost-effective from a NHS and PSS perspective. The studies by Dubinsky (2002) and Suleiman (2001) did not consider directly whether further diagnostic testing would be cost-effective in patients meeting diagnostic criteria for IBS compared to no further diagnostic testing. They did provide some evidence that where diagnostic testing does take place, it is cost-effective to use less costly and less invasive tests first in the diagnostic sequence with positive results confirmed by standard invasive testing compared to invasive testing early in the diagnostic sequence.

Having considered the evidence on the clinical utility of diagnostic tests in patients meeting IBS diagnostic criteria, the GDG decided that there was insufficient evidence of clinical utility to warrant further economic analysis on the cost-effectiveness of diagnostic testing, except for serological testing for coeliac disease. It was not considered necessary to carry out further economic analysis to estimate the cost-effectiveness of routine laboratory investigations, such as FBC, ESR and CRP. They are unlikely to result in a significant cost burden for the NHS and it would be difficult to estimate their cost-effectiveness due to their non-specific nature which means that an abnormal result may be due to a variety of causes. Therefore, further economic modelling focused on the cost-effectiveness of serological testing for coeliac disease.

Cost-effectiveness of screening for coeliac disease in patients meeting IBS diagnostic criteria – adaptation of a published economic evaluation

Further analysis was carried out to adapt the cost-effectiveness estimate provided by Mein (2004) to make it more applicable to the NHS in England and Wales. UK specific data was obtained for the prevalence of undiagnosed coeliac disease, diagnosis costs, and HRQoL and ongoing resource use for individuals with IBS. A discounting rate of 3.5% was applied to both costs and QALYs in line with the NICE reference case for cost-effectiveness analysis (NICE 2007). Mein (2004) did not consider the additional cost of gluten-free foods in their analysis, but as gluten-free foods can be prescribed through the NHS this cost was also considered in our analysis. Mein (2004) did not allow for any increased life-expectancy that may result from adherence to a gluten-free diet in patients diagnosed with coeliac disease. This was considered to be overly conservative as one of the main aims of adherence to a gluten-free diet in coeliac disease is to reduce the risk of malignant diseases associated with coeliac disease such as Non-Hodgkin Lymphoma (West 2004). The model was therefore adapted to include an estimated survival difference between patients with diagnosed and undiagnosed coeliac disease. The economic model reported by Mein (2004) compared serological testing for IgA tissue transglutaminase (TTG) antibodies against a strategy of no testing. However IgA EMA testing is more commonly used in the UK than IgA TTG so this was used in the UK adaptation and TTG was considered in a sensitivity analysis.

The prevalence of undiagnosed coeliac disease in patients meeting IBS diagnostic criteria was taken from a cross-sectional study conducted in a UK primary care setting (Saunders 2003). The study population was randomly sampled from all adults entering the GP premises on study days. A subgroup of individuals meeting the ROME II diagnostic criteria for IBS was identified. The prevalence of undiagnosed coeliac disease was 3.3% (4/123) in individuals who fulfilled the ROME II criteria for IBS. This estimate was used in the model as the prevalence of undiagnosed coeliac disease in patients meeting IBS diagnostic criteria. The prevalence from the primary care sample as a whole (1%) was used in a sensitivity analysis as the expected lower limit for the prevalence in the IBS population.

Sensitivity and specificity values for IgA EMA were taken from a published health technology assessment which included a systematic review of autoantibody testing in children with type I diabetes (Dretzke 2004). This systematic review included studies carried out in symptomatic populations or populations at a higher risk of developing coeliac disease but not exclusively type I diabetes. The sensitivity and specificity estimates used in the model were the Q values (overall best test performance with equal sensitivity and specificity) from the well-described studies as given in Table 17 of Dretzke (2004).

The NHS cost of an IgA EMA antibody test was also taken from Dretzke (2004). The cost of esophagogastroduodenoscopy (EGD) with biopsy to confirm coeliac disease was taken from the

NHS references costs (2005-06) for day case endoscopic procedures on the stomach or duodenum (Department of Health 2006). The cost for an EGD with complications was assumed to be equal to the NHS reference cost for the same procedure as a non-elective in patient (average length of stay of 1 day). The cost of care for IBS was taken from a study by Akehurst (2002) which estimated the NHS costs for IBS patients and matched controls. As in the cost-effectiveness analysis by Mein (2004), it was assumed that the NHS costs of managing coeliac disease are equal to the costs of managing IBS except that there is the additional cost of gluten free foods on prescriptions. This may be an overestimate if IBS-like symptoms are reduced when patients with coeliac disease are established on a gluten-free diet.

The NHS cost of supporting a gluten-free diet by providing foods on prescription was calculated by estimating the total cost of gluten-free foods prescribed by the NHS in England in 2005 (£21.2million) from the Prescription Cost Analysis (NHS Health and Social Care Information Centre 2006) and the number of people diagnosed with coeliac disease based on a population for England of 50.4million and a prevalence for diagnosed coeliac disease of 0.26%.(Fowell 2006). This gave an annual cost of £162 per diagnosed case of coeliac disease.

The health utility of IBS was taken from the study by Akehurst (2002) which estimated health utility for IBS patients using the EQ-5D. Mein (2004) attempted to estimate the utility gain associated with diagnosing coeliac disease in patients with IBS-like symptoms. However, this estimate was considered to be unreliable as it was calculated by comparing utility values for health states estimated in different populations. No direct evidence was available on the utility gain achieved by diagnosing and treating coeliac disease in patients with IBS-like symptoms. O'Leary (2002) found that coeliac patients with IBS-like symptoms had a lower HRQoL than those without symptoms, but these symptoms were equally common in coeliac patients who did and didn't adhere to a gluten-free diet. Casellas (2005) found that recently diagnosed patients who had not started a gluten-free diet had a lower quality of life and a higher prevalence of IBS-like symptoms compared to patients who had been established on a gluten-free diet, but the study design was cross-sectional, so it was not possible to say from this whether the diet itself provided an improvement in quality of life. In the basecase analysis it was assumed that the gluten-free diet did not provide any gain in health utility, so the only benefit was from improved survival. A threshold analysis was carried out to assess the size of health utility gain that would need to be achieved by adherence to a gluten-free diet, in order to give a cost per QALY under £20,000, when assuming that the gluten-free diet does not provide a survival gain.

There is evidence that patients with coeliac disease have a significantly higher than expected mortality (SMR = 2.0, $p<0.0001$) (Corrao 2001) and that mortality risk is significantly increased for patients with a diagnostic delay of over 12 months but is not significantly increased when it is less than this. Mortality is also significantly higher than expected (SMR 2.5, $p<0.0001$) in patients with severe symptoms of malabsorption such as diarrhoea or weight loss but not

significantly increased in patients with milder symptoms which may be seemingly unrelated to coeliac disease. There is evidence that survival is significantly reduced in the first 3 years after diagnosis but not beyond. The timing of the observed excess mortality may be due to excess deaths in patients who had extended diagnostic delay and who were not diagnosed until after symptoms had become severe. It may be possible to prevent the excess mortality in patients with IBS–like symptoms by prompt diagnosis through serological screening. In order to estimate the survival gain associated with prompt diagnosis we have assumed that undiagnosed cases have a reduced survival compared to diagnosed cases. We have taken the survival ratio for coeliac patients compared to the general public and used this to estimate the reduction in mortality avoided by prompt diagnosis. This is equivalent to a relative reduction in cumulative survival of around 2% over the first 3 years of the model for patients with coeliac disease presenting with IBS-like symptoms whose coeliac disease remains undiagnosed. This may have underestimated the survival gain associated with diagnostic testing, as the SMR in the whole coeliac population is lower than in those patients with extended diagnostic delay, but it may also have overestimated the survival gain as prompt diagnosis may not result in a complete reduction of mortality to general population levels. These survival ratios were applied to UK life-tables (Office for National Statistics 2006), assuming a male to female ratio of 1:2, and gave an estimated difference in expected life-years of 1.4 LYs for patients with diagnosed and undiagnosed coeliac disease. Once discounting was applied to the expected survival this difference was reduced to 0.54 discounted LYs. A sensitivity analysis was also carried out using the upper 95% CI of the survival ratio which resulted in a lower estimated survival gain of 0.31 discounted LYs.

The parameter values used in the UK adaptation are summarised in Table 11 alongside those used by Mein (2004) in the US basecase. Univariate sensitivity analysis was used to determine whether the deterministic estimate of cost-effectiveness was sensitive to changes in the UK specific parameters. This included a threshold analysis on the utility gain associated with establishing a gluten-free diet and the cost of prescribing gluten-free foods on the NHS. The parameter values used in the sensitivity analysis are also given in Table 11. All costs were uplifted to 2005/06 values where applicable and the uplifted values are included in Table 11 in italics.

Table 11: Parameters used in Mein (2004) analysis and in the UK adaptation

Parameter	Mein (2004) basecase, (range)	UK basecase	UK range for sensitivity analysis
Age	35 (20-60)	35	20-60
Life-expectancy (IBS or diagnosed coeliac disease)	42.8LYs	45.7LYs	N/A
Prevalence of coeliac disease	3% (1-5%)	3.3%, Saunders (2003)	1%, general population prevalence, Saunders (2003)
IBS utility	0.689 (0.6-0.9)	0.675, Akehurst (2002)	0.636, lower CI from Akehurst (2002)
Utility gain resulting from correct diagnosis of coeliac disease	0.024 (0.01-0.04)	None (conservative)	Threshold analysis at £20,000 per QALY assuming no survival gain
Sensitivity of antibody test	94% (87-97%) IgA TTG	98% IgA EMA, Dretzke (2004)	92%, lower 95% CI, Dretzke (2004)
Specificity of antibody test	95% (87-98%) IgA TTG	98% IgA EMA, Dretzke (2004)	92%, lower 95%CI, Dretzke (2004)
Probability of EGD biopsy complication	0.2% (0.05 – 0.5%)	As for US model	N/A
Probability of death if complication	5% (2-10%)	As for US model	N/A
Cost of IBS care and coeliac care excluding GFD	$450 ($225-$675) *(£196)**	£123, Akehurst (2002) *(£172)**	£221, upper 95%CI, Akehurst (2002) *(£307)**
Cost of antibody test	$68 ($22-$136) IgA TTG *(£30)***	£10 IgA EMA, Dretzke (2004) *(£12)**	£11, upper 95% CI, Dretzke (2004) *(£14)**
Cost EGD with biopsy	$800 ($300-$1800) *(£348)***	£463, Department of Health (2006)	£767 upper limit, Department of Health (2006)
Cost of EGD with complication	$5,700 ($2850-$11400), *(£2482)***	£597, Department of Health (2006)	£1010 upper limit, Department of Health (2006)
Discount rate for costs and QALYs	3%	3.5%, NICE (2007)	0% (undiscounted)
Survival difference between diagnosed and undiagnosed	N/A	0.54 (discounted) Calculated using lifetables and survival ratio from Corrao (2001)	0.31 (discounted) Using upper limit of survival ratio from Corrao (2001)
Cost per annum of gluten-free foods on prescription	N/A	£162 Calculated from prescription data and lower estimate of pop prevalence	Threshold analysis at £20K per QALY

* Uplifted to 05/06 prices using Hospital and Community Health Services Pay and Prices Index, Netten (2006)

** Equivalent cost in UK£ converted from US$ using Health Care Purchasing Power Parity rates and uplifted to 05/06, OECD (2006)

A probabilistic sensitivity analysis (PSA) was carried out to estimate the uncertainty in the cost-effectiveness estimate due to the uncertainty in the model input parameters. We characterised the parameter uncertainty by using a probability distribution to describe each of the parameters, details of which can be found in Appendix H. We sampled randomly from these distributions 1000 times and estimated the model outputs (incremental costs and incremental QALYs) for each set of sampled parameters and used these to estimate the uncertainty surrounding the cost per QALY estimate. We based our PSA on 1000 samples of the parameter distributions. The results are presented as a cost-effectiveness acceptability curve (CEAC) which shows the proportion of samples that resulted in a cost per QALY value below various thresholds. It should be noted that the PSA does not account for uncertainty around the model assumptions and these have been explored separately using univariate sensitivity analysis.

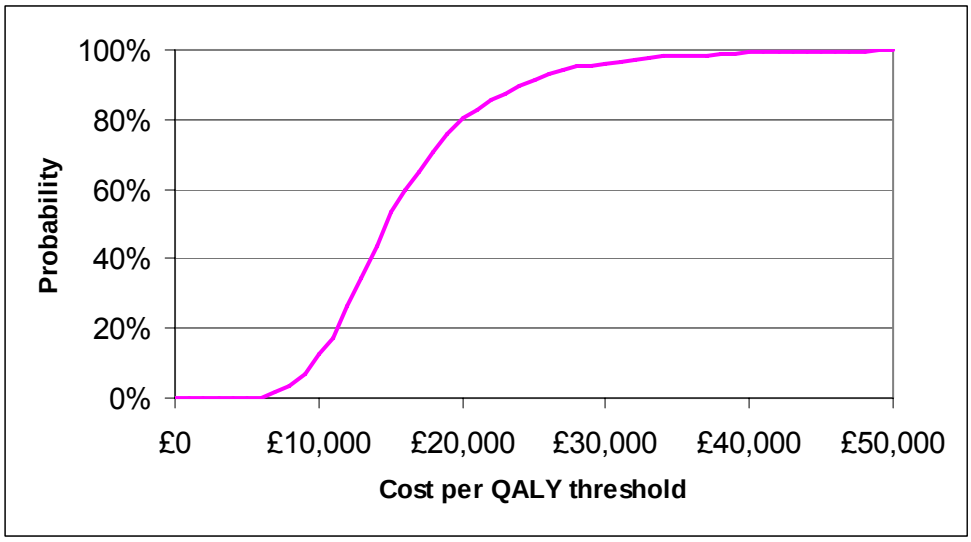
Table 12: Deterministic basecase results for 1000 patients meeting IBS diagnostic criteria. Costs, LYs and QALYs are discounted at 3.5% per annum

Outcome	No testing	Serological testing	Incremental
Number of diagnosed cases (out of 33 prevalent)	0	32	32
Total LYs	22,800	22,817	17.32
Total QALYs	15,390	15,401	11.69
Diagnostic costs	0	£36,300	£36,300
Life-time costs	£3,910,700	£4,069,300	£158,600
Cost per QALY			£13,560

The deterministic results for the UK basecase estimate are given in Table 12. The serological testing strategy identified 32 out of 33 prevalent cases of coeliac disease in the cohort of 1000 patients with IBS symptoms for a diagnosis cost of £36,300, giving a cost per correctly diagnosed case of coeliac disease of £1,122. These diagnoses resulted in an additional 43.4 LYs (undiscounted) over the lifetime of the cohort which is equivalent to 11.69 QALYs (discounted). This was associated with a further £122,300 (discounted) of treatment costs, including gluten-free products for patients diagnosed with coeliac disease, over the lifetime of the cohort. The overall cost per QALY for serological testing compared to no testing was £13,560 for a life-time horizon.

The mean cost per QALY over the 1000 samples carried out for the probabilistic analysis was £14,300. The CEAC in Figure 1 shows the probability that the cost per QALY is under various cost per QALY thresholds given the uncertainty in the parameters used to estimate cost-effectiveness. It shows that the cost per QALY had an 80% probability of being under £20K per QALY and a 96% probability of being under £30K per QALY under the basecase assumptions.

Figure 1: Cost-effectiveness acceptability curve (CEAC) for coeliac disease testing in patients with IBS-like symptoms compared to no testing



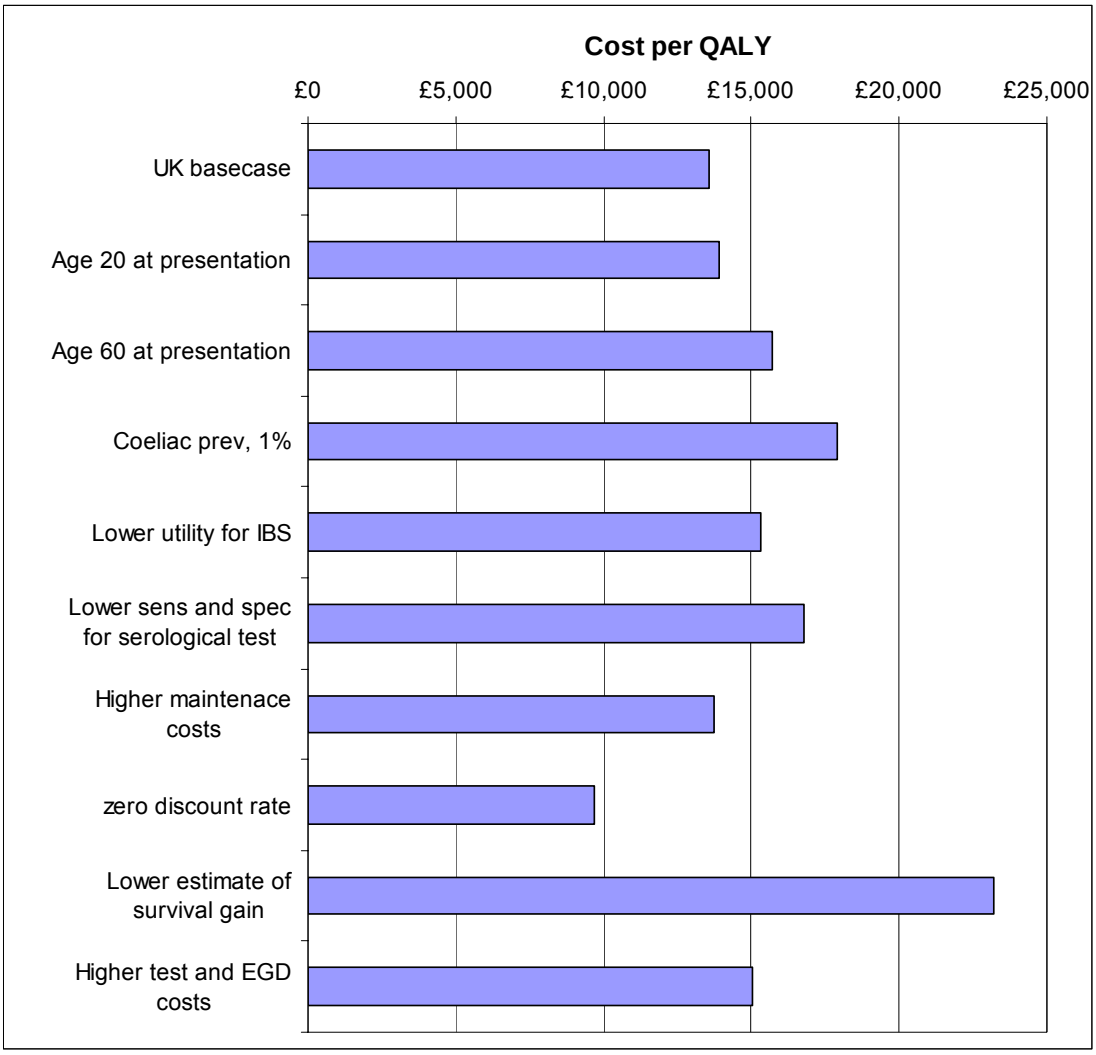
The univariate sensitivity analysis in Figure 2, shows that the cost per QALY estimate was not particularly sensitive to the age of the patient at presentation. This may be because younger patients have a longer life-expectancy, but this increases both their lifetime cost of care and their survival gain from preventing excess mortality. Cost-effectiveness was not significantly impacted by higher testing costs, higher costs for ongoing IBS / coeliac disease management, lower health state utility values for patients with IBS / coeliac disease or lower sensitivity and specificity values for serological testing. Using a zero discounting rate lowered the cost per QALY as the majority of the survival benefit was gained over the long-term whilst the upfront diagnosis costs occurred early in the model.

The cost-effectiveness estimate was sensitive to the survival gain attributed to identifying patients with coeliac disease and establishing them on a gluten-free diet, as this was the only benefit included in the basecase model. Using the lower estimate of survival benefit increased the cost per QALY to £23,000. The threshold analysis on utility gain demonstrated that establishing patients with coeliac disease on a gluten-free diet would need to produce a utility gain of 0.011 in order for the cost per QALY to remain under £20,000, when assuming that there is no survival gain. This is a small utility gain compared to the difference in health utility between IBS patients and matched controls (0.135, Akehurst 2002). These two sensitivity analyses on the survival and QALY gain demonstrated that whilst there is some uncertainty surrounding the expected benefits of identifying individuals with coeliac disease and initiating a gluten-free diet, testing is likely to be cost-effective in patients with IBS-like symptoms, so long as there is a small improvement in quality of life or a small reduction in mortality risk as a result of a correct diagnosis of coeliac disease.

The threshold analysis on the cost of prescribing gluten-free foods shows that up to £263 per patient per annum could be spent on gluten-free foods before the cost per QALY reached the threshold of £20,000. The estimated cost for providing gluten-free foods on prescription is based on the total costs of prescriptions for gluten-free foods in 2005 and an estimate of the prevalence of diagnosed coeliac disease. Using the lower estimate of prevalence from Fowell (2006) gave a higher cost of £234 per patient per annum, which based on our threshold analysis, would still provide a cost per QALY under £20,000.

We have estimated the cost-effectiveness of testing with EMA compared to no testing as this is the test most commonly available to primary care clinicians in the UK. However, TTG is also available in some areas of the NHS. Sensitivity and specificity values were available for TTG (96%, 95% CI of 92%-98%) from the Dretzke (2004) HTA, but a direct cost estimate for TTG was not available. In the economic analysis conducted as part of the HTA, the cost of TTG was assumed equal to the cost of testing for anti-gliadin antibodies (AGA) as these tests use similar techniques. The cost for these tests was estimated to be slightly higher than the cost of EMA. We carried out a sensitivity analysis to see whether testing using TTG would also be cost-effective when using the evidence on test cost and accuracy from the HTA (Dretzke 2004). The slightly lower accuracy for TTG resulted in a slightly lower QALY gain of 11.53 per 1000 people tested, for testing compared to no testing. The slightly higher test cost (£14 compared to £12) resulted in a slightly higher total cost £164,683 per 1000 people tested. The overall cost per QALY for TTG compared to no testing was therefore, £14,283. This suggests that testing with TTG would also be cost-effective compared to no testing. We have not carried out an analysis to consider which antibody test is the more cost-effective test to use as we did not feel that the cost data was sufficiently robust to allow a reliable comparison. In addition, TTG is a relatively new technology and the evidence base may have improved since the searches carried out by Dretzke (2004). There are also other factors that must be taken into account when deciding which tests should be available to primary care clinicians in the NHS, which we have not considered. Therefore we did not feel that our cost-effectiveness analysis was sufficiently robust to recommend the use of either test in preference to the other. However, there is good evidence that using either of these tests is cost-effective compared to no testing in people with IBS.

Figure 2: Univariate sensitivity analysis results for coeliac disease testing in patients with IBS-like symptoms compared to no testing



SUMMARY OF THE EVIDENCE

There is a good evidence base for the application of diagnostic criteria in the diagnosis of people presenting with IBS symptoms, allowing primary care clinicians to make a positive diagnosis with confidence. This is illustrated in Table 1. This has potential to change the current approach to diagnosis, avoiding unnecessary diagnostic tests of limited or in many cases no value. Economic analysis supported by GDG interpretation demonstrates that only four investigations from the included studies for this review are of use to the clinician, in either augmenting their positive diagnosis of IBS or related co morbidity such as Coeliac disease. The cost-effectiveness of two different antibody tests for coeliac disease (EMA and TTG) was considered as both are available within the NHS but access to these tests varies across the NHS. We did not consider which of the two antibody tests is most cost-effective as there was insufficient evidence on the relative cost to make a fair assessment of the incremental cost-effectiveness. The GDG recognised the potential need to clarify which is the better diagnostic test and

determine which test was more cost effective, but it was agreed that this was not a clinical priority for this guideline.

There was limited evidence on the clinical utility of routine laboratory investigations such as a FBC, ESR or CRP. However, GDG consensus was that these low cost tests were clinically useful in supporting a positive diagnosis and were unlikely to significantly increase the cost burden to the NHS.

For all other diagnostic investigations (ultrasound, sigmoidoscopy, colonosocopy, barium enema, thyroid function test, faecal ova and parasite tests, faecal occult blood test, hydrogen breath test) the GDG felt that there was insufficient evidence of their clinical utility to support the routine use of these tests in individuals meeting the IBS diagnostic criteria who did not have any red flag symptoms. They also felt that repeated testing could undermine confidence in the positive diagnostic approach. Whilst the cost-effectiveness of these tests was not explicitly estimated, the GDG felt that they were unlikely to be cost-effective given the lack of evidence of clinical utility in this population. The GDG recognized the importance of early and appropriate investigations in individuals with red flag symptoms. They were also mindful that the recommendations should not discourage the use of investigations in patients who do not meet the IBS diagnostic criteria or who have symptoms suggestive of organic disease.

The clinical significance of this review is two fold. Patient experience is often determined by the first exposure to healthcare, and the use of diagnostic criteria offers people who may have IBS the potential for symptom based condition to be diagnosed and managed confidently from the first consultation. The potential for cost saving is a real possibility, by determining the small number of investigations which offer primary care clinicians added benefit to confirm their clinical diagnosis. Identifying tests which are routinely requested but have little or no diagnostic value has real potential for disinvestment within the NHS. The validation of the ‘Positive Diagnostic Criteria’ is a clear step towards addressing the current variations in diagnostic practice within primary care for people presenting with IBS symptoms. Contemporised language previously used in the Manning criteria aligns closely to ROME III criteria. The diagnostic criteria recommended in this guideline implicitly acknowledges their contribution, in strengthening a contemporary IBS diagnostic approach.

GDG COMMENTARY

Duration of symptom profile

Having reviewed the evidence and analysed application of the criterion referenced diagnostic tools, duration of symptom profile was recognised to be an important aspect to consider in making recommendations for practice. Three, six and twelve month durations were all discussed and the consensus of the group was that a duration of 6 months was the most appropriate.

Entry filter for use of the diagnostic tool

Primary care clinicians should consider assessment for IBS if the patent reports any of the following symptoms for at least 6 months:

- Change in bowel habit
- Abdominal pain/discomfort and or bloating.

Positive Diagnostic Criteria

For a positive diagnosis to be made, the patient must present with at least 3 of the agreed diagnostic criteria. Language used in the tool was contemporised as follows:

- Pain was modified to include discomfort
- Pain/discomfort was changed to recurrent/episodic, experienced for at least 6 months duration
- Abdominal distension/bloating/abdominal tension was added.

Supportive investigations

Appropriate investigations identified were:

- FBC (full blood count)
- ESR (erythrocyte sedimentation rate)
- CRP (inflammatory marker)
- Antibody testing for Coeliac disease (EMA or TTG)

Follow-up

Once a positive diagnosis has been made, patient follow up is a key aspect of longer term management in managing and evaluating the response to first line therapy interventions. Giving patients the opportunity either to re-attend as required or possibly making regular appointments was discussed. It was agreed by the GDG that follow up should be explicitly stated within the recommendations, and in the absence of any evidence supporting this, consensus agreement would be used.

EVIDENCE STATEMENTS

1. There is good evidence to support the use of positive diagnostic criteria in making a diagnosis of Irritable Bowel Syndrome.

2. There is limited evidence demonstrating that patients who meet symptom based criteria for IBS, are unlikely to have organic gastrointestinal disease. The majority of diagnostic testing in this population adds little or no clinical value, with the exception of serological testing for celiac disease.

3. There are two published studies providing evidence on the cost-effectiveness of screening for Coeliac disease in patients with suspected IBS although only one presented the results

in terms of the cost per QALY gained. This study provided a cost per QALY for celiac testing vs no testing from a US perspective. This published decision analytic model was adapted to consider the cost-effectiveness of serological screening for coeliac disease from a UK perspective. This showed that antibody testing (EMA or TTG) is likely to be cost-effective in patients with IBS-like symptoms when taking into account the potential for improved survival or a modest gain in quality of life following diagnosis.

4. There is evidence from published literature that where diagnostic testing does take place, it is cost-effective to use less costly and less invasive tests first in the diagnostic sequence with positive results confirmed by standard invasive testing compared to invasive testing early in the diagnostic sequence.

RECOMMENDATION

Healthcare professionals should consider assessment for IBS if the person reports having had any of the following symptoms for at least 6 months:

- Abdominal pain or discomfort
- Bloating
- Change in bowel habit.

RECOMMENDATION

All people presenting with possible IBS symptoms should be asked if they have any of the following “red flag” indicators and should be referred to secondary care for further investigation if any are present (see ‘Referral guidelines for suspected cancer’, NICE clinical guideline 27, for detailed referral criteria where cancer is suspected).

- Unintentional and unexplained weight loss
- Rectal bleeding
- A family history of bowel or ovarian cancer
- A change in bowel habit to looser and / or more frequent stools persisting for more than 6 weeks in a person aged over 60 years.

RECOMMENDATION

All people presenting with possible IBS symptoms should be assessed and clinically examined for the following “red flag” indicators and should be referred to secondary care for further investigation if any are present (see ‘Referral guidelines for suspected cancer’, NICE clinical guideline 27, for detailed referral criteria where cancer is suspected).

- Anaemia
- Abdominal masses
- Rectal masses

- Inflammatory markers for inflammatory bowel disease.

If there is significant concern that symptoms may suggest ovarian cancer, a pelvic examination should also be considered.

RECOMMENDATION

A diagnosis of IBS should be considered only if the person has abdominal pain or discomfort that is either relieved by defaecation or associated with altered bowel frequency or stool form. This should be accompanied by at least two of the following four symptoms:

- Altered stool passage (straining, urgency, incomplete evacuation)
- Abdominal bloating (more common in women than men), distension, tension or hardness
- Symptoms made worse by eating
- Passage of mucus.

Other features such as lethargy, nausea, backache and bladder symptoms are common in people with IBS, and may be used to support the diagnosis.

RECOMMENDATION

In people who meet the IBS diagnostic criteria, the following tests should be undertaken to exclude other diagnoses:

- Full blood count (FBC)
- Erythrocyte sedimentation rate (ESR) or plasma viscosity
- C-reactive protein (CRP)
- Antibody testing for coeliac disease (endomysial antibodies [EMA] or tissue transglutaminase [TTG]).

RECOMMENDATION

The following tests are not necessary to confirm diagnosis in people who meet the IBS diagnostic criteria:

- Ultrasound
- Rigid/flexible sigmoidoscopy
- Colonoscopy; barium enema
- Thyroid function test
- Faecal ova and parasite test
- Faecal occult blood
- Hydrogen breath test (for lactose intolerance and bacterial overgrowth).

RECOMMENDATION

Follow-up should be agreed between the healthcare professional and the person with IBS, based on the response of the person's symptoms to interventions. This should form part of

the annual patient review. The emergence of any ‘red flag’ symptoms during management and follow-up should prompt further investigation and/or referral to secondary care.

Appendix 1: Sensitivity and specificity values offered as Odds Ratios

Table 3. Summary of Studies Validating Standard Diagnostic Criteria*

Criteria	Source, y	Scoring Method	Gold Standard	Type of Control	Controls, No.	IBS Patients, No.	Sensitivity, %	Specificity, %	Diagnostic Odds Ratio	Score† Raw	Score† Weighted
Manning	Manning et al,[7] 1978	≥2 of 4 criteria	Clinical	Organic GI	33	32	91	70	22.2	6	10.9
		≥2 of 6 criteria	Clinical	Organic GI	33	32	94	55	12.5		
	Talley et al,[15] 1989	No. of warnings	Clinical	Healthy	154	82	65	86	11.4	6	7
				Organic GI	101	82	58	74	3.9		
				NUD-OGD	134	82	42	85	4.1		
	Talley et al,[16] 1991; Talley,[17] 1992	≥2 of 4 criteria	Clinical	Organic GI	33	32	91	70	NC	6	9.1
		≥2 of 6 criteria					94	55	NC		
		≥3 of 4 criteria					63	85	NC		
		≥3 of 6 criteria					84	76	NC		
	Jeong et al,[18] 1993	≥2 of 6 criteria	Clinical	Non-IBS referrals	114	58	84	54	6.5	7	12.3
		≥3 of 6 criteria					67	70	4.8		
	Rao et al,[19] 1993	≥3 of 6 criteria	Clinical	Healthy	45	65	66	93	27.4	8	13.2
				Organic GI	23	65	66	61	3.0		
				NUD	35	65	66	91	20.9		
	Dogan and Unal,[20] 1996	≥3 of 6 criteria	Clinical	Organic GI	182	165	90	86	57.4	7	12.3
	Thompson,[21] 1997	≥2 of 6 criteria	Clinical	None	NC	156	NC	NC	NC	1	3
Kruis	Kruis et al,[10] 1984	Kruis ≥44	Clinical	Organic GI	209	108	64	99	183.1	8	13.2
	Frigerio et al,[22] 1992	Kruis (male) ≥44	Clinical	Organic GI	93	15	47	94	12.7	8	13.2
		Kruis (female) ≥44			108	37	59	95	30.2		
		Kruis (male + female) ≥44			201	52	56	95	21.8		
		Modified Kruis (male) ≥44			93	15	67	90	18.7		
		Modified Kruis (female) ≥44			108	37	68	92	23.8		
		Modified Kruis (male + female) ≥44			201	52	68	91	21.5		
	Dogan and Unal,[20] 1996	Kruis ≥44	Clinical	Organic GI	182	165	81	91	44.8	7	12.3
Rome	Thompson,[21] 1997	Rome guidelines	Clinical	None	NC	156	NC	NC	NC	1	3
	Vanner et al,[23] 1999	Rome guidelines	Clinical	Non-IBS referrals	52	46	65	100	18.8	6	9

*IBS indicates irritable bowel syndrome; GI, gastrointestinal; NUD-OGD, nonulcer dyspepsia–oesophagogastroduodenoscopy; and NC, not calculable.
†Sums of scores from Table 1.

From Fass et al (2001) Evidence and consensus based practice guidelines for the diagnosis of Irritable Bowel Syndrome.

Appendix 2: Comparison table for Rome Criteria

Table 1. Results of Studies Comparing Gastrointestinal Symptoms in Irritable Bowel Syndrome (IBS) and Organic Diseases

Study	Rome Criteria (%)							
	Abdominal Pain/Discomfort Relieved by Defecation	Abdominal Pain/Discomfort Associated with Change in Stool Frequency	Abdominal Pain/Discomfort Associated with Change in Stool Consistency	Altered Stool Frequency	Altered Stool Form	Altered Stool Passage	Passage of Mucus	Bloating or Feeling of Distension
Manning et al, 1978[4]								
IBS	81	81	81	—	—	59	47	53
Organic	30	30	27			33	21	21
Thompson, 1984[11]								
IBS	82	61	64	—	37	88	60	84
Organic	78	52	48		35	73	71	59
Talley et al, 1990[6]								
IBS	43	38	40	32	57	56	49	43
Organic	33	13	20	15	28	32	20	23
Poynard et al, 1992[7]								
IBS	69	23	42	—	—	78	23	66
Organic	52	20	33			54	28	45
Jeong et al, 1993[9]								
IBS	59	57	59	—	—	78	19	40
Organic	32	26	33			53	10	26
Rao et al, 1993[8]								
IBS	66	35	48	—	—	85	79	22
Organic	44	9	13			65	65	13

Table 2. Number of Patients with Specified Organic Diseases in Studies Comparing Gastrointestinal Symptoms in Irritable Bowel Syndrome and Organic Diseases

Study	No. of Subjects with Organic Disease	Upper GI Disorders	Lower GI Disorders				
			IBD	Other Colitis	Colonic Cancer	Diverticulitis	Other GI Disorders
Manning et al, 1978[4]	33	19	5	—	2	Excluded	7
Thompson, 1984[11]	98	49	49	—	—	—	—
Talley et al, 1990[6]	101	65	6	—	4	—	26
Poynard et al, 1992[7]	94	23	18	4	?*	6	43
Jeong et al, 1993[9†]	87	51			16†		20
Rao et al, 1993[8]	23	—	16	—	7	—	—
Dogan and Unal, 1996[10]	182	140	9	—	16	—	17

* Specific number of upper versus lower gastrointestinal carcinoma not specified in this investigation.
† Type of colonic disease was not specified in this study.

Appendix 3: PATIENT PROFILES FOR SIMULATED GP CONSULTATION

IBS GDG MEETING 30th November- 1st December 2006

Patient 1

Female, aged 37yrs, married 2 children.
Recurrent abdominal discomfort approximately a week out of every month – sometimes worse pre-menstrual, worse if eats cauliflower or spicy foods.
Tired and lethargic – has tried different diets to help energy levels but nothing works.
Bowel – change in bowel habits, had diarrhoea after holiday abroad now seems to have constipation followed by diarrhoea.

Patient 2

Male, aged 44 yrs, divorced, 4 children, 2 ex wives.
Frequent abdominal pain, most days of the week.
Bloating worse by end of day with increased flatulence.
Constipation, thinks there has been a little rectal bleeding but not sure. Worse since new job – very stressful over last six months.
Social life diminished because embarrassed to go out, becoming increasingly depressed.
Worried he may have something serious.

Patient 3

Female, aged 51yrs, single.
Diarrhoea on and off for last 2 years.
Abdominal pain.
Back ache.
Nausea.
Weight loss.
2 x visit to Doctors with urinary symptoms – no UTI but symptoms recur intermittently
describes herself as fed up – not depressed.

Patient 4

Female, aged 24yrs
Altered bowel habit – diarrhoea and constipation – changes all the time feels she never empties her bowels, passes mucus in diarrhoea, pale bulky stools when constipated. Has had 'sensitive tummy' since she was a child.
Mother has long term problems with constipation. Abdominal pain better after bowel movement.
Some foods make it worse she wonders if she has food allergy – sometimes gets a rash and frequently has mouth ulcers.
Drinks a lot of milk when 'off' food.

7 DIET AND LIFESTYLE

Clinical Questions

1. What associations are there between diet and IBS?
2. What dietary interventions improve symptoms/quality of life?
3. Does Aloe Vera have a role in managing symptoms?
4. What associations are there between physical activity and IBS?
5. Does physical activity improve IBS or related symptoms?

BACKGROUND

Diet and lifestyle may be factors that trigger or exacerbate symptoms of IBS so they are factors that need to be given due consideration both at the initial and later stages of management. This chapter includes all the reviews in the guideline pertaining to diet and lifestyle interventions.

DIET

A healthy diet, as based on the 'Balance of Good Health', is promoted for the UK population. Some aspects of this are appropriate for people with IBS, e.g. regular meals, drinking plenty of fluid (e.g. 8 cups of non-caffeine based fluid per day) and encouraging a wide variety of foods. However, people with IBS often find that following healthy eating advice exacerbates symptoms and, in particular, this may relate to dietary fibre and lactose (milk and dairy foods). Wheat, resistant starch, caffeine, fructose, sorbitol, alcohol and fizzy drinks have also been reported to commonly affect symptoms. Potential beneficial components of the diet include probiotics and prebiotics and water soluble dietary fibre. Diet and nutrition are fundamental in the management of IBS to avoid malnutrition and to contribute to achieving optimal symptom control.
Food products have been reported as causing, contributing to and perpetuating Irritable Bowel Syndrome. The term 'food intolerance' includes effects of pharmacologically active constituents (e.g. caffeine in coffee); enzyme deficiencies (e.g. lactose intolerance) and demonstrable immunological response (allergy or hypersensitivity to peanut, cow's milk, gluten, soya bean). The notion of food intolerance and food allergy is not new and many IBS patients give a history of food intolerance, although few clinicians consider food hypersensitivity to be a cause of IBS. There are no objective tests available to identify food intolerance and few to confirm food allergy. Data from dietary elimination and food challenge studies are contradictory.

Dietary intolerance is defined as a non-immunologically mediated response to particular foods, which resolve following dietary elimination and re-occur with food challenge. An exclusion diet is defined as a diet in which specific food products are totally excluded for a specified period of

time. The excluded food products are then gradually re-introduced one by one to confirm response.

Diagnostic testing for food intolerance includes hydrogen breath testing and diagnostic testing for Coeliac Disease. Hydrogen breath tests are based on the fact that the only source of hydrogen gas in humans comes from the bacterial metabolism of carbohydrates. Different carbohydrates are given orally to patients and the amount of hydrogen in the expired air is measured. Patients need to be fasted and to have had at least one day of a low fibre diet. Smoking and exercise alters the hydrogen concentrations so are not permitted during the tests.

Potential sources of error are:

- Carbohydrate malabsorption in chronic pancreatitis and Coeliac disease
- False positive for small intestinal bacterial overgrowth due to colonic fermentation
- Delayed gastric emptying may cause false negative
- Oral bacterial flora, failure to follow low fibre diet and rapid transit through small intestine may produce false positive.

Testing for Coeliac disease involves a blood test for immunoglobulin A (IgA) antigliadin antibodies; endomysial antibodies (EMA) and TTG anti-tissue transglutaminase antibodies. The sensitivity and specificity for IgA, EMA and TTG are 95% and 89%; 100% and 97%; and 100% and 97%, respectively in patients with GI symptoms. For general population screening, EMA and TTG have a positive predictive value of 15.7% and 21.8%. A positive blood result requires an endoscopy with duodenal biopsy to confirm a diagnosis of Coeliac disease.

People with IBS may alter their diet to alleviate symptoms of IBS. Guidance may either be sought from inadequately qualified nutritionists or be self directed. Excluding individual foods or complete food groups without appropriate dietetic supervision can lead to inadequate nutrient intake and ultimately malnutrition, e.g. calcium. In addition, symptoms often remain unresolved leading to further inappropriate dietary restriction. The gold standard diagnosis for intolerance to a food is by elimination and reintroduction. Intolerance would be demonstrated if symptoms resolved on elimination and reappeared on reintroduction. Importantly, dietary advice will vary depending on symptoms, e.g. diarrhoea and/or constipation, abdominal bloating and therefore needs to be tailored to the individual to manage symptoms. Expert professional advice on diet and nutrition for IBS should be obtained from a registered dietitian or an appropriately qualified nutritionist.

Dietary Fibre

Fibre is defined as non-starch polysaccharides in agreement with FAO/WHO/DOH measurement methods. Dietary fibre is food material that is not hydrolysed by enzymes secreted by the human gastrointestinal tract. Soluble fibre dissolves in water forming a gel and may be digested by the colonic microbiota increasing bacterial numbers and thus faecal bulk. It

includes β-glucans, pectins, gums, mucilages and some hemicelluloses. Dietary sources include oats, psyllium, ispaghula, nuts and seeds, some fruit and vegetables and pectins. Insoluble fibre is not readily broken down by the gastrointestinal microbiota and it increases faecal bulk, shortening colonic transit. It includes celluloses, some hemicelluloses and lignin and is chiefly found in corn (maize) and wheat bran and some fruit and vegetables.

An increase in fibre has often been suggested as an initial treatment for IBS, although more recently there are conflicting data to support its effectiveness and a range of views on its usefulness. The dietary reference value for non-starch polysaccharides (fibre) is 18g per day for adults. A high fibre diet is defined as 18g or more per day in recognition of the fact that many people in the UK eat on average 10 to 12g per day. Dietary manipulation of the fibre content in practice is dependent on the presenting symptom profile (constipation dominant, diarrhoea dominant or alternating symptoms) and whether abdominal bloating and flatus is present.

Wheat

Wheat is a grass and is cultivated worldwide as a food grain, ranking second in total production as a cereal crop behind maize. Whole wheat is made up of 14% bran, 2.5% germ and the rest is starchy endosperm. Wheat bran has a faecal bulking effect, delays gastric emptying and accelerates small bowel transit (McIntyre 1997). Wheat is found in bread, many breakfast cereals, pasta, cakes and biscuits and is one of the major cereals consumed in the UK. In IBS, wheat consumption is often associated with increased symptoms which may be due to the content of fibre, fructans or resisitant starch. Increasing the variety of other cereals and reducing, but not necessarily, excluding wheat may be beneficial in IBS.

Resistant Starches

Resistant starch comprises starch polymers that are not readily digested in the stomach or small intestine Resistant starches are the total amount of starches, and the products of starch degradation that resist digestion in the small intestine of healthy people (Asp 1982) and therefore reach the colon intact. The extent of resistance is influenced by the structure of naturally occurring starch polymers and food processing methods employed, e.g. how starch changes during cooking and cooling. People with IBS may benefit from a reduction of foods high in resistant starch to alleviate symptoms of wind and bloating.Common dietary sources of resistant starch are cold or re-heated potatoes, bread, cereal products containing modified starch (e.g. cakes, biscuits and breakfast cereals.

Lactose

Lactose is a sugar found in milk of all mammalian varieties including cow, goat, sheep and human and it is also used in processed foods, particularly slimming products. Approximately 10% of people with IBS have lactose intolerance (BSG Guidelines). The symptoms of IBS are brought on by undigested lactose passing into the small intestine causing an increase in the

secretion of fluid into the small bowel through osmotic mechanisms. It then passes into the colon undigested and is available for colonic fermentation as described above (Mascolo 1998).

Removing lactose from the diet may not lead to complete symptom relief in IBS and exclusion needs careful monitoring due to other nutritional inadequacies in the diet e.g. calcium. Often people with lactose intolerance can manage 10 to 12g lactose per day if spread throughout the day. Milk contains the highest level of lactose (cow's milk 5g per 100ml), foods that are lower include butter (trace), cheese (cottage cheese: 1g per tablespoon, processed cheese: 1g per slice, Cheddar, edam, brie, Danish blue: trace), yoghurts (trace – 4g per pot) and low lactose milk. It is therefore relatively easy to include a sufficient amount of dairy foods to maintain a balanced diet in diagnosed and self reported people with lactose intolerance.

Fructose

Fructose intake has increased considerably as a result of an increased consumption of high fructose corn syrup, fruits and juices and crystalline fructose. Fructose is almost twice as sweet as normal table sugar (sucrose). Fructose is an important source of energy for humans, but incomplete absorption in the small bowel can lead to colonic fermentation causing diarrhoea, wind and bloating.

Up to 80% of healthy subjects incompletely absorb 50g of fructose (Scoog 2004). In real terms 25g fructose is equivalent to that found in 200ml apple juice or 2 bananas. A regular consumption of dried fruit and high juice squash will easily add another 25g.

Sorbitol

Sorbitol is a natural component of fruits and significant amounts are found in dried apple and apricots, prunes, cherries and pears. Produced from maize it is also used as an artificial, low calorie sweetener for its low cariogenicity, e.g. in sugar-free chewing gum, mints and cough syrups and as a humectant and thickener in confectionary, frozen desserts and toothpaste. It is poorly absorbed in the small bowel and in the colon has a laxative effect if consumed in quantities of around 30g/day, although some individuals, particularly people with IBS may be sensitive to much less (Thomas 1992).

Caffeine

Caffeine is found naturally in many plant-derived foodstuffs and beverages, chiefly coffee, tea, cocoa and chocolate confectionary, cola and other stimulant drinks. It is also found in many pharmacological agents. Caffeine has many reported effects on the body: negative effects include raised blood pressure, increased heart rate, arrhythmias, dehydration, anxiety, insomnia, headaches and heartburn. Caffeine can also stimulate the central nervous system, improve alertness and mental efficiency and improve athletic performance (Thomas 2003). There is a general consensus that a moderate intake of caffeine (up to 300mg/day in adults) is not harmful.

Caffeine has stimulatory effects on the digestive system but there is little evidence that it will cause gastrointestinal dysfunction (Thomas 2003). Heartburn is the most commonly reported symptom from drinking coffee. It may promote gastrointestinal reflux and stimulate gastrin release and gastric acid secretion but does not appear to affect gastric emptying or small bowel transit.

Probiotics and Prebiotics

In IBS, the gastrointestinal flora may undergo both qualitative and quantitative changes and the most common finding is a decrease in the population of 'good bacteria' such as *Bifidobacteria* and *Lactobacilli* and the faecal microflora has increased numbers of facultative organisms (Madden and Hunter 2002; Quigley 2007). Probiotics may be useful in the management of IBS, however dose and specific bacterial strain are important. In vivo studies have identified some of the variables that determine the survival of probiotics through the GI tract, and some have attempted to quantify the degree of survival of the dose administered. This was found to vary from 10 to 50% depending on the probiotic species used and the dose administered.

For the purposes of this guideline probiotics are defined as microbial food supplements which, when administered in adequate amounts, have a beneficial effect on the host. Prebiotics are defined as a non-digestible food ingredient that affects the host by selectively targeting growth and/or activity of one or more bacteria in the colon that can improve health. Synbiotics are defined as a combination of pre and probiotics which beneficially affects the host by improving survival and implantation of live microbial dietary supplements in the gastrointestinal tract.

Fermented milks and yoghurts have been the most commonly used carrier of probiotics. The probiotic organism is added at the end of the milk fermentation process. The range of probiotic products is expanding to include cheese, frozen yoghurt, ice cream and non-dairy foods, liquids, powders, capsules and drinks. It should be noted that many available probiotics have not had their health benefits identified or been scientifically proven to be beneficial to the host (Reid 2001).

In vivo studies have identified some of the variables that determine the survival of probiotics through the GI tract, and some have attempted to quantify the degree of survival of the dose administered. This was found to vary from 10 to 50% depending on the probiotic species used and the dose administered. The GDG defined the minimum acceptable dose to be $1x10^{6}$ (one million) bacteria per day. The duration of the intervention is also considered important. To avoid concerns regarding possible effects during the menstrual cycle, four weeks was thought to be the minimum duration of intervention.

Colonic Fermentation

Some of the symptoms of IBS (e.g. abdominal bloating, flatus and diarrhoea) may be due to colonic fermentation by intestinal microflora of certain dietary constituents to short chain fatty acids (acetate, butyrate and propionate) and gases (hydrogen, carbon dioxide and methane). The short chain fatty acids have been shown to stimulate ileal and colonic smooth muscle contractility (Barbara 2005). Watery diarrhoea may also happen due to the increased osmotic load. The dietary constituents include non absorbed lactose (as in lactose intolerance), dietary fibre/non-starch polysaccharides, resistant starches and oligosacchaides from wheat and other grains.

Aloe vera

Aloe vera (*Aloe barbadensis* Miller) belongs to the Liliaceal family of which there are approximately 360 species. Aloe vera is a cactus like plant; cosmetic and medicinal products are derived from the leaf tissue and called aloe vera gel. Aloe sap or juice, often referred to as aloes, are derived from the peripheral bundle sheath cells of aloe vera. Aloe vera sap contains anthraquinones that are known to have laxative effects. These are not found in the gel but may be present in total leaf extracts (Vogler and Ernst 1999). The use of aloe vera is being promoted for many conditions including IBS. Most of the evidence is based on anecdotal, historical use rather than scientific evidence.

PHYSICAL ACTIVITY

The relationship between physical activity and chronic disease

There is strong evidence from observational studies that moderate to high levels of physical activity can have a substantial impact on major non communicable diseases, such as coronary heart disease (CHD), hypertension, diabetes and certain types of cancer (US Department of Health and Human Services, 1996; Department of Health, 2004a; WHO, 2004). People who are physically active typically experience 30 to 50% reductions in relative risk of CHD compared with people who are sedentary, after adjustment for other risk factors (Murphy 2003).

The Chief Medical Officer (CMO) recently published a report stating the importance of physical activity for health (Department of Health, 2004a). As well as linking chronic disease with physical inactivity the report also described how physical activity can reduce the risk of musculoskeletal health conditions, including osteoporosis, back pain and osteoarthritis. It stated that regular physical activity can reduce the risk of depression and promotes many other positive mental health benefits including reducing anxiety and promoting self esteem (Department of Health, 2004a). The CMO's report also presented a series of recommendations for the amount of physical activity that should be undertaken by different population groups. These recommendations mimicked similar recommendations from other international bodies (Pate et al, 1995; US Department of Health and Human Services, 1996; Department of Health, 2004a). The report advised that adults should undertake at least 30 minutes of moderate intensity

physical activity on at least five days of the week (Department of Health, 2004a). In 2002 the cost of physical inactivity was estimated to be £8.2 billion annually in terms of mortality, morbidity and quality of life (Department for Culture Media and Sports and London Strategy Unit, 2002). A more accurate estimate of the direct costs of physical inactivity to the UK health service was £1.06 billion annually (Allender et al, 2006a). Physical activity has been described as a good investment for public health, not only because of the great potential for benefit, but also because 'it is inexpensive and has few side-effects' (Morris 1992, in Marmot and Elliot 1992).

In 2006, NICE published guidance (Public Health Intervention Guidance No. 2) on exercise interventions in primary care, pedometers, exercise referral schemes and community-based exercise programmes for walking and cycling to increase physical activity. Two specific recommendations were made for primary health care professionals:

Recommendation 1
Primary care practitioners should take the opportunity, whenever possible, to identify inactive adults and advise them to aim for 30 minutes of moderate activity on 5 days of the week (or more)*. They should use their judgement to determine when this would be inappropriate (for example, because of medical conditions or personal circumstances). They should use a validated tool, such as the Department of Health's forthcoming general practitioner physical activity questionnaire (GPPAQ), to identify inactive individuals.

* The practitioner may be a GP or another professional with specific responsibility for providing encouragement or advice. This will depend on local conditions, professional interest and resources. Health trainers are likely to have a role in offering brief advice. 'Inactive' is used as shorthand for those failing to reach the CMO's recommendation. 'Advise' is used as shorthand for 'encourage, advise, discuss, negotiate'.

Recommendation 2
When providing physical activity advice, primary care practitioners should take into account the individual's needs, preferences and circumstances. They should agree goals with them. They should also provide written information about the benefits of activity and the local opportunities to be active. They should follow them up at appropriate intervals over a 3 to 6 month period.

The NICE public health intervention advisory committee determined that there was insufficient evidence to recommend the use of exercise referral schemes to promote physical activity, other than as part of research studies where their effectiveness can be evaluated.

This guidance aims to help practitioners deliver effective interventions that will increase people's physical activity levels and therefore benefit their health.

The use of physical activity as part of a non-pharmacological therapy for IBS is described as "reasonable" despite the relationship between exercise and gastrointestinal system being unclear (Bi and Triadafilopoulos 2003). For example, moderate physical activity (e.g. brisk walking) is reported to improve gut transit time, whereas vigorous physical activity (e.g. running) can result in "runners trots" (Oettle, 1991). Physical activity has been associated with improved outcomes in uncontrolled studies (Colwell et al, 1998).

7.1 General dietary and lifestyle advice

This section is concerned with the effect of diet and lifestyle on IBS and its management. Five reviews are addressed, fibre, probiotics, aloe vera, exclusion diets and physical activity. In addition, the GDG made some consensus recommendations, partly informed by dietary advice leaflets. These are listed below.

RECOMMENDATION

Healthcare professionals should encourage people with IBS to identify and make the most of their available leisure time and to create relaxation time.

RECOMMENDATION

Diet and nutrition should be assessed for people with IBS and the following general advice given.

- Have regular meals and take time to eat.
- Avoid missing meals or leaving long gaps between eating.
- Drink at least eight cups of fluid per day, especially water or other non-caffeinated drinks, for example herbal teas.
- Restrict tea and coffee to three cups per day.
- Reduce intake of alcohol and fizzy drinks.
- It may be helpful to limit intake of high-fibre food (such as wholemeal or high-fibre flour and breads, cereals high in bran, and whole grains such as brown rice).
- Reduce intake of 'resistant starch' (starch that resists digestion in the small intestine and reaches the colon intact), which is often found in processed or re-cooked foods.
- Limit fresh fruit to three portions per day (a portion should be approximately 80g).
- People with diarrhoea should avoid sorbitol, an artificial sweetener found in sugar-free sweets (including chewing gum) and drinks, and in some diabetic and slimming products.
- People with wind and bloating may find it helpful to eat oats (such as oat-based breakfast cereal or porridge) and linseeds (up to one tablespoon per day).

7.2 Physical activity

SELECTION CRITERIA

The selection criteria described in the general methodology section were to be used, but some were specific to the physical activity review and are reported below.

Types of studies

For intervention studies, randomised trials (RCTs) examining the use of physical activity for the treatment or management of IBS were to be included. In the absence of randomised trials, quasi randomised studies were to be considered. Crossover trials with a washout period of less than 2 weeks were to be excluded. All study designs were to be included for adverse effects, but specific searches for adverse effects will not be carried out. Studies were restricted to the English language.

Types of intervention

Studies were included if they had one or more of the following interventions:

- The use of physical activity alone or in combination with other therapies
- 12 weeks minimum length of intervention

A physical activity intervention is defined as the use of physical activity or exercise as a therapeutic and/or preventative medical procedure used to support the management and treatment of IBS. Physical activity is usually defined as *any force exerted by skeletal muscles that results in energy expenditure above resting level* whereas exercise is defined as *a subset of physical activity, which is volitional, planned, structured, repetitive and aimed at improvement or maintenance of any aspects of fitness or health* (Casperson et al, 1985). The GDG defined the minimum acceptable dose of physical activity to be at least 30 minutes per week of at least moderate intensity physical activity. The duration of the intervention is also considered important, and the minimum duration of intervention was set at twelve weeks.

Types of comparisons

The following comparisons were to be included

- Physical activity versus attention control
- Combination of physical activity with another non-pharmacological intervention (e.g. diet advice) versus control.

Types of participants

Studies were to be included if the participants were:

- Adults (18 years and over)
- Had symptoms of IBS
- No serious diseases (e.g. cancer, heart disease) other than IBS
- Did not have a single symptom of IBS only (e.g. not constipation only)

In the absence of studies in patients with IBS, we extended the review to cover studies in people with single symptoms such as constipation or diarrhoea. Studies in these participants were regarded as indirect as far as the population was concerned.

SEARCH STRATEGY FOR IDENTIFICATION OF STUDIES

Searches were performed on the following core databases: MEDLINE, EMBASE, CINAHL and *The Cochrane Library (*1966 to current day with guidance from the GDG). An additional database searched for this review only was SPORTS DISCUS. The search strategies are listed in Appendix B.

Subgroup analyses

Subgroup analyses were proposed to examine any heterogeneity as follows:

- Dose
- Type of physical activity
- Symptom severity.

Sensitivity analyses

The following sensitivity analyses may be considered:

- Setting (primary/secondary care).

DESCRIPTION OF STUDIES INCLUDED IN THE REVIEW

The search strategy identified 2608 studies. The titles and abstracts of these studies were assessed. Of these, 19 that were potentially relevant to the review were identified on the basis of the title and abstract – these papers were retrieved in full. All reference lists of these studies were inspected for potential papers for inclusion in the review, but none was found.

None of the studies identified met the primary inclusion criteria. Therefore, we included some studies with indirect evidence, and considered other studies to aid GDG discussions. One systematic review was identified (Bi and Triadafilopoulos 2003). This review examined the relationship between exercise and gastrointestinal function for eight disease types.

RESULTS

Evidence from Systematic Reviews

Bi and Triadafilopoulos (2003) reviewed the relationship between exercise and gastrointestinal function for eight disease types. The authors described their review as systematic but provided no methods in the paper.

1. Gastroesophageal reflux disease
2. Gastric emptying and gastric acid production
3. Peptic ulcer disease
4. Inflammatory bowel disease

5. Constipation and gastrointestinal motility
6. Colorectal cancer
7. Gastrointestinal bleeding
8. Liver disease

The authors attempted to identify if there were any differential effects of physical activity (by intensity or type) on gastrointestinal function. IBS was not identified as a separate class, but it may be possible to extrapolate from the indirect evidence in section 5 of the Bi and Triadafilopoulos (2003) review. Participants in these studies tended to be young, fit and active males, rather than typical clinical populations. The review found that physical activity could improve gastric emptying and lower the risk of bowel cancer. However, there was insufficient evidence to suggest that exercise can relieve chronic constipation. The authors also noted consistent improvements in aerobic fitness and general health for all subjects participating in regular physical activity programmes and that this outcome is a notable behavioural goal for sedentary patients. The majority of risks to gastrointestinal organs relate to very high levels of sustained physical activity (performed at elite levels). However these risks do not outweigh the benefits of light and moderate physical activity.

Evidence from intervention studies

One randomised trial was included as an indirect study as it examined the impact of physical activity upon adults with chronic constipation only (De Schryver 2005). However this study was not included in the Bi and Triadafilopoulos (2003) review.

The aim of the study was to investigate the effect of regular physical activity on colonic transit time and defecation in middle aged inactive patients suffering from chronic idiopathic constipation. Forty three adults aged 51 to 61 were recruited from general practice lists and pharmacies. Using Rome I criteria all were categorised as suffering from constipation, with IBS patients excluded. Participants' physical activity levels were also assessed using a self report measure and all the participants were categorised as sedentary if they failed to reach the current physical activity recommendation (under 30 minutes or more of moderate physical activity on most days of the week).

Other baseline measures included food consumption, assessed by self report using a diary, in order to determine the average daily fibre and water intake. Defecations patterns were recorded in a 7-day diary, at the start of the study and at 12 weeks follow up. Colonic transit time was measured using radiopaque markers and x-rays. Transit time was calculated based on the number of markers visible in the colon, segmented into three (right colon, left colon and rectosigmoid).

Participants were randomised in to two groups, physical activity versus waiting list control. Group A maintained their normal lifestyle for 12 weeks, and then started their 12 week physical

activity programme. Group B started their physical activity programme immediately after randomisation. Both groups were given dietary advice by a dietician concerning the consumption of fluid and fibre at the start of the study. Group A received a second dietary advice after 12 weeks, before starting the physical activity programme. This programme consisted of both aerobic and strength/flexibility exercises. Brisk walking was chosen for aerobic training and strength/ flexibility exercises were chosen for a home based programme. Brisk walking was performed at least twice a week for at least 30 minutes per session, performed at 70 to 80% of the subject's maximal heart rate. Participants were able to monitor their heart rates using a Polar sports tester (a heart rate monitor worn on the wrist, in conjunction with a chest sensor). Maximal heart rate was assessed for all patients at baseline using a maximal heart test performed on a cycle ergometer. Participants were also asked to perform a walking test on a treadmill at 70% of their heart rate for 5 minutes to establish an average heart rate for their brisk walking.

The number of defecations did not change in either of the study groups (Table 1). However in Group B the percentage of incomplete stools decreased significantly, compared to Group A at 12 weeks (Group A from 58.8% to 39.5% whereas in Group B from 54.3% to 27.4%).

Table 1. Defecation patterns at baseline and after 12 week physical activity programme for 41 adult participants aged 51-61 years old (De Schryver et al, 2005)

	Group A (12 weeks inactive, 12 weeks PA)			Group B (12 weeks PA)	
	Week 0	Week 12	Week 24	Week 0	Week 12
No. of defecations/wk	7.1 ±0.8	7.5 ±1.1	7.8 ±1.1	7.5 ±1.1	7.8 ±1.0
% Hard stools	53.8 ±8.5	51.9 ±9.5	35.1 ±9.2	59.5 ±8.7	39.5 ±6.8*
% Straining at defecation	65.7 ±7.7	69.2 ±7.9	54.3 ±9.8	71.2 ±4.6	40.4 ±6.4*
% Incomplete stools	51.3 ±7.9	58.8 ±8.5	39.5 ±8.9	54.3 ±7.2	27.4 ±6.0*
No. of Rome criteria	2.3 ±0.1	2.6 ±0.2	1.7 ±0.3*	2.7 ±0.1	1.7 ±0.2*
% Patients with ≥2 Rome criteria	100	89	61*	100	64*

PA = physical activity.
Data are given as means ± SEM.
* $p < 0.05$

Despite randomisation, there were considerable differences between right and total colonic transit times at baseline between groups (Table 2). No significant changes in right or left colonic transit time were observed in either group at the end of the physical activity programme. In Group B there was an observed acceleration in rectosigmoid mean transit time compared to Group A. Total colonic transit time also improved with a significant reduction in Group B. The

authors reported that there was no correlation between fibre intake and improvements in defecation patterns and colonic transit times.

The GDG noted that the normal total colonic transit time is 72 hours and concluded that group B was significantly different from group A, so that the study was considered to be at least partially confounded.

The evidence from this study was assessed to be low, using GRADE criteria. Limitations included (i) the study was conducted in secondary care (ii) there were important differences in baseline characteristics, (iii) IBS patients were excluded. This study was also limited because the participants had relatively high levels of baseline physical activity, which equates to over 2 hours of walking per week, and may not be representative. The study did show that moderate physical activity could deliver a consistent reduction in total colonic transit time and improvements in ROME I symptoms amongst older adults with chronic constipation.

Table 2. Colonic transit times (hours) at baseline and after 12 week physical activity programme for 41 adult participants aged 51-61 years old (De Schryver et al, 2005)

	Group A (12 weeks inactive, 12 weeks PA)			Group B (12 weeks PA)	
	Week 0	Week 12	Week 24	Week 0	Week 12
RCTT	15.1 ±2.2	14.0 ±2.7	13.8 ±2.1	27.5 ±4.7	22.2 ±2.8
LCTT	27.5 ±4.9	29.5 ±6.1	33.9 ±6.9	33.8 ±5.0	27.6 ±4.9
RSTT	16.9 ±3.0	18.9 ±3.0	14.3 ±3.2	17.5 ±2.5	9.6 ±1.6
Total CTT	59.5 ±8.4	62.4 ±9.5	61.0 ±9.9	79.2 ±9.1	58.4 ±7.7

RCTT = right colonic transit time; LCTT = left colonic transit time; RSTT = rectosigmoid transit time; PA = physical activity.
Data are given as means ± SEM.
* $p < 0.05$

Studies used to aid GDG discussions

One pre-post intervention study examined the impact of a lifestyle education programme upon IBS symptoms. This study design was judged inadequate to make recommendations on interventions, but was considered useful to inform GDG discussions, and does illustrate a suitable approach for evaluating a lifestyle intervention for IBS patients.

Colwell et al (1998) assessed the impact at one and six months of a patient education class, that included exercise, on 52 adult outpatients with IBS (definition of IBS not stated). Patients were advised to increase their physical activity by walking or basic stretching exercises during one 3 hour structured class, delivered by a specialist nurse. Pre-class data was compared with results for physical activity levels at follow up. Exercise scores increased significantly at one month but

not at 6 months, compared with baseline, using a self-rating scale. It is difficult to assess if this increase was clinically significant because the physical activity variable was assessed using a categorical scale, and so the physical activity change scores were not adjusted for baseline values. Pain scores at 1 and 6 months reduced significantly (see Table 3). The Manning score also decreased significantly, on a scale of 0 to 6 using Manning criteria.

Table 3. Symptom scores at 1 and 6 months for 57 adult participants in an IBS educational class aged 21-79 years old (Colwell et al, 1998, page 903)

Score	Median Scores (ranges)		
	Baseline	1 month	6 months
Pain*	3.0 (1.9-3.9)	2.4 (0.0-3.7)§	2.6 (0.0-4.0)§
Manning∇	4.0 (1.0-6.0)	3.0 (0.0-6.0)§	3.0 (0.0-6.0)§

* Pain score: a weighted average of severity, frequency, and duration of pain on a scale from 0-4

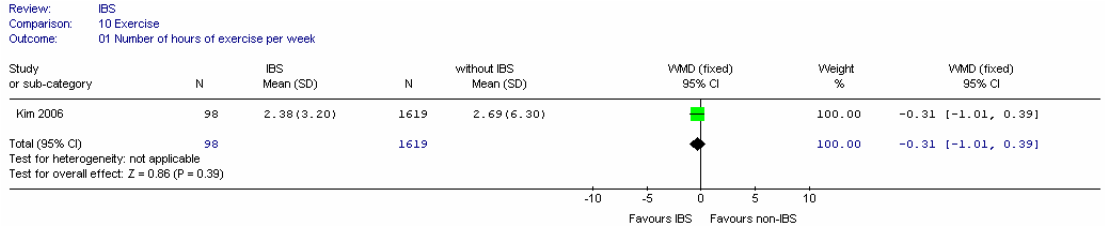
∇ Manning score: On a scale of 0 to 6 Manning criteria: pain relief with defecation; looser stools with pain onset; abdominal distension; mucus in the stool; and a feeling of incomplete evacuation (2)

§ $p < 0.01$.

Evidence from Epidemiological studies

Three observational studies reported the prevalence and association between IBS and physical activity. In a case-control study, Kim and Ban (2006) reported a small, non-significant difference in the mean number of hours of exercise per week for students with IBS compared to students without IBS (defined by ROME 2 criteria) (students with IBS 2.38 h/week, SD 3.2 versus students with non-IBS: 2.69 h/week, SD 6.3).

Figure 1:



Lustyk et al (2001) compared prevalence and severity of IBS symptoms between active and sedentary women with IBS (defined by ROME I criteria). They found that active and inactive women reported the same level of recalled psychological and somatic symptoms as well as daily reports of GI and psychological distress. Active women (those who took at least 2.5 hours per week of moderate physical activity and meeting recommended physical activity levels) reported significantly less fatigue than sedentary women. This outcome was assessed by combining frequency and severity of fatigue using categorical scale. No differences were observed for

other somatic symptoms including backache, headache and insomnia between active and sedentary women with IBS.

Dancey et al (2002) examined gender differences in the prevalence and severity of IBS symptoms. They used a cross sectional survey to compare the prevalence and impact of IBS symptoms between 117 male and female IBS patients. IBS was assessed by self report measure with respondents rating severity of abdominal pain, constipation, diarrhoea, incomplete evacuation after bowel movement, bloating and flatulence on a 7 point severity scale (0 = no symptoms to 7 = extremely severe). Illness intrusiveness ratings were assessed across 13 life domains, using a 7 category Likert scale. Respondents were asked to rate the extent to which their illness interfered with each life domain important to quality of life (e.g. health, diet, financial situation, relationship with partner etc.). One life domain was active recreation (e.g. sports). The authors reported that in response to this item, men and women scored the interference of IBS similarly (i.e. moderate interference), with no significant differences between genders. They found that IBS inference was higher in diet, health and self expression domains than active recreation. Other domains reporting less interference than active recreation were social relations, work, community/civic life, sex life, relationship with spouse, family relations, financial situation, passive recreation and religious expression.

Two studies examined the relationship between physical activity and bowel frequency in the general population. In a cohort study, Sanjoaquin et al (2004) investigated the association between mean number of bowel movements and physical activity, adjusted for other confounding variables (e.g. age, BMI, diet, fibre intake) in 20,630 EPIC-Oxford cohort participants. The EPIC-Oxford cohort is a cohort study forming part of the European Prospective Investigation into Cancer and Nutrition (EPIC). Participants were recruited from general practice surgeries, vegetarian and health food magazines, the Vegetarian Society, the Vegan Society and from friends and relatives of participants. In a follow up study a short questionnaire was sent to all participants and included two questions relating to bowel movements, (i) “About how many bowel movements do you have each week? And (ii) How often do you take laxatives?” The number of bowel movements was counted for each participant. Respondents were then dichotomised into one of two groups, either above of below 7 movements per week.

The authors reported a positive association between increasing amounts of vigorous physical activity and mean number of bowel movements per week for both men and women. However only highly active women (more than 7 hours per week of vigorous physical activity) had a greater likelihood of reporting more than 7 bowel movements per week (OR; 1.70 [95%CI 1.42, 2.03]) compared to women who reported no vigorous physical activity. Curtin et al (1996) conducted a population survey of bowel habits in urban Swiss men but found no relationship between physical activity status and bowel habits.

EVIDENCE STATEMENTS

1. There is poor evidence to show that the percentage of incomplete stools decreased significantly in non-IBS constipated people given an exercise programme.

2. There is weak evidence that IBS Manning and pain scores at one and six months were reduced significantly in comparison with pre-intervention scores following a patient education class that included exercise for people with IBS.

3. There is mixed evidence on whether there is a positive association between physical activity and bowel habits in the general population.

GDG DISCUSSION

The GDG considered the evidence and discussed whether exercise effects were related to stress reduction. It was noted that some people may have increased stress levels because of exercise, depending on their liking for exercise. The GDG thought that exercise would not necessarily be beneficial for people with IBS-D. It was also noted that attendance at exercise classes might prove difficult for patients and a gentle exercise programme that could be carried out at home (e.g. Tai Chi, yoga, stretching) might be more beneficial.

The GDG discussed whether it was useful to recommend taking more fluid after exercise, but concluded that this would not necessarily be appropriate for people with IBS, since many have bladder problems, and taking more fluid does not help constipation.

EVIDENCE TO RECOMMENDATION

The GDG took into consideration the limited evidence and also referred to NICE public health guidance and the Chief Medical Officers report on physical activity. This led to a general recommendation for practice.

Recommendations for active living throughout the lifecourse (DoH 2004)

- For general health benefit, adults should achieve a total of at least 30 minutes a day of at least moderate intensity physical activity on 5 or more days of the week.
- The recommended levels of activity can be achieved either by doing all the daily activity in one session, or through several shorter bouts of activity of 10 minutes or more. The activity can be lifestyle activity* or structured exercise or sport, or a combination of these.
- More specific activity recommendations for adults are made for beneficial effects for individual diseases and conditions. All movement contributes to energy expenditure and is important for weight management. It is likely that for many people, 45-60 minutes of

* Lifestyle activity: activities that are performed as part of everyday life, such as climbing stairs, walking (for example to work, school or shops) and cycling. They are normally contrasted with 'programmed' activities such as attending a dance class or fitness training session.

moderate intensity physical activity a day is necessary to prevent obesity. For bone health, activities that produce high physical stresses on the bones are necessary.

- The recommendations for adults are also appropriate for older adults.
  Older people should take particular care to keep moving and retain their mobility through daily activity. Additionally, specific activities that promote improved strength, co-ordination and balance are particularly beneficial for older people.
- People with disabilities will know their abilities and should modify their physical activity accordingly e.g. chair-based exercises.

The GDG was also interested to know if exercise affects IBS symptoms and quality of life for people with IBS, and whether the type of IBS was important.

RECOMMENDATION

Healthcare professionals should assess the physical activity levels of people with IBS, ideally using the General Practice Physical Activity Questionnaire (GPPAQ; see Appendix J). People with low activity levels should be given brief advice and counselling to encourage them to increase their activity levels.

7.3 Fibre

SELECTION CRITERIA

The selection criteria described in the general methodology section were to be used, but some were specific to the fibre review and are reported below.

Types of studies

The GDG decided that the washout period for crossover studies in this review should be at least 4 weeks. Trials with shorter washout periods were not to be included in the analysis.

Types of intervention

Studies were to include the following interventions:

- Insoluble fibre (corn, wheat, fruit and vegetables)
- Soluble fibre (pectins, fruit and vegetables, oats, nuts and seeds, psyllium, ispaghula)
- Bran.

It was to be noted if the fibre was provided as a food or as a capsule/supplement. In addition, the total amount of fibre in the diet for each intervention was to be recorded where possible.

The following comparisons were to be included:

- Fibre + normal diet versus normal diet (fibre versus nothing)
- Fibre versus low fibre diet or placebo (fibre versus placebo)
- Bran versus placebo
- Insoluble fibre versus soluble fibre
- Insoluble fibre + soluble fibre versus soluble fibre
- Insoluble fibre + soluble fibre versus insoluble fibre
- Fibre level 1 versus fibre level 2
- Duration of treatment 1 versus duration 2
- Fibre versus another type of intervention
- Fibre plus another type of intervention versus another type of intervention.

In spite of the large placebo effect associated with IBS, comparisons with no treatment were to be included.

The fibre review was to be concerned only with longer-term maintenance treatment. The GDG decided that there should be a minimum duration of treatment of four weeks for this review. Studies of shorter durations were to be excluded.

Outcomes

In addition to the outcomes discussed in the general methods section, the GDG were interested in the number of people with global deterioration, other than those who withdrew because of the treatment.

Data extraction

In addition to the items given in the general section, we also extracted information on the total amount of fibre (i.e. the sum of the intervention and the fibre in the diet).

Subgroup analyses

We planned to carry out subgroup analyses by type of fibre (soluble, insoluble, mixed), dose (both intervention and total amount), duration of intervention, and, post-hoc, by means of ingestion (supplement or dietary).

SEARCH STRATEGY FOR IDENTIFICATION OF STUDIES

Searches were performed on the following core databases: MEDLINE, EMBASE, CINAHL and *The Cochrane Library* (1966 to current day with guidance from the GDG). Additional databases were not searched for this review. The search strategies are given in Appendix B.

The titles and abstracts from the search strategy were assessed. Sixty-four were identified to be potentially relevant to the review and these papers were retrieved in full. Twenty studies met the inclusion criteria for the review. The reference lists of the retrieved studies were inspected for further potential papers, but none were identified. The forty-four excluded studies are listed in the Appendix, along with reasons for exclusion.

DESCRIPTION OF STUDIES INCLUDED IN THE REVIEW

There were 20 included studies (Aller 2004; Arthurs 1983; Chapman 1990; Cook 1990; Dettmar 1999; Fielding 1984; Fowlie 1992; Kruis 1986; Longstreth 1981; Lucey 1987; Manning 1977; Parisi 2002; Parisi 2005; Prior and Whorwell 1987; Rees 2005; Ritchie 1979; Ritchie 1980; Soltoft 1976; Tarpila 2004; Vilagrasa 1991). Nine studies were conducted in the UK (Chapman 1990; Dettmar 1999; Fowlie 1992; Lucey 1987; Manning 1977; Prior and Whorwell1987; Rees 2005; Ritchie 1979; Ritchie 1980); two in Ireland (Arthurs 1983; Fielding 1984); seven in the rest of Europe, and two in the USA and Canada.

One study (Cook 1990) had fewer than 20 participants (n=14). This was a crossover study so fewer participants were required to achieve adequate power. Five studies had more than 100 participants in total (Chapman 1990; Dettmar 1999; Kruis 1986; Parisi 2002; Villagrasa 1991).

Study Design

Setting: The majority of studies took place in secondary care; one was in primary care (Dettmar 1999) and one study did not report the setting (Tarpila 2004).

There were two crossover studies (Cook 1990; Lucey 1987) in which participants were allocated to receive both the intervention and control treatments during the course of the study, in a random order. The GDG defined the minimum washout period to be four weeks for crossover studies in this review, so the only crossover study eligible was Cook (1990). However, a second crossover study (Lucey 1987) became eligible because individual patient data were reported, allowing calculation of first period results. This gave the study a 'pseudo-parallel' design, although the power was reduced. The remaining studies had a parallel design. One study had more than two arms: Kruis (1986) compared bran with mebeverine (anti-spasmodic) and placebo.

Population

The definition of IBS varied between studies: two used the Manning criteria (Chapman 1990; Cook 1990); two used Rome I (Parisi 2002; Rees 2005); two used Rome II (Aller 2004; Parisi 2005) and two met criteria defined by the authors that were similar to the above (Fielding 1984; Tarpila 2004). In five studies, the authors stated that the participants had IBS, with no further explanation (Lucey 1987; Manning 1977; Ritchie 1979; Ritchie 1980; Vilagrasa 1991). The remaining seven studies (Arthurs 1983; Dettmar 1999; Fowlie 1992; Kruis 1986; Longstreth 1981; Prior and Whorwell 1987; Søltoft 1976) did not use a formal definition but described a range of symptoms consistent with IBS.

Most studies included a combination of IBS types. Four specified constipation-predominant IBS (Cook 1990; Fielding 1984, Rees 2005; Tarpila 2004) and three were unclear (Arthurs 1963; Dettmar 1999; Fowlie 1992).

None of the studies stated that any participants had IBS as result of gastrointestinal infection. The majority of studies (13) did not state the number of participants with bloating. Four studies reported that some people had bloating (Aller 2004; Kruis 1986; Longstreth 1981; Vilagrasa 1991). Two studies (Prior and Whorwell 1987; Tarpila 2004) stated that all people had bloating.

Most of the studies did not describe symptom severity. Six studies stated that participants had symptoms of mixed severity (Dettmar 1999; Fowlie 1992; Longstreth 1981; Parisi 2002; Parisi 2005; Prior and Whorwell 1987).

The age range of participants across studies was 14 to 82 years, with the mean age (where given) ranging from 25.8 to 45 years. No study particularly identified elderly people. All studies had more women than men.

Interventions

The studies varied in the type of fibre used: six had insoluble fibre (wheatbran); eight had soluble fibre (six ispaghula, one partially hydrolysed guar gum ['PHGG'], one psyllium); five had mixed fibres: studies used a combination of fruit, vegetables and cereal.

One study gave the fibre in a capsule form (Fowlie 1992), eight gave the fibre as a supplement (Arthurs 1983; Chapman 1990; Dettmar 1999; Fowlie 1992; Longstreth 1981; Prior and Whorwell 1987; Ritchie 1979; Ritchie 1980); and the rest added fibre to the diet with food (e.g. bran-containing biscuits).

A fibre level of 18g per day is regarded as a threshold dose. When assessing dose we considered both the amount of additional fibre and the amount of total fibre (intervention plus that in the diet). The amount of additional fibre ranged from 7g per day (Dettmar 1999), although a third 3.5g sachet could be added if needed, to 40g per day (Fielding 1984). Ten studies gave additional fibre as amounts of less than 18g (Chapman 1990; Dettmar 1999; Fowlie 1992; Kruis 1986; Lucey 1987; Parisi 2005; Prior and Whorwell 1987; Rees 2005; Ritchie 1979; Ritchie 1980). Nine studies gave more than 18g (Aller 2004; Arthurs 1983; Cook 1990; Fielding 1984; Longstreth 1981; Parisi 2002; Manning 1977; Søltoft 1976; Villagrasa 1991). One study (Tarpila 2004) gave 12 to 24g daily.

Eight studies reported the total fibre in the intervention arm (Aller 2004; Arthurs 1983; Cook 1990; Fielding 1984; Fowlie 1992; Prior and Whorwell 1987; Tarpila 2004; Villagrasa 1991).

The duration of the intervention ranged from four weeks (Arthurs 1983; Dettmar 1999; Fielding 1984; Parisi 2002) to two years (Villagrasa 1991). One study reported follow-up after the end of the trial (Parisi 2005; 3 months follow-up).

Comparisons

The included studies covered the following comparisons:

- Eleven comparisons of fibre versus placebo, including one versus usual diet (Kruis 1986); and one versus reduced fibre (Manning 1977):
    - Four gave soluble fibre (Arthurs 1983; Longstreth 1981; Prior and Whorwell 1987; Ritchie 1979)
    - Six gave insoluble fibre (Cook 1990; Kruis 1986; Lucey 1987; Manning 1977; Rees 2005; Søltoft 1976)
    - One gave mixed fibre (Fowlie 1992);
- Three studies compared different classes of fibre:
    - Two studies compared soluble versus insoluble fibre
        - PHGG versus bran (Parisi 2002)

        - Ispaghula versus bran (Ritchie 1980)
    - One study compared mixed versus soluble fibre
        - Ground flax seed (containing 20% flaxseed oil) versus psyllium (Tarpila 2004);
- One study compared different types of fibre in the same class (mixed):
    - One study compared different combinations of fruit and cereal fibre (Fielding 1984);
- Two studies compared different doses of fibre:
    - One compared 30.5g with 10.4g of mixed fibre. However, the proportion of soluble fibre differed between the two groups (13% versus 19%) (Aller 2004)
    - One study compared 5 and 10g of PHGG (Parisi 2005);
- Two studies compared fibre + mebeverine versus mebeverine + dietary advice (Chapman 1990; Dettmar 1999)
- Two studies compared fibre with an antispasmodic (Kruis 1987; Villagrasa 1991).

OUTCOMES

The studies measured a range of outcomes.

1. Global symptoms

a) Number of people with improvement in global symptoms

Ten studies recorded the participants' assessment of improvement (Fowlie 1992; Kruis 1986; Longstreth 1981; Lucey 1987; Parisi 2002; Prior and Whorwell 1987; Rees 2005; Ritchie 1979; Ritchie 1980; Søltoft 1976) and one (Arthurs 1983) appeared to record a clinician's assessment.

b) Number of people with deterioration in global symptoms

Four studies recorded the participants' assessment of deterioration (Longstreth 1981; Lucey 1987; Parisi 2002; Søltoft 1976).

c) Global symptom score (mean)

Global symptom scores combined pain, bowel habits, flatulence and bloating. This outcome was recorded by five studies (Cook 1990; Fowlie 1992; Longstreth 1981; Lucey 1987; Parisi 2005). Longstreth (1981) recorded how symptoms interfered with normal activity.

2. Individual symptoms

a) Pain

Pain was reported in several ways: the number of people with pain at the end of the study; the number of people whose pain improved or worsened compared with the baseline, and; pain scores. The pain score recorded a range of features, including severity, frequency and duration, or a combination of these. In addition, studies recorded the final scores, mean daily scores or the change from baseline. The studies reporting the following outcomes are listed below:

i. Number of people with pain: three studies (Parisi 2002; Prior and Whorwell 1987; Villagrasa 1991)

ii. Number of people with more pain: one study (Chapman 1990)
iii. Number of people with no pain: two studies (Prior and Whorwell 1987; Villagrasa 1991)
iv. Number of people with less pain: four studies (Chapman 1990; Dettmar 1999; Fielding 1984; Kruis 1986)
v. Pain score (change and final): six studies (Aller 2004; Cook 1990; Fowlie 1992; Longstreth 1981; Manning 1977; Parisi 2005):
    a. Three studies reported pain severity at the end of the study (Cook 1990; Fowlie 1992; Parisi 2005)
    b. Two studies reported pain severity from daily diary readings (Longstreth 1981; Manning 1977)
    c. One study reported a combined score for pain frequency and severity (Aller 2004) and this study also reported change scores. In all cases the highest rating meant worst symptoms, although the scales used were not the same.

b) Bloating

i. Number of people with bloating: two studies (Prior and Whorwell 1987; Villagrasa 1991)
ii. Number of people with more bloating: one study (Tarpila 2004)
iii. Number of people with no bloating: two studies (Prior and Whorwell 1987; Villagrasa 1991)
iv. Number of people with less bloating: one study (Tarpila 2004)
v. Bloating score (change and final): no studies reported this outcome.

c) Combined bloating and flatulence score

Three studies measured end of study scores (Aller 2004; Longstreth 1981; Parisi 2005).

d) Bowel habits

i. Number of people with improved bowel habits

Eight studies recorded the number of people with improved bowel habits (Chapman 1990; Dettmar 1999; Fielding 1984; Kruis 1986; Manning 1977; Parisi 2002; Tarpila 2004; Villagrasa 1991). Of these, two reported normalisation of bowel habits (Parisi 2002; Villagrasa 1991), and the rest reported the patient's assessment of improvement.

ii. Stool score (aggregate)

Three studies (Aller 2004; Fowlie 1992; Longstreth 1981) measured an aggregate of frequency, consistency and straining. Fowlie (1992) reported the sum of number of stools x consistency score (1=hard; 5=watery), for people whose IBS type was unclear; we regarded this outcome as unhelpful. Longstreth (1981) reported the number of normal stools and this study was included in the analysis.

e) Quality of life

Two studies reported a measure of quality of life (Fielding 1984; Parisi 2005). Parisi (2005) reported the social functioning item on the SF-36 scale.

f) Adverse events

Two studies reported adverse effects (Chapman 1990; Villagrasa 1991).

METHODOLOGICAL QUALITY

The results of the quality assessment for included trials are shown in Appendix D. The method of randomisation was reported in one study, classified as partially adequate (Manning 1977; drawing a randomly numbered card). The other studies did not state the method of randomisation.

Allocation concealment was reported in two studies (Parisi 2002; Parisi 2005), both of which reported a partially adequate method in which randomisation and analysis were said to be 'supervised by a statistician'.

Nine studies reported that the outcome assessors were blinded to the interventions (Cook 1990; Fielding 1984; Longstreth 1981; Manning 1977; Prior and Whorwell 1987; Ritchie 1979; Ritchie 1980; Søltoft 1976; Tarpila 2004). One study stated that the outcome assessors were not blinded (Parisi 2002). The remaining studies did not report blinding of outcome assessors.

Eleven studies reported that the participants were blinded to the interventions (Arthurs 1983; Cook 1990; Fowlie 1992; Longstreth 1981; Lucey 1987; Prior and Whorwell 1987; Rees 2005; Ritchie 1979; Ritchie 1980; Søltoft 1976; Tarpila 2004). Eight studies stated that the participants were not blinded (or this was deduced from intervention differences) (Aller 2004; Chapman 1990; Dettmar 1999; Fielding 1984; Kruis 1986; Manning 1977; Parisi 2002; Villagrasa 1991). One study (Parisi 2005) was unclear about patient blinding.

Only one study (Cook 1990) described an *a-priori* power calculation. Several studies included in the review demonstrated baseline comparability of the groups, but eight did not give baseline characteristics (Arthurs 1983; Dettmar 1999; Longstreth 1981; Lucey 1987; Manning 1977; Ritchie 1979; Ritchie 1980; Søltoft 1976).

Six studies reported no withdrawals (Aller 2004; Dettmar 1999; Lucey 1987; Parisi 2002; Ritchie 1979; Ritchie 1980). Four studies reported that more than 20% of people in at least one arm (or overall) were not analysed or were lost to follow-up (attrition bias):

- Cook (1990): 5/14 (36%) of participants withdrew from the study

- Longstreth (1981): 6/40 (15%) on placebo and 11/37 (30%) on psyllium did not complete the study. 3/6 and 7/11 respectively dropped out because of dislike for the study preparation or failure to improve; 1/6 and 1/7 dropped out because their symptoms improved
- Prior and Whorwell (1987): 8/40 (20%) withdrew from ispaghula group; 15/40 (38%) withdrew from placebo group. This study reported most recent data carried forward in the analysis, but this is not an approved method of handling missing data. The study also stated that 4/8 and 10/15 withdrawals, respectively, were because of treatment failure.
- Rees (2005): 2/14 (14%) did not complete the study in the intervention arm and 4/14 (29%) on placebo. There were no further details.

Thus, Cook (1990), Longstreth (1981), Prior and Whorwell (1987) and Rees (2005) were treated with caution and examined in sensitivity analyses.

The risk of bias was assessed for each included study. Four studies were assessed as being at higher risk of bias (Cook 1990; Longstreth 1981; Prior and Whorwell 1987; Rees 2005 – attrition bias) and were treated with caution. The eight studies that reported that the participants were not blinded (Aller 2004; Chapman 1990; Dettmar 1999; Fielding 1984; Kruis 1986; Manning 1977; Parisi 2002; Villagrasa 1991) were also treated more cautiously.

RESULTS

A. Fibre versus Placebo

There were eleven studies that compared fibre with placebo (Arthurs 1983; Cook 1990; Fowlie 1992; Kruis 1986; Longstreth 1981; Lucey 1987 first period only; Manning 1977; Prior and Whorwell 1987; Rees 2005; Ritchie 1979; Søltoft 1976). Two of these studies were in people with constipation-predominant IBS (Cook 1990; Rees 2005); three did not specify the type of IBS (Arthurs 1983; Fowlie 1992; Ritchie 1979) and the remainder had mixed IBS types. Therefore the studies were not stratified by IBS type. Similarly, there was too little information to separate by severity, post-infective cause or bloating status.

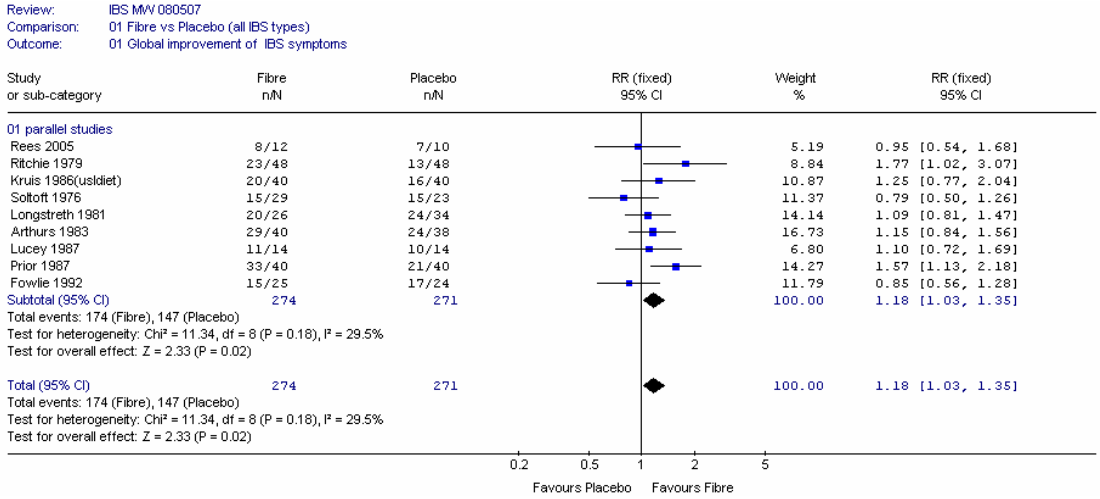
Where outcomes were measured at different times during the study, we took the end-study results unless there were significant numbers of withdrawals or problems with compliance. Therefore, for the Kruis (1986) study we took the values at four weeks. The results in Rees (2005) were collected between week 8 and week 12 (11 people were assessed at week 8; six at week 9; three at week 10; one at week 11, and; one at week 12).

1. Global symptoms

a) Number of people with improvement in global symptoms

Nine studies with 545 participants reported this outcome. Overall the relative risk was 1.18 (95% CI 1.03 to 1.35), i.e. statistically significant, in favour of fibre.

Figure 1



Subgroup analysis into soluble and insoluble fibres (Figure 2) gave some suggestion that soluble fibre was more effective than insoluble, however, this conclusion was fairly reliant on the Prior and Whorwell (1987) study, which had some attrition bias and was analysed using the last measurement carried forward method. A sensitivity analysis without Prior and Whorwell (1987), Longstreth (1981), Rees (2005 - attrition bias) and Kruis (1986 - which did not have a placebo comparator) showed little difference in global improvement between fibre and placebo overall, although the results for soluble fibre were still significant (Figure 3a).

Figure 2:

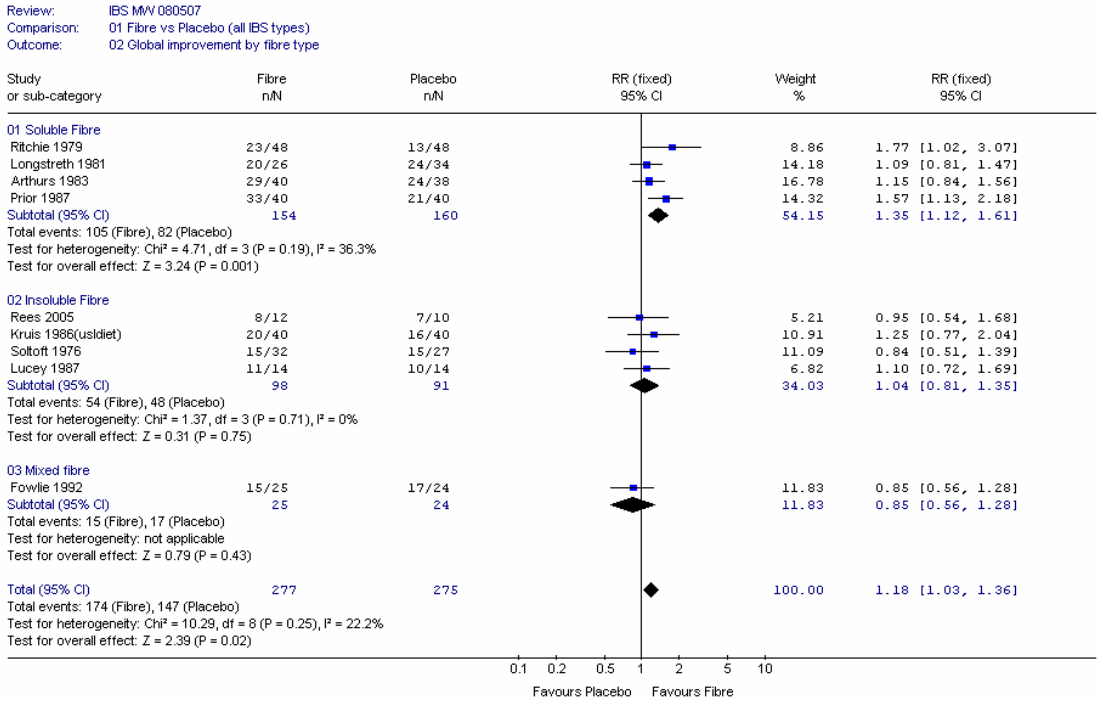
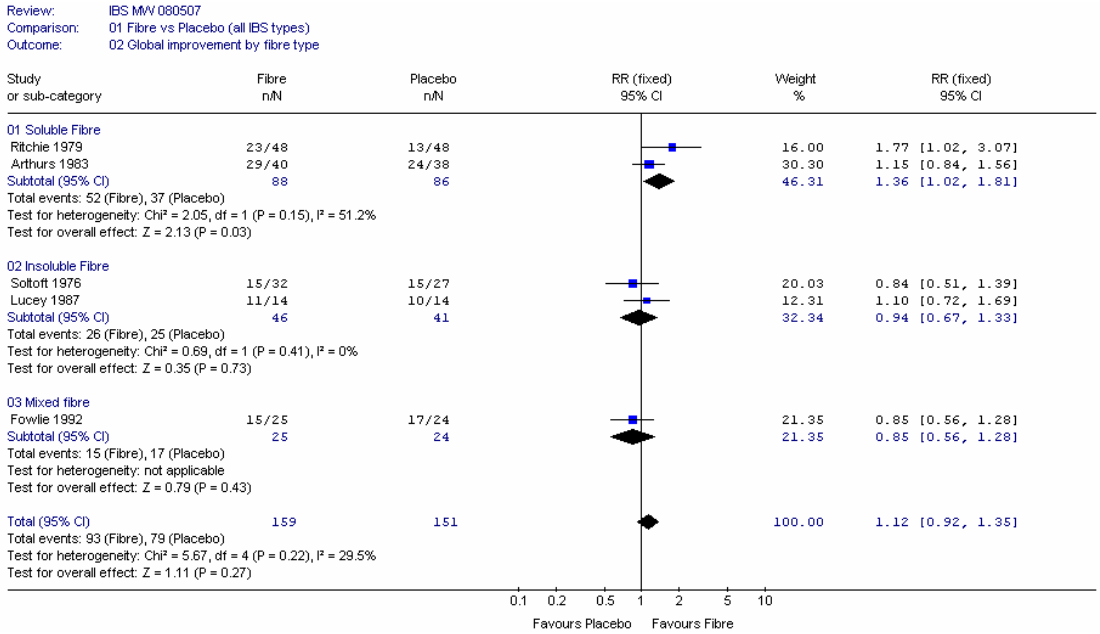


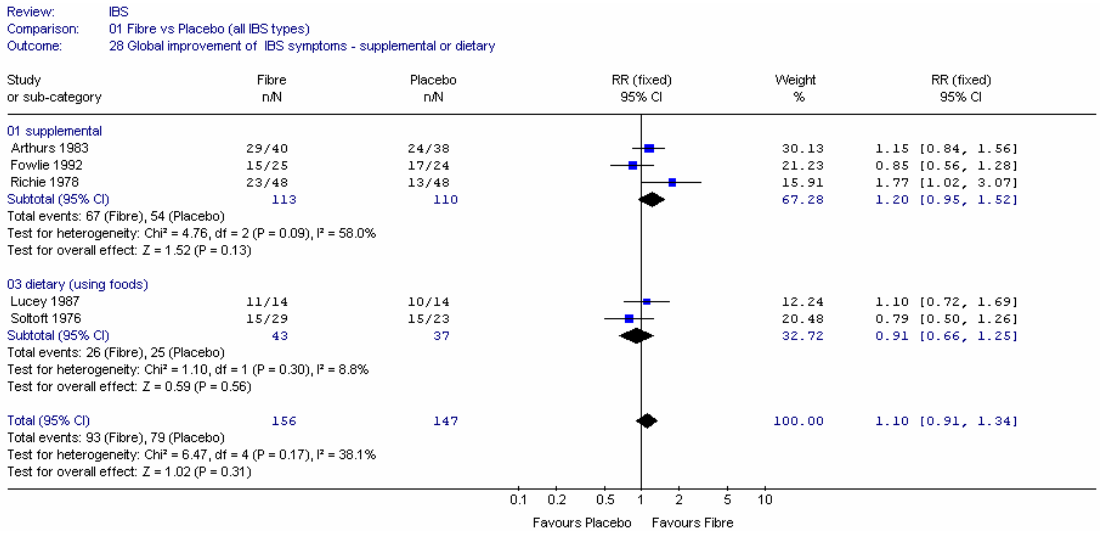
Figure 3: Sensitivity analysis



Sensitivity analysis by method of ingestion

A further sensitivity analysis was carried out on the studies that were not at risk of bias, to investigate if there was an effect of supplementary fibre compared with dietary fibre. This was examined in a subgroup analysis (Figure 3b). There was heterogeneity (I^2=58%, p=0.09) in the supplement group, which was probably caused by different types of fibre.

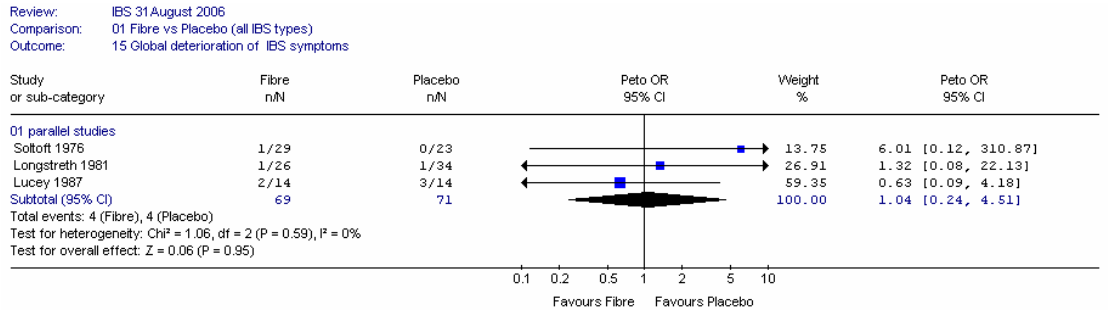
Figure 3b



b) Number of people with deterioration in global symptoms

Three studies reported this outcome, and included 140 participants (Figure 4). The numbers of events were few and there was too much uncertainty (wide confidence interval) to draw conclusions.

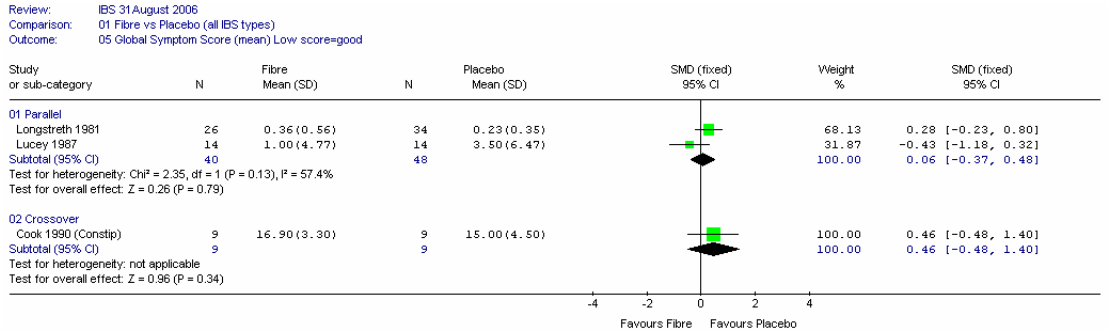
Figure 4:



c) Global symptom score (mean)

This outcome was recorded by four studies (Cook 1990; Fowlie 1992; Longstreth 1981; Lucey 1987), and different scales were used. Fowlie (1992) did not give scores for the two groups and Cook (1990) was a crossover design (and had some attrition bias). In view of the different scales it was not possible to meta-analyse the parallel and crossover studies using the generic inverse variance method, so the two remaining parallel studies and the crossover study were analysed separately using the standardised mean difference. The results were inconclusive (Figure 5).

Figure 5



2. Individual symptoms

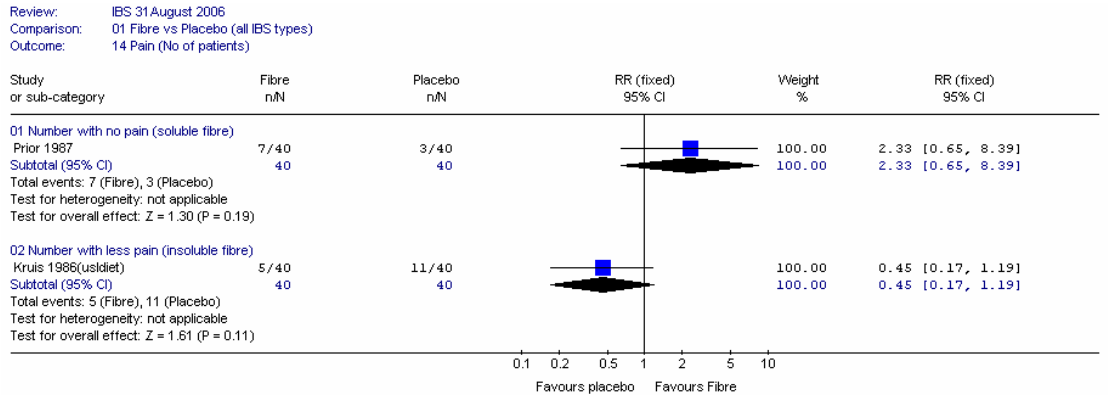
a) Pain

The following studies measured pain:

i. Number of people with no pain: one study (Prior and Whorwell 1987)
ii. Number of people with less pain: three studies (Kruis 1986)
iii. Pain score (final): four studies (Cook 1990; Fowlie et al 1992; Longstreth et al 1981; Manning 1977);
vi. Two studies reported pain severity at the end of the study (Cook 1990; Fowlie 1992)
iv. Two studies reported pain severity from daily diary readings (Longstreth 1981; Manning 1977).

Figure 6 shows the number of people with less pain and the number of people with no pain, in two single studies. The confidence intervals were too wide to draw conclusions.

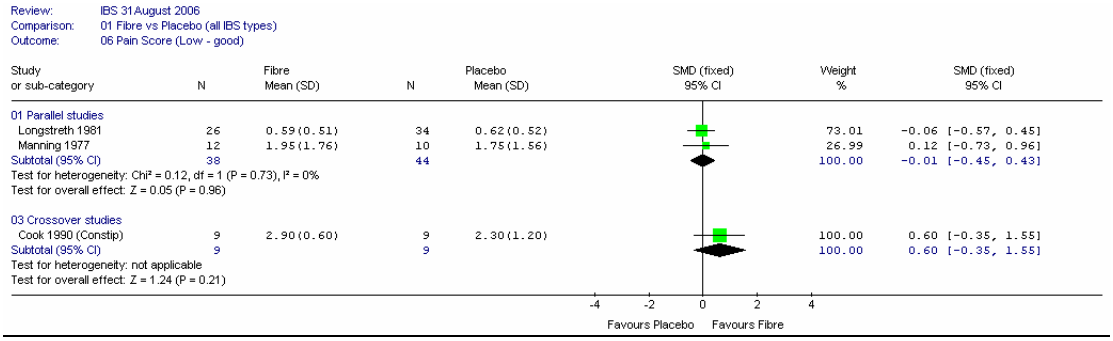
Figure 6



Fowlie (1992) only gave the difference in the mean change score from baseline and its 95%CI, which was 1 (95%CI -1.5, 4), i.e. not statistically significant.

Combining the other three studies recording pain score, using the standardised mean difference (Figure 7), showed little difference between fibre and placebo, but the data was limited.

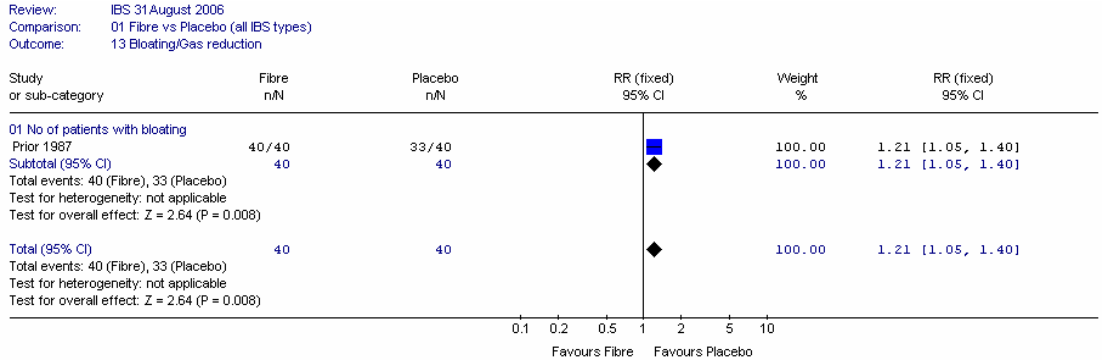
Figure 7



b) Bloating

Only one study (Prior and Whorwell 1987) reported bloating (Figure 8). This showed that statistically significantly more people had bloating when they took fibre (soluble) compared with placebo. It should be noted that this was a last measurement carried forward analysis, but that a large proportion withdrew from the study in the ispaghula group.

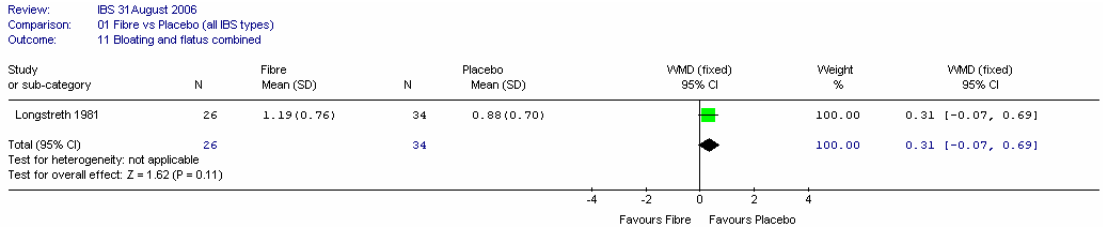
Figure 8



c) Combined bloating and flatulence score

One study reported this outcome (Longstreth 1981). The results showed a small non-significant difference (0.31 on a scale of 0 to 4) in favour of placebo. We noted that this study had attrition bias.

Figure 9

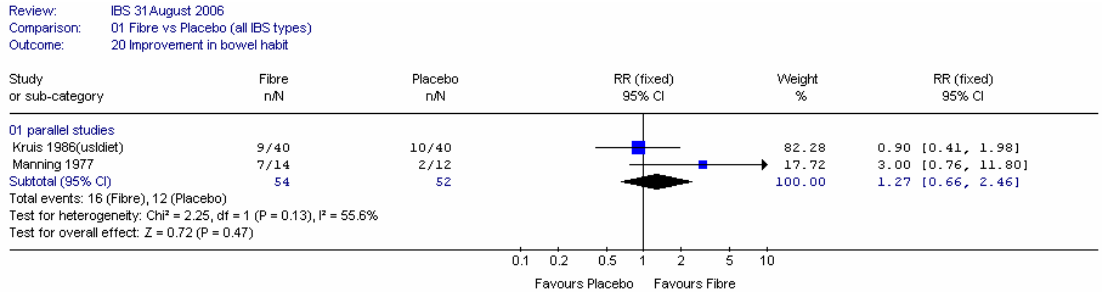


d) Bowel habits

i. Number of people with improved bowel habits

Two studies, with 106 participants, recorded the number of people with improved bowel habits (Kruis 1986; Manning 1977). Meta-analysis showed some heterogeneity between studies and a wide confidence interval. Each study was a comparison with a non-placebo comparator (low fibre or usual diet).

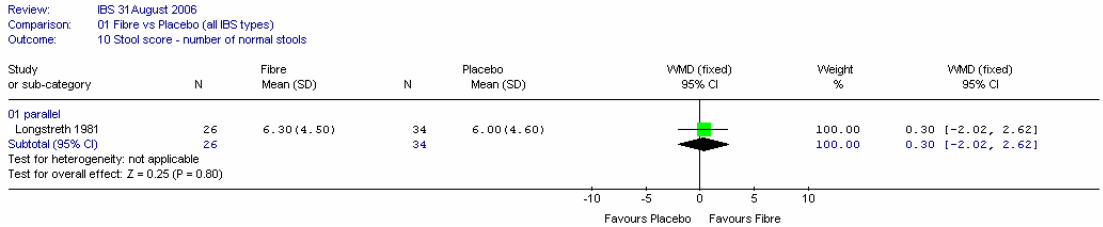
Figure 10



ii. Stool score (aggregate)

Longstreth (1981) reported the number of normal stools per week. The confidence interval was fairly wide (-2.0 to 2.6), but there was little difference between fibre and placebo. We noted that this study had attrition bias.

Figure 11



B. Fibre type 1 versus Fibre type 2

B1. Insoluble versus soluble fibre

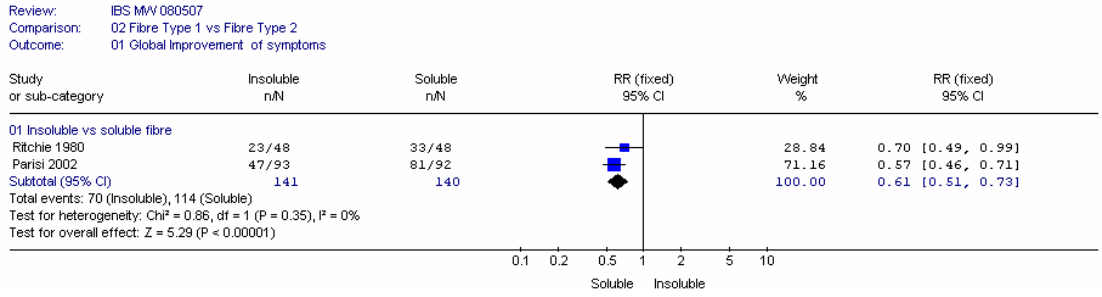
Two studies compared insoluble and soluble fibre: Parisi (2002) compared wheat bran (insoluble; 30g/day) with guar gum (soluble; 5g/day) in people with a mixture of IBS types; Ritchie (1980) compared coarse natural bran (insoluble; 20g/day) with ispaghula (soluble; Fibogel 7g/day).

1. Global outcomes

a) Global improvement of symptoms

Meta-analysis of two studies (Parisi 2002; Ritchie 1980) in 281 people, found a statistically significant increase in the number of people reporting improved global symptoms in favour of the soluble fibre (RR 0.61, 95% CI 0.51 to 0.73), with no heterogeneity. This corresponded to a number needed to harm of 3 (95%CI 2, 4), for a soluble group rate of 69 to 88%.

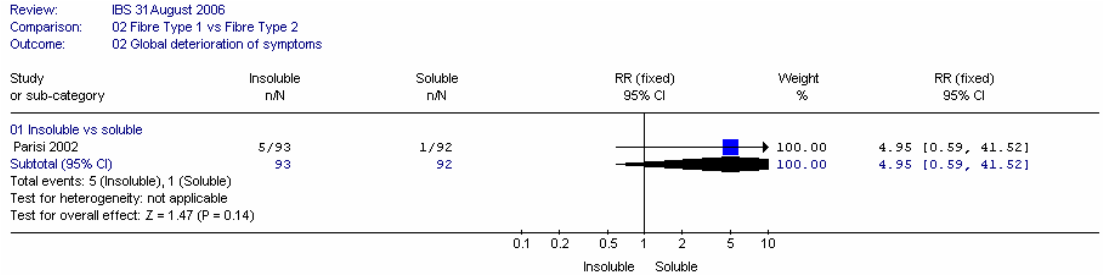
Figure 12



b) Global deterioration in symptoms

One study (Parisi 2002) showed a wide confidence interval for this outcome and conclusions could not be drawn.

Figure 13

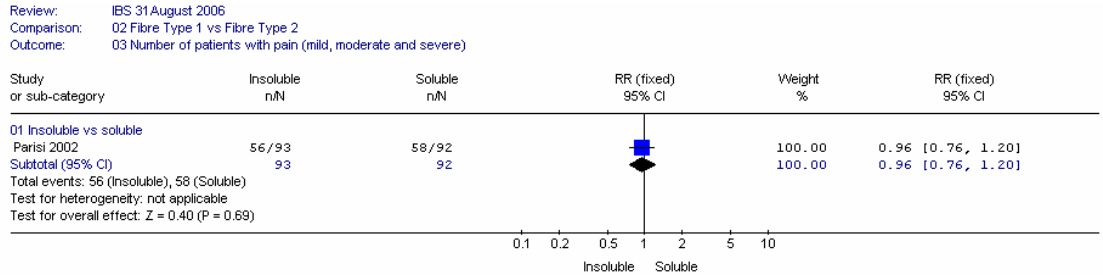


2. Individual symptoms

a) Pain

One study (Parisi 2002) showed little difference between the interventions for the number of people with pain.

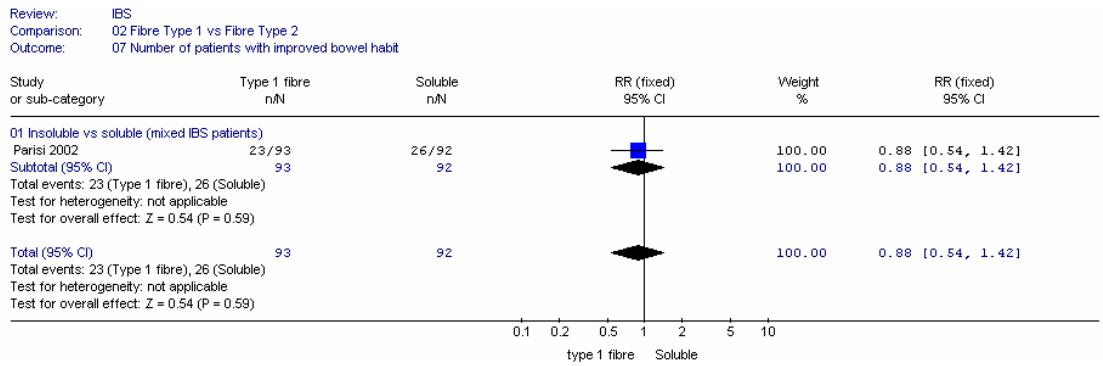
Figure 14



b) Bowel habits

There was no significant difference in the number of people with improved bowel habits.

Figure 15



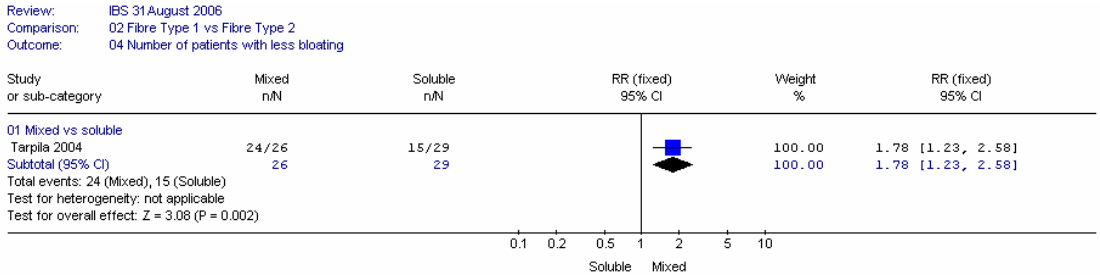
B2. Mixed fibre versus soluble fibre

Tarpila (2004) compared 6 to 24g/day flax seed (mixed fibre: 33% insoluble, 11% soluble, 20% flaxseed oil) with 6 to 24g/day psyllium (soluble), in 55 people with IBS-C.

a) Bloating

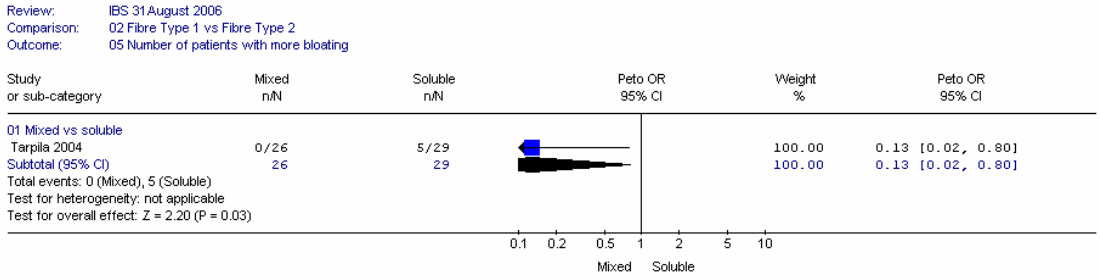
There were significantly more people with a reduction in bloating for the mixed fibres (flax seeds) group, compared to psyllium.

Figure 16a



The number of people with more bloating also significantly favoured the mixed fibre, although the confidence interval was very wide.

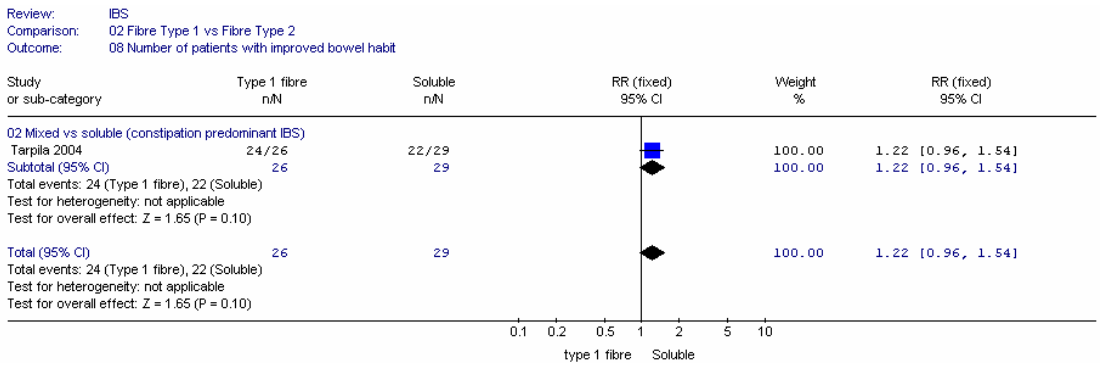
Figure 16b



b) Bowel habits

There was no significant difference in the number of people with improved bowel habits.

Figure 17



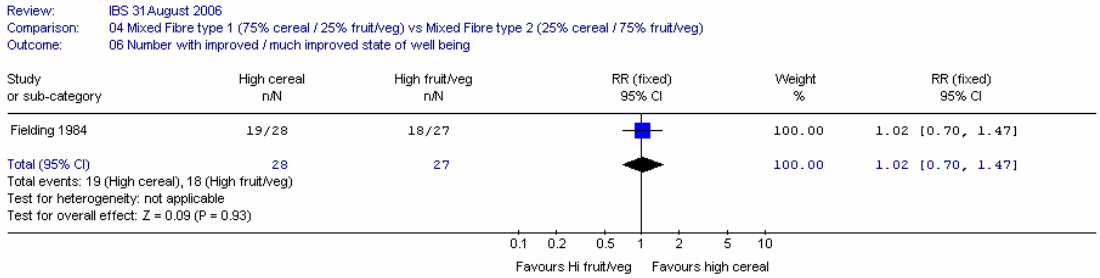
C. Mixed fibre 1 versus mixed fibre 2

One study (Fielding 1984) compared 40g of mixed fibre diet with different proportions of cereal and fruit/vegetables 75% cereal versus 25% cereal. The study recorded a state of well being score and individual symptom outcomes.

1. Number of people with an improved state of well being

There was little difference between interventions, although the confidence interval was fairly wide.

Figure 18

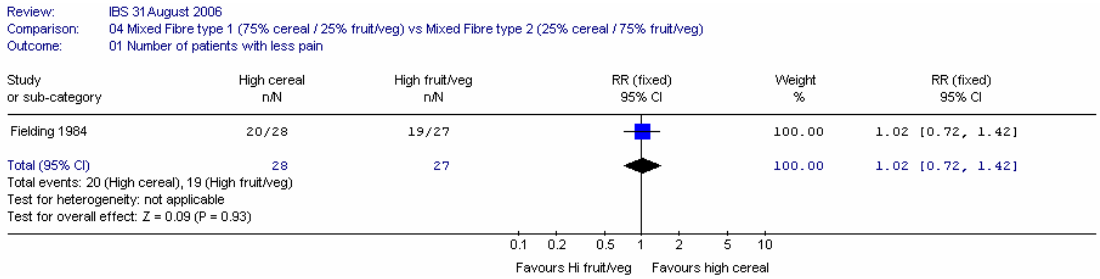


2. Individual symptoms

a) Number of people with less pain

There was little difference in pain incidence between the two types of mixed fibre.

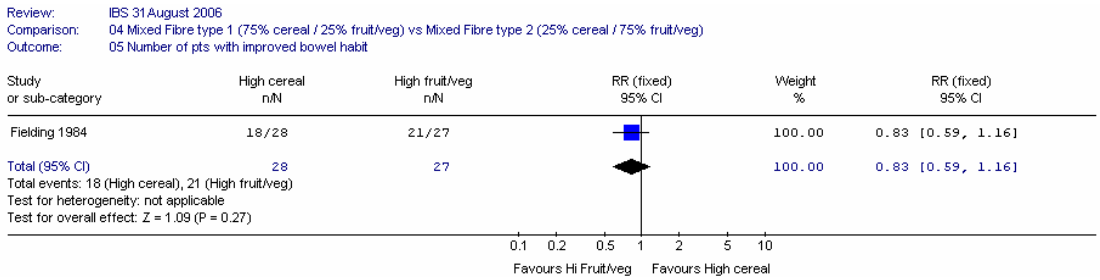
Figure 19



b) Number of people with improved bowel habit

There was little difference between interventions.

Figure 20



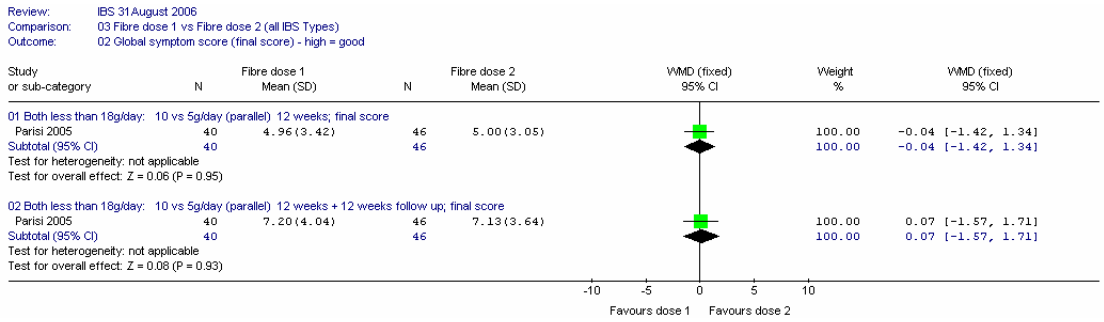
D. Fibre dose 1 versus fibre dose 2

Two studies compared different doses of fibre (Aller 2004; Parisi 2005). In the former, the comparison was 30.5 versus 10.4g /day of mixed fibre over 12 weeks (i.e. above versus below the 18g/day threshold). The latter compared 10 and 5g/day of partially hydrolysed guar gum over 12 weeks, which was then followed up for a further 12 weeks.

a) Global symptom score

There was little difference between interventions in a single study in 96 patients, and the further 12 weeks follow-up did not change this conclusion

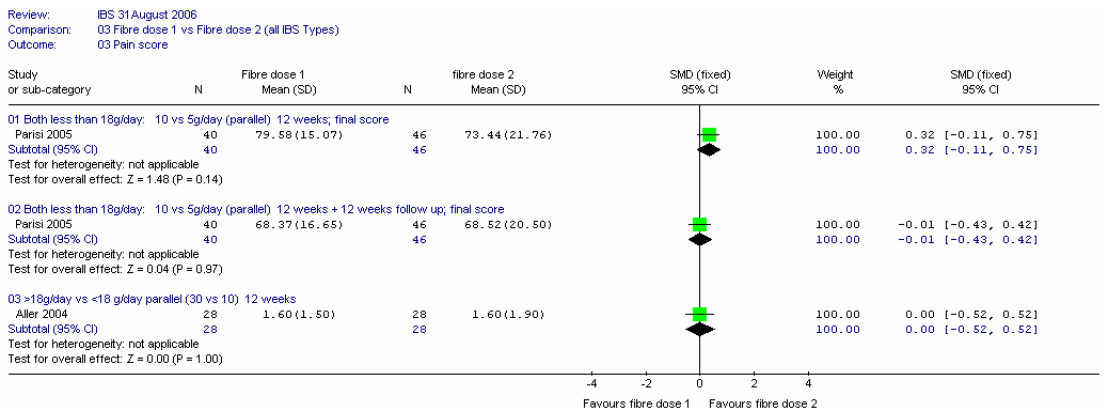
Figure 21



b) Pain score

There was a small, non-significant difference between interventions, favouring the lower dose of soluble fibre in Parisi (2005) at 12 weeks, which decreases to zero after a further 12 weeks. There was no significant difference in the two doses (above and below the threshold) for the Aller (2004) study.

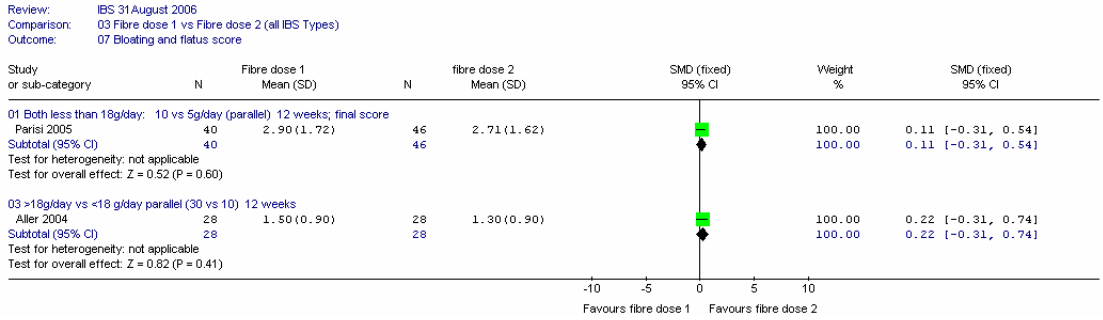
Figure 22



c) General bloating and flatus score

There is little difference between dose levels in either study.

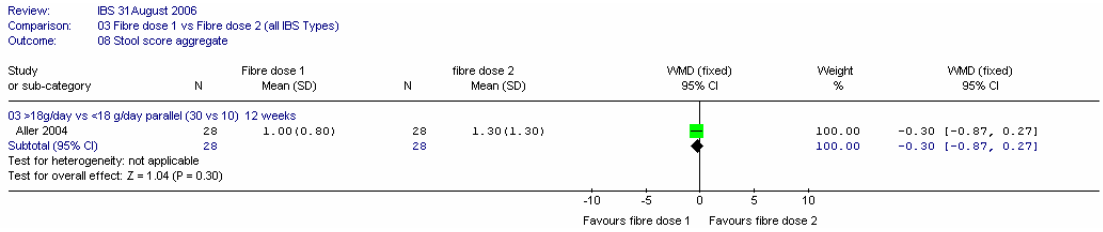
Figure 23



d) Bowel scores

There is little difference between doses for the Aller (2004) study.

Figure 24



E. Fibre plus another intervention versus another intervention alone

Two studies (Dettmar 1999; Chapman 1990) assessed ispaghula plus mebeverine (anti-spasmodic) versus mebeverine plus high fibre dietary advice. Each study reported the number of people improved in terms of abdominal pain, and in terms of improvements in bowel habit, at 4 weeks.

Figure 25

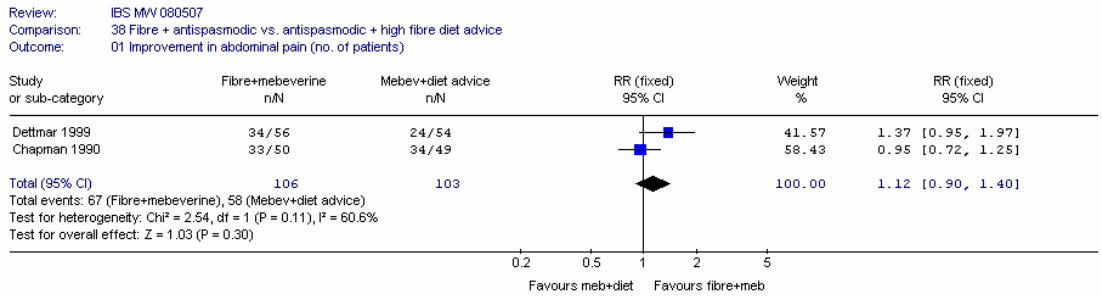
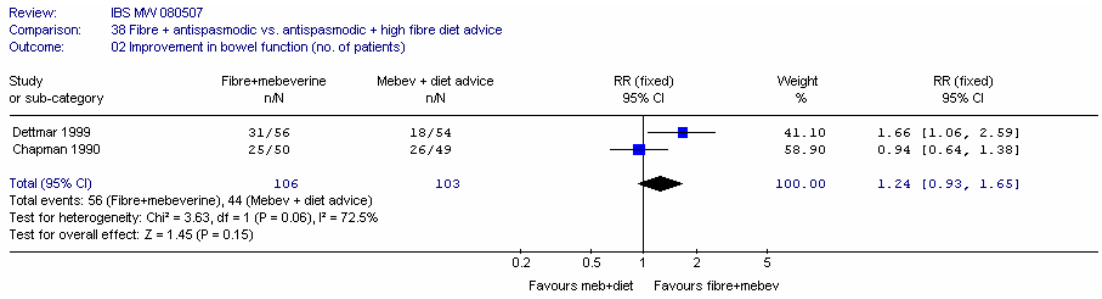


Figure 26



F. Protective effects of fibre for the prevention of colorectal adenomas and carcinomas, coronary heart disease and breast cancer

1. Colorectal Cancer

The role of diet in the development of colorectal cancer has long been hypothesised. Although there are many studies investigating the relationship between diet and colorectal cancer, the exact relationship remains unclear.

In the 1970's epidemiological studies first suggested an inverse relationship between foods rich in dietary fibre and the incidence of colorectal cancer. However, many of these studies were case-control designs, which were subject to selection bias and recall bias. Evidence from two large cohort studies (the Nurses Health Study in 88,757 women and the Health Professionals' Follow-up Study in 47,325 men) found that dietary fibre had no significant effect on the risk of colorectal cancer. A further cohort study in 61,463 people, however, found a weak association between fruit consumption and reduction in risk, but no association between cereal intake and risk. More recently a Cochrane review (Asano 2002) of five large randomised trials showed no significant protective effect of fibre on the development of colorectal adenomas within two to four years.

2. Coronary Heart Disease (CHD)

Prior to 2000, a number of reviews investigated the relationship between diet and CHD and Stroke. Since 2000 several studies have concentrated on the relationship between wholegrain dietary intake and CHD, and there is a body of evidence to support a 20 to 40% risk reduction of CHD for those who consume a diet rich in wholegrains compared to those who do not. However many studies have not shown an independent effect of fibre alone. The only RCT in secondary prevention of CHD that advised participants to eat more cereal fibre showed no reduction in the reinfarction rate, but there was no data on primary prevention. There was strong evidence to suggest that wheat fibre does not lower cholesterol.

Cereal products provide around 30% of total energy intake in British adults. Several nutrients contained in cereals have the potential to reduce the risk factors for CHD (linoleic acid, fibre vitamin E, selenium and folate, phytoestrogens of the lignan family, phenolic acids with antioxidant properties). It should be noted that some processed cereal foods are high in salt and could contribute to raising blood pressure.

Over 40 human trials have shown that oat fibre tends to lower plasma total and LDL cholesterol but wheat fibre does not. Rice bran and barley may also lower cholesterol but intake of barley tends to be too low to have an effect.

There is no clear association, negative or positive, between total cereal consumption and CHD.

The intake of wholegrain foods may protect against heart disease and stroke but the exact mechanism is not clear. Fibre, magnesium, folate and vitamins B6 and E may be important.

The Joint Health Claims Initiative states that the evidence supports the association between regular consumption of wholegrains and a healthy heart but that it is insufficient to demonstrate cause and effect.

3. Breast Cancer

In the mid 1980's the role of fibre in breast cancer was suggested. There have been many studies including case control studies in several populations reporting a reduced risk for breast cancer for individuals with a high intake of dietary fibre. Other studies were contradictory and the positive effect of fibre for breast cancer risk reduction was not confirmed by prospective cohort studies in the US (Holmes 2004; Terry 2002). A recent study (Cade 2007) investigated the relationship between dietary fibre intake and breast cancer in a large cohort of British women. The conclusions were that total fibre of more than 30g/day was protective against breast cancer in pre-menopausal women relative to an intake of less than 20g/day, but was not significant in post-menopausal women. After assessing this study we had some reservations.

- The population were highly selected and not necessarily representative
- Lower levels of fibre intake were not protective and subgroup analysis according to fruit, vegetable and cereal fibre showed no significant effect
- There was no data available on the effects of soluble and insoluble fibre (Cade, personal communication to GDG).

A recent large RCT (Pierce 2007) in 3088 women investigated the effect on prognosis, following treatment for breast cancer, of a diet very high in vegetables, fruit and fibre and low in fat, plus telephone counselling, in comparison to dietary guidelines. The trial found no reduction of breast cancer events (recurrence or new primary) or any improvement in survival over a 7.5 year follow-up period.

There is currently insufficient evidence to demonstrate a causal relationship between total cereal consumption and breast cancer prevention. Studies have not investigated the specific effects of soluble and insoluble fibre.

In summary, the protective effects of fibre for the prevention of colorectal adenomas and carcinomas, coronary heart disease and breast cancer remain uncertain.

GDG DISCUSSION

The GDG discussed the use of fibre at some length, also taking into account a survey of the use of bran in people with IBS in primary and secondary care (Miller 2006). This paper suggested that bran was not especially effective in primary care, improving symptoms in 27/100 people with IBS, with 22/100 reporting an exacerbation of symptoms. This was significantly fewer than found in people in secondary care. The effects of soluble fibre were similar in both primary care and secondary care. The study highlighted the issues of extrapolating the response to treatment in IBS from different care settings.

The GDG unanimously agreed that the practice in primary care of recommending high fibre diets to people with IBS should cease. They suggested that GPs should investigate the person's usual fibre intake with a view to modifying fibre levels to suit the symptom profile and they should monitor the person's response to dietary modification. GDG consensus was that wheat bran should not be recommended for people with IBS as it is ineffective in the management of symptoms and may even increase symptoms in some people. It may be preferential for the dietary fibre intake to be closer to 12g/day rather than 18g/day. If an increase in fibre were needed, this should be in the form of soluble fibre. Although the RCT evidence for the beneficial effect of soluble fibre was based on trials using supplements such as ispaghula, the GDG wished to give an example of a dietary food that is high in soluble fibre in their recommendation. They also took into consideration the protective effect of oats on cholesterol levels. GDG consensus was that oats should be given as an example of a food high in soluble fibre.

The GDG noted that any protective effect of fibre is from food rich in dietary fibre as opposed to supplemental fibre, because the former contain other nutrients and phytochemicals and the roles these play may be more important than the fibre alone.

HEALTH ECONOMIC EVIDENCE

The cost effectiveness of fibre was not estimated as fibre is not prescribed but purchased by people with IBS as part of their food or as an over the counter food supplement.

EVIDENCE STATEMENTS

1. There is a moderate amount of weak evidence to show that significantly more patients have improved global symptoms when taking soluble fibre compared with placebo, and that there is no significant difference for insoluble fibre compared with placebo.

2. There is weak evidence to show no significant effect on global symptoms of the means of delivery of fibre, whether given as a food or as a supplement.

3. There is good evidence to show that significantly more patients have improved global symptoms when taking soluble fibre compared with insoluble fibre; however there is no significant difference in pain or in improvement in bowel habits.

4. There is a fair evidence to show that flax seed containing flaxseed oil gave significantly less bloating than psyllium in people with IBS, but there was no significant difference in the number of people with improved bowel habits.

5. There is a moderate amount of fair evidence to show no significant difference in the state of well being and the number of patients with reduced pain, or improved bowel habit, when comparing a mixed diet containing 25 % or 75% cereal.

6. There is limited evidence to show little effect of fibre dose on pain, bloating and bowel scores in people with IBS.

7. There is inconsistent evidence of a protective effect of fibre on colorectal cancer, breast cancer and coronary heart disease, and a causal protective relationship has not been demonstrated.

EVIDENCE TO RECOMMENDATION

The GDG took into consideration the clinical evidence on the effectiveness of high fibre diets, together with their clinical experience of deleterious effects of a high fibre diet; they balanced these with a consideration of the protective nature of fibre against cancers and heart disease, as determined in the general population. The GDG was unanimous that the practice of recommending that people with IBS eat a diet high in fibre should cease, and recommended that the first stage in improving a person's diet was to review the fibre intake and adjust accordingly. The improvement in IBS symptoms due to soluble fibre was noted, and its possible protective effect against heart disease, so that the GDG recommended soluble fibre if an increase in fibre was required. Soluble fibre should be either in the form of supplements (as in the RCT evidence) or as foods high in soluble fibre, such as oats (from GDG consensus).

RECOMMENDATION

Healthcare professionals should review the fibre intake of people with IBS, adjusting (usually reducing) it while monitoring the effect on symptoms. People with IBS should be discouraged from eating insoluble fibre (for example, bran). If an increase in dietary fibre is advised, it should be soluble fibre such as ispaghula powder or foods high in soluble fibre (for example, oats).

7.4 Probiotics and prebiotics

SELECTION CRITERIA

The selection criteria described in the general methodology section were used, but some were specific to the probiotics review and are reported below.

Types of studies

The GDG decided that crossover studies should not be included in this review because it was unclear whether probiotics effected longer term changes or how long they were retained in the gut.

Types of intervention

Studies should include the following interventions:

- Single probiotics
- Combination probiotics
- Single prebiotics
- Synbiotics.

Probiotics may be given as a food or as an enteric coated capsule. Prebiotics should fulfil three criteria: (a) resistance to gastric acidity, hydrolysis by mammalian enzymes and gastrointestinal absorption; (b) fermentation by intestinal microflora; (c) selective stimulation of the growth and/or activity of intestinal bacteria associated with health and well-being. Acceptable prebiotics are mainly fructo-oligosaccharides, galacto-oligosaccharides and lactulose.

The following comparisons were included:

- Single probiotic versus placebo
- Combination probiotic versus placebo
- Single prebiotic versus placebo
- Synbiotics versus placebo
- Probiotic 1 versus probiotic 2
- Probiotic dose 1 versus dose 2
- Intervention duration 1 versus duration 2.

The probiotics review was concerned only with longer-term maintenance treatment.

In spite of the large placebo effect associated with IBS, comparisons with no treatment were included, and the minimum duration of treatment was four weeks.

Stratification and Subgroup analyses

Pre and probiotics were to be treated separately. We planned to carry out subgroup analyses as follows:

- Type of probiotic (single, combination)
- Nature of bacteria, including the strain (e.g. Lactobacillus salivarius, Bifidobacterium infantis, Streptococcus faecium)
- Dose (above and below 1 x 10^6 bacteria per day; this was later revised to 10^6, 10^8, 10^{10} subgroups and the GDG later excluded studies with levels below 1 x 10^6)
- Duration of intervention (5-8, 9-12, 13-16, 16+ weeks).

We also planned to investigate the effect of enteric coated capsules compared with the addition of probiotics as a food.

SEARCH STRATEGY FOR IDENTIFICATION OF STUDIES

Searches were performed on the following core databases: MEDLINE, EMBASE, CINAHL and *The Cochrane Library* (1966 to current day with guidance from the GDG). The search strategies are listed in Appendix B.

The titles and abstracts from the search strategy were assessed. Thirty-seven were identified to be potentially relevant to the review and these papers were retrieved in full. Thirteen studies met the inclusion criteria for the review. The reference lists of these were inspected for further potential papers, but none were identified. The excluded studies are listed in Appendix E, along with reasons for exclusion.

DESCRIPTION OF STUDIES INCLUDED IN THE REVIEW

Thirteen studies met the inclusion criteria for the review (Bittner 2005; Gade 1989; Kajander 2005; Kim 2003; Kim 2005; Niedzielin 2001; Niv 2005; Nobaek 2000; Olesen 2000; O'Mahony 2004; Saggioro 2004; Tsuchiya 2004; Whorwell 2006). One study was conducted in the UK (Whorwell 2006) and one was carried out in Ireland (O'Mahony 2004). Two were conducted in Italy, three in the USA, two in Denmark and one each in Finland, Sweden, Poland and Israel.

The majority of studies had fewer than 100 patients. Two studies (Kajander 2005; Whorwell 2006) had more than 100 patients in total.

Study Design

Setting: The majority of studies took place in secondary care, but three were carried out in primary care (Bittner 2005; Gade 1989; Whorwell 2006) and one was assumed to be primary care (Nobaek 2000; recruited by newspaper advertisement). One study had patients from both primary and secondary care (O'Mahony 2004; patients from gastroenterology clinics and newspaper advertisement).

All the studies included in the review had a parallel design.

One study (O'Mahony 2004) had 3 arms comparing Lactobacillus salivarius UCC4431, Bifidobacterium infantis 35624 and placebo malted milk. Whorwell (2006) compared three different doses of encapsulated Bifidobacterium infantis 35624 with placebo in women with IBS. This gave a total of 20 comparisons in the review.

Population

The definition of IBS varied between studies: two used the Manning criteria (Niedzielin 2001; Olesen 2000); one used the Rome I criteria (Kajander 2005); one met criteria defined by the authors that were similar to the above (Gade 1989); and the rest used the Rome II criteria.

All studies but one included patients who had a range of IBS types; the other study specified diarrhoea predominant IBS symptoms (Kim 2003). Only one study (Niv 2005) stated that the participants had IBS as result of gastrointestinal infection.

The majority of studies (12) did not state the number of participants with bloating. Five studies had some patients with bloating measured as an outcome (Kajander 2005; Kim 2003; Olesen 2000; Tsuchiya 2004; Whorwell 2006). Two studies (Kim 2005; Niedzielin 2001) identified all patients as having bloating.

Most of the studies described symptom severity as mixed; one study described the symptoms as mild (Nobaek 2000). Two studies did not state symptom severity (Kajander 2005; O'Mahony 2004). Three studies suggested that the patients had refractory IBS: Saggioro (2004) reported that the patients had been treated with drugs without success; Niedzielin (2001) stated that all patients had been referred to secondary care because of problems with management; Tsuchiya (2004) reported that all patients had undergone a number of treatments without significant and lasting benefit.

The age range of participants across studies was 19 to 78 years, with the mean age (where given) ranging from 34 to 48 years. No study particularly identified elderly participants.
All studies had a ratio of women to men greater than one. Whorwell (2006) included only women participants.

Interventions

The studies varied in the type of probiotics used:

- Six used a single probiotic (Gade 1989; Niedzielin 2001; Niv 2005; Nobaek 2000; O'Mahony 2004; Whorwell 2006)
- Five used a combination of probiotics (Kajander 2005; Kim 2003; Kim 2005; Saggioro 2004; Tsuchiya 2004)
- One study used a prebiotic (Olesen 2000)
- One gave a pre/probiotic combination (Bittner 2005).

A range of different bacteria was used, and included various strains of Lactobacillus, Bifidobacterium and Streptococcus. Further details are available in the Appendix.

Three studies gave the probiotic in a capsule form (Kajander 2005; Whorwell 2006; Bittner 2005), two gave a tablet (Gade and Thorn 1989; Niv 2005) and the remainder used a food source or solution as the means of ingestion. The food sources used included milk or milk products, yoghurt, oatmeal soup and fruit drinks. The GDG considered the medium in which the probiotics were ingested to be an important difference and decided to consider, as subgroups, capsules versus other delivery routes. Whether the intervention was given with food was also considered important because of the increased levels of bile salts, as a result of digestive process, which are a serious obstacle to probiotic survival. However only three studies gave details as to when the probiotics were taken: Niedzielin (2001) directed that they should be taken before breakfast and two hours after the evening meal; in Gade (1989) the dose was given in the morning and evening with meals; and Olesen (2000) required the dose of prebiotics be taken with breakfast.

The GDG defined the minimum dose of probiotic as 1 $x10^6$. The doses of probiotic varied considerably, and ranged from $8x10^6$ (Gade 1989) to $4x10^{10}$ (Niedzielin 2001) for single probiotics, and $5x10^9$ to $5x10^{11}$ for combination probiotics. It is noted that the activity of the probiotics vary according to strain.

The duration of the intervention ranged from four weeks (Gade 1989; Niedzielin 2001; Nobaek 2000; Saggioro 2004; Whorwell 2006) to six months (Kajander 2005; Niv 2005). Three studies had durations of eight weeks (Kim 2003; Kim 2005; O'Mahony 2004), and two studies had interventions lasting 12 weeks (Olesen 2000; Tsuchiya 2004). One study followed the patients for 12 months (Nobaek 2000).

Comparisons

The included studies covered the following comparisons:

- Nine comparisons of a single probiotic versus placebo (Gade 1989; Niedzielin 2001; Niv 2005; Nobaek 2000; O'Mahony 2004 x 2; Whorwell 2006 x3)
    - Lactobacillus salivarius UCC4331 ($1x10^{10}$) in malted milk drink (O'Mahony 2004)
    - Lactobacillus plantarum DSM 9843 ($5x10^7$ CFU) in oatmeal soup (Nobaek 2000)
    - Lactobacillus plantarum 299V ($5x10^7$) in oatmeal soup (Niedzielin 2001)
    - Lactobacillus reuteri ATCC 55730 ($1x10^8$) tablet (Niv 2005)
    - Two used Bifidobacterium infantis 35624 (O'Mahony 2004 ($1x10^{10}$) in malted milk drink; Whorwell (2006) $1x10^6$, $1x10^8$, $1x10^{10}$ CFU in capsule)
    - Streptococcus faecium (dose estimated as $8x10^6$) tablet (Gade 1989);
- Five comparisons of a combination of probiotics versus placebo:

    - Two studies used VSL3 powder sachet (Bifidobacterium 3 strains, Lactobacillus 4 strains, Streptococcus 1 strain) (Kim 2003; Kim 2005)
    - SCM-III solution (Lactobacillus acidophilus1.25x10^6 CFU; Lactobacillus helveticus 1.3x10^9; bifidobacterium 4.95x10^9) (Tsuchiya 2004)
    - Lactobacillus rhamnosus GG, L. rhamnosus LC705, Bacillus breve Bb99, P.freudenreichii ssp.shermanii JS capsule (Kajander 2005)
    - Lactobacillus plantarum LPO1 & Bifidobacterium Breve BRO 5x10^9 CFU sachet dissolved in water (Saggioro 2004);
- One study compared two different probiotics (Lactobacillus salivarius UCC4331 versus Bifidobacterium infantis 35624) (O'Mahony 2004)
- One study compared three doses of probiotics (Whorwell 2006; 3 comparisons)
- One comparison of Prebiotic versus placebo (Oleson and Hoyer 2000)
- One comparison of a pre/probiotic capsule versus placebo, but this study contained no analysable data (Bittner 2005).

OUTCOMES

The studies measured a range of outcomes.

1. Global symptoms

a) Number of patients with an improvement in global symptoms

Seven studies recorded the patients' assessment of improvement (Gade 1989; Kajander 2005; Kim 2003; Niedzielin 2001; Olesen 2000; Tsuchiya 2004 – overall clinical effectiveness; Whorwell 2006 – adequate symptom relief) and two (Gade 1989; Tsuchiya 2004) also recorded a clinician assessment.

b) Global symptom score (mean)

The global symptom score was recorded by seven studies (Kajander 2005; Kim 2003; Niv 2005; Nobaek 2000; O'Mahony 2004; Saggioro 2004; Whorwell 2006), but Saggioro (2004) recorded the percentage change in global symptom score.

c) Global improvement in symptoms score (mean)

This outcome was recorded by two studies (Kim 2003; Olesen 2000).

d) Number of patients with deterioration in global symptoms

This outcome was recorded by three studies (Gade 1989; Olesen 2000; Tsuchiya 2004).

2. Individual symptoms

a) Pain

Pain was reported in several ways, either giving the number of patients with pain at the end of the study, the number of patients whose pain improved or worsened compared with the

baseline, and pain scores. The latter recorded a range of features, including severity, frequency and duration, or a combination of these. In addition, studies recorded the final scores, mean daily scores or the change from baseline. The studies reporting the following outcomes are listed below:

- Number of patients with pain: three studies (Gade 1989; Olesen 2000; Niedzielin 2001)
- Pain score: eight studies recorded a pain score (Kajander 2005; Kim 2003; Kim 2005; Nobaek 2000; O'Mahony 2004; Saggioro 2004; Tsuchiya 2004; Whorwell 2006), although Saggioro (2004) recorded the percentage change in pain score.
  In all cases the highest rating meant worst symptoms, although the scales used were not the same.
- Number of patients with less pain: one study (Niedzielin 2001).

b) Bloating

- Number of patients with more bloating (Olesen 2000)
- Number of patients with less bloating (Kim 2005; Olesen 2000)
- Bloating score (Kajander 2005; Kim 2003; Kim 2005; O'Mahony 2004; Tsuchiya 2004; Whorwell 2006).

c) Bowel habits

- Stool frequency (change and final) (Kajander 2005; Kim 2003; Kim 2005; Tsuchiya 2004). We decided that stool frequency was an unreliable measure of improvement if the type of IBS was not given. Only one of these studies specified the type of IBS (Kim 2003, which was in patients with diarrhoea predominant IBS), and the other studies were disregarded for this outcome.
- Stool score which was an aggregate score including stool frequency, consistency, ease of passage and completeness of evacuation (Kim 2003; Kim 2005; Nobaek 2000; O'Mahony 2004).

3. Quality of Life

- Two studies reported quality of life as an outcome (Niv 2005; Whorwell 2006).

METHODOLOGICAL QUALITY

The quality assessment for included trials is shown in Appendix D. The method of randomisation was reported in four studies, all of which gave an adequate method: computer generated numbers (Gade 1989; Kajander 2005; Olesen 2000) and one picking a card from a pack (O'Mahony 2004). The other studies did not state the method of randomisation (Kim 2003; Kim 2005; Niedzielin 2001; Niv 2005; Nobaek 2000; Tsuchiya 2004; Whorwell 2006).

Allocation concealment was reported in three studies (Kim 2005; Olesen 2000; O'Mahony 2004), one of which reported a partially adequate method (O'Mahony 2004), in which

randomisation and analysis were said to be 'supervised by a person independent from the study'. The other two were classified as having adequate concealment because the sequence was retained by a third party.

All the studies reported that the outcome assessors and the patients were blinded to the interventions. All described in detail the appearance and taste of the placebo and active intervention.

Four studies (Kajander 2005; Kim 2003; Kim 2005; Tsuchiya 2004) described an *a-priori* power calculation. Five studies used an intention to treat analysis (Kim 2003; Kim 2005; Olesen 2000; O'Mahony 2004; Whorwell 2006). All studies included in the review demonstrated some level of baseline comparability of the groups, but two provided limited data regarding baseline characteristics (Gade 1989; Nobaek 2000).

One study had no loss to follow-up (Niedzielin 2001). Three studies reported that more than 20% of patients in at least one arm (or overall) were not analysed or were lost to follow-up (Kim 2005; Niv 2005; Olesen 2000). For the Kim (2005) study we used four week data instead. In Niv (2005), 9/27 (33%) in the control group withdrew; and in Olesen (2000), 14/52 (27%) did not complete the 12 week comparative phase in FOS group.

The risk of bias was assessed for each included study and only Niv (2005) and Olesen (2000) were considered to be at higher risk of bias. These were considered, where possible, in sensitivity analyses.

RESULTS

A. Probiotics versus placebo

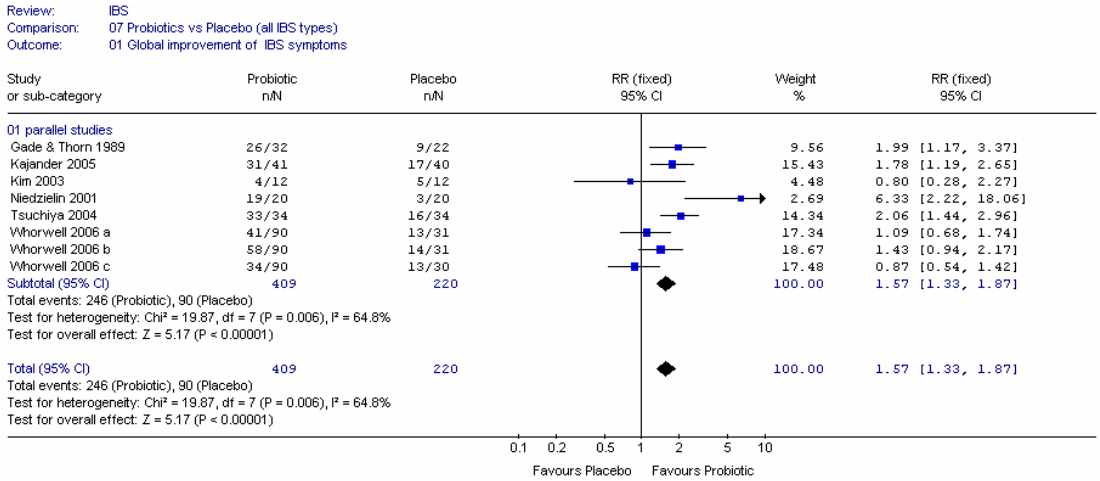
Ten studies compared probiotics (singly or in combination) with placebo (Gade 1989; Kajander 2005; Kim 2003; Kim 2005; Nobaek 2000; Niedzielin 2001; Niv 2005; O'Mahony 2004; Tsuchiya 2004; Whorwell 2006).

1. Global symptoms

a) Number of patients with an improvement in global symptoms

Six studies (eight comparisons), with 629 patients, recorded the patients' assessment of global improvement (Gade 1989; Kajander 2005, Kim 2003, Niedzielin 2001, Tsuchiya 2004, Whorwell 2007). Meta-analysis showed significant heterogeneity (I^2=65%; p=0.006).

Figure 1

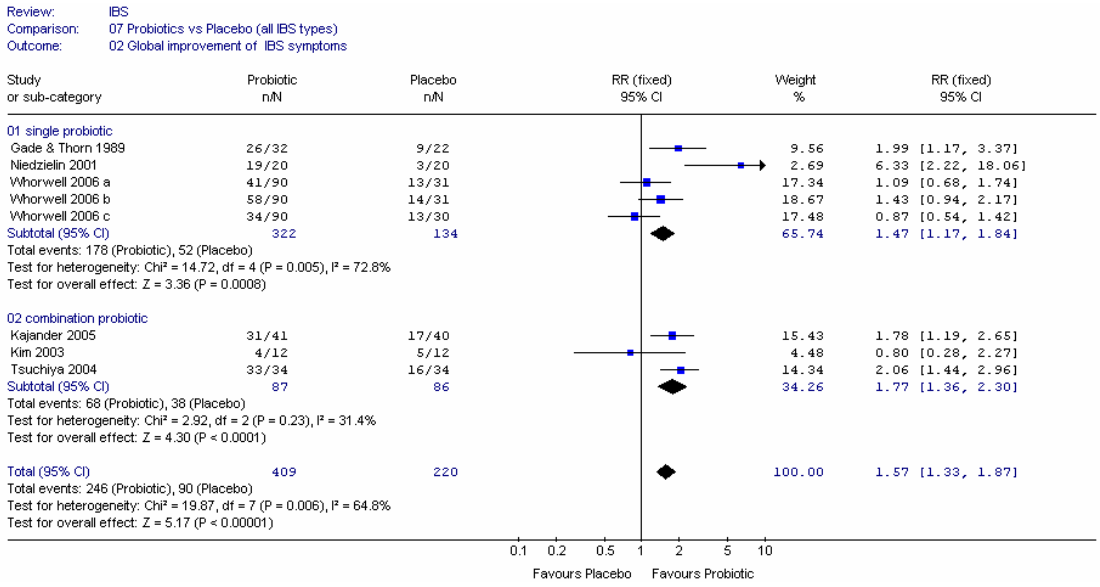


This heterogeneity was investigated in terms of the pre-specified subgroup analyses: by type of probiotic (single, combination), by duration and by dose and strain of bacterium (Figures 2 to 3).

Type of probiotic (Figure 2)

There was still significant heterogeneity in the single probiotic group, but it was not significant in the combination probiotic group (I^2=31%, p=0.23). Meta-analysis of three studies in 173 patients showed a statistically significant improvement in global symptoms. This corresponded to an NNT of 3 (95%CI 3, 5), for a control group rate of 42 to 47%. We noted there was significant heterogeneity for the risk difference (I^2=74%, p=0.02), which may have been an indication that the particular combination of probiotics was important.

Figure 2: Subgroup analysis by type of probiotic



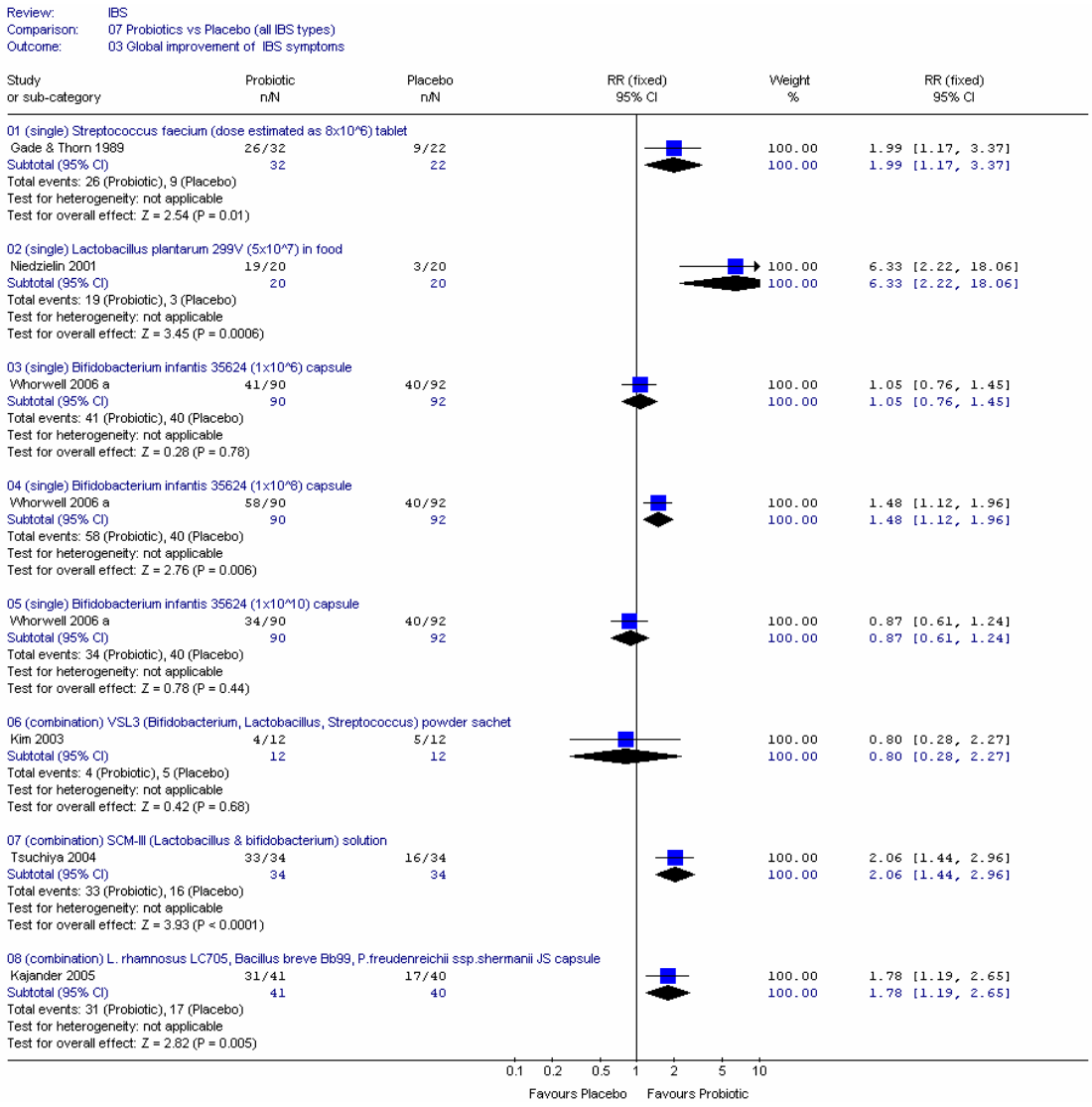
Duration

The Kajander (2005) study was six months duration, Tsuchiya (2004) was 12 weeks and the others were four or eight weeks. This did not account for the heterogeneity amongst studies.

Strain and dose of probiotic (Figure 3)

All the studies had different strains and/or doses, and the confidence intervals are wide in some cases. The heterogeneity may be indicative of different efficacies of the different probiotics; most of the probiotics tested in the trials gave a greater improvement in symptoms than placebo, but there were some exceptions. Whorwell (2006) showed a maximum in the improvement of global symptoms with increasing dose, with only the 10^8 dose of Bifidobacterium infantis being significant at four weeks. The authors attributed this effect to dissolution problems of the capsule for particular concentrations (see GDG discussion at the end of this review).

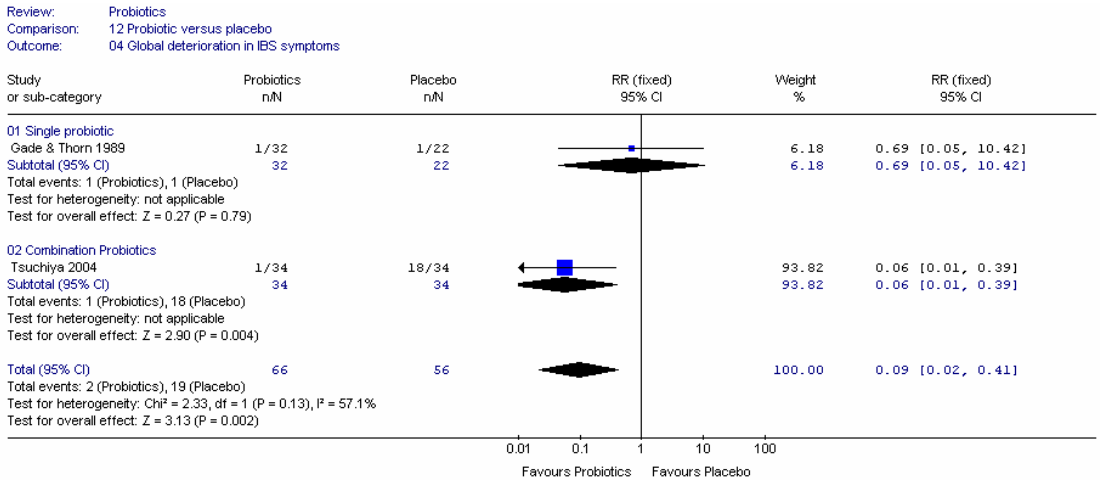
Figure 3: By type and dose of bacterium



b) Number of patients with deterioration in global symptoms

This outcome was recorded by two studies (Gade 1989; Tsuchiya 2004). The confidence intervals were very wide, although Tsuchiya (2004) was statistically significantly in favour of probiotics.

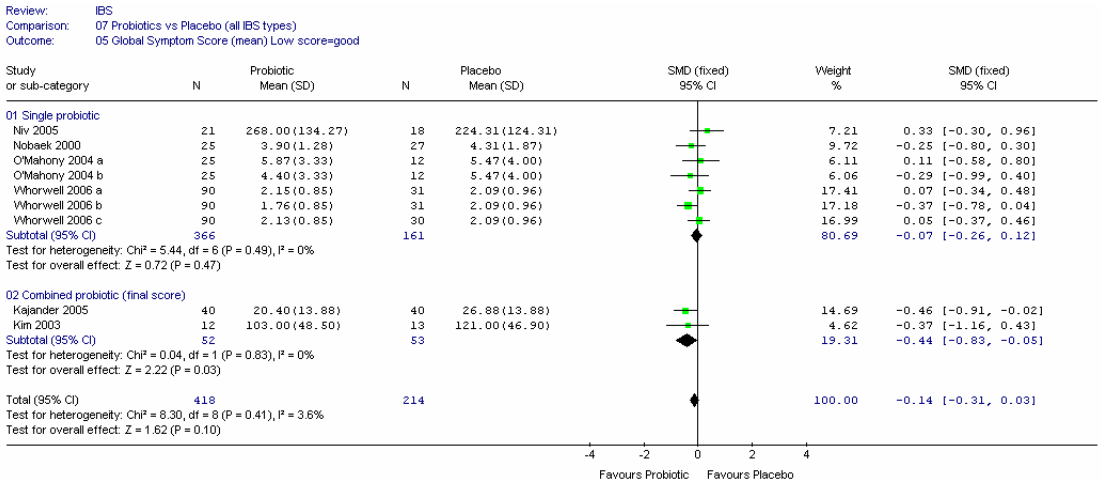
Figure 4: (NB 0.01 to 100 scale)



c) Global symptom score (mean)

This outcome was recorded by seven studies (Kajander 2005; Kim 2003; Niv 2005; Nobaek 2000; O'Mahony 2004; Saggioro 2004; Whorwell 2006). One study (Saggioro 2004) reported percentage change scores, with p values, so these results are given separately. The other studies reported the global symptom score, but on different scales, so the standardised mean difference was used to analyse the data (Figure 5). The Niv (2005) values were taken from a graph and it was assumed that the standard error was given. This study also had some attrition bias, so a sensitivity analysis was repeated excluding this study (Figure 6).

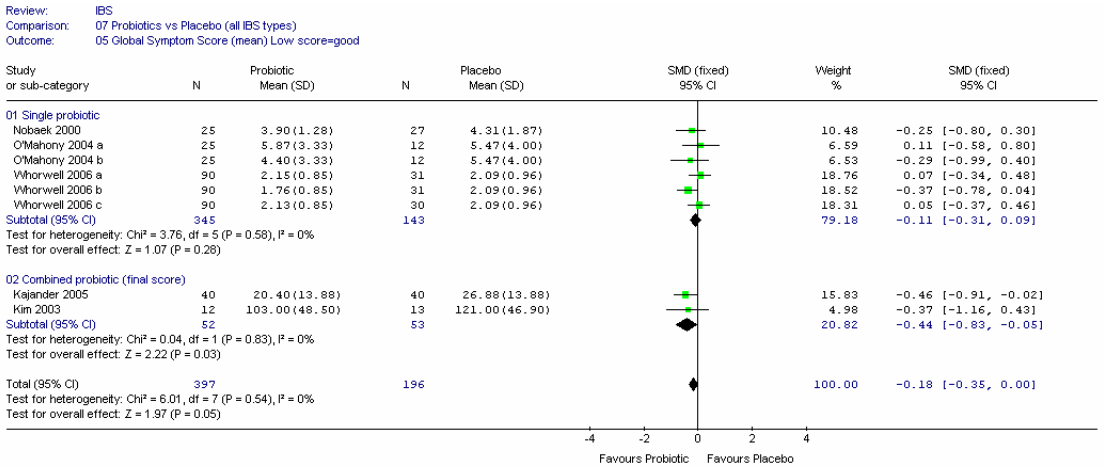
Figure 5



Meta-analysis of eight comparisons in 624 patients showed no significant difference between probiotics and placebo overall, with little heterogeneity (I^2=4%, p=0.41). However, there was a statistically significant difference for the combined probiotic subgroup in 105 patients. Meta-analysis of seven single probiotics showed no significant difference between probiotic and placebo, with no heterogeneity. Sensitivity analysis without Niv (2005) made a small difference.

The Saggioro (2004) study in 40 patients reported a statistically significant difference in the percentage change in IBS symptom severity (-44% versus -8.5% after 28 days; p<0.001 for the combined probiotic versus placebo).

Figure 6: Sensitivity analysis without Niv (2005)

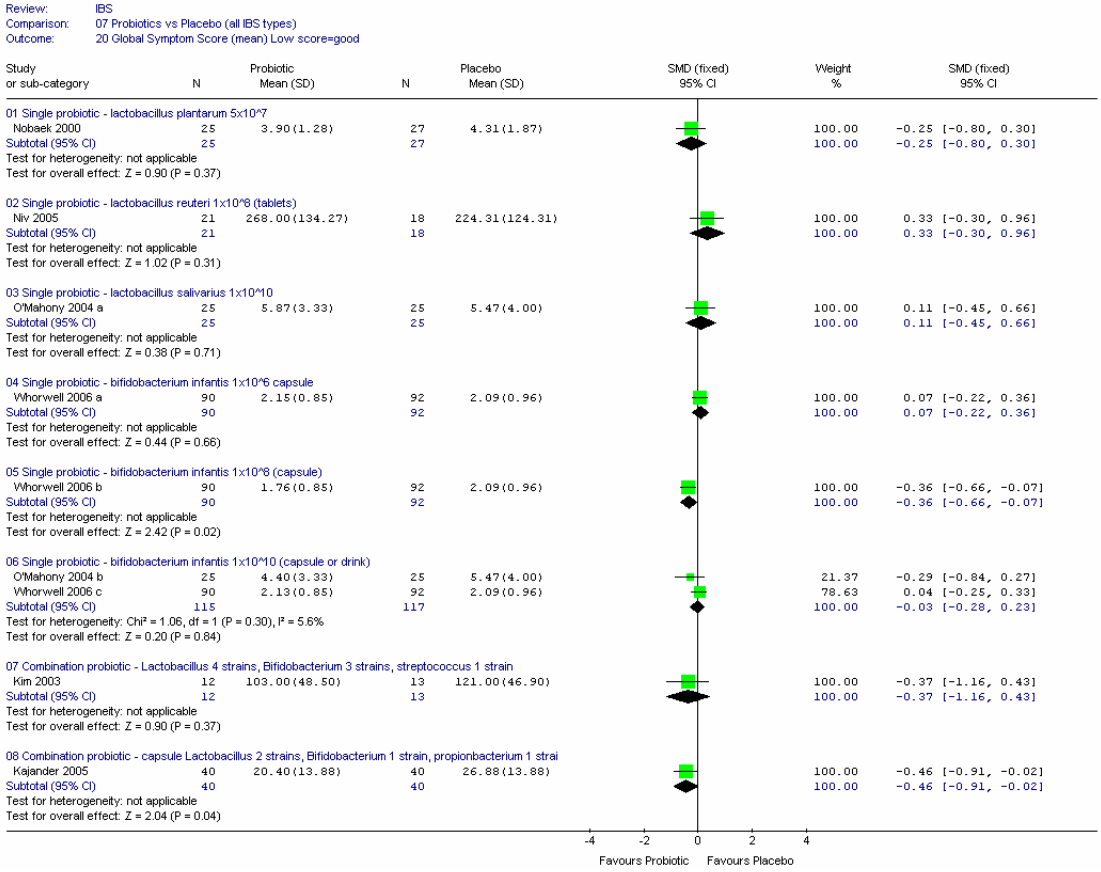


Subgroup analyses were carried out by strain and dose of bacterium because the GDG was uncertain whether studies using different bacteria should be combined. Figure 7 shows the studies by bacterium and dose. Most comparisons showed no significant difference compared with placebo, including the meta-analysis of two studies in 232 patients, receiving Bifidobacterium infantis at a dose of $1x10^{10}$ CFU; there was no significant heterogeneity for these two studies (I^2=6%, p=0.30). There were only two statistically significant comparisons:

- Encapsulated Bifidobacterium infantis at a dose of $1x10^8$ CFU versus placebo, in 182 patients. This had a mean difference of -0.33 (95%CI -0.59, -0.07) on a scale of 0 to 15 (i.e. a fairly small effect)
- Encapsulated combined probiotic versus placebo in 81 patients. This had a mean difference of -6.48 (95%CI -12.56, -0.40) on a scale of 0 to 112.

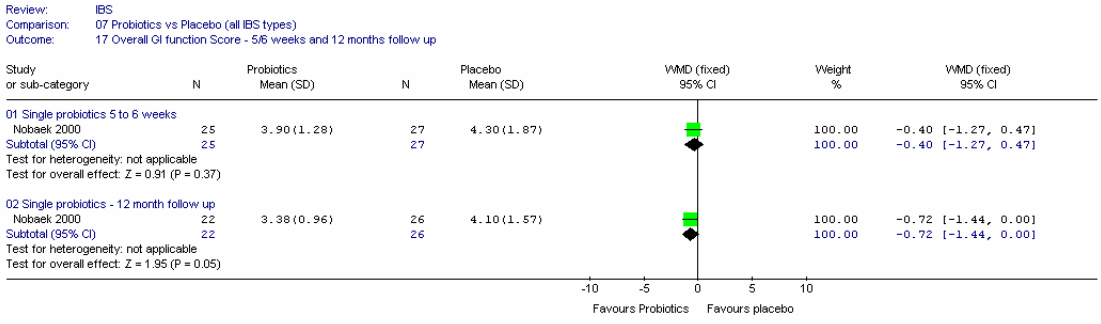
This may, however, be a size effect; most of the non-significant studies had around 50 patients or fewer.

Figure 7a: Global symptom score



Nobaek (2000) also reported 12 month follow-up, but it was unclear if the patients continued to modify their diet after the trial had ended. There was a borderline significant effect of probiotics at 12 months, but not at 5 to 6 weeks. The scale was 0 to 10.

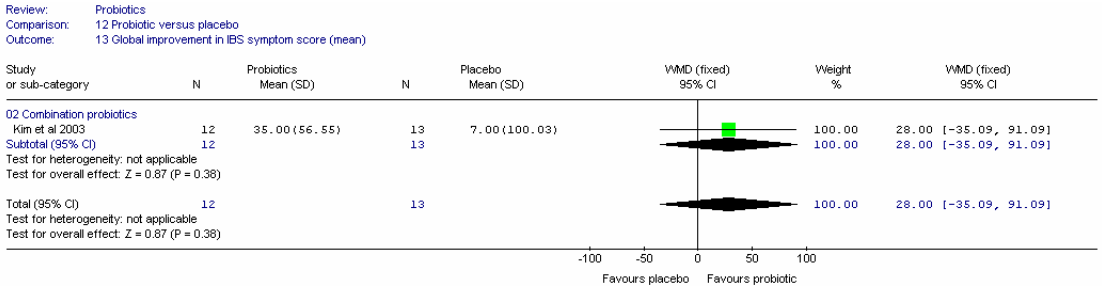
Figure 7b: Global symptom score – 5/6 weeks and 12 month follow-up



e) Global improvement in symptoms score (mean)

This outcome was recorded by one study (Kim 2003), which showed too much uncertainty to draw conclusions. It is unclear what scale is used.

Figure 8



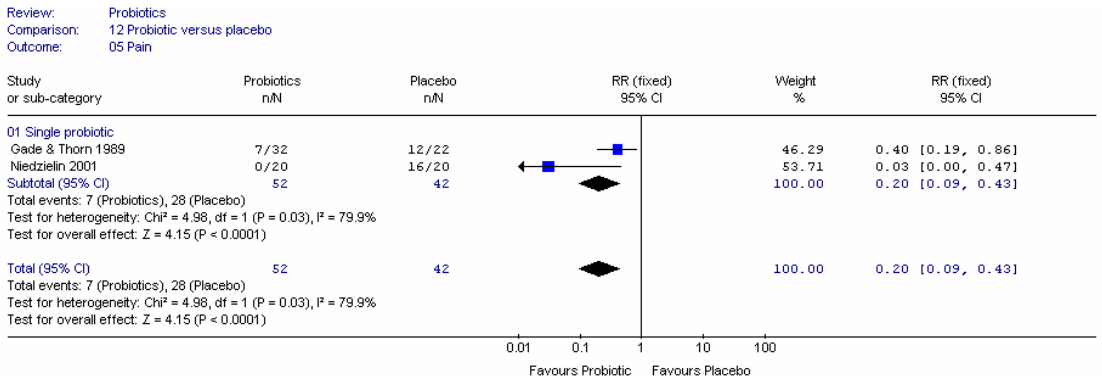
2. Individual symptoms

a) Pain

i. Number of patients with pain

Two studies measured this outcome (Gade 1989; Niedzielin 2001) and both separately were statistically significantly in favour of probiotic. The relative risk ranged from 0.03 to 0.2 (i.e. 5 to 33 times less risk of pain with the probiotic). However, combining the studies gave heterogeneity (I^2=80%; p=0.03).

Figure 9



ii. Pain score

Eight studies (Kajander 2005; Kim 2003; Kim 2005; Nobaek 2000; O'Mahony 2004; Saggioro 2004; Tsuchiya 2004; Whorwell 2006) reported a pain score. Saggioro (2004) reported percentage change scores, with p values, so these results are given separately.

This outcome showed no significant difference between interventions for the single probiotic group (although it is difficult to estimate the width of the confidence interval because the standardised mean difference was used) and a highly heterogeneous result for the combined probiotics group (I^2=93%, p=0.00001), attributable to the Tsuchiya (2004) study, from which data were extracted from a graph, which may not have been to scale for the standard deviations. In the absence of this study the meta-analysis of three studies gave a statistically significant reduction in pain for the combined probiotic group, and no heterogeneity (I^2=0%; p=0.94).

Saggioro (2004) reported a statistically significant difference in the percentage change in pain score (-38% versus -18% after 28 days; p<0.05 for the combined probiotic versus placebo).

Figure 10a

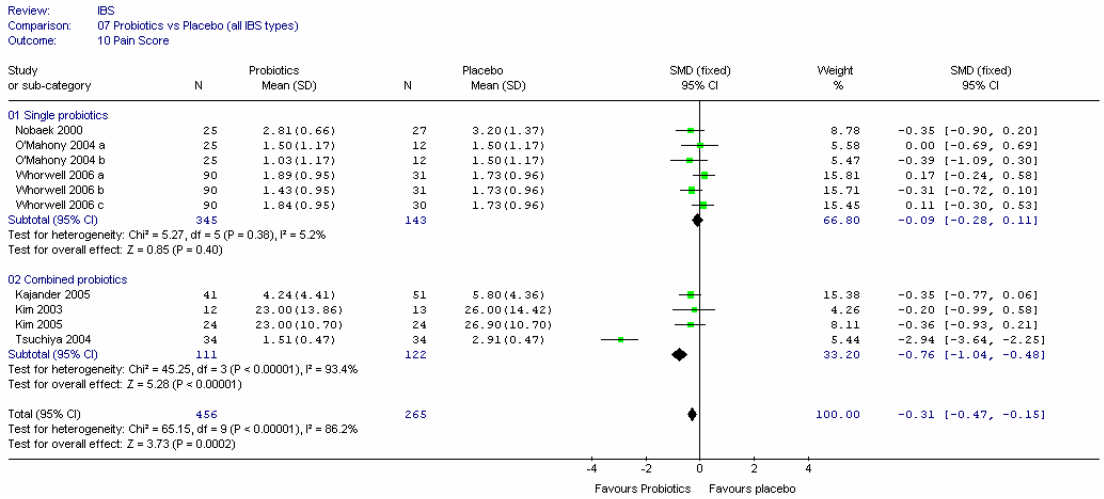
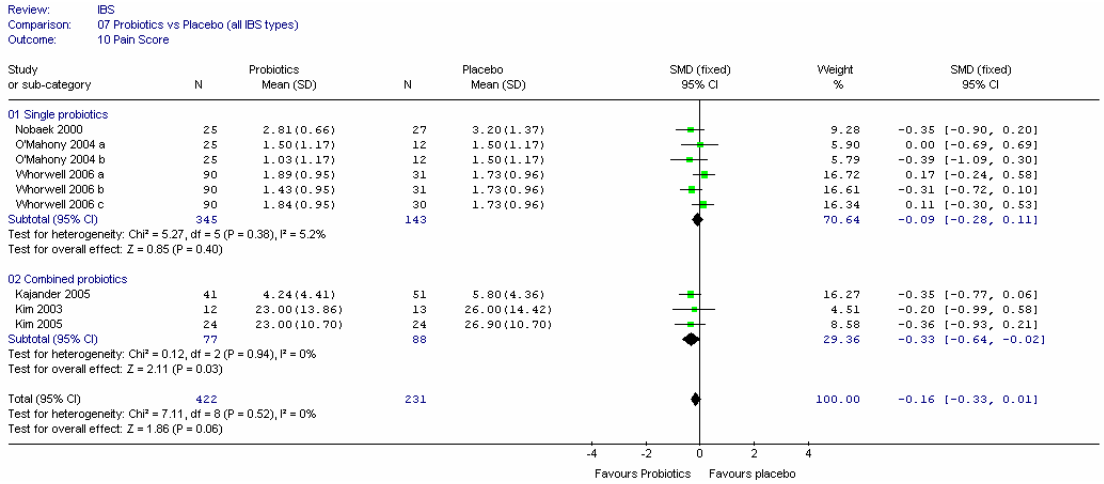
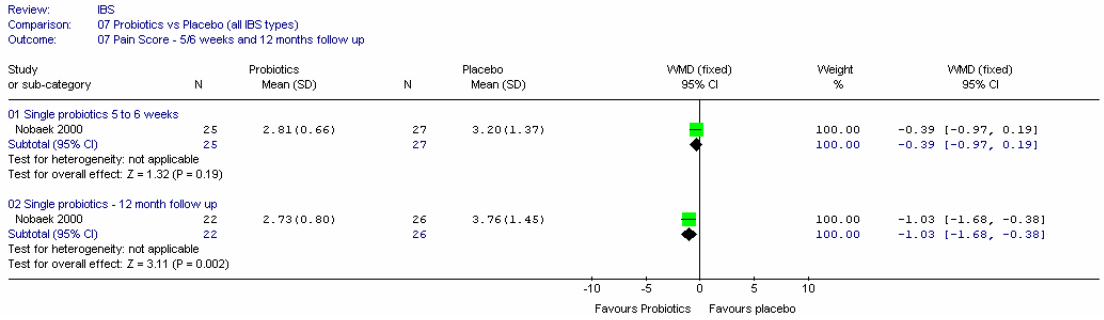


Figure 10b: Without Tsuchiya 2004



Nobaek (2000) also reported 12 month follow-up data, shown in Figure 10c. The scale is a visual analogue scale of 0 to 10. There was no significant difference at 5 to 6 weeks, but a statistically significant difference after 12 months. It was unclear if the patients in the intervention group changed their dietary habits following the trial or if there was a long-term effect.

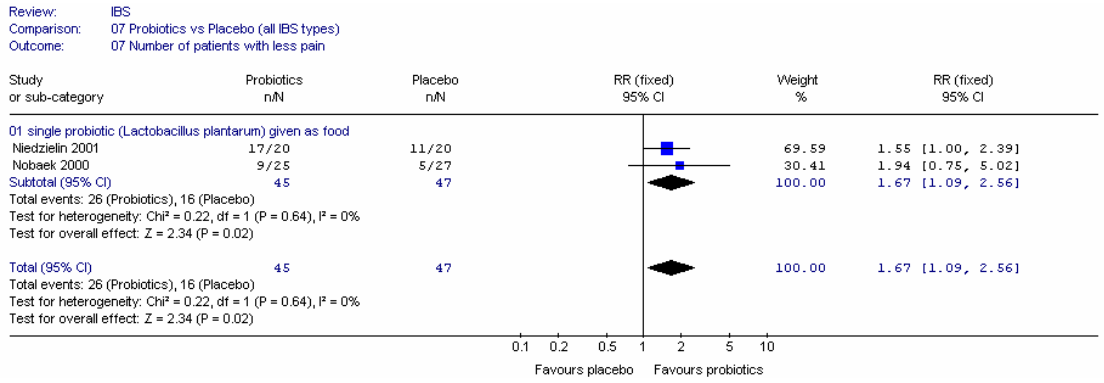
Figure 10c



iii. Number of patients with less pain

Two studies compared Lactobacillus planetarum, given in food, with placebo (Niedzielin 2001; Nobaek 2000) and reported the number of patients with reduced pain. There was a statistically significant reduction in pain; RR 1.67 (95%CI 1.09, 2.56), with no heterogeneity (I^2=0, p=0.64). This corresponded to a number needed to treat of 5 (95%CI 3, 20) for a control group rate of 19 to 55%.

Figure 11

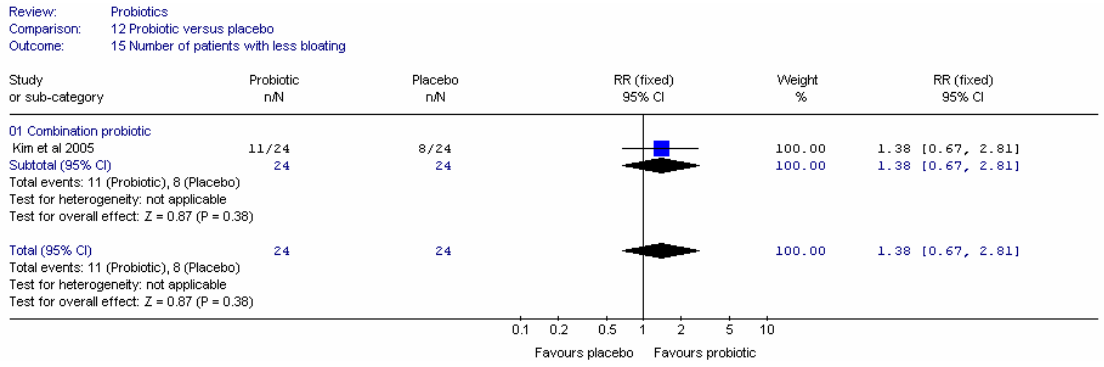


b) Bloating

i. Number of patients with less bloating (Kim 2005)

In a single study in 48 patients, there was no significant difference between probiotics and placebo in the number of patients with less bloating, although the confidence interval was fairly wide.

Figure 12



ii. Bloating score (Kajander 2005; Kim 2003; Kim 2005; O'Mahony 2004; Tsuchiya 2004; Whorwell 2006)

This outcome showed no significant difference between interventions for the single probiotic group and a highly heterogeneous result for the combined probiotics group, attributable to the Tsuchiya (2004) study, from which data were extracted from a graph, which may not be to scale for the standard deviations. The authors of this study reported that there was no significant difference between groups, which belies the data on the graph, suggesting that the standard deviations on the graph were inaccurate. In the absence of this study, meta-analysis of the three studies in 73 patients gave a statistically significant reduction in bloating score for the combined probiotic group, MD -0.42 (95%CI -0.73, -0.10), with no heterogeneity (I^2=0%; p=0.87).

Figure 13a: Bloating score (final scores)

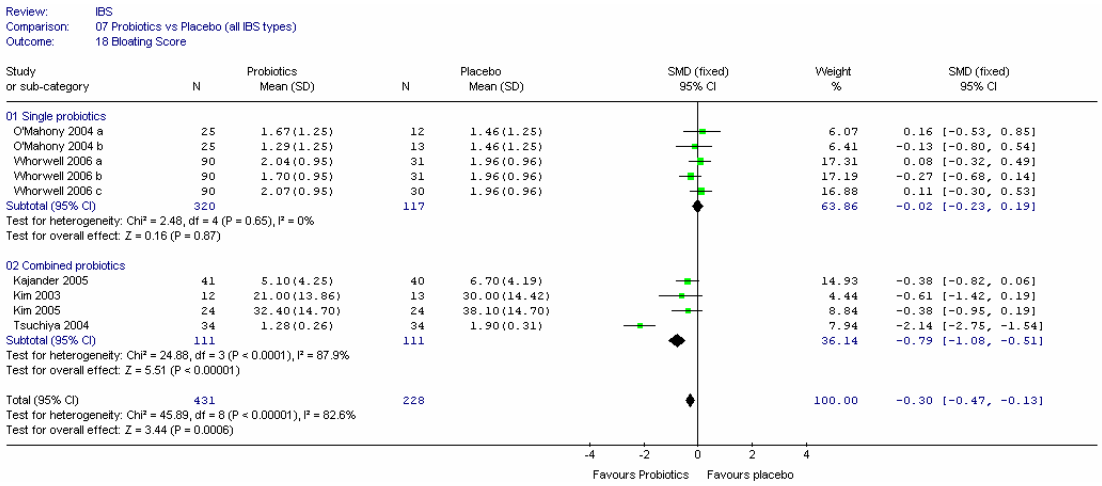
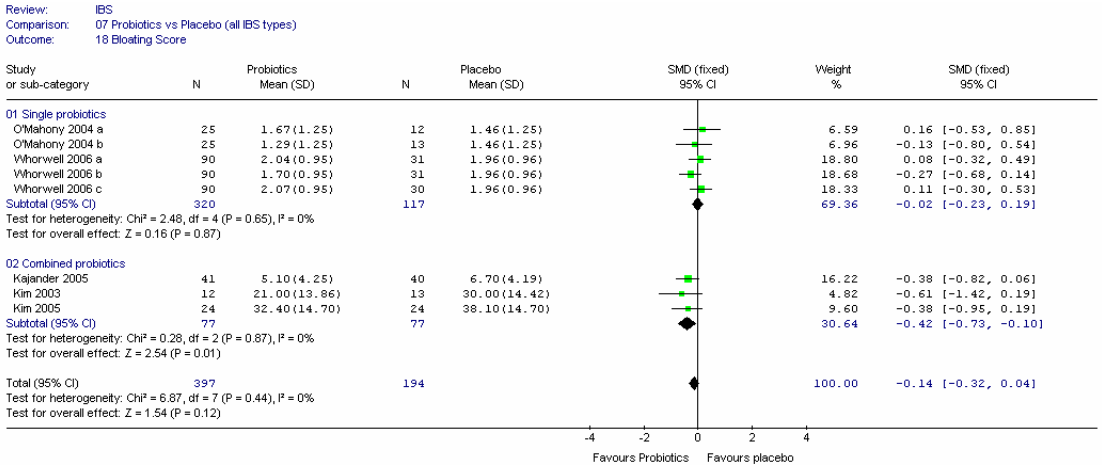


Figure 13b: Sensitivity analysis without Tsuchiya (2004)

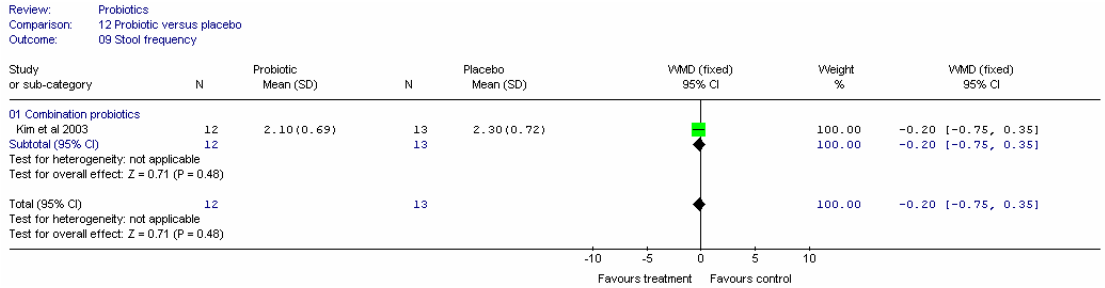


c) Bowel habits

i. Stool frequency

Only one study specified the type of IBS (Kim 2003), which was in patients with diarrhoea predominant IBS. For this study, the frequency was seen as a negative outcome and there was no significant difference between probiotic and placebo.

Figure 14

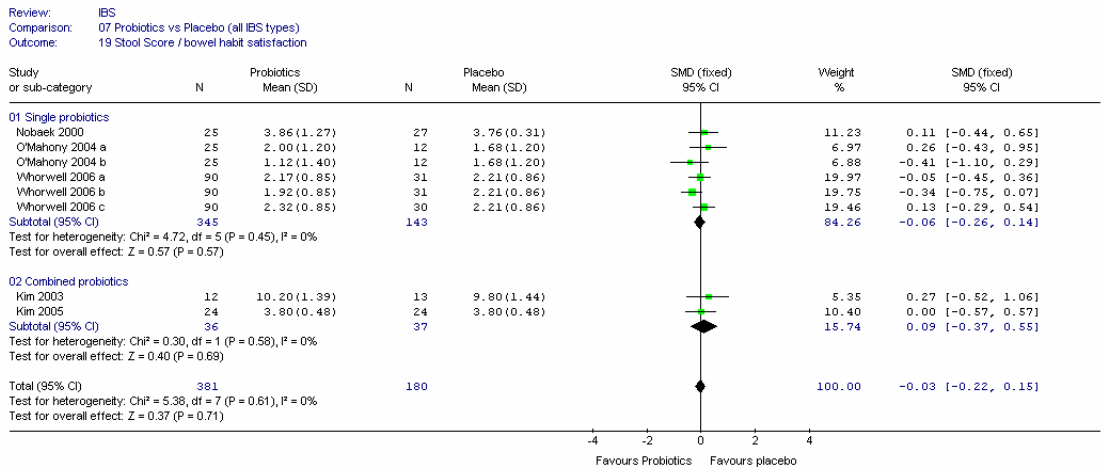


ii. Stool score

This was aggregated to include stool frequency, consistency, ease of passage and completeness of evacuation (Kim 2003; Kim 2005; O'Mahony 2004; Nobaek 2000; Whorwell 2006 – bowel habit satisfaction). Tsuchiya (2004) also reported assessment of bowel habits, but these values were not included in the meta-analysis in view of the uncertainties in the standard deviation described above.

In the meta-analysis of eight comparisons (562 patients) there was no significant difference between probiotics and placebo for this outcome, either overall, or for single or combined probiotics, and there was no significant heterogeneity.

Figure 15

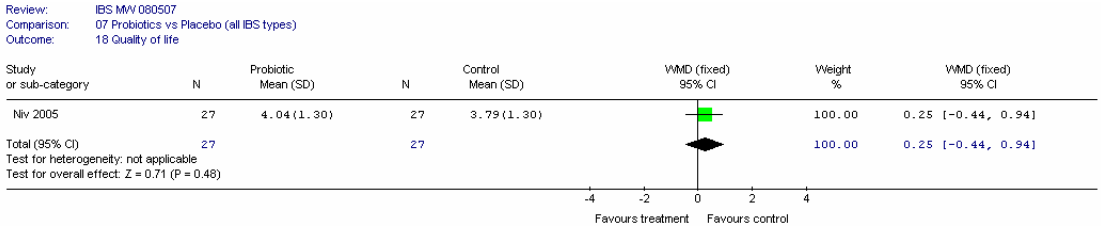


3. Quality of Life

Only one study reported quality of life as an outcome (Niv 2005). This showed no significant difference in the quality of life score. The scale used was unclear, however: the study reported

that there were 26 questions, each rated from mild (1) to severe (7), and the sum of all of them yielded the total QoL score, but the baseline scores for the total were similar to the individual components and were about 4 to 5 points.

Figure 16

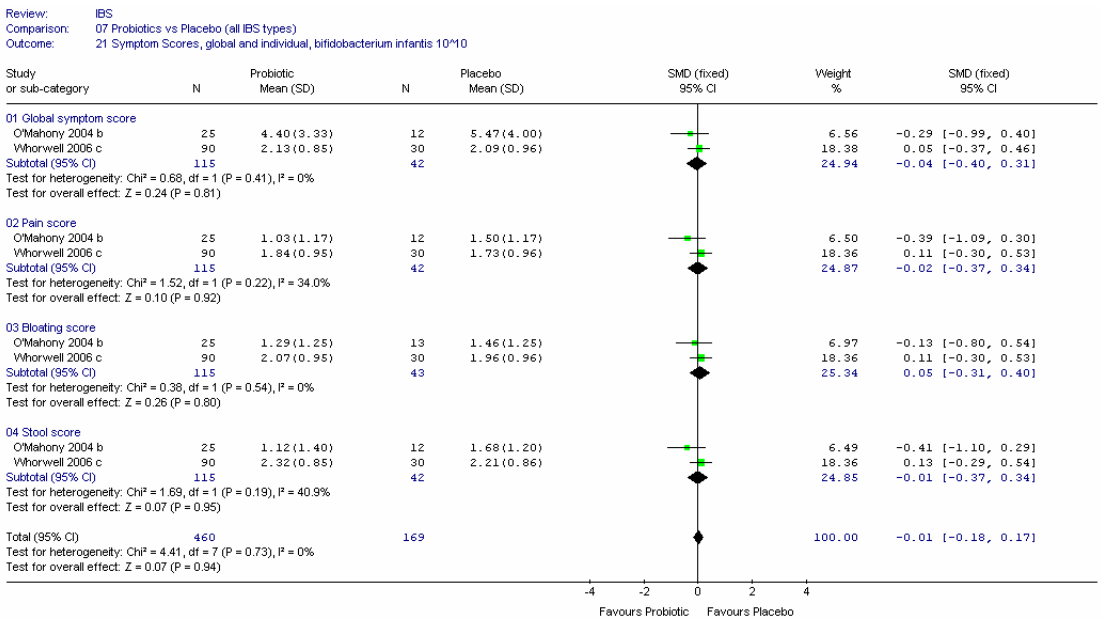


Examination of the two studies using Bifidobacterium infantis 35624

Two studies compared Bifidobacterium infantis 35624, at a dose of $1x10^{10}$ CFU per day, versus placebo. One study (Whorwell 2006) gave the probiotic in a capsule and the other (O'Mahony 2004) in a malted drink.

The outcomes are summarised in Figure 17. There was some heterogeneity between studies for the outcomes of pain and stool score, with the encapsulated probiotic having less effect. This is discussed further in the next section.

Figure 17

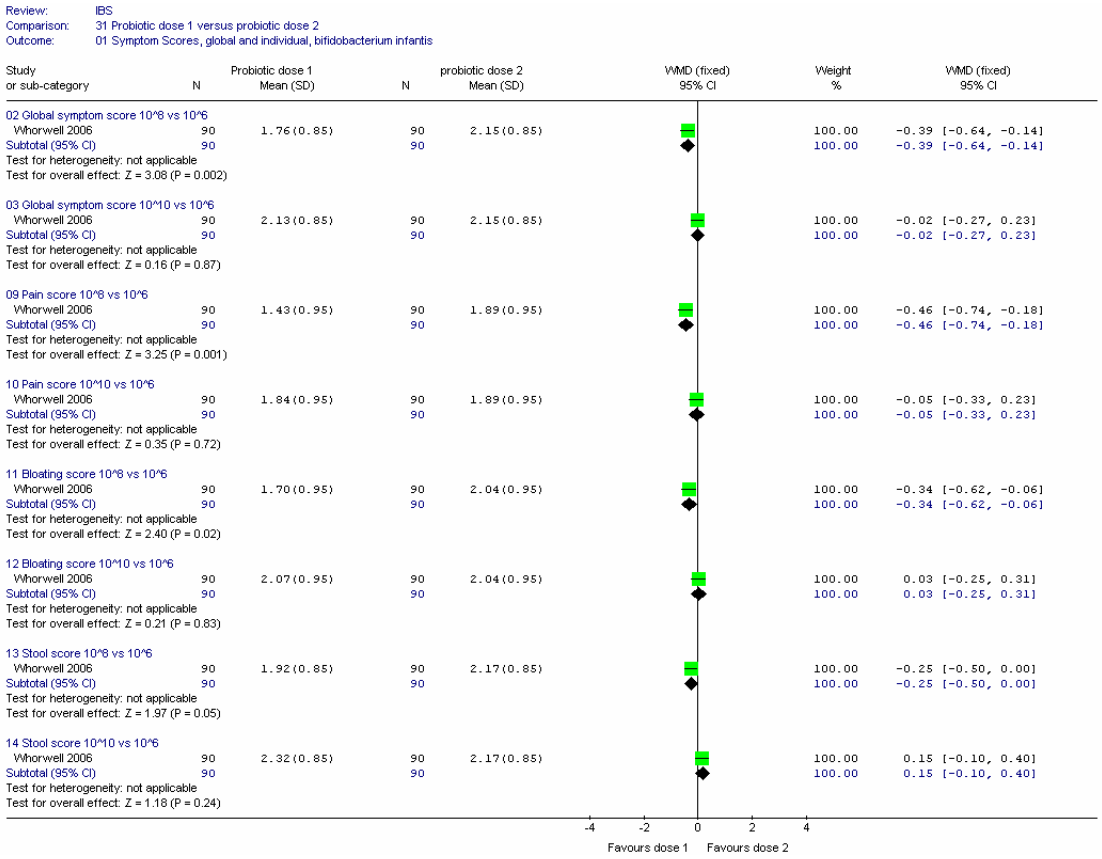


B. Probiotic dose 1 versus probiotic dose 2

One study (Whorwell 2006) compared three doses of Bifidobacterium infantis 35624, $1x10^{6}$, $1x10^{8}$, $1x10^{10}$, with approximately 90 patients in each arm. The outcomes compared are reported in Figure 18.

Head-to-head comparison of the doses $1x10^8$ and $1x10^6$ showed there was a significant difference in global symptoms, pain and bloating scores and a borderline difference in stool score, favouring the $1x10^8$ dose. However, there was no significant difference between the $1x10^{10}$ and $1x10^6$ doses, an unexpected dose effect.

Figure 18



Whorwell (2006) explained this using in-vitro dissolution experiments, showing that the highest concentration of probiotic coagulated on exposure to moisture, making dissolution very difficult, such that the probiotic was not bioavailable to the patient.

This effect also explains the differences between Whorwell (2006) and O'Mahony (2004); in the latter, the probiotic was bioavailable because it was present in a drink.

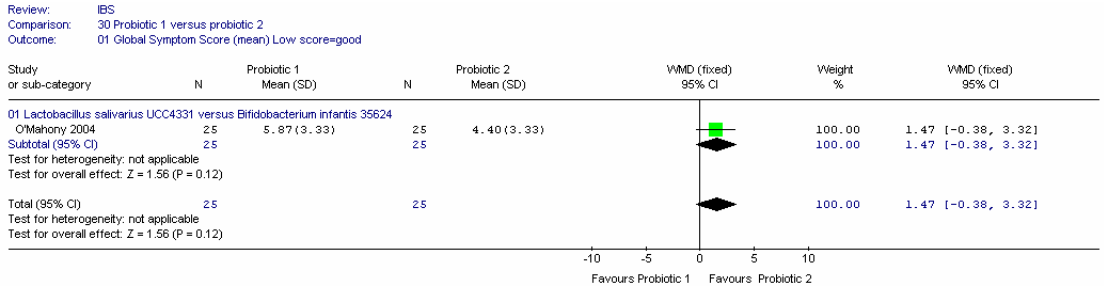
C. Probiotic 1 versus probiotic 2

One study compared two strains of bacteria, Lactobacillus salivarius UCC4331 versus Bifidobacterium infantis 35624 (O'Mahony 2004) directly in a randomised trial of 50 patients. The results are presented below for the different outcome measures.

1. Global symptom score

There was no significant difference in global symptoms at eight weeks, but the Bifidobacterium is favoured. A 10cm visual analogue scale was used for individual symptoms and combined to give a global score (maximum 30).

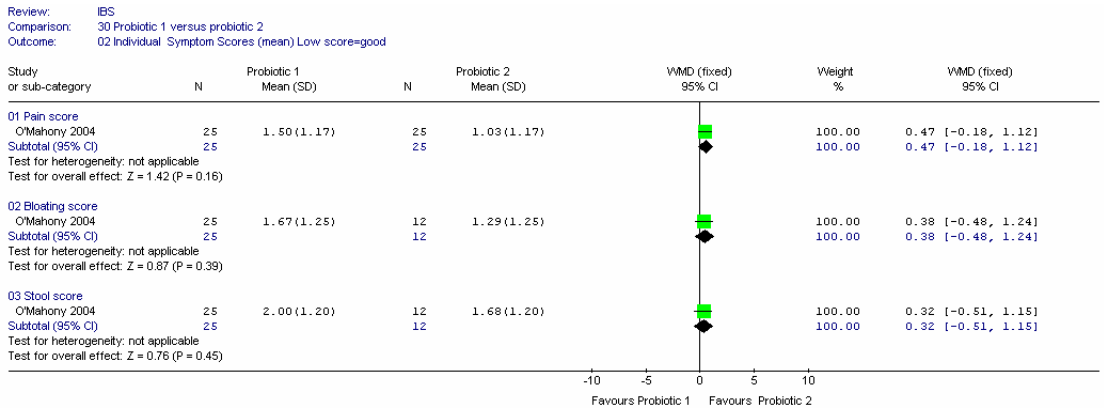
Figure 19



2. Individual symptoms

There was no significant difference between the two types of bacteria for pain, bloating or stool score. Likert scales were used for each component with a maximum of 7.

Figure 20



D. Prebiotics versus placebo

One study (Olesen 2000) compared a prebiotic (Fructooliogsaccharide given as a 10g sachet for 2 weeks then 20g for 10 weeks) with placebo in 98 patients. The results are given below and generally showed no significant differences between prebiotics and placebo, in either global symptoms or bloating (although the confidence interval was fairly wide in the latter). The confidence interval was too wide to determine if there was a difference for the pain outcome. We noted that there was some attrition bias for this study.

Figure 21

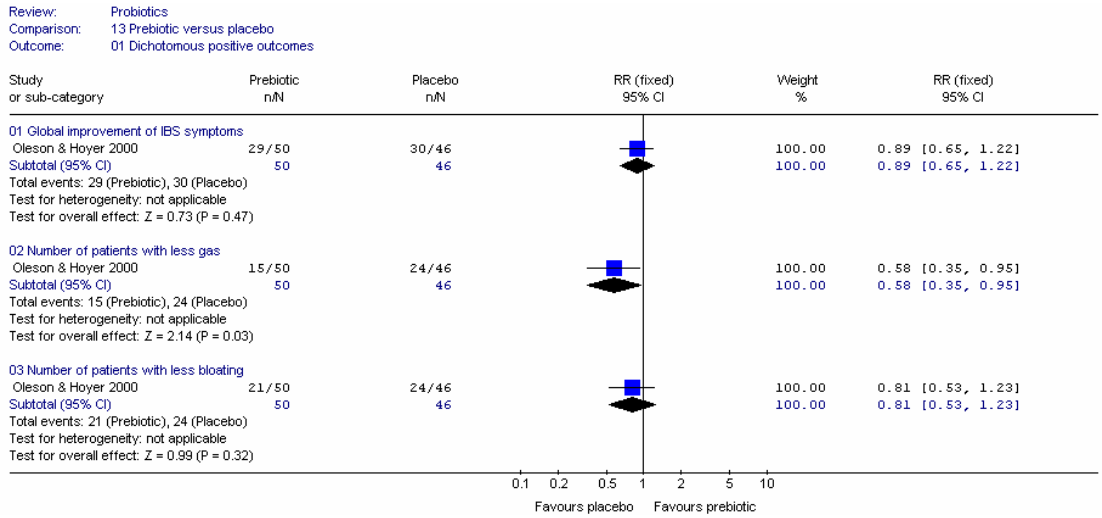
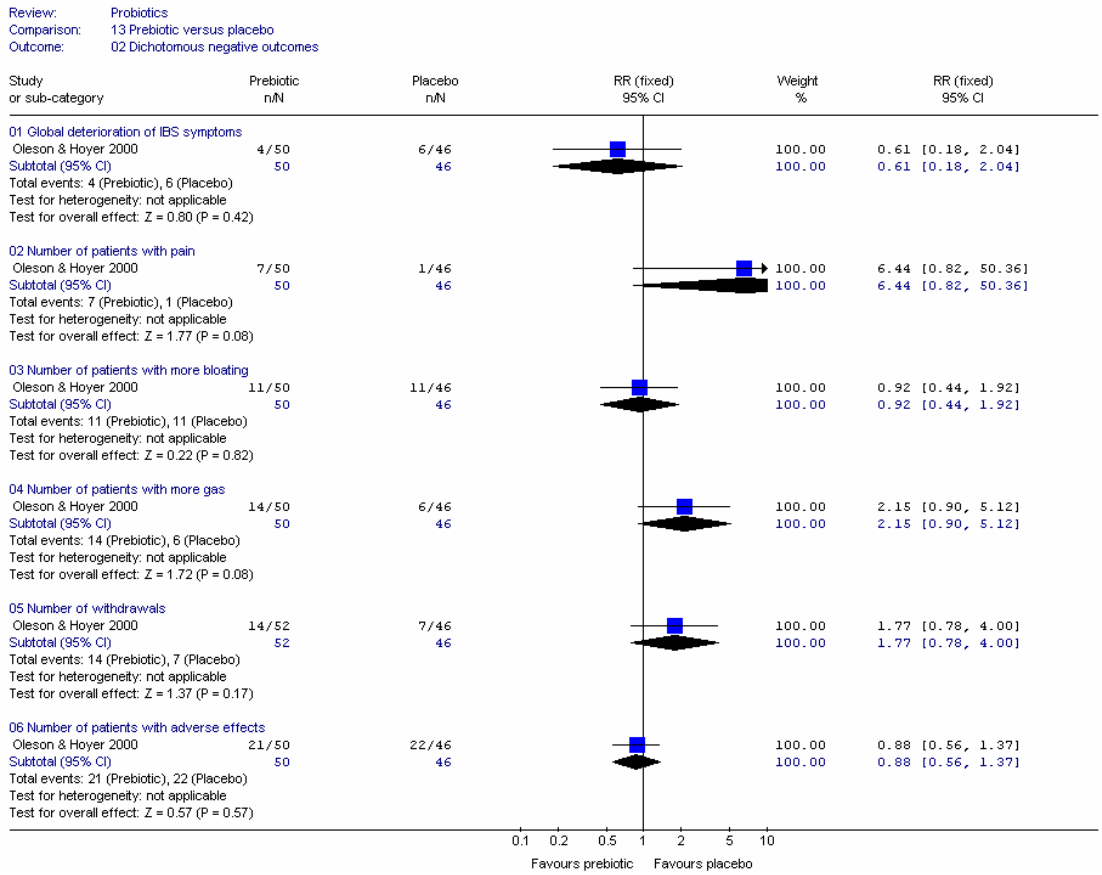


Figure 22



HEALTH ECONOMIC EVIDENCE

The cost effectiveness of pre and probiotics was not estimated as they are not prescribed, but currently purchased by patients as a food supplement.

GDG DISCUSSION

The GDG discussed the use of pre and probiotics at some length. They were unanimous in their view that different types and doses of probiotic should not be combined together in an analysis because they all have different effects. The main issues raised for discussion were dose, method of ingestion and quality of products available to patients. Probiotics are not generally prescribed by GPs. Patients purchase them and there was concern that sources are not always reliable or safe. There was agreement that there is insufficient information for patients about the quality of products and insufficient information on packaging regarding dose and quality of individual products.

The studies that investigated Bifidobacterium infantis 35624 (Whorwell 2006; O'Mahony 2004) were discussed with regard to the observed maximum in the dose response in Whorwell (2006) and the inconsistencies between the two studies. This was explained by the method of ingestion. In Whorwell (2006), a capsule was used as the means of ingesting the different doses of probiotic. For the $1x10^{10}$ CFU concentration of probiotic, contact with water led to the probiotic coagulating so that it was no longer bioavailable to the patient. The same dose of probiotic was found to be effective in O'Mahony (2004) because the probiotic was ingested in the form of a milk based drink so the concentration of probiotic was evenly dispersed through the fluid and therefore bioavailable to the patient.

EVIDENCE STATEMENTS

1. There is fair evidence to show that some probiotics (single or combination) give a significantly greater improvement in global symptoms of IBS than placebo. However, this is bacterium dependent, in terms of both dose and strain.

2. There is good evidence to show a significant difference in global symptom score for combined probiotics compared with placebo, favouring probiotics, but no significant difference for single probiotics as a group in people with IBS.

3. There is fair evidence to show a significant reduction in the number of people with pain for those taking single probiotics compared with placebo; there is weak evidence to suggest the extent of this depends on the bacterium strain and/or dose.

4. There is good evidence to show no significant difference in pain score or bloating score for single probiotics, both as a group and individually, compared with placebo. There is a significant difference for combined probiotics, with the probiotic giving significantly less pain and bloating.

5. There is weak evidence to show no significant difference in the number of people with bloating for combined probiotics compared with placebo.

6. There is good evidence to show that the use of probiotics (single or combination) resulted in participants reporting no significant difference in bowel habit.

7. There is good evidence to show that high doses of Bifidobacterium infantis (10^{10} CFU) in capsule form are significantly less effective than moderate doses (10^{8} CFU); moderate doses are more effective than low doses (10^{6}). There is weak indirect evidence to show that this reduction in effect at high doses does not occur when probiotics are delivered in a drink.

8. There is fair evidence to show no significant difference between Lactobacillus salivarius UCC4331 and Bifidobacterium infantis 35624, in global symptoms, pain, bloating or stool scores.

9. There is a moderate amount of weak evidence to show no significant difference in the number of people with improvement in global symptoms or with bloating, between those given the prebiotic, Fructooliogsaccharide, in comparison with placebo.

EVIDENCE TO RECOMMENDATION

The review evidence suggests that some probiotics are effective in people with IBS, but others are not. The effect is dose and strain dependent, and the method of ingestion is also important. Although, there is some evidence from single trials, the GDG did not feel able to recommend named bacteria or probiotic products. On the other hand, it was the view of the GDG that probiotics were not harmful (unless they came from an unreliable source), they were widely available and it might benefit people with IBS if they experimented with probiotics as part of their diet. The GDG agreed there was insufficient evidence to make a recommendation on prebiotics.

RECOMMENDATION

People with IBS who choose to try probiotics should be advised to take the product for at least 4 weeks while monitoring the effect. Probiotics should be taken at the dose recommended by the manufacturer.

7.5 Aloe vera

SELECTION CRITERIA

The selection criteria described in the general methodology section were used.

DESCRIPTION OF STUDIES

Types of Studies

Two randomised trials were included (Odes and Madar 1991; Davis 2006) and two excluded studies are listed in Appendix E, along with reasons for exclusion.

Types of participants

All participants in Davis (2006) had IBS (28% IBS-C, 52% IBS-D, 20% IBS-A); participants had to be between 18 and 65 years, have no other co-morbidities and had to have previously failed conventional management of IBS defined as antispasmodics, bulking agents and dietary interventions. Constipation was defined as per Rome II criteria.

Odes and Madar (1991) had 11/32 people with IBS-C (the rest had simple constipation); people with IBS-D or IBS-A were excluded; participants had to have been receiving laxative therapy for constipation for a minimum of two years as an indication of severity. Participants had previously received other treatments including diet and enemas, but it is not stated if they were refractory to treatment.

Types of intervention

Davis (2006) used aloe vera gel made up in a pink mango flavoured syrup. The dose was 50 ml taken four times a day for one month. The placebo was a matching pink mango flavoured inert syrup.

Odes and Madar (1991) used a capsule laxative preparation made up of celandin, aloe vera and psyllium in ratio of 6:3:1 (total fibre content 47%) given for 28 days. The aloe vera fibre was derived from leaves of *Aloe socotrine* and contains anthraquinone. The dose was one 500mg capsule per day taken with water at bedtime increasing to a maximum of three capsules a day. The placebo capsule was of identical appearance but contained no active ingredient. Participants in Odes and Madar (1991) were given no dietary modification advice. No additional medication was prescribed throughout the treatment period but people could continue with prescribed laxative medication, provided that the dose and frequency were recorded in the study data sheet. Davis (2006) did not state if other medications could be continued.

METHODOLOGICAL QUALITY

Davis (2006) used a computerised random numbers table to generate the randomisation schedule. Allocation concealment was implemented in this study; the pharmacist held the

randomisation code. Both studies were double blind. Davis (2006) carried out an *a-priori* sample size calculation.

In Davis (2006), 58 people were randomised. 49 completed the protocol to one month and 41 to three months (i.e. data missing for 17/58 (29%) overall; 33% in the placebo group and 26% in the active group). In Odes and Madar (1991), 35 people were randomised. Three people (placebo) withdrew citing lack of benefit as reason and were excluded from the analysis because of incomplete data.

The groups in both trials were comparable at baseline as regards age, gender, duration and severity of condition, but Odes and Madar (1991) reported that the treatment group had significantly higher pain scores at baseline.

Overall, neither study was considered to have higher potential for bias.

RESULTS

In view of the differences in population and interventions, these two studies were reported separately.

A. Aloe vera gel versus placebo

One study (Davis 2006) in compared aloe vera gel with placebo in 58 people with IBS.

1. Global improvement of symptoms

The primary outcome was the number of people with an improvement in global symptom score (pain; distension; bowel habit, and; quality of life). The symptom score was derived by adding the scores of individual symptoms and the proportion of days symptoms occurred with a maximum score of 500. A reduction of 50 points was defined as improvement. Participants were assessed at one month and at three months post-intervention. The forest plots below illustrate that there was no significant difference between the active and placebo treatment for global improvement of symptoms, although the confidence interval was fairly wide.

Figure 1a: Global improvement of symptoms at one month

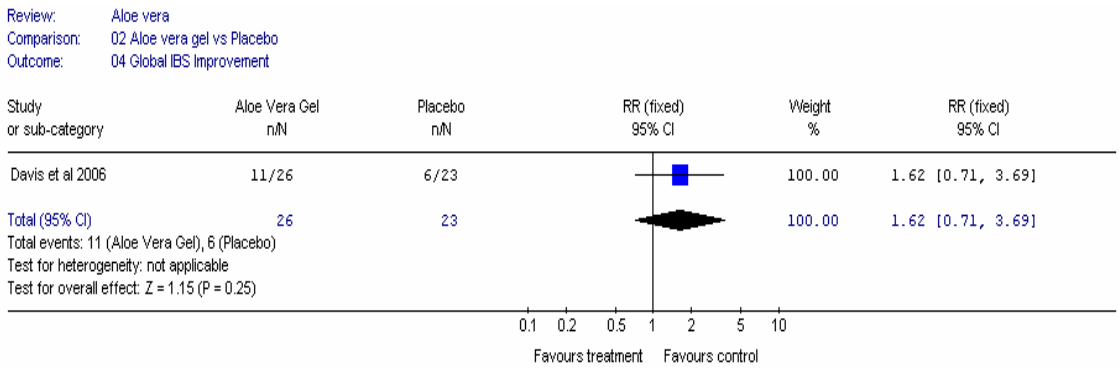
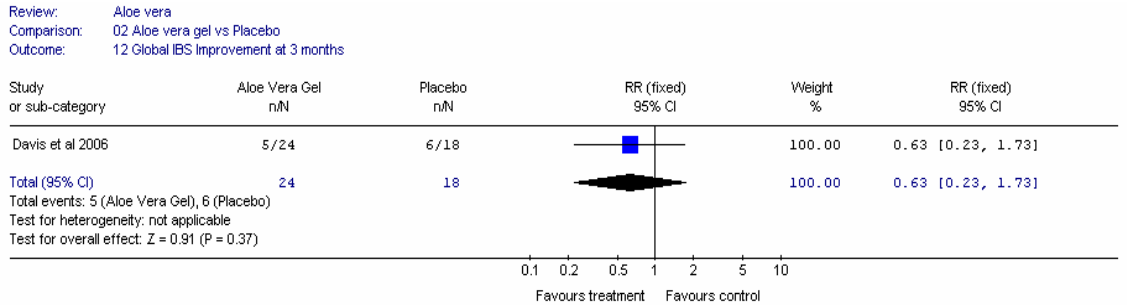


Figure 1b: Global improvement of symptoms at three months



2. Individual symptoms

a) Pain

There was no significant difference, either at 1 month or at 3 months, in the change in pain score, on a scale of 0 to 100%, for which a positive change represented an improvement over baseline.

Figure 2a: Pain at one month

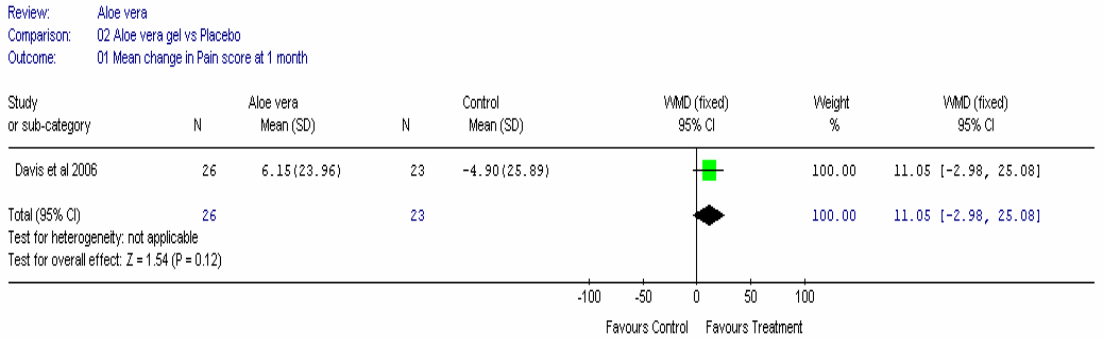
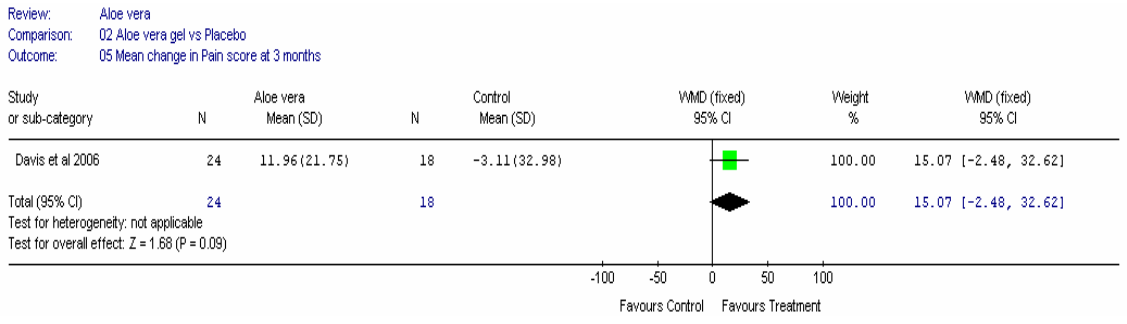


Figure 2b: Pain at three months



b) Bloating

There was no significant difference either at 1 month or at 3 months, in the change in distension score, on a scale of 0 to 100%, for which a positive change represented an improvement over baseline.

Figure 3a: Distension at one month

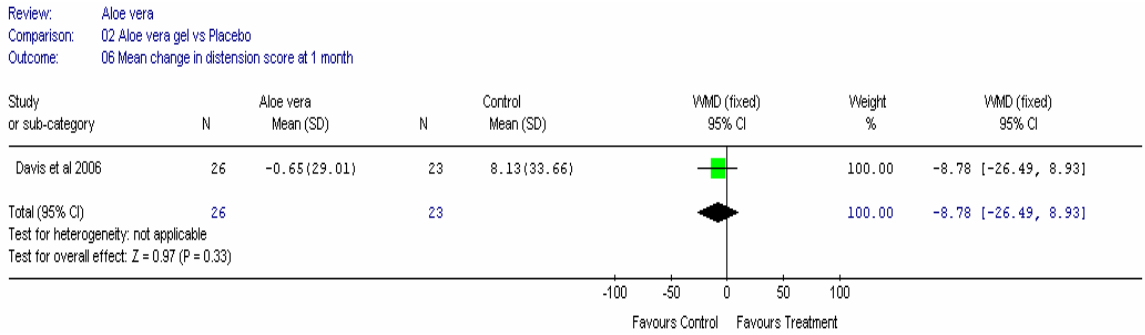
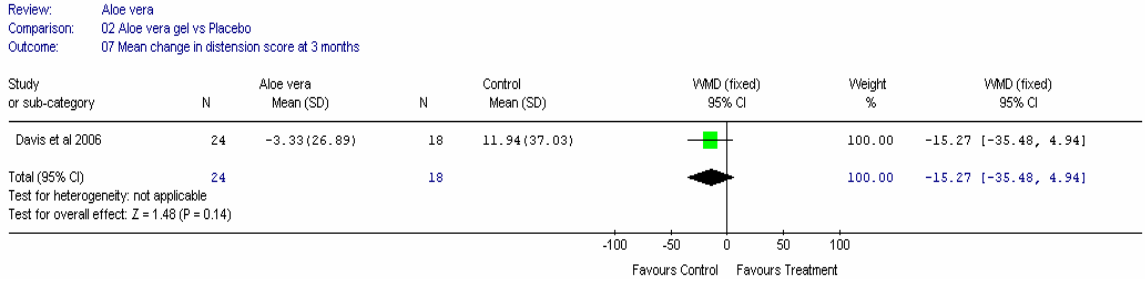


Figure 3b: Distension at three months



c) Bowel Habit

There was no significant difference, either at 1 month or at 3 months, in the change in bowel score, on a scale of 0 to 100%, for which a positive change represented an improvement over baseline.

Figure 4a: Change in bowel score at one month

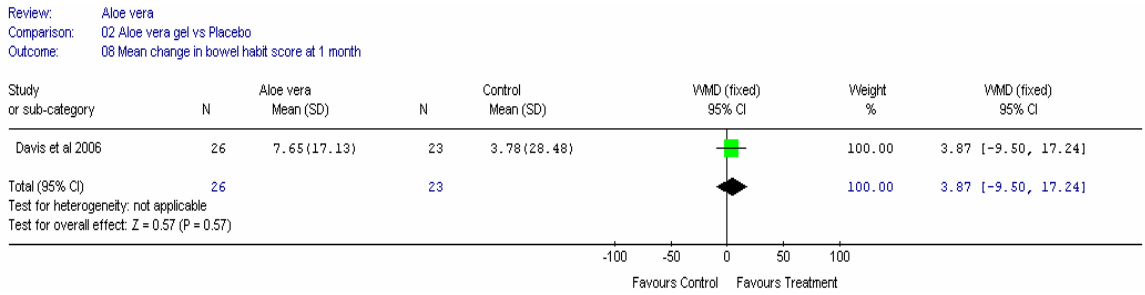
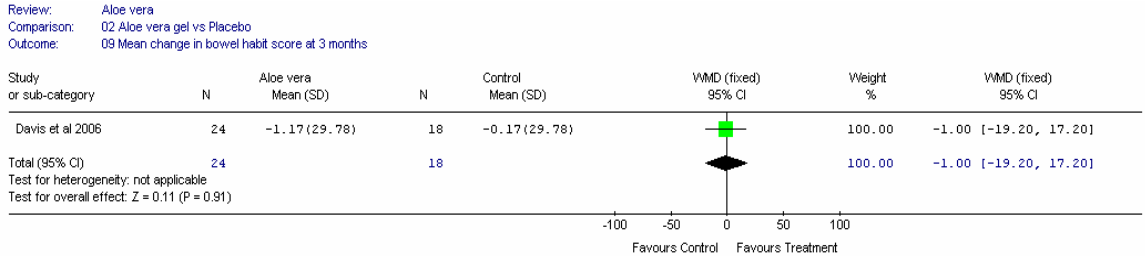


Figure 4b: Change in bowel score at three months



3. Quality of Life

There was no effect on quality of life at one month or at three months. The scale used was not stated.

Figure 5a: Change in quality of life at one month

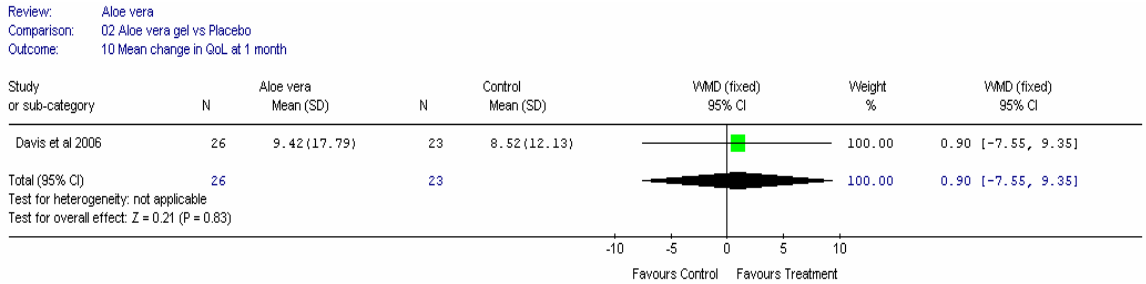
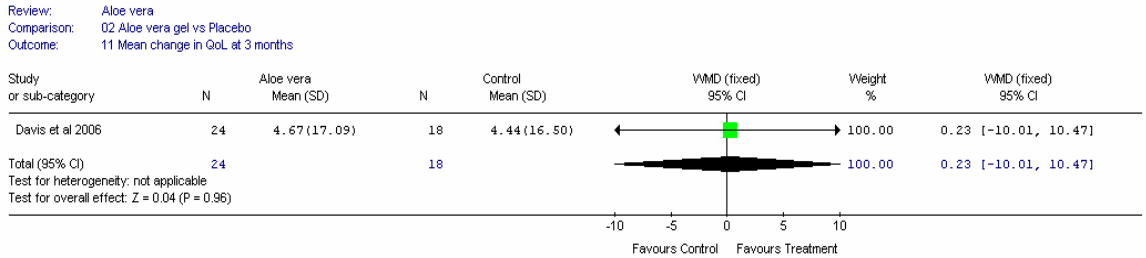


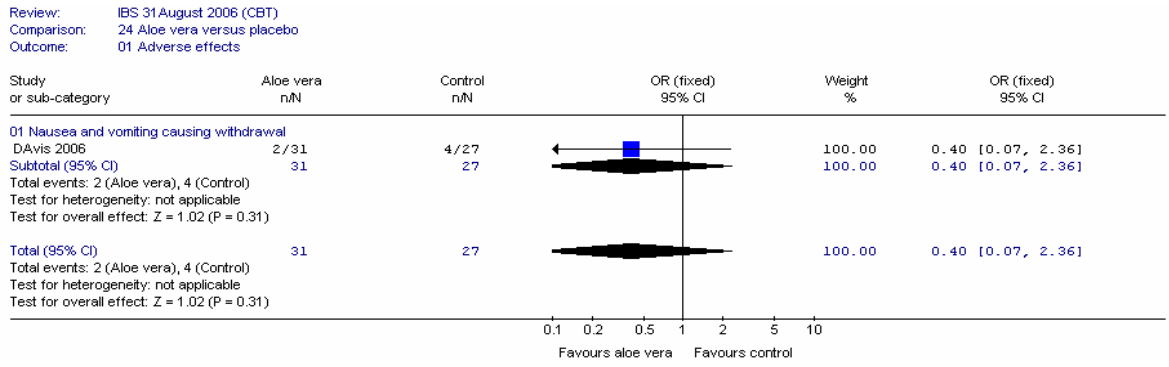
Figure 5b: Change in quality of life at three months



4. Adverse effects

2/31 people withdrew from the active group and 4/27 from the placebo group because of nausea and vomiting. The confidence interval was too wide to determine if there was a difference between groups.

Figure 6: Adverse effects



B. Combined capsule of celandin, aloe vera and psyllium versus placebo

1. Global improvement of symptoms

Odes and Madar (1991) did not report global symptoms.

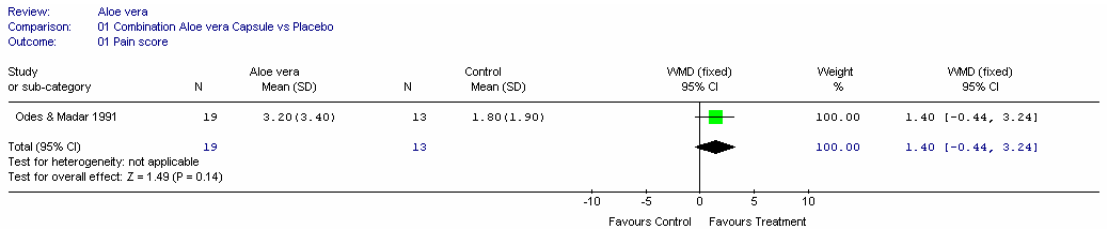
2. Individual symptoms

One study with 32 participants reported differences in bowel habits (including frequency and consistency) and pain scores for the final two weeks of treatment compared with those in the 14 day pre-intervention run in period (Odes and Madar 1991). Eleven participants (34%) were identified as having IBS-C; the rest had simple constipation.

a) Pain

There was no significant difference in pain scores (number of episodes of pain per week) between groups.

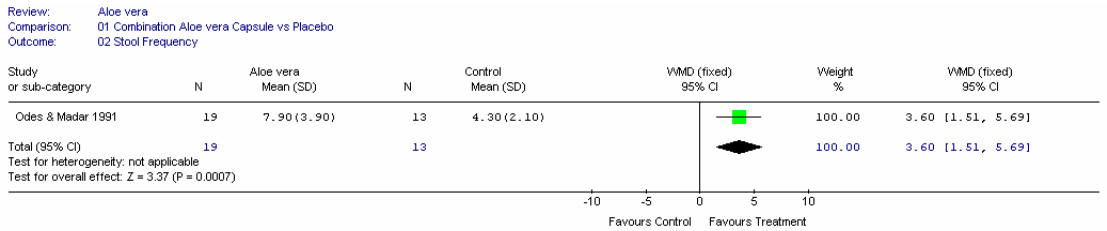
Figure 7: Number of episodes of pain per week



b) Bowel Habits

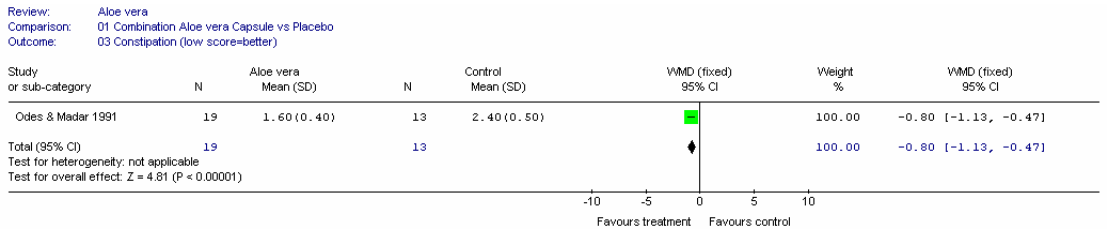
Compared to the placebo group, people in the intervention arm of the trial experienced a significant increase of 3.6 (95%CI 1.51, 5.69) in the mean number of bowel movements per week.

Figure 8: Stool frequency



The consistency of the stools also improved. There was a statistically significant decrease in laxative use in the intervention group of -0.8 (95%CI -1.12, -0.47) on a scale of 1 to 3 and 16/19 people considered their bowel symptoms improved compared to 4/13 of the control group.

Figure 8: Stool consistency



No adverse effects were reported and all participants reported that the capsules were easy and convenient to use.

Comment

Whilst this study shows a significant positive effect for bowel habit, we noted that this was a small study (35 patients) in a population of which only one-third had IBS. In addition, the intervention used a combination of aloe vera (30%), celandin and psyllium (soluble fibre). Therefore, it was not possible to attribute the effect to aloe vera alone, and this study was not included in the evidence statements.

SAFETY DATA

The following safety data is based on a systematic review of the scientific literature (case reports and systematic reviews) edited and peer reviewed by contributors to the US Natural Standard Research Collaboration (2006).

Adverse effects

The use of aloe by mouth for laxative effects can cause abdominal cramps and diarrhoea. Adverse effects, reported in a small number of studies, include low blood sugar levels and electrolyte imbalance, particularly lowered potassium levels.

Drug interaction

Use of aloe with laxative drugs may increase the risk of dehydration, electrolyte imbalance, potassium depletion and changes in blood pH.

Oral preparations of aloe have been reported to lower potassium levels, which may impact on the effectiveness of drugs used to manage heart rhythm disturbances, heart disease and renal disease.

Oral preparations of aloe may lower blood sugar, so have the potential to interact with drugs used in the management of diabetes.

Aloe vera should not be used by individuals who may be at increased risk from the aforementioned adverse effects, particularly people with heart disease, kidney disease, diabetes and blood disorders.

GDG DISCUSSION

The GDG expressed concerns that people with IBS purchase aloe vera products at considerable expense without evidence of effectiveness. The GDG also expressed concerns about the adverse effects of oral preparations of aloe vera, about which there was little awareness.

HEALTH ECONOMIC EVIDENCE

The cost-effectiveness of aloe vera was not estimated as it is not prescribed, but purchased by patients as a food supplement.

EVIDENCE STATEMENTS

1. There is fair evidence to show no significant effect of aloe vera, in comparison with placebo, in global improvement of symptoms, pain, bloating, bowel score or quality of life.

2. There is limited evidence of potentially serious adverse effects associated with oral aloe preparations.

EVIDENCE TO RECOMMENDATION

There is only one trial of aloe vera in people with IBS, but this gave fair evidence to show a lack of effectiveness. The GDG took this into account, together with aloe vera's potentially serious adverse effects, especially for people with comorbidities. Since aloe vera is a commercially available product that people with IBS pay for at considerable expense, the GDG wished to highlight these points by discouraging its use. Clinicians and people with IBS should be made aware of the lack of effectiveness and potential adverse effects.

RECOMMENDATION

Healthcare professionals should discourage the use of aloe vera in the treatment of IBS.

7.6 Exclusion Diets

SELECTION CRITERIA

The selection criteria described in the general methodology section were used, but some were specific to this review and are reported below.

Types of studies

For intervention studies, randomised trials (RCTs) and quasi-randomised studies, examining the use of dietary manipulation/exclusion for the treatment of IBS were preferred. Crossover trials with a washout period of less than 2 weeks were included but treated with caution. Double-blind placebo controlled studies are technically difficult and most elimination diet studies use a non-randomised open dietary elimination and re-challenge design. This has the potential to introduce bias due to the large placebo effect identified in IBS patients. For this review non-randomised studies were also permitted. Studies were restricted to the English language, but the date was not restricted.

Types of intervention

Interventions were to be included if they referred to an exclusion diet (excluding certain foods) or an elimination diet (only allowing certain foods):

- Lactose restricted diet
- Elimination diet based on foods with IgG4 titres >250µg/l
- Elimination diet based on food challenge and re-challenge
- Elimination diet based on patient-reported intolerance and re-challenge
- Elimination diet using lamb, rice and pears
- Fasting therapy.

Types of comparisons

The following types of comparisons were to be included:

- True diet versus sham diet
- Elimination diet and food challenge with foods that had been identified as potential causes of intolerance
- Fasting therapy versus usual treatment.

Sensitivity analyses

The following sensitivity analyses may be considered:

- Setting (primary/secondary care)
- Blinding of patients.

SEARCH STRATEGY FOR IDENTIFICATION OF STUDIES

Searches were performed on the following core databases: MEDLINE, EMBASE, CINAHL and *The Cochrane Library* (1966 to current day with guidance from the GDG). Additional databases were not searched for this review. The search strategies are listed in Appendix B.

The search strategy identified 957 studies. The titles and abstracts of these studies were assessed. Of these, 33 that were potentially relevant to the review were retrieved in full. The reference lists of the retrieved studies were inspected for potential papers for inclusion in the review but none were identified. Sixteen studies were included in the review. The excluded studies are listed in Appendix E, along with reasons for exclusion.

DESCRIPTION OF STUDIES INCLUDED IN THE REVIEW

There were two randomised trials included (Atkinson 2004; Symons 1992). There were three reviews: one of which examined the evidence for the role of food hypersensitivity in IBS (Zar 2001) and the others were systematic reviews of non-randomised evidence for the dietary treatment of IBS (Niec 1998; Burden 2001). The remaining fourteen included studies were non-randomised studies (Bentley 1983; Böhmer and Tuynman 1996; Drisco 2006; Hawthorn 1991; Hunter 1985; Jones 1982; Kanazawa and Fukudo 2006; McKee 1987; Nanda 1989; Parker 1995; Petitpierre 1985; Smith 1985; Zar 2005; Zwetchkenbaum and Burakoff 1988).

Study Design

One study had a crossover design: Symons (1992) stated that the patients were randomised to interventions on two days, following a 12 hour fast, but the washout period was not clear.

Setting: all the studies included patients in secondary care, many of whom had not responded to previous treatment for IBS symptom management.

The majority of studies took place in the UK (Atkinson 2004; Bentley 1983; Hawthorn 1991; Hunter 1985; Jones 1982; McKee 1987; Nanda 1989; Parker 1995; Smith 1985; Zar 2005; Zwetchkenbaum and Burakoff 1988). One took place in Japan (Kanazawa and Fukudo 2006), two in Europe (Böhmer and Tuynman 1996; Petitpierre 1985), two in the US (Drisko 2006; Zwetchkenbaum and Burakoff 1988) and one in Australia (Symons 1992).

Population

All studies included patients with a diagnosis of IBS, although the definition varied between studies. Four studies used Rome criteria: Rome I (Hawthorne 1991); Rome II (Atkinson 2004, mean duration of IBS over 10 years; Drisko 2006; Zar 2006); Zar (2006) also predefined the IBS type. Two studies used the Manning Criteria (Kanazawa and Fukudo 2006; Symons 1992). Two studies used a definition described by the author (Böhmer and Tuynman 1996; Parker 1995). Seven studies simply said the patients ‘had IBS’ (Jones 1982; Bentley 1983; McKee 1987; Petitpierre 1985; Smith 1985; Nanda 1989; Zwetchkenbaum and Burakoff 1988). None of the studies stated that any patients had IBS as result of gastrointestinal infection.

Atkinson (2004) did not state whether patients had bloating and/or pain but described the symptom severity to be severe. Another study described the duration and frequency of symptom episodes (Nanda 1989), and one study reported duration of symptoms and the percentage of patients with pain, bloating and urgency (Hawthorne 1991). The remaining studies did not state the severity of symptoms. The age range of patients was 18 to 80 years with the average mean age being approximately 28 to 44 years. None of the studies particularly identified elderly patients. All studies had more women than men.

Interventions

Fructose-Sorbitol Dose 1 versus Dose 2

The RCT, Symons (1992), compared the difference in symptom provocation in IBS patients using two different doses of fructose–sorbitol solution. The lower dose solution was made up of 20g fructose and 3.5g sorbitol in 200 ml water; the higher dose contained 25g fructose and 5g sorbitol in 250ml water, i.e. a comparison of 17.5 and 20g/litre of sorbitol, for a constant concentration of fructose 100g/litre. Thirty-nine patients (15 IBS patients and 24 healthy controls) were randomised to receive the higher or lower dose on different days, and results were reported separately for the two population groups.

Exclusion diets

The other RCT, Atkinson (2004), tested patients' blood for IgG antibodies against 29 foods. A true and a sham diet sheet were then prepared for each patient. The true intervention diet excluded those foods to which the patient had antibodies; the sham diet excluded an equal number of foods but not those to which the patients had antibodies. The sham diet also included an equally difficult-to-exclude staple food as the true diet (for example, cow's milk was replaced by potato, wheat with rice, yeast with whole egg, etc.).

Exclusion diets (non-randomised studies)

The majority of studies used a low allergenic diet, and initially excluded a range of foods, including dairy products, wheat, corn, yeast, eggs, rye, potatoes, onions, cocoa, citrus, coffee, tea spices, alcohol, peas, banana, additives, preservatives and tomatoes. Then an open or single-blinded food challenge re-introduced foods 2 to 7 days apart.

- One study used a diet of one meat, one fruit and distilled water (Jones 1982)
- One study used only lamb, rice and pears (Bentley 1983)
- One study used lamb, white fish, cabbage, carrots, peas, 'Ryvita', weak black tea and dairy free margarine (Smith 1985)
- Two studies used IgG4 antibody and mould guided exclusion diets (Drisko 2006; Zar 2006)
- One study used a lactose restricted diet, but gave no further details. Low lactose consumption was defined as less than 9 g per day (Böhmer and Tuynman 1996)
- One study used starvation followed by 5 days of re-feeding in hospitalised IBS patients (Kanazawa and Fukudo 2006).

Comparisons

One RCT compared true diet with sham diet (Atkinson 2004).

One RCT compared two different doses of fructose-sorbitol solution (Symons 1992).

The remaining studies used diet and food challenge in all patients. The duration of the exclusion diet ranged from seven days (Jones 1982) to six months (Zar 2006). The challenge tests used in the studies involved patients being placed on a diet excluding foods believed to provoke symptoms and then re-introducing the foods in a double-blind or controlled way.

OUTCOMES

I. RANDOMISED TRIALS

1. Global symptoms score

a) Global improvement of IBS score

Atkinson (2004) used a validated IBS symptom severity score with a range from 0 to 500. The scale took into consideration scores for pain, distension, bowel function and general well-being, with mild, moderate and severe cases indicated by scores of 75-175, 175-300 and >300 respectively. A reduction in score of 50 or more was regarded as a clinically significant improvement.

Atkinson (2004) also reported a global rating of IBS using the question: 'Compared with your IBS before you started the food elimination diet, are you now: terrible, worse, slightly worse, no change, slightly better, better or excellent?' Significant improvement was defined as 'better' or 'excellent'.

Symons (1992) used a symptom score composite: abdominal pain/discomfort, bloating, distension, belching, nausea, bowel frequency, flatulence and borborygmi were each scored on a scale of 0 to 3 with 0 = absent and 3 = severe.

2. Quality of Life

Atkinson (2004) assessed the patients using a validated quality of life scale that is sensitive to change in IBS (range 0 to 500).

3. Mental health

Atkinson (2004) assessed the patients using the Hospital Anxiety and Depression (HAD). This instrument scores anxiety and depression up to a maximum score of 21 for each parameter, and a score above 9 indicates significant psychopathology.

Symons (1992) did not record other outcomes.

METHODOLOGICAL QUALITY OF RANDOMISED TRIALS

The quality assessment for included studies is shown in Appendix D.

The methods of randomisation and allocation concealment were reported in one randomised study, both of which were classified as adequate (computer generated and the sequence was retained by a central telephone centre: Atkinson 2004). Symons (1992) gave no details of the methods of randomisation or allocation concealment.

Atkinson (2004) described an *a-priori* power calculation and used an intention to treat analysis. The groups were mainly comparable, except that the baseline IBS symptom score was higher in the intervention group (331.9 (SD 70.8) versus 309.0 (SD 78.5), which is not a significant difference (p=0.06)). The number of patients who withdrew from the studies or were lost to follow-up was minimal. Atkinson (2004) reported data from 131 of the original 150 patients (65/75 true and 66/75 sham diet groups) at 12 weeks (87%).

Symons (1992) did not describe an *a-priori* power calculation. All patients completed the study. The study reported no baseline data so it was not possible to judge whether the groups were comparable.

RESULTS

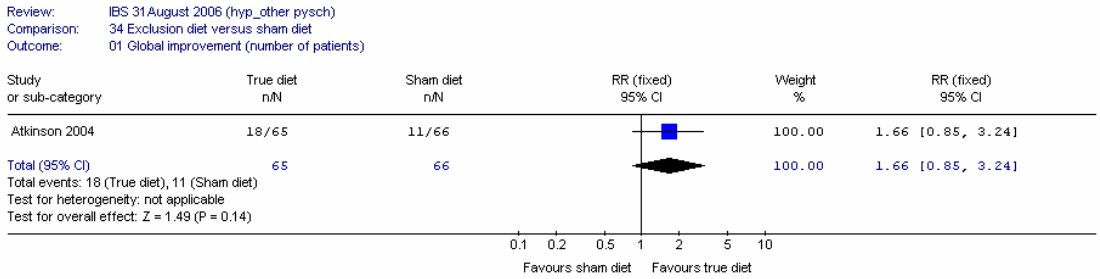
A. True diet versus sham diet

1. Global symptoms

a) Number of patients with improvement in global symptoms

Atkinson (2004) randomised 150 patients to true and sham exclusion diets. They reported the number of patients with improvement in global symptoms. There was no significant difference between true and sham diets; however, the confidence interval was fairly wide.

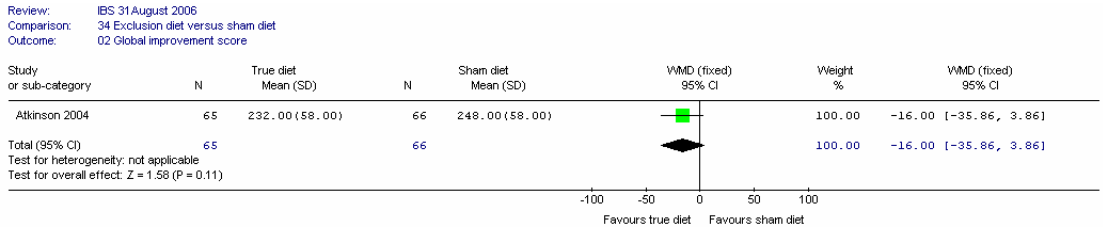
Figure 1



b) Global improvement of symptoms score

Atkinson (2004) reported the final global symptom score on a scale from 0 to 500 (where lower scores are better). There was no significant difference between true and sham diets, although the true diet was favoured.

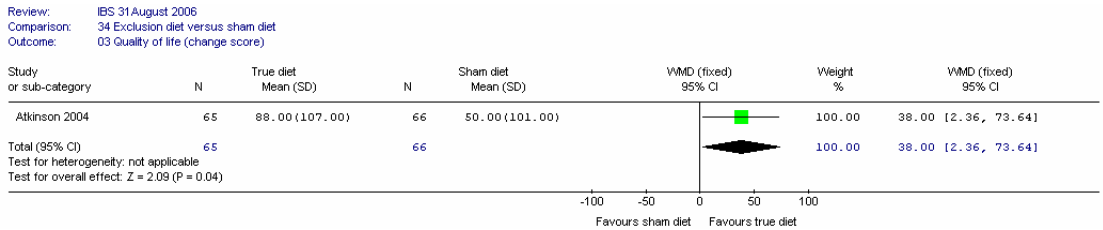
Figure 2



2. Quality of life

Atkinson (2004) reported a significant improvement in quality of life change-from-baseline scores for the true diet compared with sham diet, but the confidence interval was fairly wide. The mean difference was 38.0 (95%CI 2.36, 73.64), for a sham diet change from baseline of 50 points. The scale was 0 to 500.

Figure 3



3. Mental health

There was a small significant difference between the sham and true diet groups in the HAD anxiety scores (scale 0 to 21), but no significant difference in the depression scores.

Figure 4: HAD anxiety

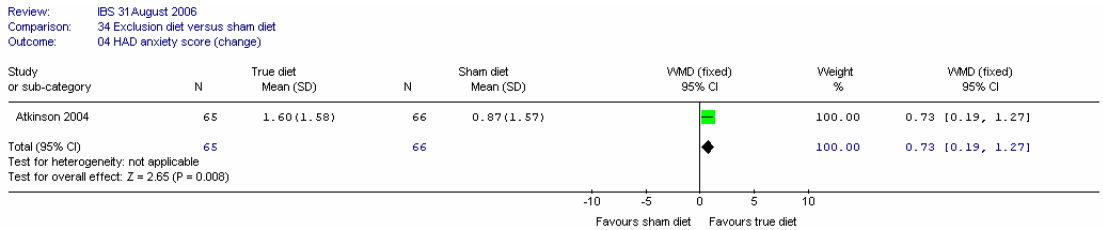
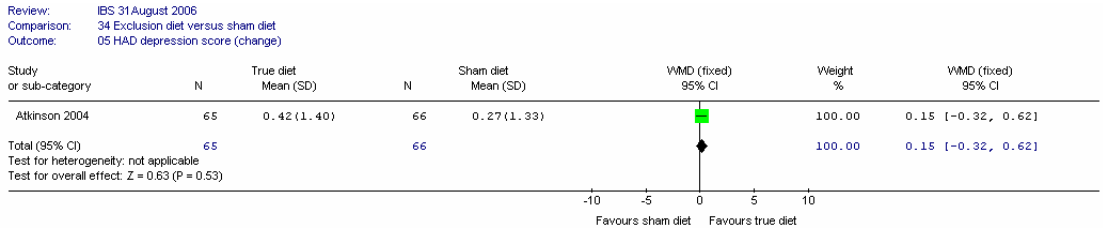


Figure 5: HAD depression



Symptoms on reintroduction of excluded foods at end of trial period

Of the 131 patients who gave data at the end of the trial period in Atkinson (2004), 93 (41 in the true diet group and 52 in the sham diet group) agreed to attempt reintroduction of eliminated foods. The mean IBS symptom score significantly increased (i.e. worsened) more in the true diet group (83.3 points) than in the sham diet group (31 points, p=0.003; standard deviations not given).

The change in global symptom score also showed that significantly more patients in the true diet group worsened on reintroduction of foods to which they had IgG antibodies (i.e. those that had been excluded during the diet): 41.5% of these patients worsened on reintroduction of these foods, versus 25% worsening in the sham diet group on reintroduction of similar foods (to which they had not been shown to have antibodies), p=0.047. We noted though that the self-selecting group taking part in this section of the trial may not have been representative of the randomised groups.

B. Fructose-sorbitol solution dose 1 versus fructose-sorbitol dose 2

Fructose and sorbitol, when ingested together, are thought to provoke symptoms of IBS. Sorbitol is found naturally in fruits, particularly peaches, pears, and plums. It is also added to soft drinks and diet products. One study (Symons 1992) compared two concentrations of sorbitol in a mixed solution of fructose and sorbitol. Concentrations compared were 17.5 and 20 g/litre sorbitol (the fructose concentration was kept constant). We noted that the duration of the study was very short – two days in each phase.

1. Global symptoms

Symons (1992) used a symptom score composite: abdominal pain/discomfort, bloating, distension, belching, nausea, bowel frequency, flatulence and borborygmi were each scored on a scale of 0 to 3 with 0 = absent and 3 = severe. It is unclear what the maximum score is, but it could be 21. The data were expressed as median (interquartile range). For the IBS patients the total symptom score was significantly greater (i.e. more severe) following consumption of the higher concentration solution, compared to the lower concentration solution (p=0.04).

Intervention	Median symptom score (range) (n=15)
Lower F-S dose	1.5 (0 to 4)
Higher F-S dose	3.5 (1 to 9) *

***** p = 0.04

II. NON-RANDOMISED STUDIES

All thirteen studies identified food intolerance with varying degrees of response to exclusion diets (Bentley 1983, Böhmer and Tuynman 1996, Drisco 2006, Hawthorn 1991, Hunter 1985, Jones 1982, Kanazawa and Fukudo 2006, McKee 1987, Nanda 1989, Parker 1995, Petitpierre 1985, Zar 2005, Zwetchkenbaum and Burakoff 1988), illustrated in Table 1.

Table 1: Non-randomised studies; exclusion diets and results

Study (Drop out rate)	No. of Patients	Diet	Results
LAMB, PEARS AND RICE DIET			
Bentley 1983 8/27 (29.6%)	27	**Diet:** 2 weeks duration; initially only lamb, pears and rice, then other foods introduced individually. **Challenge**: identified foods reintroduced on 3 occasions, 3 days apart	14/21 remission after ED. This is just significant, but wide CI. Taking into account drop outs and assuming they are treatment failures makes the result non significant. 10/21identified specific food intolerance – 8 had double blind challenge and 3/8 confirmed food intolerance originally identified.
Parker 1995 53/253(21%) 33/129 (25%)	253 (phase 1) 129 (phase 2)	**Diet**: 2 weeks ED comprising of lamb, pears, white rice and spring water **Challenge**: single food re-introduction at daily intervals **Phase 2**: less restricted diet	100/200 improved on diet Phase 2: 39/96 improved on diet
1 MEAT, 1 FRUIT AND DISTILLED WATER			
Jones 1982 4/25 (20%)	25 (6 = food challenge)	**Diet**: 1 week of single meat, 1single fruit & distilled water **Challenge**: hospital double blind challenge	4/25 refused diet. 14/21 improved and identified foods that provoked symptoms – this is just significant, but wide CI. Food challenge: 10/12 test solutions identified correctly – majority of foods that patients had identified as provoking symptoms were confirmed by food challenge.

Study (Drop out rate)	No. of Patients	Diet	Results
LOW ALLERGENIC DIET AND SIMILAR			
McKee 1987 (not stated)	40	**Diet**: 1 week low allergenic diet, excluded all sources of salicylates, amines, glutamates, additives **Challenge**: Open, frequency not stated	6/40 remission during exclusion diet
Nanda 1989 11/200 (5.5%)	200	**Diet**: 3 week low allergenic, excluded dairy, cereals, citrus fruit, potato, tea, coffee, additives. **Challenge**: open challenge every 2 days	91/189 remission during ED 73/189 found specific foods by open food challenge Follow up approx 14 months 73/91 responders still compliant with ED
Petitpierre 1985 0% drop out	24	**Diet**: 3 weeks Low allergenic **Challenge**: open and single blind, Frequency not stated.	3/24 remission with ED but challenges negative 14/24 specific foods identified and confirmed by blind challenge 7/24 symptoms unchanged
Hawthorne 1991 5/38 (9.5%)	38	**Diet**: 2 weeks exclusion of dairy, cereals, yeast, eggs, citrus fruits, tea, coffee, alcohol, potato, onion, tomato, banana, peas. **Challenge**: foods re-introduced at 2 day intervals following set protocol	5/38 refused to try diet 18/33 improved: 16/18 identified foods which exacerbated symptoms, 2/18 did not. 15/33 had no improvement from diet Follow-up of 16 improvers at 3 to 45 months (results not reported).
Smith 1985 Not stated	28	**Diet**: 2 weeks diet allowed, lamb, white fish, cabbage, carrots, peas, Ryvita, dairy free margarine, black tea. **Challenge**: foods were reintroduced at 2 day intervals in responders	11/28 improved Follow-up at 1yr: 7/9 responders were still well and maintaining diet.

Study (Drop out rate)	No. of Patients	Diet	Results
FOOD EXCLUSION BASED ON IgG ANTIBODIES			
Drisko 2006 All patients completed study and follow up at 1 year.	20	**Diet**: 2-3 weeks duration; tailored food exclusion based on IgE and IgG food and mould panels. **Challenge**: food reintroduced over several months	Statistically significant reduction in stool frequency (diarrhoea) from 4.29 (2.49) stools per day to 3.43 (1.22) Pain score (1 to 5 scale) 3.65 (1.12) to 2.71(1.38) p>0.5 (not significant) Overall QoL scores (100 point scale, high = better) 46.51(21.08) to 67.22(20.92) p<0.001
Zar 2005	25	**Diet**: 6 months duration; IgG4 antibody titres to 16 common foods. These were excluded if titres >250µg/l – most common exclusions: milk, cheese, eggs, beef, lamb, wheat and tomato. On average patients excluded 8 (3 -13) foods	Symptom score (scale 1-100) 21/25 showed statistically significant improvement in pain severity p<0.001, pain frequency p=0.034, bloating severity p=0.001, improved bowel habit p=0.004, QOL p=0.008 Follow up at 6 months: 6/15 lost to follow-up, the remaining patients maintained improvement
FOOD EXCLUSION PARTLY BASED ON IgG ANTIBODIES			
Zwetchkenbaum and Burakoff 1988 1/10 (10%)	10	**Diet**: 2 week exclusion of foods identified from patient food diaries, skin testing and IgG testing. **Challenge**: open for 2 days, 2 days apart Double blind provocation for patients showing persistent exacerbation of symptoms on open food re-introduction.	3/9 remission of symptoms with ED; 6/9 had no change in symptoms. Challenges did not identify provoking food

Study (Drop out rate)	No. of Patients	Diet	Results
STARVATION DIET			
Kanazawa and Fukudo 2006 No drop out	58 hospitalised pts.	**Diet**: 10 days starvation diet followed by 5 days re-feeding (from 225 – 2100kca). Patients were allowed 2 litres of water + 500 ml xylitol solution. Patients also received brief psychotherapy for 12 weeks hospital stay.	Starvation significantly decreased the following symptoms: abdominal pain/discomfort, distension, diarrhoea, anxiety and QOL (p=0.001), nausea (p<0.01), anorexia p=0.02)
LACTOSE RESTRICTED DIET			
Böhmer and Tuynman 1996 No drop out.	105 (70 IBS patients, 35 healthy controls)	**Diet**: 6 week duration; lactose restricted diet (no details given)	17/70 IBS patients had positive hydrogen breath test and glucose blood test compared to 2/35 controls. There was no difference in symptom score between groups at baseline. After dietary therapy, statistically significant decrease in symptom score in lactose intolerant group p<0.001. The lactose tolerant group had no change in scores. The incidence of lactose malabsorption was 4 times higher in IBS group than in healthy controls.

The non-randomised studies have been grouped according to the type of diet, and the following general conclusions can be drawn:

- There is some evidence to suggest that a simple diet of lamb, pears and rice or one meat and one fruit may improve symptoms
- A low allergenic diet does not appear to give remission in IBS symptoms
- Food exclusion diets based on IgG antibody testing appear to be effective in improving symptoms
- A starvation diet significantly decreased symptoms, but this was in a group of hospitalised patients, and is not applicable to primary care
- A lactose restricted diet gave a significant decrease in symptom score for lactose intolerant patients, but not for the lactose tolerant group.

It should be remembered that this evidence is from non-randomised studies, so its overall quality is reduced.

GDG DISCUSSION

The GDG discussed this review at length. They noted that lifestyle change and adjustment of diet according to symptoms can offer relief to people with IBS. Further dietary manipulation in the form of avoidance of specific foods offers improvement for up to two-thirds of people suffering from IBS. However, the GDG was concerned that exclusion diets undertaken without the advice of a dietician could lead to malnourishment and deficiencies.

Diet and nutrition are fundamental in the management of IBS to avoid malnutrition and to achieve optimal symptom control. The gold standard diagnosis for intolerance to a food is by elimination and reintroduction. Intolerance is demonstrated if symptoms resolve on elimination and reappear on reintroduction. Importantly, dietary advice will vary depending on symptoms, e.g. diarrhoea and/or constipation, abdominal bloating and therefore needs to be tailored to the individual to manage symptoms. Consequently, the GDG did not wish to produce a list of possible suspect foods, or to encourage patients to adopt a trial-and-error approach.

The GDG also emphasised that the dietitian should be registered and therefore trained to work in clinical settings and able to advise on all aspects of diet. The GDG noted that, currently, anyone can call themselves a nutritionist, regardless of qualifications. The Nutrition Society is the professional organisation for nutritionists; registration can be checked at www.hpcheck.org.

The GDG commented that an implementable dietary assessment tool would be useful, but accepted that such a tool had to be validated before it could be recommended.

Finally, the GDG recommended that the term, 'balanced diet' should be avoided because it was not specific. They commented that the 5-a-day public health recommendation could be problematic, especially for IBS-D patients.

The consensus was as follows:

- Patients should have a dietary assessment at initial consultation, and this should include examining eating patterns and when patients are eating
- Regular eating patterns should be encouraged
- Exclusion diets should be reserved for severe cases of IBS and should be carried out only under the advice of a dietician
- Dietary referral would be a useful option for mild IBS.

Several of these consensus points have been included in recommendations in the general dietary lifestyle and advice section.

EVIDENCE STATEMENTS

1. There is fair evidence to show no significant difference in global symptoms, between true and sham exclusion diets (i.e. foods excluded for which the patient had or had not IgG antibodies).

2. There is fair evidence to show a significant difference in quality of life, favouring a true exclusion diet, in comparison with a sham diet.

3. There is weak evidence to show that reintroduction of excluded foods to patients previously given a true exclusion diet resulted in significant worsening of global symptoms in comparison with those given a sham diet.

4. There is weak evidence to suggest that food exclusion diets based on IgG antibody testing are effective in improving symptoms, but a low allergenic diet does not appear to be effective.

5. There is weak evidence to suggest that a simple diet of lamb, pears and rice or 1 meat and 1 fruit may improve symptoms.

6. There is weak evidence that a lactose restricted diet gave a significant decrease in symptom score for lactose intolerant patients, but not for lactose tolerant patients.

7. There is limited evidence to show significantly more severe symptoms following consumption of a solution containing 20 g/litre sorbitol, compared to one with 17.5 g/litre, in the presence of fructose.

EVIDENCE TO RECOMMENDATIONS

The GDG took into consideration the clinical effectiveness evidence. Although there was some evidence to support the use of exclusion diets, the GDG believed that such diets should only be undertaken with the specialist help of a dietitian to ensure the diet remains well balanced.

RECOMMENDATION

If diet continues to be considered a major factor in a person's symptoms and they are following general lifestyle/dietary advice, they should be referred to a dietitian for advice and treatment, including single food avoidance and exclusion diets. Such advice should only be given by a dietitian.

8 PHARMACOLOGICAL INTERVENTIONS

Clinical Questions

1. Are antispasmodics effective in managing IBS symptoms?
2. Are laxatives effective in the management of IBS?
3. Are anti-motility agents effective in symptom control in IBS?
4. Do tricyclics and SSRI's have a role in the management of IBS symptoms?

BACKGROUND

The pharmacological management of IBS can provide clinicians with a major therapeutic challenge. People with IBS may present with a multi-symptom profile and it is unlikely that all patients will respond in the same way to the same single agent. There have been no new drugs specifically developed for the treatment of IBS in the last twenty years and the quality of the trials in the majority of pharmacological agents currently available is variable and often conducted on secondary populations. The drug management strategy should be based on the nature and severity of the symptoms and individual or combinations of medication directed at the predominant symptom/s. Irritable bowel syndrome can present with pain, constipation, or diarrhoea. Antispasmodic, TCA and SSRI drugs may relieve IBS pain. Antimotility drugs may relieve diarrhoea. Opioids with a central action such as codeine are better avoided because of the risk of dependence. Laxatives may be needed to relieve constipation. It is important to be sure that the patient *is* constipated. People who complain of constipation need to understand that bowel habit can vary considerably in frequency without doing harm. Some people tend to consider themselves constipated if they do not have a bowel movement each day. Misconceptions about 'normal' bowel habits have led to excessive or inappropriate laxative use. Laxative abuse may lead to hypokalaemia.

In some people with IBS there may be important psychological aggravating factors which respond to reassurance and possibly specific treatment e.g. with an antidepressant.

Antispasmodics

The abdominal pain experienced by people with IBS may be a result of irregular and intermittent intestinal contractions along the length of the colon. This may lead to symptoms of abdominal pain, bloating and gas. Pain is most common after a meal and may last for several hours.

Antispasmodics can be separated into two main categories: antimuscarinics, and smooth muscle relaxants. Antimuscarinics reduce intestinal motility; smooth muscle relaxants directly

relax intestinal smooth muscle. The use of antispasmodics is primarily to relax the smooth muscles of the gut, helping to prevent or relieve the painful cramping spasms in the intestines. They are typically taken 30 to 45 minutes before meals.

Antimotility agents

Diarrhoea is associated with alterations of fluid and electrolyte movement in either the small intestine or the colon. This can be due to decreased intestinal absorption, altered intestinal motility, or increased intestinal secretions (e.g. due to bacterial enterotoxins or laxatives). Antimotility agents are used to manage acute or chronic diarrhoea or exacerbations of chronic diarrhoea and work by altering one or more of these mechanisms.

Antimotility agents for IBS can be separated into four main categories: codeine phosphate; co-phenotrope (mixture of diphenoxylate hydrochloride and atropine sulphate in the mass proportions 100 parts to 1 part); loperamide and morphine-containing preparations. Prolonged codeine use can lead to dependency. Loperamide is considered especially useful as it tends to increase anal sphincter tone.

Laxatives

Laxatives can be separated into four main categories: bulk forming laxatives; stimulant laxatives; faecal softeners and osmotic laxatives. Bulk-forming laxatives relieve constipation by increasing faecal mass, which stimulates peristalsis; adequate fluid intake should be maintained to avoid intestinal obstruction. Stimulant laxatives work by increasing intestinal motility, but they often cause abdominal cramps. Faecal softeners may lubricate the passage of stools and/or soften them. Osmotic laxatives increase the amount of water in the large bowel, either by drawing fluid from the body into the bowel or by retaining the fluid with which they were administered. The route of adminstration for laxatives may be oral or rectal. Laxatives can be used in two ways: as short-term rescue medication or as longer-term maintenance treatment. There is no evidence that long term laxative use damages the bowel.

Tricyclics and Antidepressants

Since their introduction approximately fifty years ago, antidepressants have been used in a variety of gastrointestinal (GI) conditions. In the last twenty years antidepressants have been increasingly used in the treatment of functional GI disorders such as IBS. The prevalence of anxiety and depressive disorders is high in patients with severe and/or intractable IBS and may be present to some degree in all IBS patients. Antidepressants appear have an analgesic effect separate to their antidepressant effect. Visceral pain syndromes including IBS may be effectively treated by a range of therapies, including antidepressants that modulate the interactions between the central and enteric nervous systems. Tricyclics also have a peripheral anticholinergic action in addition to their central analgesic and antidepressant actions.

Antidepressants can be divided into three major classes: tricyclics and related antidepressants; selective serotonin re-uptake inhibitors (SSRIs), and monoamine oxidase inhibitors (MAOIs). There are other antidepressants that do not fit easily into these categories: Duloxetine (Cymbalta); Flupentixol (Fluanxol); Mirtazapine (Zispin Soltab); Reboxetine (Edronax); Tryptophan (Optimax), and; Venlafaxine (Efexor).

8.1 Laxatives

SELECTION CRITERIA

The selection criteria described in the general methodology section were used, but some were specific to the laxatives review and are reported below.

Types of studies

For longer-term studies, the GDG decided that the washout period for this review should be at least two weeks. Trials with no washout were not included in the analysis and trials with one week washout were considered if there was no other information. Crossover studies are not appropriate for short-term (rescue) medication.

Types of participants

For this review, participants with IBS were included, but the review was extended to include people with simple constipation as well because the same drugs are used. Studies in these participants were regarded as indirect as far as population was concerned.

Types of intervention

Studies were to include the following interventions:

- **Bulk-forming laxatives**, which, as a class, include some dietary fibres (see fibres review), but here we consider only non-dietary bulk forming agents:
    - Ispaghula husk (trade names: Fibrelief®; Fybogel®; Isogel®; Ispagel Orange®; Regulan®)
    - Methylcellulose (trade name: Celevac®)
    - Sterculia (trade names: Normacol®; Normacol Plus®).
- **Stimulant laxatives:**
    - Biascodyl (trade name: *Dulco-lax®), given as either oral tablets or rectal suppositories
    - Docusate sodium (synonym: dioctyl sodium sulphosuccinate; trade names: Dioctyl® (oral); Docusol® (oral); Norgalax Micro-enema® (rectal))
    - Glycerol (synonym: glycerine), given as rectal suppositories
    - Senna (non proprietary tablets; trade names: Senokot® granules; Manevac® granules (senna fruit 12.4%, ispaghula 54.2%)), given as an oral preparation

- Sodium picosulphate (Trade names: Laxoberal® (oral elixir); *Dulco-lax® Liquid (oral elixir); *Dulco-lax Perles® (oral capsules)), given as an oral preparation.

  * note that the trade name Dulco-lax is used for different drugs, but with different qualifiers.

- **Faecal softeners:**
  - Arachis oil (Trade name: Fletchers' Arachis Oil Retention Enema®), given as a rectal preparation
  - Liquid paraffin (Liquid Paraffin Oral Emulsion, BP), given as oral preparation.
- **Osmotic laxatives:**
  - Lactulose (trade names include: *Duphalac*®; *Lactugal*®; *Regulose*®), given as oral solution
  - Macrogols (synonyms: polyethylene glycols, PEG; trade names: Idrolax® (oral powder, PEG 4000); Movicol® (oral powder, PEG 3350); Movicol®-Half (oral powder, PEG 3350))
  - Magnesium salts (Magnesium Hydroxide Mixture, BP, oral aqueous suspension; Liquid Paraffin and Magnesium Hydroxide Oral Emulsion, BP (oral aqueous suspension), Magnesium Sulphate (Epsom Salts); trade name: *Milpar*®)
  - Sodium phosphate – this is not in the BNF but is in routine use and so was included by the GDG.

The following comparisons were included:

- Laxative versus placebo (or nothing)
- Laxative type 1 versus type 2
- Laxative dose 1 versus dose 2
- Laxative + another intervention versus the other intervention alone
- Laxative route of delivery 1 versus route 2
- Duration of treatment 1 versus duration 2.

NB: In spite of the large placebo effect associated with IBS, comparisons with no treatment are included.

The laxatives review was concerned with both longer-term maintenance treatment and short-term symptom relief.

The GDG decided that there should be a minimum duration of treatment of four weeks for maintenance in this review. Maintenance studies of shorter durations were not included in the analysis.

Subgroup analyses

We carried out subgroup analyses by type of laxative (bulk forming laxatives; stimulant laxatives; faecal softeners, and; osmotic laxatives); dose; route of delivery (oral, rectal), and; duration of intervention.

SEARCH STRATEGY FOR IDENTIFICATION OF STUDIES

The initial search identified a Cochrane Review (Quartero 2005, *Bulking agents, antispasmodic and antidepressant medication for the treatment of irritable bowel syndrome*). Searches were partly based on the terms in this review. Searches were performed on the following core databases: MEDLINE, EMBASE, CINAHL and *The Cochrane Library (*1966 to current day with guidance from the GDG).

Additional databases were not searched for this review. For this review, the search was extended to cover the population with simple constipation as well as IBS. The search strategies are listed in Appendix B.

The Cochrane review identified 11 studies, ten of which are included in the fibres review. The remaining study (Piai 1987) used a cellulose material, glucomannan, which is not used in the UK. The titles and abstracts identified by the NCC search strategy were assessed and fifty studies were retrieved in full. The reference lists for each of the retrieved studies were inspected for further potential papers, but none were identified. The 38 excluded studies are listed in Appendix E, along with reasons for exclusion. Searches were updated to June 2007 and a further two papers were identified and obtained from the authors with some further information (Wulkow 2007; Kienzle-Horn 2007).

DESCRIPTION OF STUDIES INCLUDED IN THE REVIEW

Study Design

There were four crossover studies (Cleveland 2001; Connolly 1975; Quah 2006; Sobhani 1996) in which participants were allocated to receive both the intervention and control treatments during the course of the study, in a random order. Two of these studies (Cleveland 2001; Sobhani 1996) had either no washout period or it was not reported, in which case this was assumed to be none. The other two studies had a washout period of one week. The GDG had specified a washout period of two weeks minimum, but would consider the two one-week studies if there was no other data. No crossover studies reported first-period results only or individual patient data.

The remaining 15 studies had a parallel design (Attar 1999; Bouhnik 2004; Chaussade 2003; Corazziari 1996; Corazziari 2000; Dettmar 1998; DiPalma 2000; Hamilton 1988; Kienzle-Horn 2006; Kienzle-Horn 2007; Marlett 1987; Medoff 2004; Rouse 1991; Wang 2004; Wulkow 2007).

The GDG had specified a minimum treatment period of four weeks for each intervention in the maintenance studies. Two studies had a treatment duration of one week (Connolly 1975; Marlett 1987); one had ten days (Hamilton 1988); three had two weeks (Cleveland 2001; DiPalma 2000; Wang 2004); one had three weeks (Sobhani 1996). All these studies were transferred to the excluded studies table.

The remaining studies had durations of four weeks (Attar 1999; Bouhnik 2004; Chaussade 2003; Dettmar 1998; Kienzle-Horn 2007; Medoff 2004; Quah 2006 (1-week washout crossover); Rouse 1991); eight weeks (Corazziari 1996), and; 20 weeks (Corazziari 2000).

Two studies investigated the use of laxatives for acute constipation (Kienzle-Horn 2006; Wulkow 2007).

Twelve studies were therefore included in the analysis (11 parallel and one 1-week washout crossover trial: Attar 1999; Bouhnik 2004; Chaussade 2003; Corazziari 1996; Corazziari 2000; Dettmar 1998; Kienzle-Horn 2006; Kienzle-Horn 2007; Medoff 2004; Quah 2006; Rouse 1991; Wulkow 2007).

One of the remaining studies had more than two arms: Chaussade (2003) compared four PEG interventions; there were thus 14 comparisons in the laxatives review. The rest of the description of studies will focus on these studies/comparisons.

Two were conducted in the UK (Dettmar 1998 and Rouse 1991); one in sites in the UK and France (Attar 1999); seven in the rest of Europe, one in each of the USA and China.

Setting: Seven studies took place in primary care (Bouhnik 2004; Chaussade 2003; Dettmar 1998; Kienzle-Horn 2006; Medoff 2004; Rouse 1991; Wulkow 2007); and five were in secondary care (Attar 1999 (with 31% from geriatric institutions); Corazziari 1996; Corazziari 2000; Kienzle-Horn 2007; Quah 2006).

The majority of studies (7/12) had fewer than 100 patients, with two having 25 or fewer in the intervention arm (Corazziari 1996; Medoff 2004). Two studies had more than 200 patients in total (Chaussade 2003; Dettmar 1998).

Funding: Six studies had some industry sponsorship: Bouhnik (2004) was sponsored by Solvay Pharmaceuticals, manufacturers of lactulose; Chaussade (2003) was supported by a grant from by Hoffmann La Roche, the manufacturers of PEG 3350, and; the Dettmar (1998) authors were from Reckitt & Colman, manufacturers of Fybogel. Kienzle-Horn (2006), Kienzle-Horn (2007) and; Wulkow (2007) were all funded by Boehringer-Ingelheim GmbH, manufacturers of Bisacodyl, and Sodium Picosulphate.

Population

- Only one study (Medoff 2004) definitely included patients with IBS: 7/43 patients had a diagnosis of constipation predominant IBS, but separate results were not reported. All the other studies stated they had patients with simple constipation, usually defined as 3 or less, or 2 or less bowel movements per week. Most studies defined a minimum period of constipation symptoms, ranging from 3 weeks (Rouse 1991) to 12 months (Corazziari 1996; Corazziari 2000). The GDG suspected, however, that many of these studies may have had the classification of 'simple constipation' because this was the primary symptom being treated by laxatives, rather than the only symptom. Indeed, they thought it was quite likely that the patients had IBS. This was further investigated. Communication with the authors of one study (Kienzle-Horn 2007) revealed that abdominal pain was not excluded and the author believed that some patients entering the studies would have had IBS if they had been checked for it by their physician. Seven of these studies (Attar 1999; Bouhnik 2004; Corazziari 1996; Corazziari 2000; Chaussade 2003; Dettmar 1998; Rouse 1991) reported that some patients had pain and/or bloating. However, Dettmar (1998) and Rouse (1991) did not report sufficient duration to be defined as IBS. Two studies did not mention the incidence of pain or bloating before treatment (Kienzle-Horn 2006; Quah 2006) but the patients had had constipation for at least 3 months.
- In Attar (1999), 20% and 35% of the control group had pain and bloating respectively during the trial. The patients were stated to have had chronic idiopathic constipation for at least 3 months.
- In Bouhnik (2004), in the washout period, 45 and 53% had bloating at washout and 30 and 45% had pain for lactulose and PEG respectively. The patients were stated to have had chronic idiopathic constipation for at least 6 months.
- In Chaussade (2003), at baseline, the bloating score was ~ 3 points on a scale of 1 to 4 (considerable) and pain was 2.6. There was an implied use of the Rome II criteria for chronic idiopathic constipation, which the patients were to have had for at least 3 months
- In Corazziari (1996), in the run-in period 52-60% pts had pain and 84-91% had bloating. The patients were stated to have chronic non-organic constipation and had had this for at least 12 months.
- In Corazziari (2000), the pain and bloating scores were non zero, even after the patients had received PEG for 4 weeks. Chronic constipation was defined using Rome criteria and the patients had had chronic constipation for at least 12 months.
- Dettmar (1998) reported that the majority of the patients experienced abdominal symptoms, including pain, distension or flatulence. The patients were said to have 'simple constipation' and there were no details about the duration of constipation.
- In Rouse (1991) 53-54% patients in both groups had abdominal pain after seven days. Bloating was not mentioned. The patients were treated for chronic constipation, which they had had for at least 3 weeks.

The GDG concluded that all of these studies, with the exception of Dettmar (1998) and Rouse (1991) were likely to have some, if not all, patients with IBS. It was unclear if Kienzle-Horn (2006) and Quah (2006) included patients with IBS. Further details are given in the included studies table (Appendix C).

One study (Corazziari 2000) gave PEG electrolyte to patients for 4 weeks and then randomised only the responders (at least two bowel movements per week with no other defaecatory disturbances or more than three bowel movements per week) to PEG electrolyte or placebo.

The age range of participants across the studies was 18 to 89 years, with the mean age (where given) ranging from 42 to 58 years. All the studies had more women than men.

Interventions

The studies varied in the type of laxatives used:

- Two used stimulant laxatives:
    - One bisacodyl (Kienzle-Horn 2006)
    - One sodium picosulphate (Wulkow 2007).
- Eight had osmotic laxatives:
    - Four lactulose (Attar 1999; Bouhnik 2004; Quah 2006; Rouse 1991)
    - Five polyethylene glycol (Attar 1999; Chaussade 2003; Corazziari 1996; Corazziari 2000; Bouhnik 2004)
    - One sodium phosphate (Medoff 2004).
- One study (Dettmar 1998) allowed the patient any laxative (which was mainly lactulose) and also reported the lactulose patients as a subgroup.

Comparisons

The included studies covered the following comparisons:

- Four comparisons of laxatives versus placebo:
    - Two gave stimulant laxatives (Kienzle-Horn 2006; Wulkow 2007 treatment for acute episodes)
    - Two gave osmotic laxatives (Corazziari 1996; Corazziari 2000).
- Three studies compared a laxative with fibre:
    - Two compared an osmotic laxative (lactulose) with fibre (ispaghula), (Quah 2006; Rouse 1991)
    - One compared usual laxatives (mainly lactulose) with fibre (ispaghula) (Dettmar 1998).
- Seven comparisons of different types of laxative in the same class:
    - Two studies (Attar 1999; Bouhnik 2004) compared lactulose with PEG electrolyte (Osmotic Laxatives)

    - Four comparisons of PEG 3350 (Transipeg) plus electrolytes versus PEG 4000 without electrolytes (Forlax) (Chaussade 2003 x4) (Osmotic Laxatives)
    - One comparison of Bisacodyl versus Sodium Picosulphate (Kienzle–Horn 2007).
- Three comparisons of different doses of an osmotic laxative:
    - One comparison of 11.8g versus 5.9g PEG 3350 (Transipeg) plus electrolytes (Chaussade 2003)
    - One comparison of 20g versus 10g PEG 4000 (Forlax) (Chaussade 2003)
    - One comparison of 10.56g (mean) versus 6.84g (mean) sodium phosphate.

METHODOLOGICAL QUALITY

The results of the quality assessment for included trials are shown in Appendix D.

An adequate method of randomisation was reported in four studies (Attar 1999; Medoff 2004; Quah 2006; Wulrow 2007), all of which used a computer generated method. The other studies did not state the method.

Allocation concealment was reported in three studies (Attar 1999; Bouhnik 2004; Quah 2006), both of which reported an adequate method, in which the statistician prepared the list and the investigators were unaware of the allocation (Attar 1999) or by telephoning a central office (Bouhnik 2004; Quah 2006).

Six studies reported that the patients were blinded to the interventions (Chaussade 2003; Corazziari 1996; Corazziari 2000; Kienzle-Horn 2006; Kienzle-Horn 2007; Wulrow 2007); these included all the placebo controlled studies. The remaining studies stated that the patients were not blinded, or could not have been because of differences between drugs in appearance and taste.

Five studies (Attar 1999; Bouhnik 2004; Kienzle-Horn 2006; Kienzle-Horn 2007; Wulrow 2007) described an *a-priori* power calculation. All studies included in the review demonstrated baseline comparability of the groups, apart from one study which was not comparable at baseline (Medoff 2004) for rectal irritation, which was greater in the group receiving four tablets.

There was loss to follow-up in the majority of studies, and all but one had less than 20% drop-outs. One study (Corazziari 2000) reported that more than 20% of patients in at least one arm (or overall) were not analysed or were lost to follow-up (attrition bias). In Corazziari (2000), for the first eight weeks 1/33 (3%) PMF and 4/37 (11%) placebo did not complete the period, but 10/33 (30%) PMF and 22/37 (59%) placebo did not complete the 20 weeks. Consequently, results at eight weeks only were taken for this study. In Quah (2006), 8/50 (22%) withdrew before receiving the interventions, then 3/21 (14%) withdrew from fibre group and 0% on lactulose. The GDG did not regard this level of missing data as significant.

Seven studies stated that they did not permit any concomitant medication that would change the GI motility (Bouhnik 2004; Chaussade 2003; Corazziari 1996; Kienzle-Horn 2006; Kienzle-Horn 2007; Quah 2006; Wulrow 2007). Five studies allowed the patients to have laxatives as relief medication: in two studies (Corazziari 1996; Corazziari 2000) there had to be five consecutive days without a bowel movement; in one study (Chaussade 2003) there had to be three consecutive days, after which the patients could have suppositories. In the other studies (Attar 1999; Medoff 2004) patients could use suppositories or microenemas for relief, apparently without restriction. In another study (Rouse 1991) 12/124 patients took other laxatives during the study and were considered to be protocol violators.

The risk of bias was assessed for each included study and no studies were excluded from the analysis (although the 20 week results for Corazziari 2000 were disregarded). The two studies in which laxatives could be taken apparently without restriction (Attar 1999; Medoff 2004) were regarded with caution.

RESULTS

I. Treatment for acute episodes of constipation

A. Laxatives versus placebo

Two studies (Kienzle-Horn 2006; Wulkow 2007) in 112 patients compared laxatives with placebo for the treatment of acute episodes of constipation. It was unclear if the patients had IBS. Stimulant laxatives 10mg bisacodyl (Kienzle-Horn 2006) or 7mg sodium picosulphate (Wulkow 2007) or placebo was given once-a-day for three days.

1. Global symptoms

Global symptoms (pain, bloating and bowel habit) were not reported.

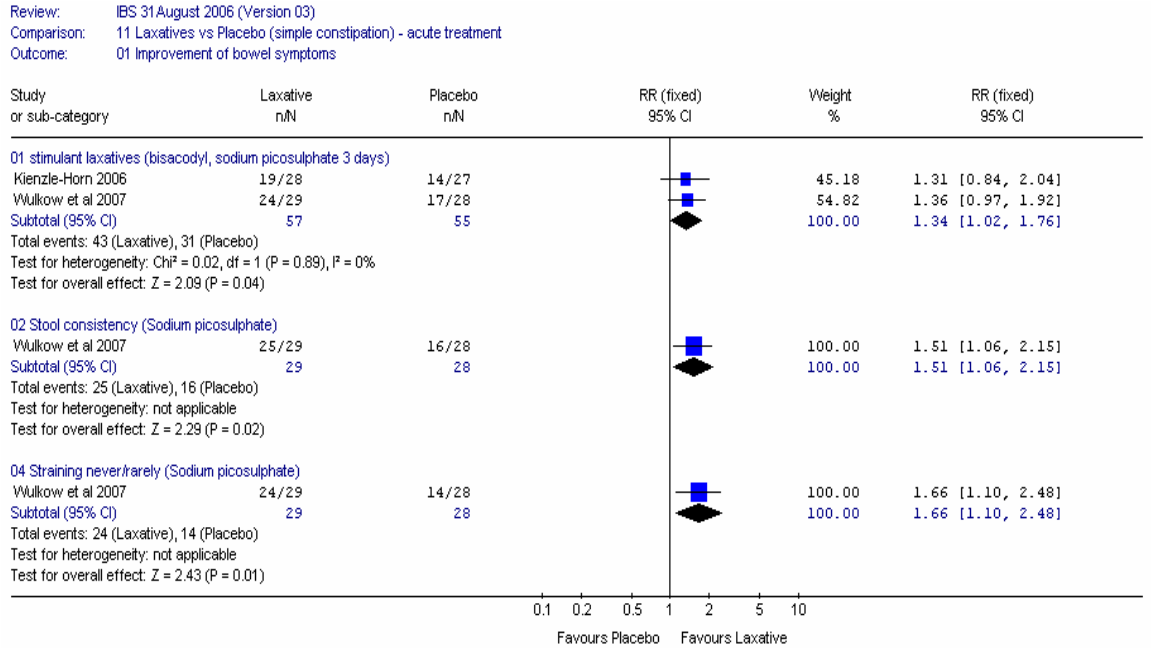
2. Individual symptoms

a) Bowel habits

i. Number of patients with improvement in bowel habit assessed by investigators

The investigators assessed the improvement in bowel habit, based on diary recordings of the patients. Overall, the relative risk was 1.34 (95%CI 1.02, 1.76) (Figure 1), i.e. statistically significant difference between laxative and placebo (p=0.04). This corresponded to a number needed to treat (NNT) of 6 (95%CI 3, 50) for a control group risk of 52 to 61%. There was no heterogeneity.

Figure 1:

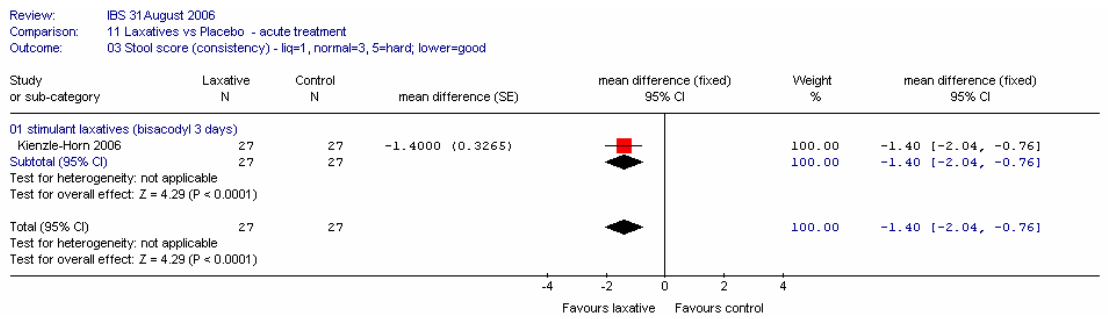


ii. Stool score - consistency

The consistency of stool was measured on the scale of 1 to 5, where 5=hard, 4=moderately hard, 3=well-formed, 2=soft, 1=liquid (Kienzle-Horn 2006) and on a 4 point scale where 4=hard, 3=well-formed, 2=pasty,1=liquid (Wulkow 2007). The Wulkow study reported the number of patients with soft and/or well formed stools. The relative risk was 1.51 (95%CI 1.06, 2.15) i.e. statistically significant difference between laxative and placebo (p=0.02) favouring laxative (Figure 1).

Kienzle-Horn (2006) reported baseline mean scores which were 5.0 for each group, so any decrease in score constituted an improvement. The study did not report the standard deviation for the placebo group, but gave the difference in change score between the two groups and the 95%CI (Figure 2). This was -1.4 (95%CI -2.0, -0.76), for a placebo group score of 4.2, i.e. a statistically significant difference between groups, such that the bisacodyl group had a value between soft and well-formed.

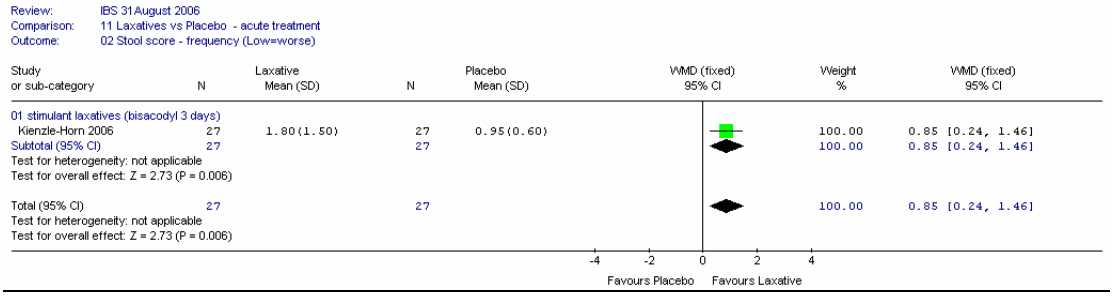
Figure 2:



iii. Stool frequency

The stool frequency per day was statistically significantly higher for the bisacodyl group: mean difference 0.85 (95%CI 0.24, 1.46) for a placebo group mean of 0.95 stools/day (Figure 3).

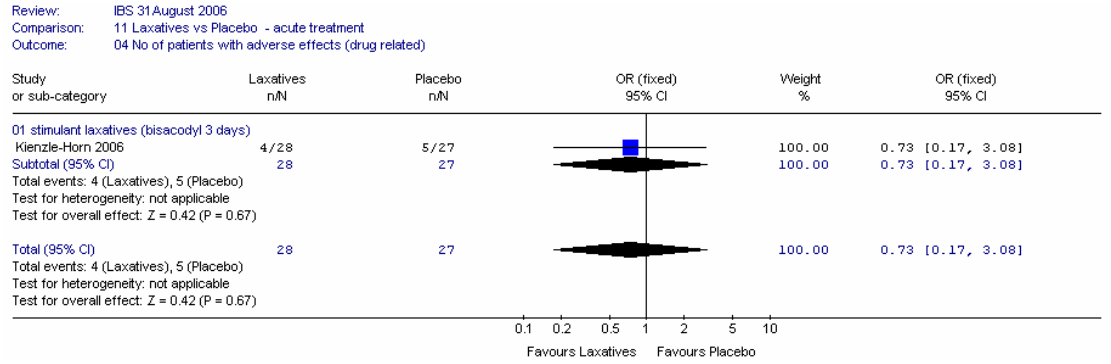
Figure 3:



3. Adverse effects

The confidence interval was too wide to decide if there was a difference in the number of patients reporting adverse effects that could have been drug related (Figure 4).

Figure 4:



II. Laxatives for maintenance treatment

A. Laxatives versus Placebo

There were two studies included in the analysis that compared laxatives with placebo in patients with constipation (Corazziari 1996 and Corazziari 2000). Both studies gave the patients an isosmotic PEG electrolyte balanced solution (PMF-100) containing 14.6g PEG 4000, twice a day. However, in Corazziari (2000), all patients received 4 weeks of PMF-100 initially, with responders (more than 3 bowel movements per week) then randomised to PEG or placebo for a further 20 weeks. Thus the populations were different in the two trials, and Corazziari (2000) was regarded as an investigation of the effects of stopping the laxative. Their results are therefore reported separately. Both studies had patients who were outpatients in secondary care. The GDG considered it likely that both studies had at least some patients with IBS.

In both trials, patients were allowed other laxatives when they had no bowel movements for at least 5 consecutive days, and they were allowed to adjust the intervention dose downwards (but not upwards above 2 sachets per day).

Where outcomes were measured at different times during the study, we took the end-study results unless there were significant numbers of withdrawals or problems with compliance. Therefore, for the Corazziari (2000) study we took the values at eight weeks (i.e. from the start of randomisation).

1. Global symptoms

Neither study reported global symptoms.

2. Number of patients using additional laxatives / not using additional laxatives as rescue medication

The GDG considered this to be an important outcome for this review and gave it the status of primary outcome measure. We gave both the number of patients using additional laxatives (as reported in the papers), and the number not using additional laxatives (calculated).

The comparison of PEG and placebo over 8 weeks in 48 patients (Corazziari 1996) showed a statistically significant decrease in the number of patients using other laxatives as rescue medication; Figure 5; RR 0.33 (95%CI 0.12, 0.90), although the confidence interval was wide. This corresponded to a number needed to treat of 4 (95%CI 2, 15) for a placebo group risk of 48%.

For the outcome measure, the number of patients not using rescue medication was calculated for Corazziari (1996) (Figure 6). There was a statistically significant difference between PEG and placebo, favouring the former; RR 1.61 (95%CI 1.05, 2.47), which gave an NNT of 4 (95%CI 2, 15) for a control group risk of 52%.

Figure 5: Number of patients taking rescue laxatives

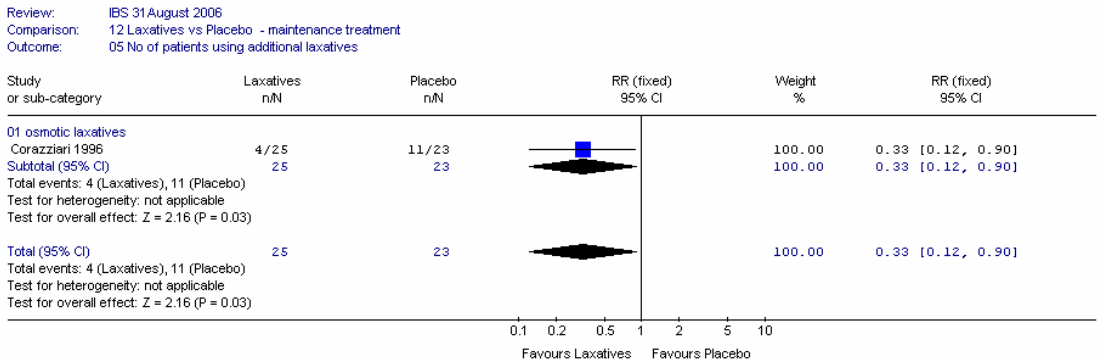
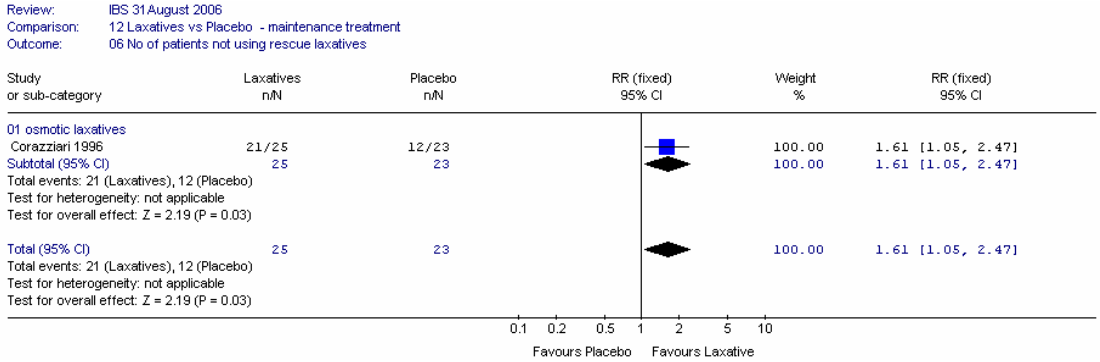
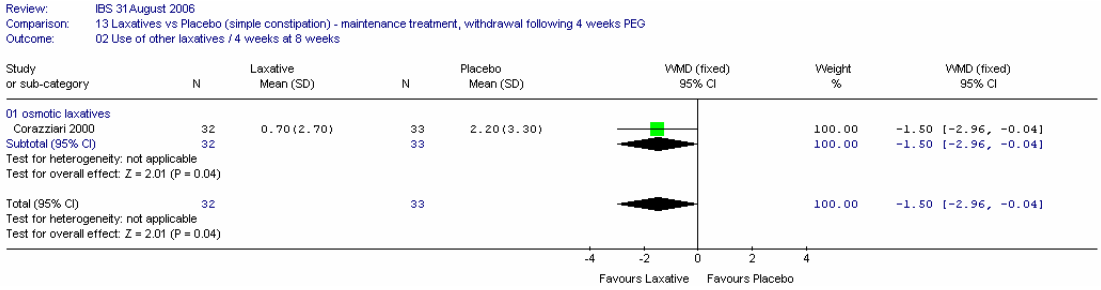


Figure 6: Number of patients not taking rescue laxatives



Corazziari (2000) (withdrawal of laxative following four weeks PEG electrolyte solution, in responders) reported that the use of other oral laxatives, rectal evacuants, suppositories and enemas was more frequent in the placebo group compared to the PEG group. At eight weeks the difference in number of other laxatives used per four weeks was statistically significant (Figure 6), but the confidence interval was fairly wide.

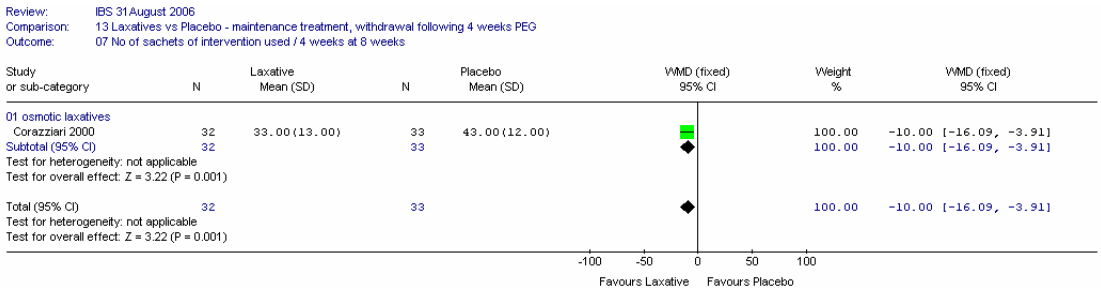
Figure 7:



At the same time, statistically significantly more sachets of the intervention were used in the placebo group (even though the more severely constipated patients dropped out), compared with the PEG group (Figure 7).

In the PEG group, the authors reported that the use of other laxatives progressively decreased in the PEG group but increased in the placebo group.

Figure 8:

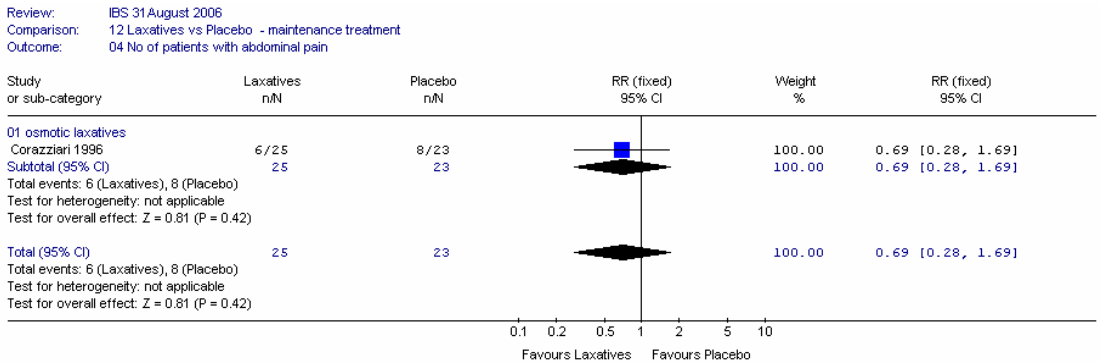


3. Individual symptoms

a) Pain

There was no significant difference between PEG and placebo for this outcome (Corazziari 1996) in 48 patients. The confidence intervals were fairly wide so there was some uncertainty over the results for the difference between groups in the number of patients with abdominal pain (Figure 8).

Figure 9:

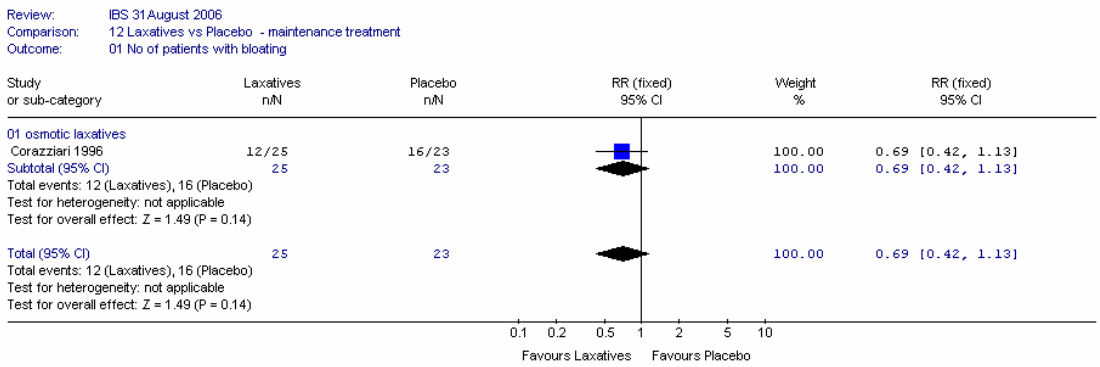


Corazziari (2000) (withdrawal of laxative following 4 weeks PEG electrolyte solution, in responders) reported that the abdominal pain score progressively decreased in the PEG group and increased in the placebo group. No data were given.

b) Bloating

The comparison of PEG and placebo (Corazziari 1996) in 48 patients showed no statistically significant difference between groups in the number of patients with bloating (Figure 9).

Figure 10:



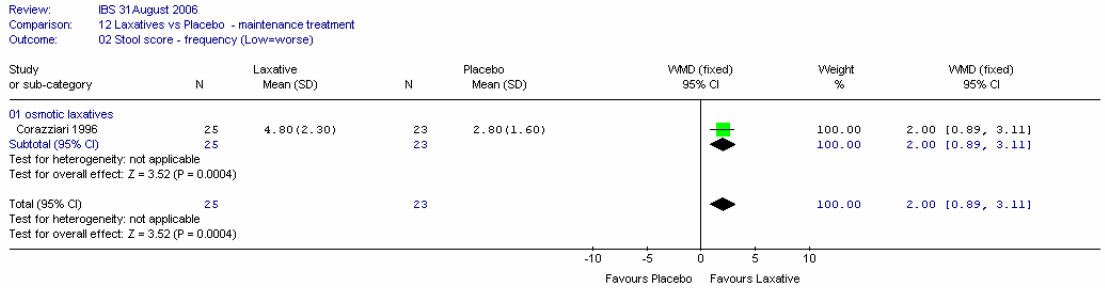
Corazziari (2000) (withdrawal of laxative following 4 weeks PEG electrolyte solution, in responders) reported that bloating was less severe in the PEG group compared to the placebo group throughout the study. At 8 weeks the difference was statistically significant: p<0.001. No other statistics were given.

c) Bowel habits

i. Stool frequency

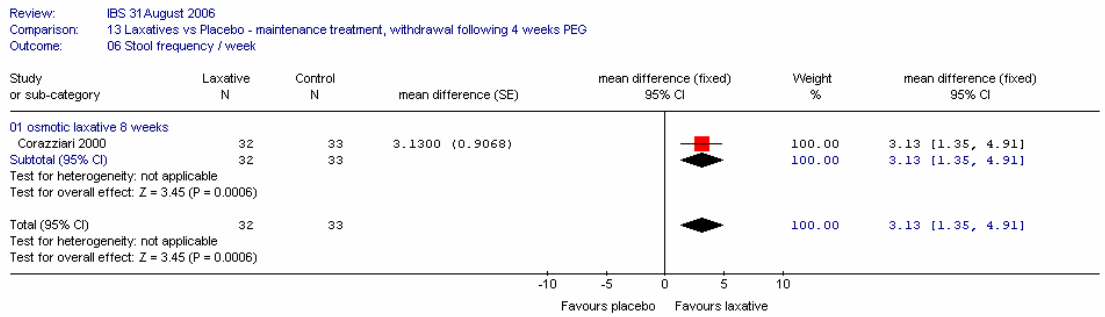
The comparison of PEG and placebo over 8 weeks in 48 patients (Corazziari 1996) showed a statistically significant increase in stool frequency per week (figure 10) of 2.00 (95%CI 0.89, 3.11), for a placebo group value of 2.8 stools per week.

Figure 11:



Corazziari (2000) (withdrawal of laxative following 4 weeks PEG electrolyte solution, in responders) found a statistically significant increase in stool frequency per week for the PEG group compared to the placebo group throughout the study. At 8 weeks (Figure 11) the difference was 3.13 (95%CI 1.35, 4.91) for a placebo group value of 4.39 stools per week.

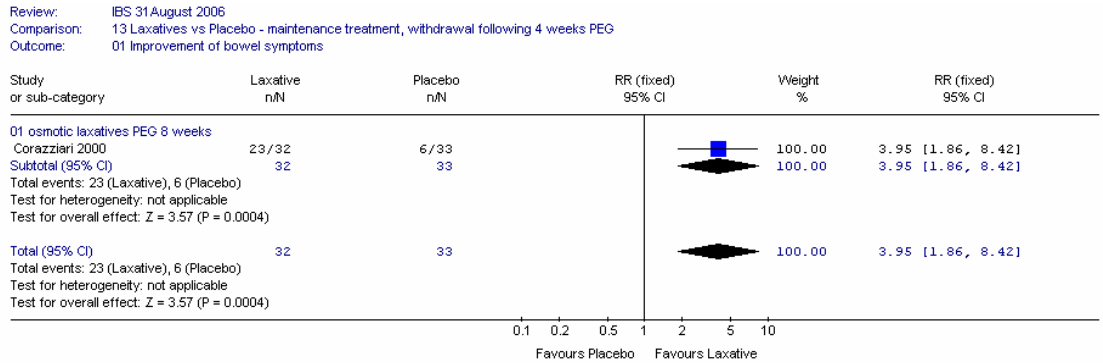
Figure 12:



ii. Improvement in bowel habit

Corazziari (2000) (withdrawal of laxative following 4 weeks PEG electrolyte solution, in responders) found a statistically significantly greater number of patients with complete remission of constipation symptoms (more than three bowel movements per week, no use of other laxatives, no straining at defecation, no feeling of incomplete evacuation, no hard/pellety stools) for the PEG group compared to the placebo group throughout the study. At 8 weeks (Figure 12) the RR was 3.95 (95%CI 1.86, 8.42); this corresponds to an NNT of 2 (95%CI 2, 3) for a control group rate of 18%.

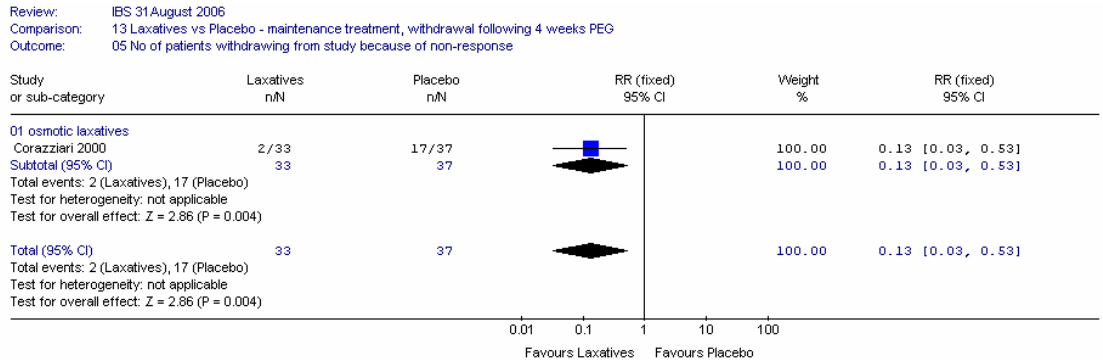
Figure 13:



iii. Number of patients withdrawing from study

Corazziari (2000) (withdrawal of laxative following 4 weeks PEG electrolyte solution, in responders) reported statistically significantly more patients withdrew from the study by 20 weeks because of non-response to treatment in the placebo group compared to the PEG group. At the end of the study the RR was 0.13 (95%CI 0.03, 0.53), i.e. statistically significantly in favour of the PEG group, although the confidence interval was very wide. This corresponded to an NNT of 3 (95%CI 2, 5) for a placebo group rate of 46%.

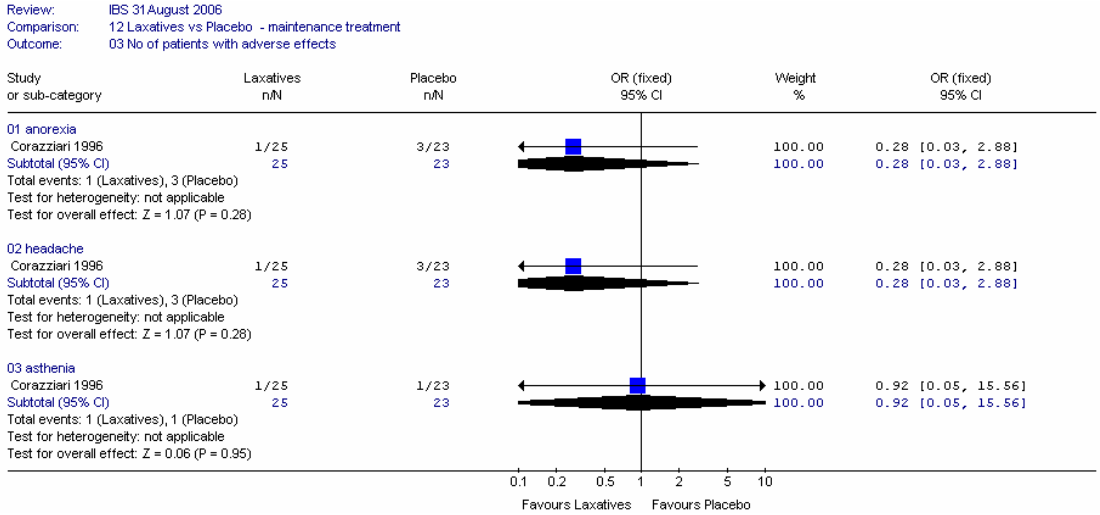
Figure 14:



4. Adverse effects

In the comparison of PEG and placebo over 8 weeks in 48 patients (Corazziari 1996), there was too much uncertainty to determine if there was a difference in the number of patients reporting anorexia, headache or asthenia (Figure 15).

Figure 15:



Corazziari (2000) reported that there were no significant differences between groups in the incidence of adverse effects.

B. Osmotic Laxative type 1 versus Osmotic laxative type 2

Three studies compared different types of osmotic laxatives: two (Attar 1999; Bouhnik 2004) compared lactulose with PEG, and one compared different types of PEG: PEG 3350 plus electrolytes versus PEG 4000 without electrolytes (Chaussade 2003). We noted that the Bouhnik (2004) was sponsored by Solvay Pharmaceuticals, manufacturers of lactulose, and Chaussade (2003) was supported by a grant from by Hoffmann La Roche, the manufacturers of PEG 3350. The Attar (1999) study was in secondary care (of which 31% were in geriatric institutions), and the Chaussade (2003) and Bouhnik (2004) studies were in primary care. The GDG thought it likely that all of these studies had some patients with IBS.

B1. Lactulose versus PEG

Attar (1999) compared PEG 3350 plus electrolytes (Movicol) versus lactulose, and Bouhnik (2004) compared PEG 4000 plus electrolytes (Forlax) versus lactulose. Both studies had a duration of four weeks. The doses of PEG differed in the two studies: the patients in Attar (1999) started with 26.24 g (2 sachets) for the first two weeks, but could change to 1 or 3 sachets for the second two weeks. Patients in Bouhnik (2004) started at a dose of 20g (2 sachets) for the first week and then this could be varied to 10 or 30g. The lactulose dose in both studies was 20g which could also be varied as above.

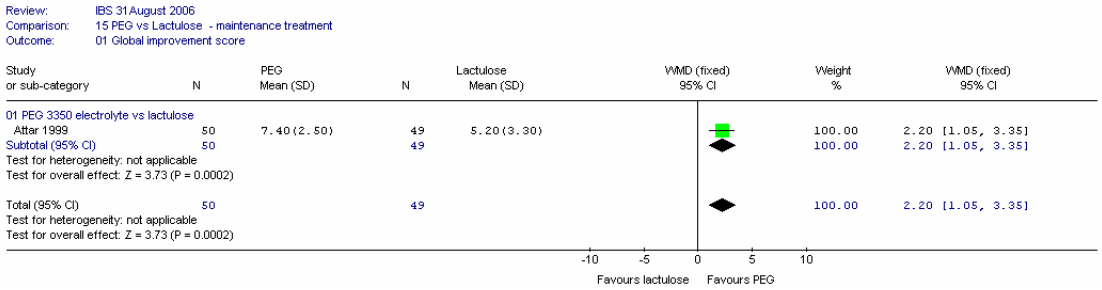
In Attar (1999) patients could take suppositories or microenemas for relief of constipation, apparently without restriction. However, in Bouhnik (2004) patients were asked to stop enema/suppositories 48 hours before the first stool collection.

1. Global outcomes

a) Global improvement in symptoms score

One study (Attar 1999) in 99 patients recorded a global improvement score at four weeks on a VAS of 0 to 10 (0=no change, 10=excellent); comprising pain, bloating and bowel habit. The global improvement score was statistically significantly in favour of PEG electrolyte; mean difference 2.20 (95%CI 1.05, 3.35) for a control group value of 5.20.

Figure 16



2. Use of microenemas as rescue medication

Attar (1999) also reported the number of patients using microenemas as rescue medication after four weeks, and we also calculated the number of patients not using rescue medication. The study found that statistically significantly more patients used microenemas in the lactulose group than in the PEG group; RR 0.48 (95%CI 0.25, 0.95), which corresponded to an NNT of 6 (95%CI 3, 50) for a lactulose group risk of 35% (Figure 17a). The confidence interval was fairly wide.

There was a statistically significant difference, favouring PEG, for the number of patients *not* using microenemas; RR 1.27 (95%CI 1.02, 1.59). This corresponded to an NNT of 6 (95%CI 3, 50) for a lactulose risk of 65% (Figure 17b).

Figure 17a: Number of patients using microenemas

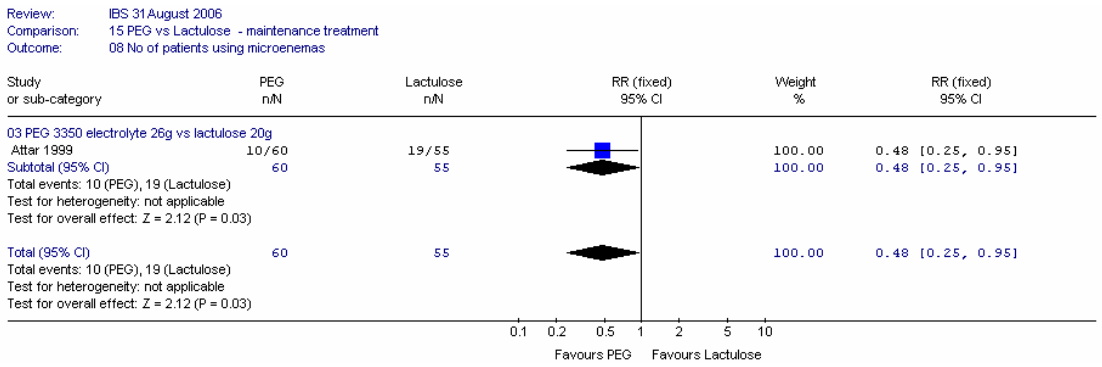
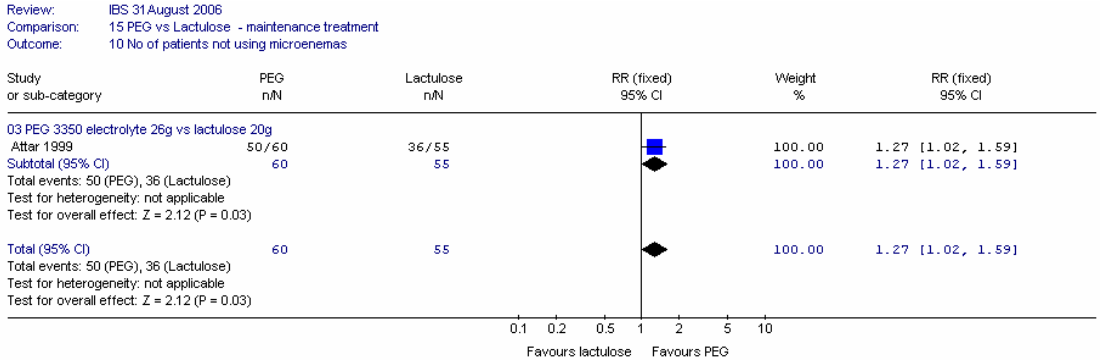


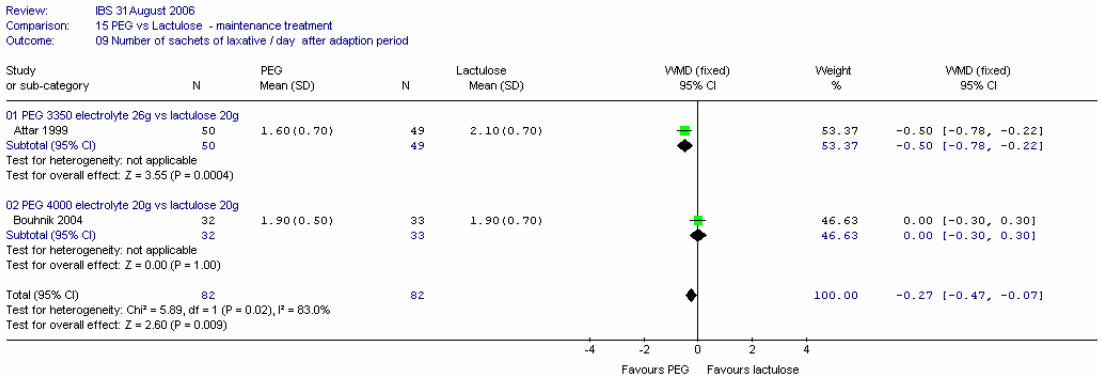
Figure 17b: Number of patients not using microenemas



3. Number of sachets of intervention used

In Attar (1999) the number of sachets of laxative used over four weeks was statistically significantly lower for the PEG group (Figure 18), but there was no difference between groups in Bouhnik (2004). This led to significant heterogeneity between studies (I^2=83%, p=0.02). It is unclear if this was an effect of dose; type of PEG; use of other laxatives, or; any other reason.

Figure 18:

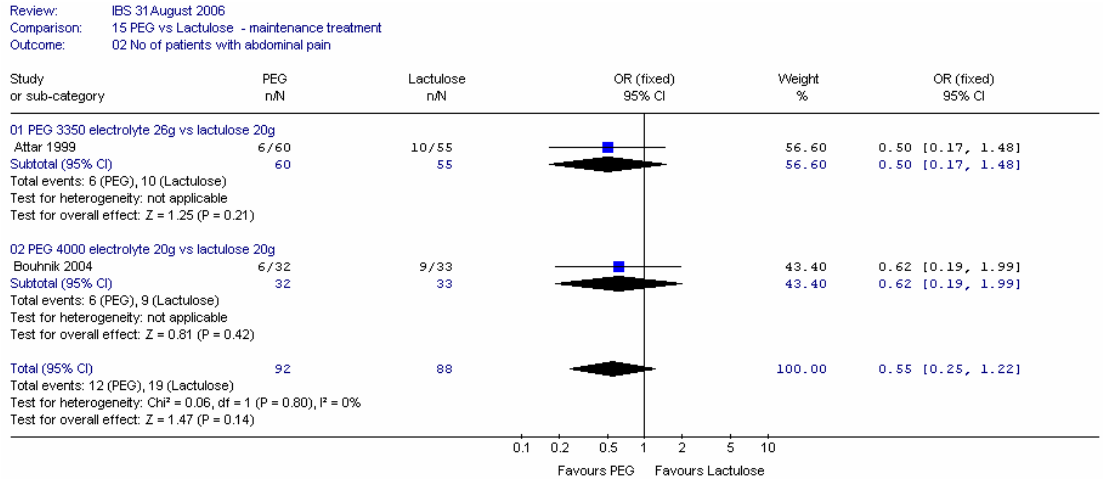


4. Individual symptoms

a) Pain

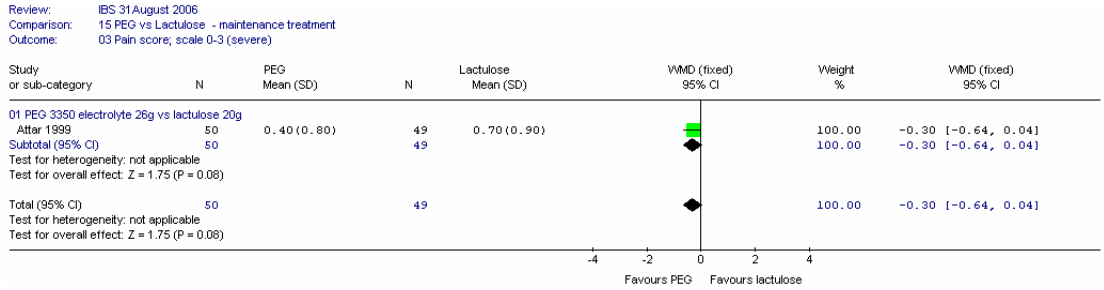
Both studies reported the number of patients with abdominal pain at four weeks. Meta-analysis of 180 patients gave a wide confidence interval.

Figure 19:



One study (Attar 1999) recorded pain on a scale of 0 to 3 (severe). The difference was not statistically significant.

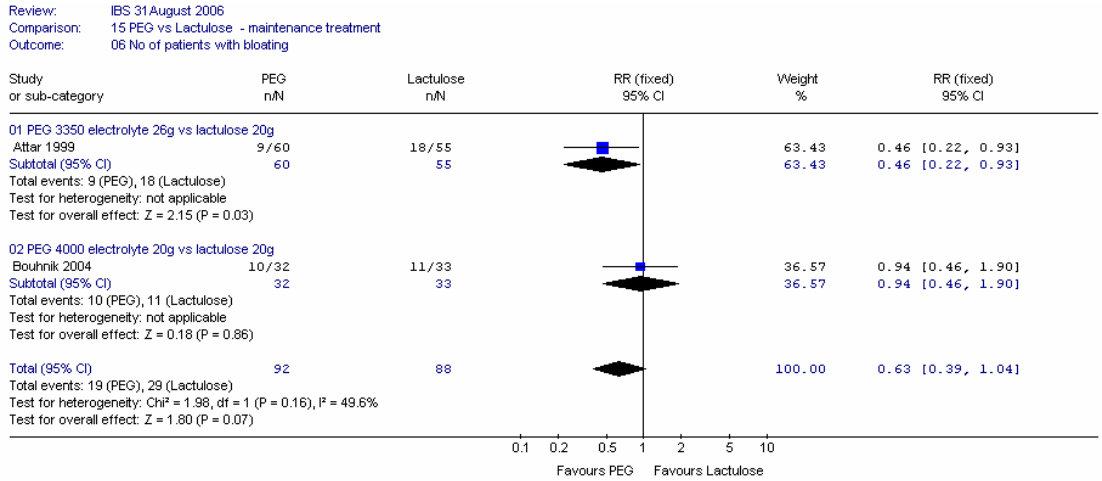
Figure 20:



b) Bloating

Both studies reported the number of patients with bloating at four weeks. Meta-analysis of 180 patients gave a fairly wide confidence interval and some heterogeneity (I^2=50%; p=0.16). This difference may be an effect of dose or type of PEG. It is also noted that Bouhnik (2004) was sponsored by the manufacturers of lactulose and Attar (1999) allowed the patients to use other laxatives *ad libitum*.

Figure 21:

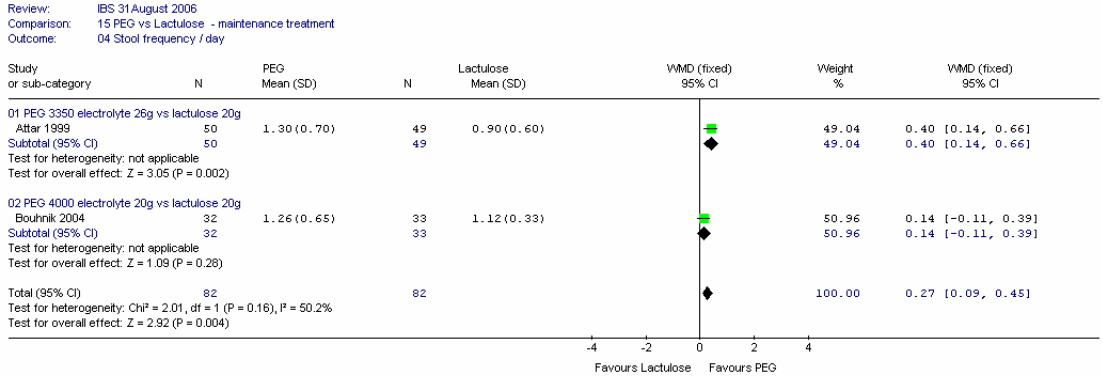


c) Bowel habits

i. Stool frequency

Both studies reported the stool frequency per day at four weeks. Meta-analysis of 180 patients gave a statistically significant difference of 0.27 (95%CI 0.09, 0.45) stools/day, favouring PEG, but there was some heterogeneity (I^2=50%; p=0.16).

Figure 22:



5. Adverse effects

Both studies reported the number of patients with adverse effects at four weeks. Meta-analysis of 180 patients gave a wide confidence interval and no heterogeneity (Figure 22). One study (Attar 1999) reported the number of patients with liquid stools, but this also had a wide confidence interval (Figure 23).

Figure 23:

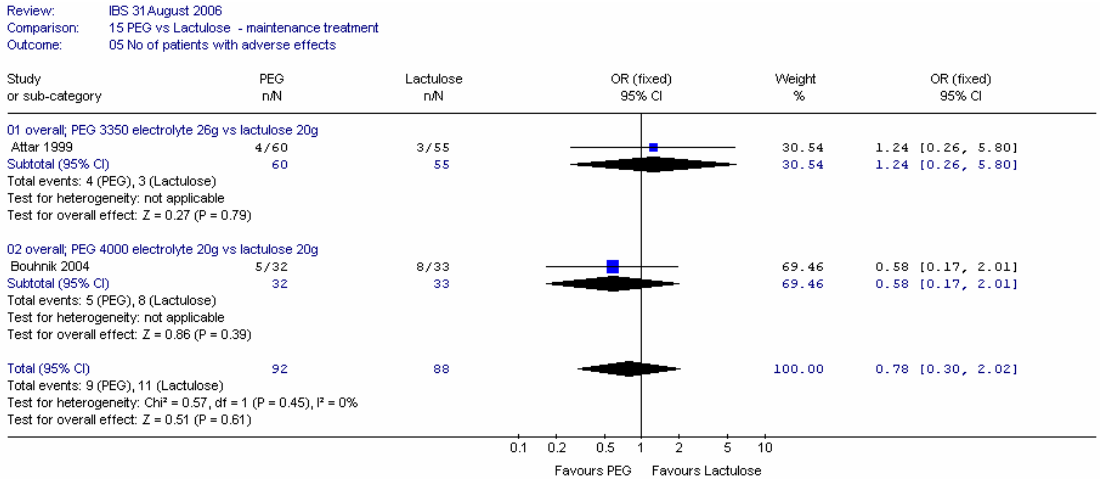
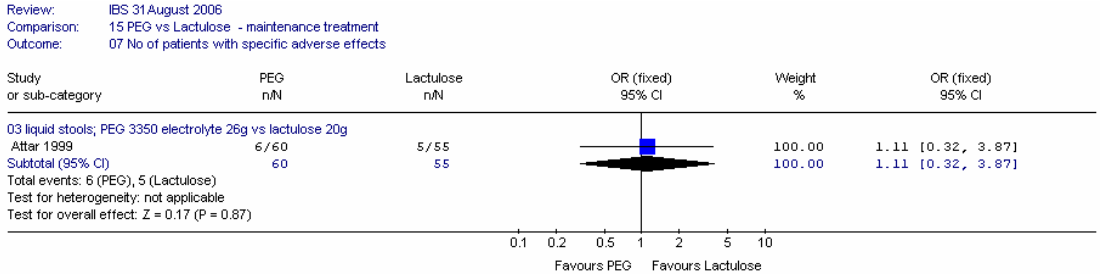


Figure 24:



B2. Comparison of different PEG laxatives

One study (Chaussade 2003) compared two doses of each of two types of PEG solution for a duration of four weeks. The PEG species were PEG 4000 (Forlax) without electrolytes and PEG 3350 plus electrolytes. Doses used were the maximum and standard recommended by the manufacturers.

1. Global improvement of symptoms

The study measured the patients' global impression of efficacy on a VAS, but the results are not reported. The authors state that there was no significant difference between groups.

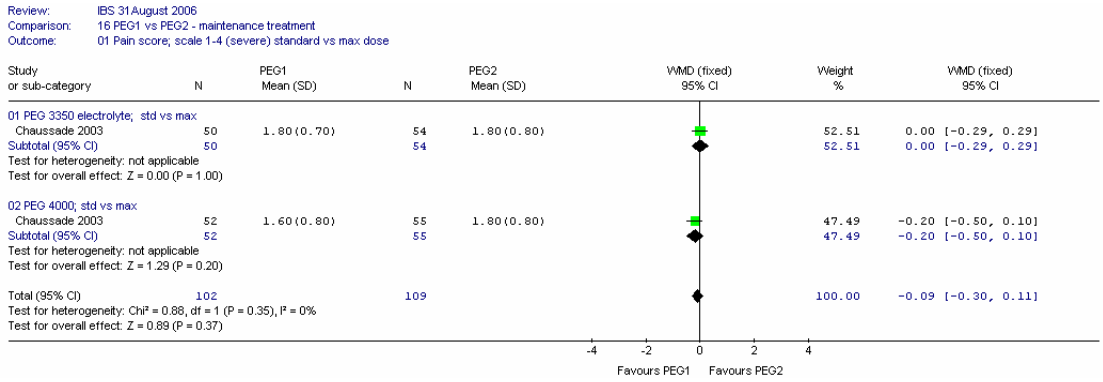
2. Individual symptoms

a) Abdominal pain

Pain scores at four weeks were recorded on a scale of 1 (none) to 4 (considerable).

There was no significant difference between the two types of PEG for this outcome at either dose, and there was no heterogeneity (I^2=0%).

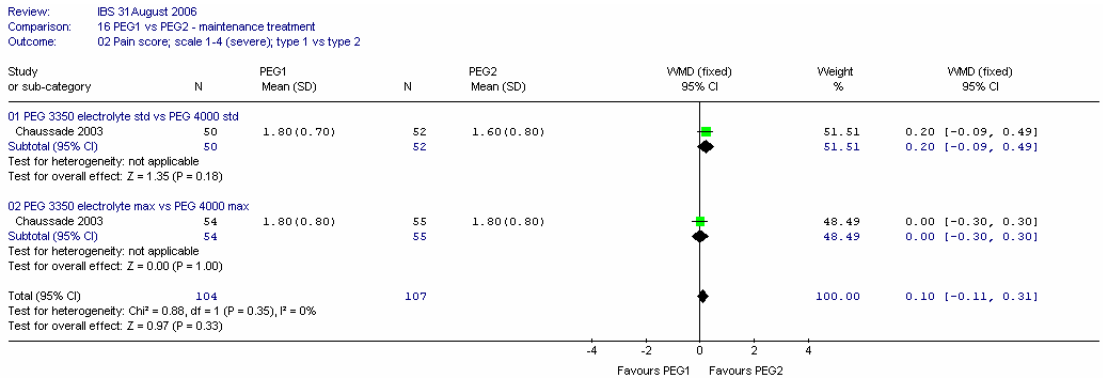
Figure 25:



b) Bloating

Bloating scores at four weeks were recorded on a scale of 1 (none) to 4 (considerable). There was no significant difference between the two types of PEG for this outcome at either dose, and no heterogeneity (I^2=0%).

Figure 26:

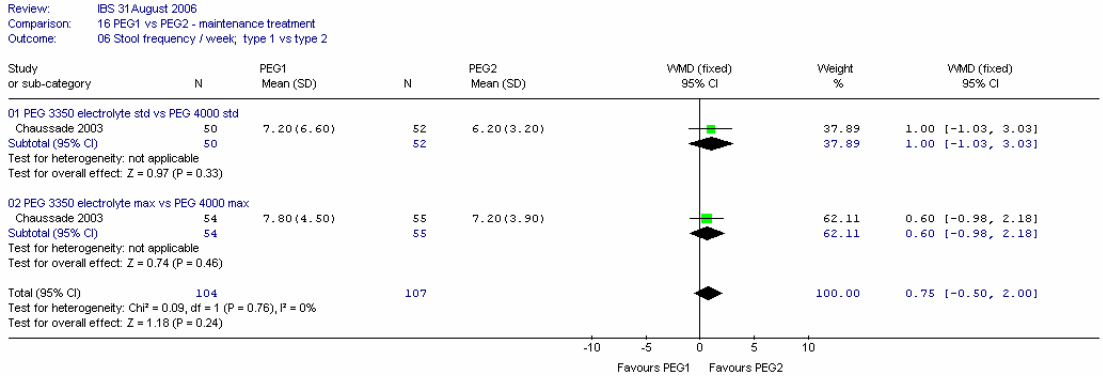


c) Bowel habits

i. Stool frequency per week

There was no significant difference between the two types of PEG for this outcome at four weeks at either dose, and no heterogeneity (I^2=0%).

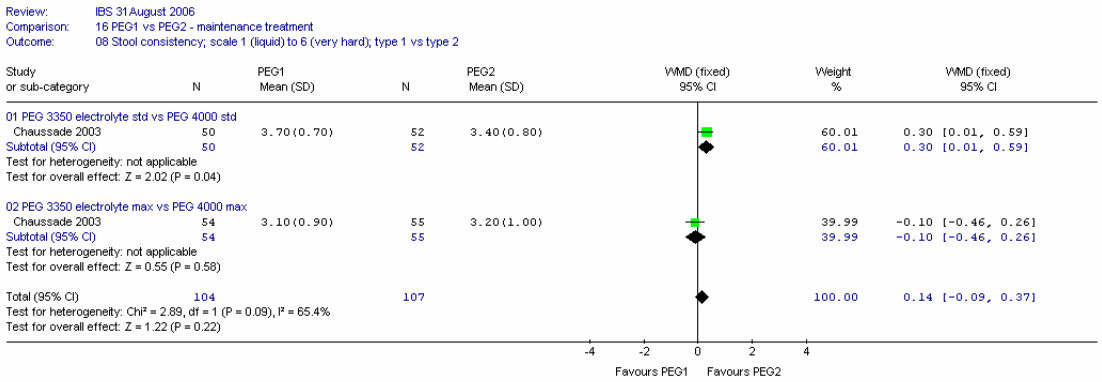
Figure 27:



ii. Stool consistency

Consistency of stools at four weeks were recorded on a scale of 1 (liquid) to 6 (very hard). Meta-analysis of the two comparisons revealed heterogeneity (I^2=65%, p=0.09). For the standard dose, there was a statistically significant difference between the two PEG solutions, favouring PEG 4000; mean difference 0.30 (95%CI 0.01, 0.59). This was a fairly small change. There was no significant difference for the maximum dose.

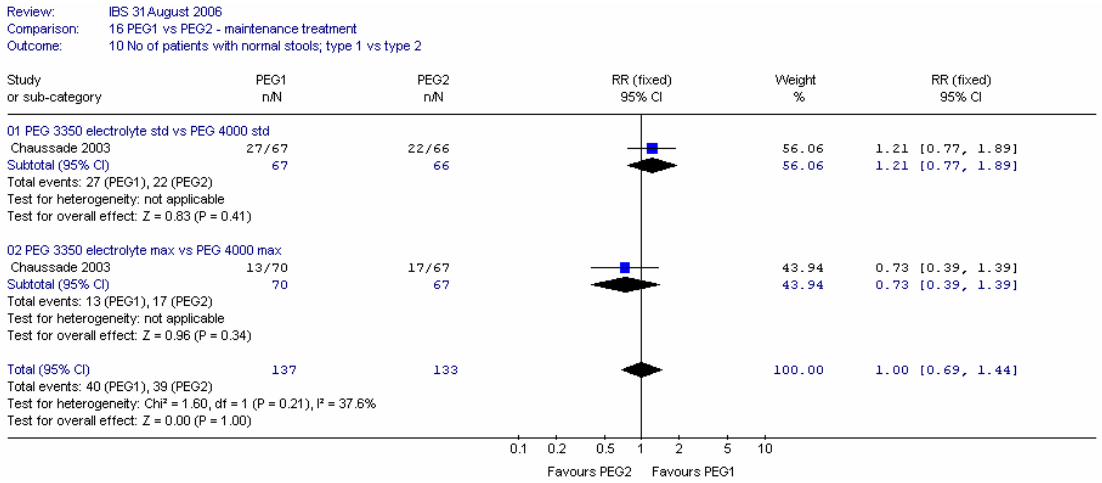
Figure 28:



iii. Number of patients with normal stools

Meta-analysis showed no significant difference at four weeks between types of PEG.

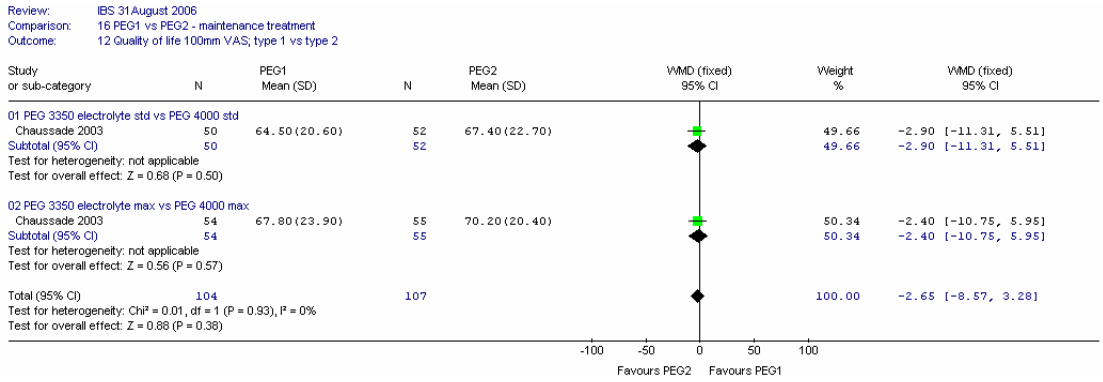
Figure 29:



3. Quality of life

The study measured quality of life on a 100mm VAS at four weeks. Meta-analysis showed no significant difference between types of PEG and no heterogeneity (I^2=0%, p=0.93).

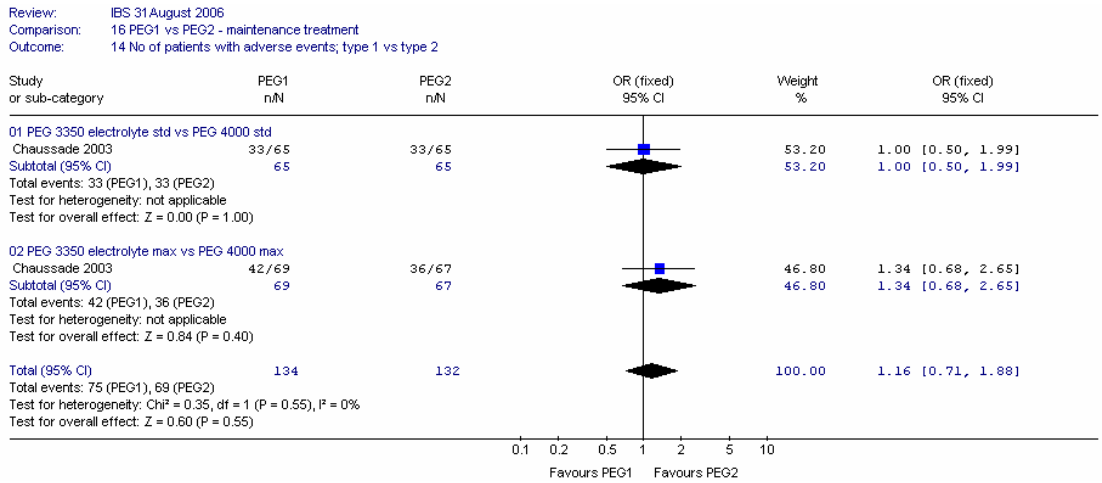
Figure 30:



4. Adverse effects

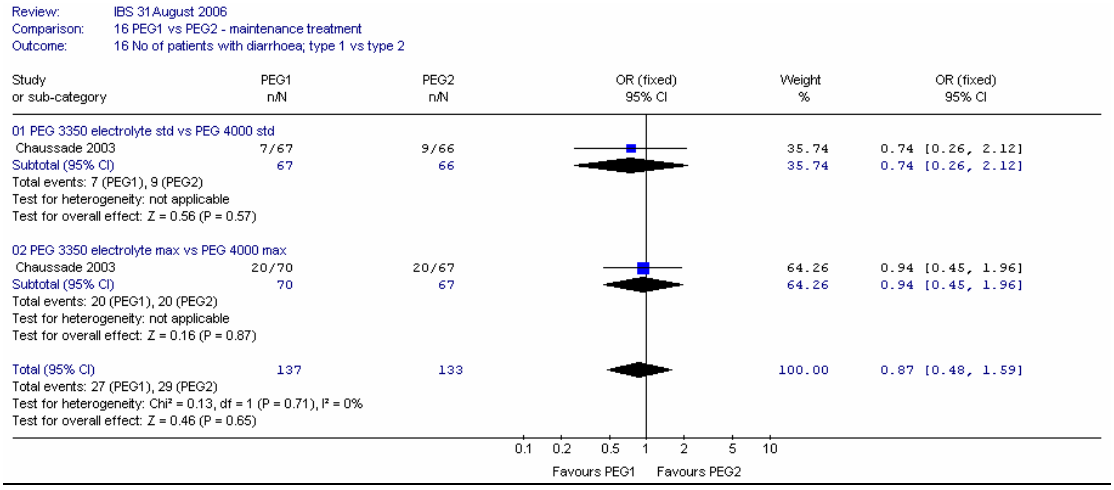
For overall adverse effects at four weeks, the majority of which were gastrointestinal, meta-analysis showed no significant difference between types of PEG and no heterogeneity (I^2=0%, p=0.55).

Figure 31:



For the specific adverse effect of diarrhoea, there was no significant difference between types of PEG and no heterogeneity (I^2=0%, p=0.71).

Figure 32:



B3. Comparison of different doses of PEG laxatives

One study (Chaussade 2003) compared two doses of each of two types of PEG solution for a duration of four weeks. The PEG species were PEG 4000 (Forlax) without electrolytes and PEG 3350 plus electrolytes. Doses used were the maximum and standard recommended by the manufacturers.

1. Global improvement of symptoms

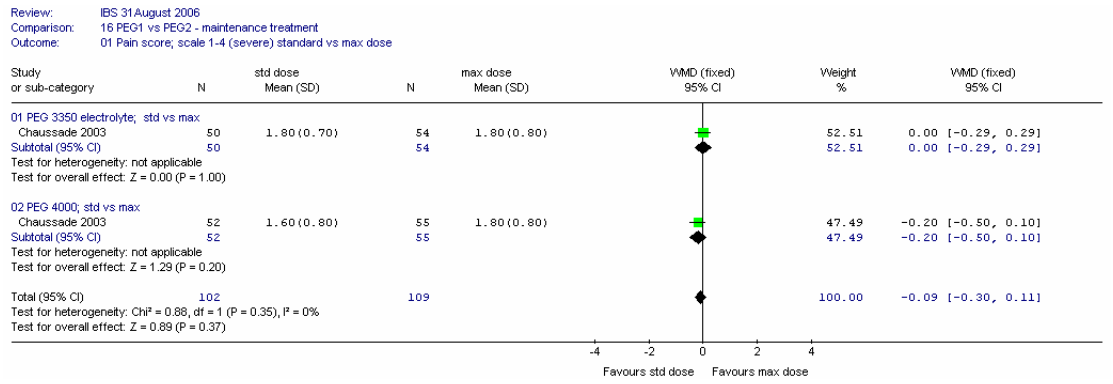
The study measured the patients' global impression of efficacy at four weeks on a VAS, but the results are not reported. The authors state that there was no significant difference between groups.

2. Individual symptoms

a) Abdominal pain

Pain scores at four weeks were recorded on a scale of 1 (none) to 4 (considerable). Meta-analysis showed no significant difference between the two doses for this outcome, and no heterogeneity (I^2=0%).

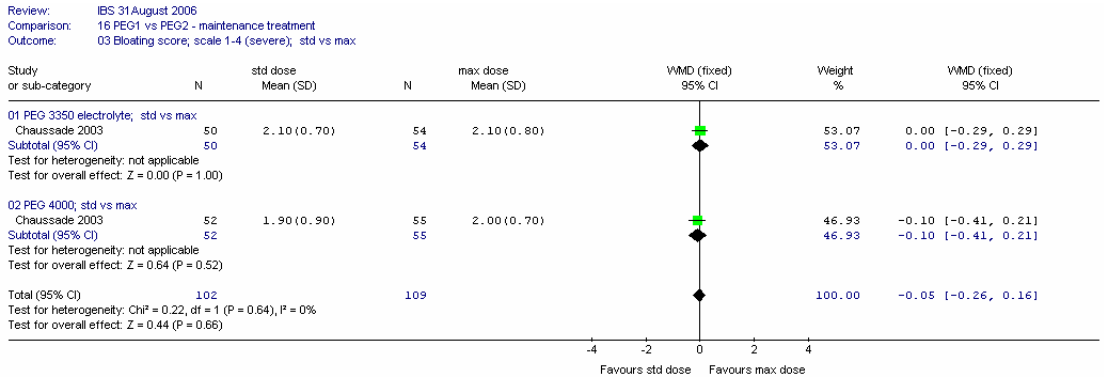
Figure 33:



b) Bloating

Bloating scores at four weeks were recorded on a scale of 1 (none) to 4 (considerable). There was no significant difference between the two doses for this outcome, and no heterogeneity (I^2=0%).

Figure 34:

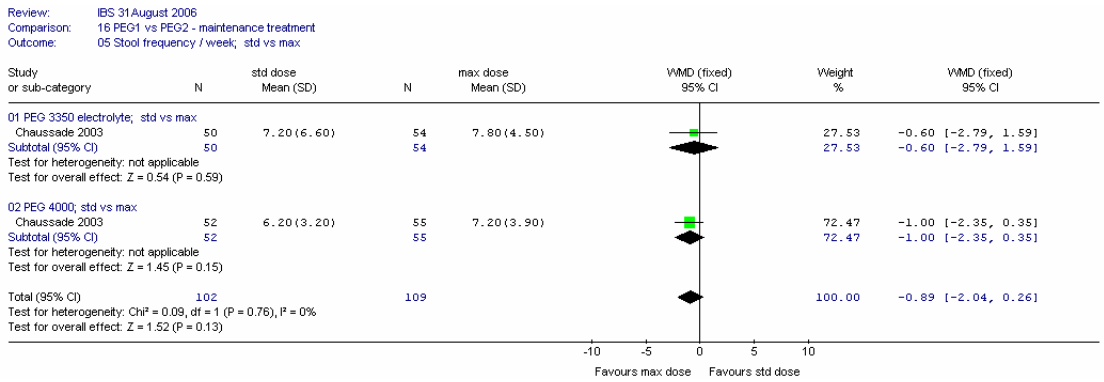


c) Bowel habits

i. Stool frequency

There was no significant difference between the two doses for this outcome at four weeks, and no heterogeneity (I^2=0%).

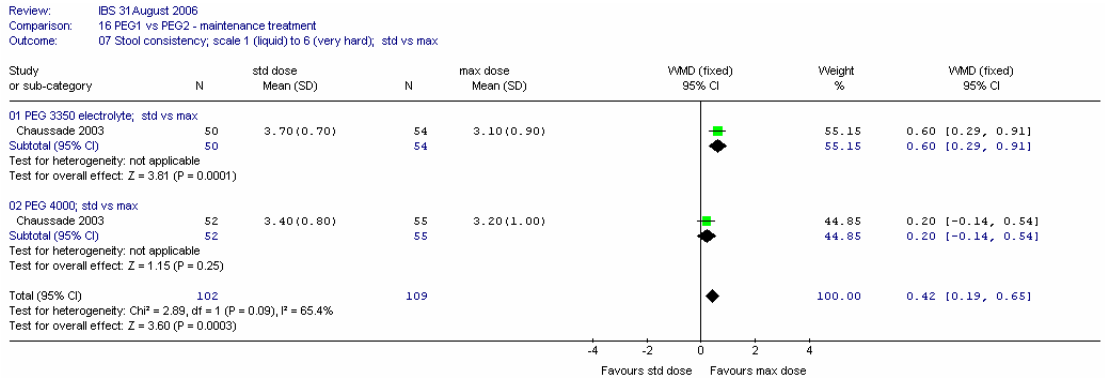
Figure 35:



ii. Stool consistency

Consistency of stools at four weeks was recorded on a scale of 1 (liquid) to 6 (very hard). Meta-analysis of the two comparisons revealed some heterogeneity (I^2=65%, p=0.09). For the PEG 3350 electrolyte dose, there was a statistically significant difference between the two doses, favouring the maximum dose; mean difference 0.60 (95%CI 0.29, 0.91). There was no significant difference for the PEG 4000.

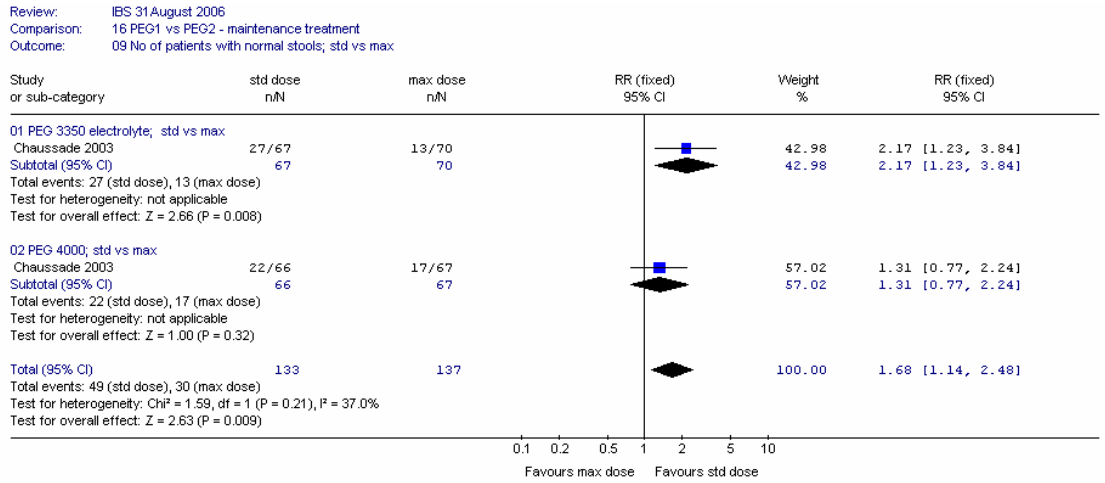
Figure 36:



iii. Number of patients with normal stools

Meta-analysis of the two comparisons reveals statistically significantly more patients with normal stools at four weeks for the standard dose groups. The RR was 1.68 (95%CI 1.14, 2.48), which corresponded to an NNH of 7 (95%CI 4, 25) for the higher dose rate of 19% or 25%.

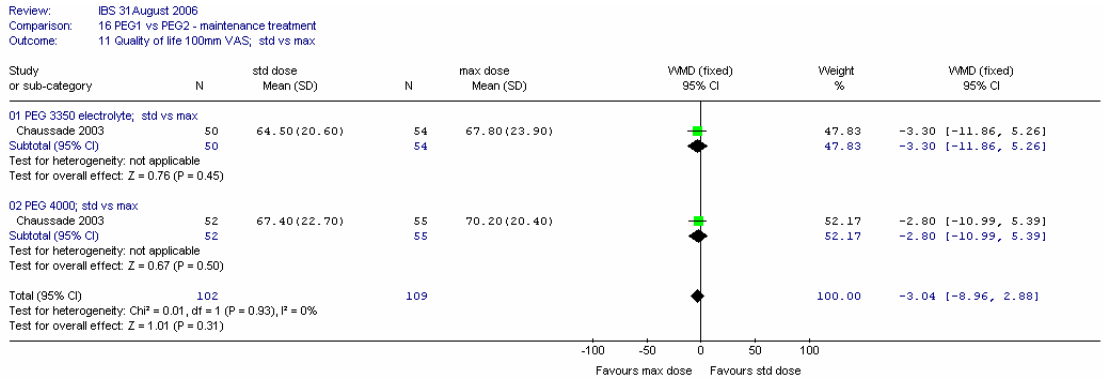
Figure 37:



3. Quality of life

The study measured quality of life at four weeks on a 100mm VAS. Meta-analysis showed no significant difference between doses and no heterogeneity (I^2=0%, p=0.93).

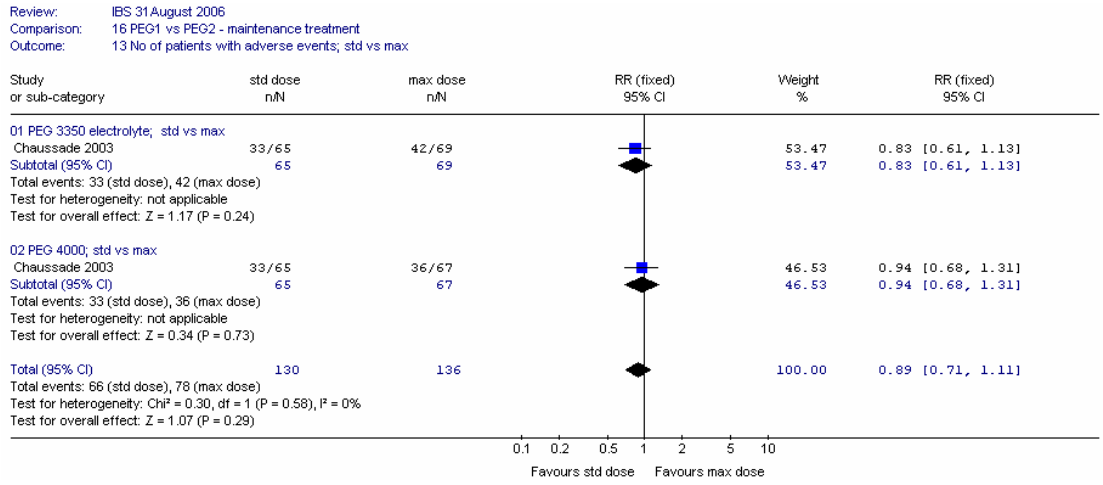
Figure 38:



4. Adverse effects

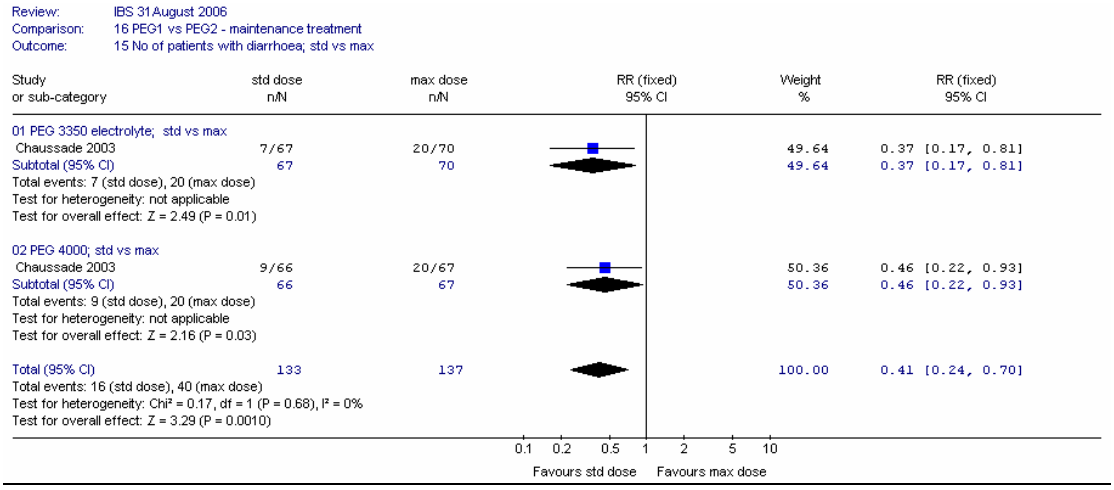
For overall adverse effects at four weeks, the majority of which were gastrointestinal, meta-analysis showed no significant difference between doses and no heterogeneity (I^2=0%, p=0.55).

Figure 39:



For the specific adverse effect of diarrhoea, there was a statistically significant difference, favouring the standard dose, and no heterogeneity (I^2=0%, p=0.68). The RR was 0.41 (95%CI 0.24, 0.70); this corresponded to an NNT of 6 (95%CI 4, 13) for the higher dose rate of 30%.

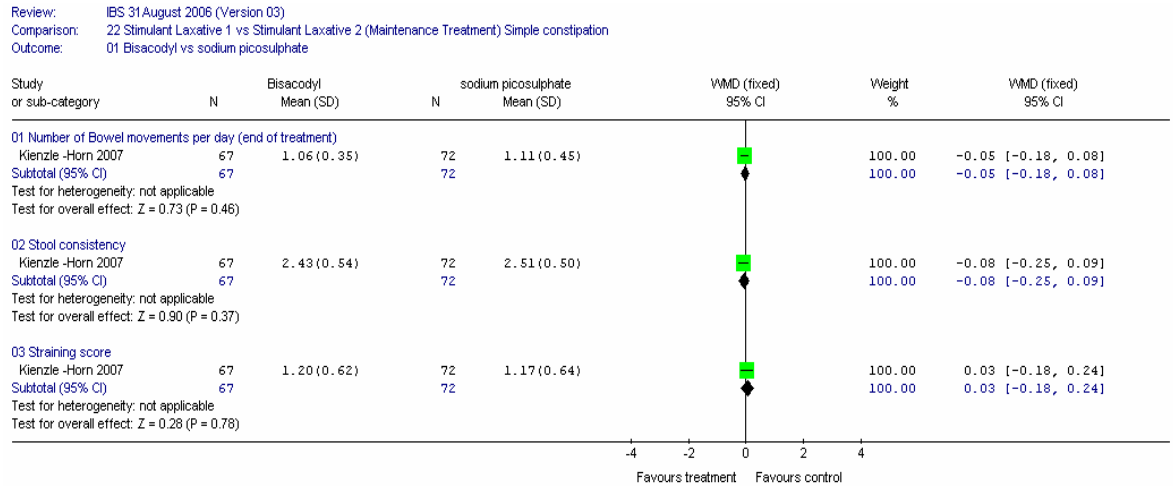
Figure 40:



B4. Stimulant Laxative Type 1 versus Stimulant Laxative Type 2

One study compared two stimulant laxatives, bisacodyl versus sodium picosulphate (Kienzle-Horn 2007). Patients were treated daily for 4 weeks with 5 to10mg of either bisacodyl or sodium picosulphate. The primary outcome was the change in bowel habit recorded as the mean number of bowel movements per day and stool consistency measured on a 5 point scale where 5=hard, 4= moderately hard,3= well formed,2=soft, 1=liquid. Secondary outcomes included straining scored on a 4 point scale with 4 = severe and 0=absent. There was no statistically significant difference between the two laxatives for the number of bowel movements per day, WMD: -0,05 (95%CI -0.18, 0.08), and similarly for the stool consistency and straining score. Both were equally effective in treating constipation.

Figure 41:



C. Laxative versus fibre

Three studies compared a laxative with fibre: two compared an osmotic laxative (lactulose) with fibre (ispaghula), (Quah 2006; Rouse 1991) and one compared usual laxatives (mainly lactulose) with fibre (ispaghula) (Dettmar 1998). Quah (2006) had a crossover design, with a

washout period of 1 week, and this study was treated separately. Quah (2006) and Rouse (1991) compared respectively: 20 ml lactulose with 3.5g ispaghula husk, and 30 ml lactulose with 7g ispaghula husk. Dettmar (1998) did not record the dose of lactulose (other laxatives), but 7g ispaghula husk was given. Dettmar (1998) also reported results for the lactulose subgroup of 'other laxatives'. Rouse (1991) and Dettmar (1998) were in primary care and Quah (2006) in secondary care. The authors of Dettmar (1998) were from Reckitt and Colman, manufacturers of Fybogel. The GDG considered it unlikely that the patients in Dettmar (1998) and Rouse (1991) had IBS. It was unclear if the patients in Quah (2006) had IBS.

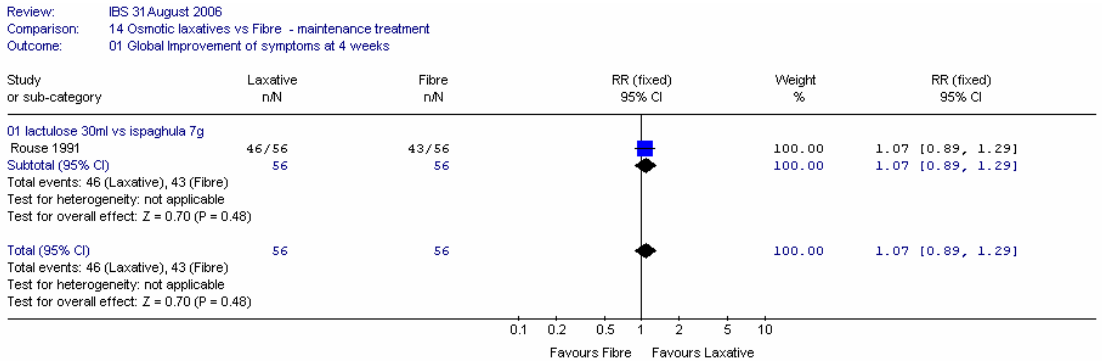
1. Global symptoms

Two studies reported an outcome of global symptoms (Rouse 1991; Dettmar 1998).

a) Global improvement of symptoms

One study (Rouse 1991) in 112 patients showed little difference in global improvement of symptoms at four weeks between patients given 30ml lactulose and 7g ispaghula husk (figure 40).

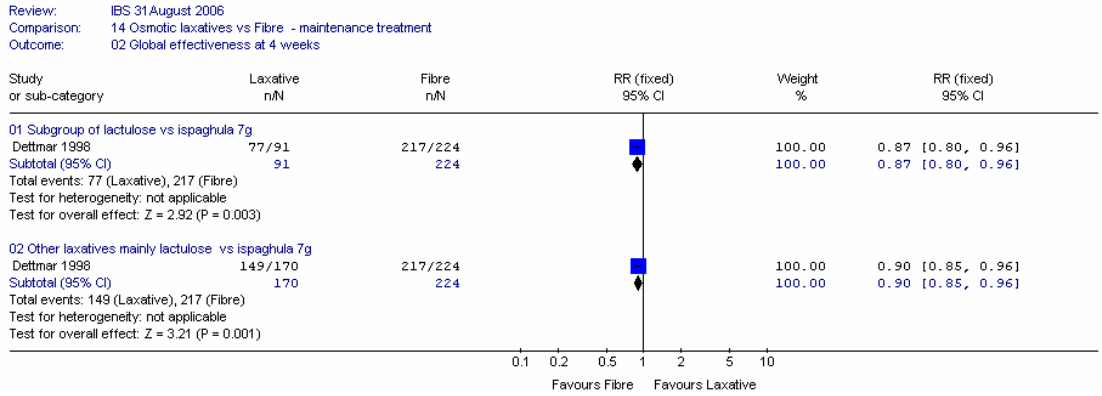
Figure 42:



a) Global effectiveness

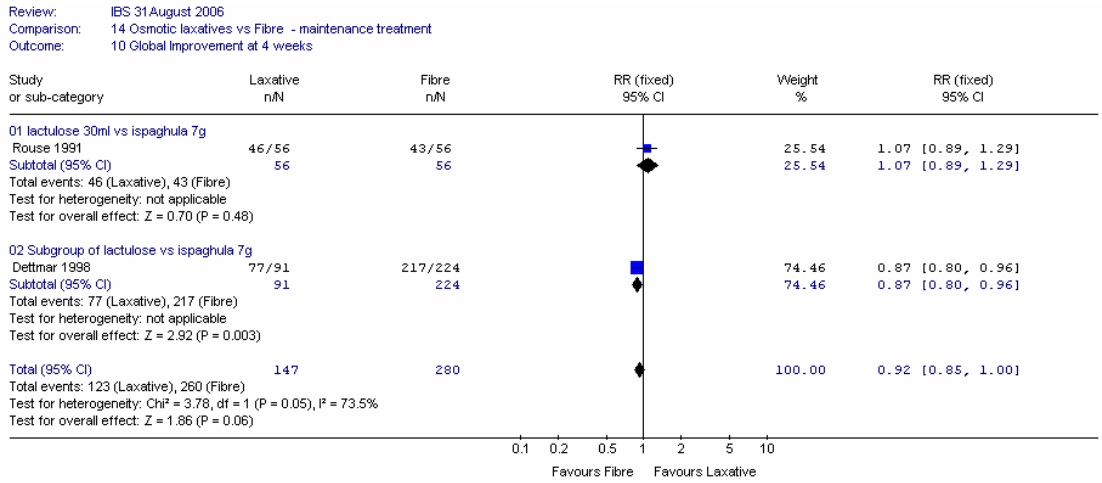
Dettmar (1998), in 315 patients, asked the patients to rate the effectiveness at four weeks of treatment with ispaghula 7g and other laxatives, mainly lactulose. Statistically significantly more patients given ispaghula rated the effectiveness as excellent, good or satisfactory. RR (all other laxatives versus fibre) was 0.87 (95%CI 0.80, 0.96) and for the subgroup with lactulose the RR was 0.90 (95%CI 0.85, 0.96). It was noted that authors of Dettmar (1998) were from the manufacturers of ispaghula (Reckitt and Colman).

Figure 43:



When these two studies were combined in a meta-analysis, the RR was 0.92 (0.85, 1.00) and there was a significant heterogeneity $I^2 = 73.5\%$, p=0.05. It is unclear what caused this, but the overall effect was small.

Figure 44:

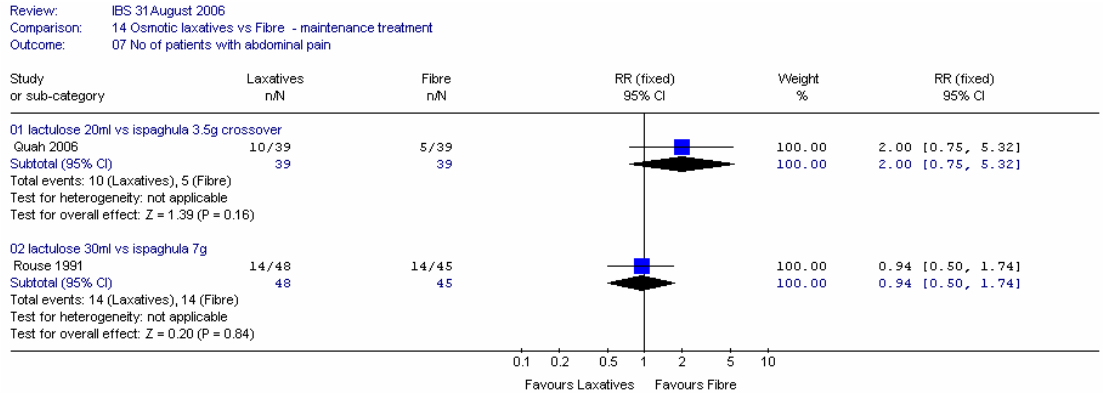


2. Individual symptoms

a) Pain

Two studies (Rouse 1991; Quah 2006) in 93 and 78 patients respectively, recorded the number of patients with abdominal pain at four weeks. We did not combine these studies because one was a crossover study and the other parallel. We did not draw conclusions for the crossover study because the confidence interval was too wide; there was also only 1 week washout for this study. The confidence interval was fairly wide for Rouse (1991), but there was no significant difference between lactulose and ispaghula.

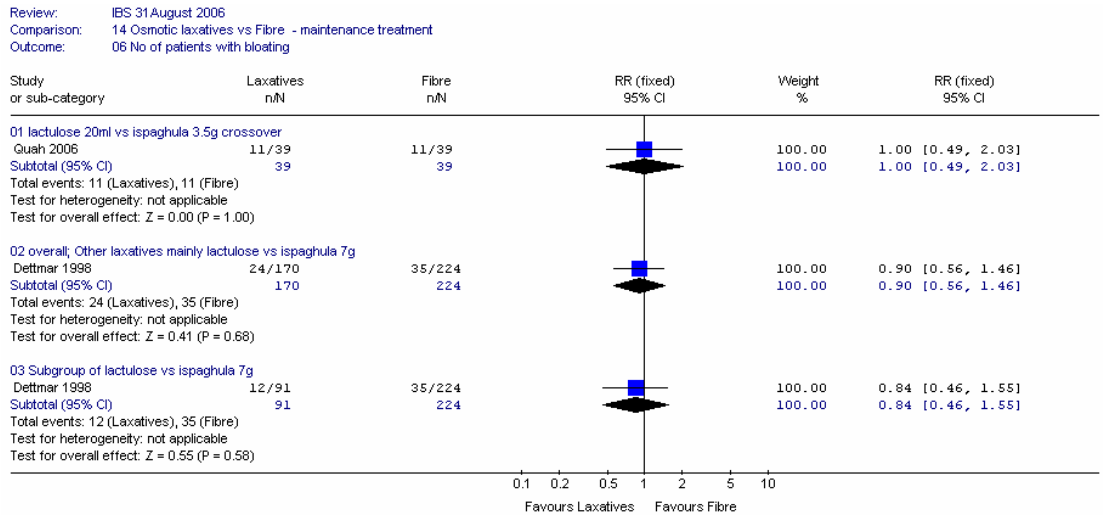
Figure 45:



b) Bloating

Two studies recorded the number of patients with bloating at four weeks: Quah (2006) in 76 patients, and; Dettmar (1998) in 394 patients. There was little difference in the numbers with bloating, although the confidence intervals were fairly wide.

Figure 46:

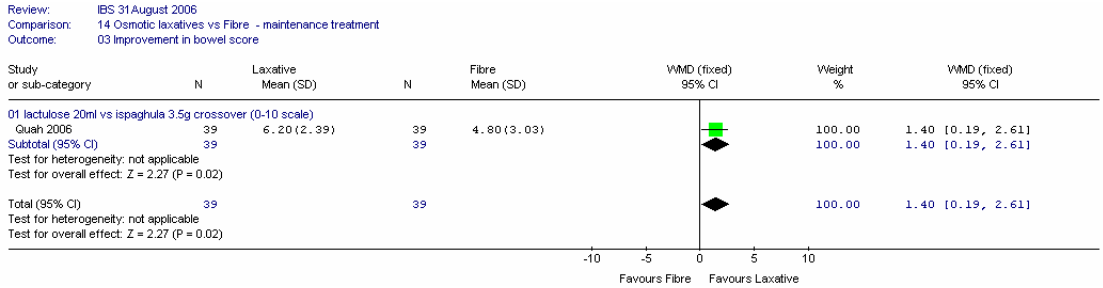


c) Bowel habits

i. Improvement in bowel score

One crossover study (Quah 2006) with 78 patients recorded improvement in bowel score at four weeks compared with baseline on a scale of 0 (no effect) to 10 (excellent) (Figure 45). There was a statistically significantly greater improvement with lactulose compared to ispaghula; mean difference 1.40 (95%CI 0.19, 2.61). It was noted that this crossover study had a washout period of only 1 week, so the results were treated with caution.

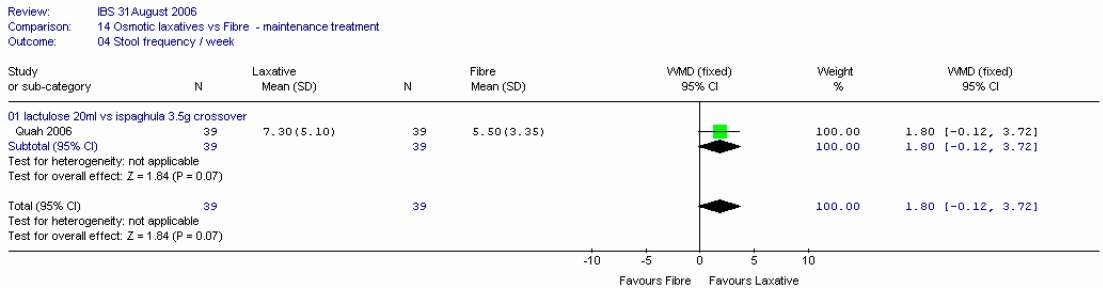
Figure 47:



ii. Stool frequency

One study reported the stool frequency at four weeks (Quah 2006). There was a non-significant difference between lactulose and ispaghula, favouring the former; WMD 1.80 (95%CI -0.12, 3.72). It was noted that this crossover study had a washout period of only 1 week, so the results were treated with caution.

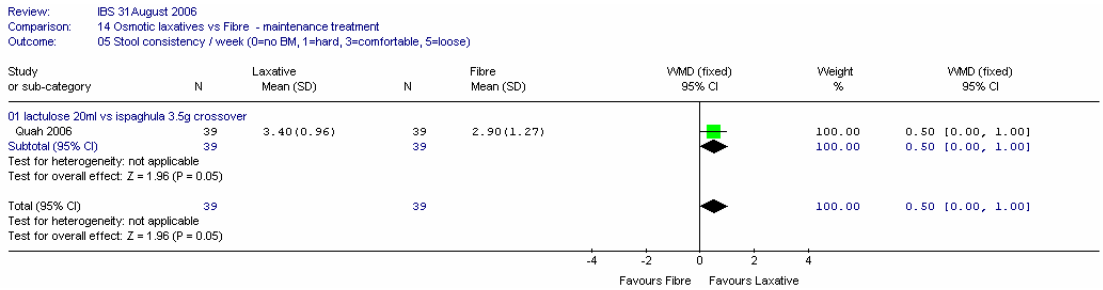
Figure 48:



iii. Stool consistency

One study reported the stool consistency at four weeks on a scale of 0 (no bowel movement) to 3 (comfortable and solid) to 5 (loose) (Quah 2006). There was a borderline significant difference of 0.50 (95%CI 0.00, 1.00; p=0.05) between lactulose and ispaghula, favouring the former. However, since the normal rating is 3 and the fibre group is closer to this value (2.9) it could be argued that fibre is more favourable. It was noted that this crossover study had a washout period of only one week, so the results were treated with caution.

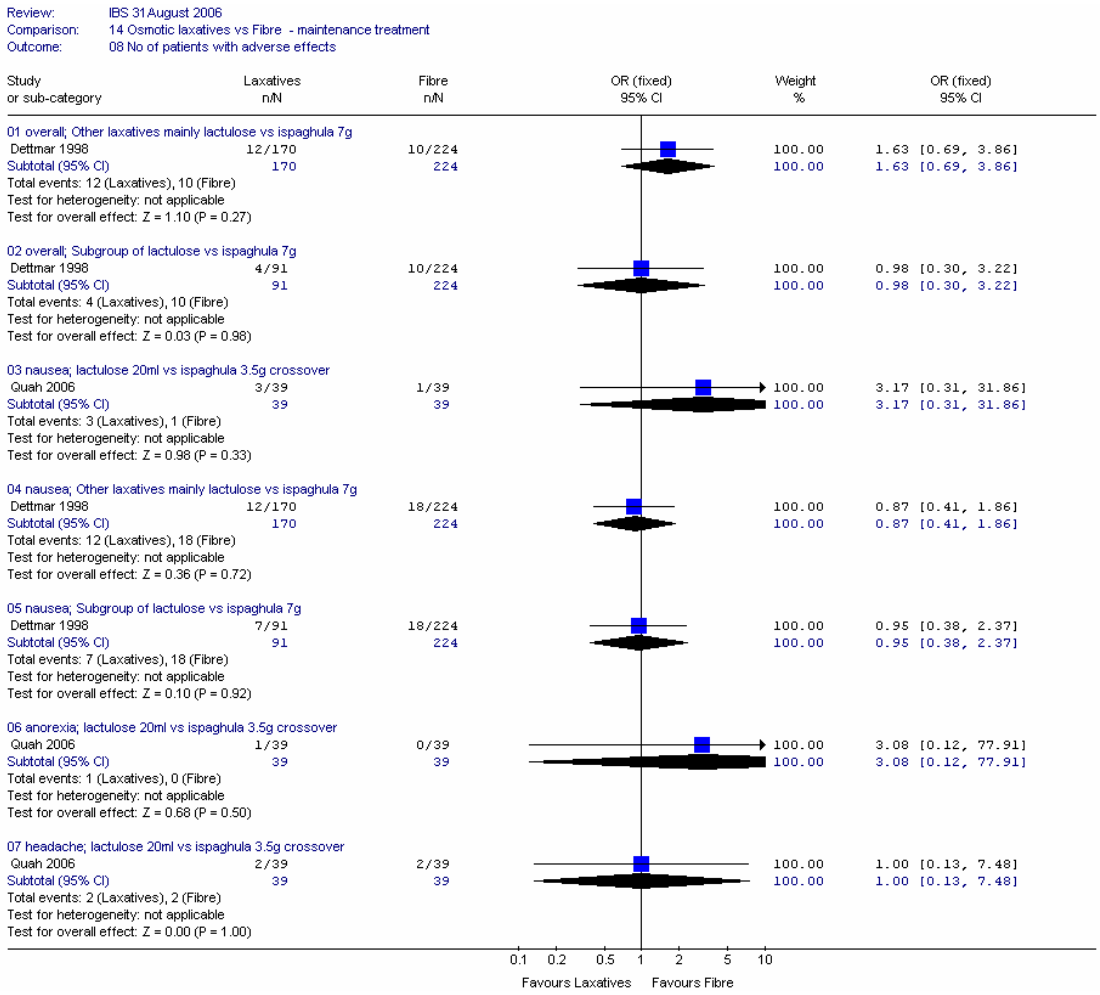
Figure 49:



3. Adverse effects

Two studies reported the number of patients with adverse effects at four weeks. In all cases there were wide confidence intervals (Figure 48).

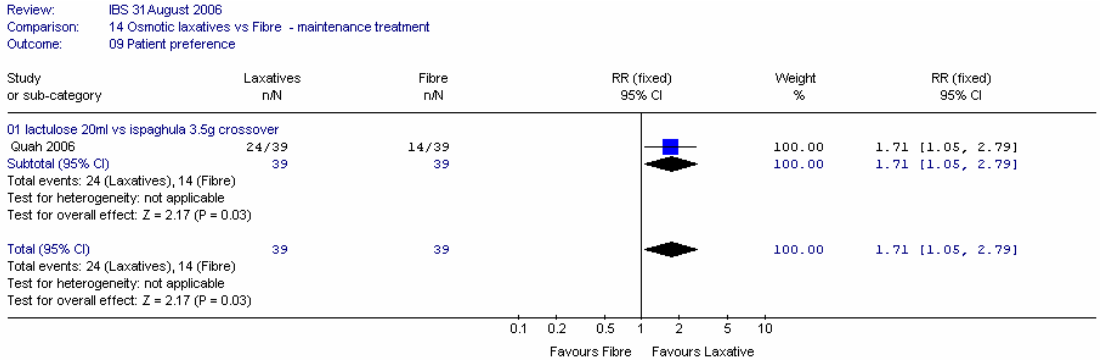
Figure 50:



4. Patient preference

The crossover study, Quah (2006), recorded patient preference at four weeks between lactulose and ispaghula. Statistically significantly more patients preferred lactulose; RR 1.71 (95%CI 1.05, 2.79). This gave an NNT of 4 (95%CI 3, 25). It was noted that this crossover study had a washout period of only one week, so the results were treated with caution.

Figure 51:



Adverse Effects

An adverse effects review has been carried out and is reported in section 8.5.1. The review included six RCTs (Quah 2006; Ferguson and Attar 1999; Bouhnik 2004; Corazziari 1996; Corazziari 2000; Chaussade 2003), and their results are reported in this effectiveness review. The RCTs were primarily aimed at assessing and reporting on the efficacy of the drug treatments. Evaluation of safety and reporting of adverse effects data was often cursory or non-existent. Even in instances where the methods sections had explicitly stated the intention of monitoring for adverse effects, trial reports did not follow a structured format (e.g. by WHO system organ class) of reporting adverse effects. The interventions and comparators were extremely varied, as was the reporting of adverse effects.

One non-randomised study in the US reported a series of adverse effects of laxatives, but did not distinguish laxative class, and used doses higher than in the UK.

Many of the adverse outcomes of interest are very similar to the symptoms of the IBS itself. For instance, laxatives are associated with flatulence, cramps and abdominal pain – all of which are commonly seen in untreated IBS patients and also form part of the efficacy assessment. It is not always possible to determine whether deterioration in these symptoms is due to lack of efficacy, or the natural history of the disease, or the adverse effect of the drug. Generally, though, the RCT data on lactulose was consistent with the findings of the non-randomised data with regards to increased risk of abdominal symptoms. The GDG's clinical experience of lactulose was that it caused bloating and other side effects.

ECONOMIC LITERATURE FOR LAXATIVES

One relevant health economic analysis was identified on the cost-effectiveness of laxatives in the treatment of IBS. Christie (2002) was a model based economic evaluation from a UK perspective which used efficacy data from a secondary care trial comparing two laxatives conducted in Scotland and France. The population included in the trial was patients with idiopathic constipation of greater than three months duration and the population included some elderly patients living in institutions. Whilst data from elderly residential patients is not directly

relevant to the IBS population, this paper was included as indirect evidence for the IBS population.

This study aimed to assess the economic impact of using low dose polyethylene glycol 3350 plus electrolytes (PEG+E) compared to lactulose in the treatment of idiopathic constipation using a decision analytic model. The economic analysis was carried out from an NHS perspective. As discussed earlier, this study was considered to be indirect evidence as the patient population was not restricted to patients with IBS but may have included some patients with IBS-C. The effectiveness inputs used in the model were obtained from a randomised controlled trial conducted in primary care. In this trial patients were randomised to treatment with either PEG+E or lactulose for one month. After this initial comparator controlled phase, patients aged over 65 continued on their allocated treatment for two months but those aged under 65 received lactulose for a further 2 months regardless of their initial allocation. The model considered the probability of various clinical outcomes over 2 weekly intervals for a 3 month period. The outcomes considered by the model were; successful treatment, discontinuation of treatment due to an adverse event, switching laxatives due to an adverse event, discontinuation of treatment due to lack of efficacy, switching laxatives due to lack of efficacy, not complying with either treatment and discontinuing treatment, not complying with either treatment and switching to another laxative. Resource use estimates were provided by a panel of experts.

PEG+E had a higher probability of achieving successful treatment at 3 months (53% versus 24%) but a higher acquisition cost (£25.42 versus £10.05 over 3 months). This was offset by a reduced number of GP appointments (2.9 visits versus 4.4 visits), resulting in an overall lower cost in patients initially treated with PEG+E (£85 versus £96). The sensitivity analyses showed that the overall costs were particularly sensitive to changes in the efficacy of first-line treatment with either treatment, the mean daily dose for PEG+E, the probability of senna being co-prescribed with lactulose, the probability of discontinuing treatment with lactulose and the number of GP appointments. Given that the costs were sensitive to dose it is important that this study is considered along-side evidence on the effective dose in patients with IBS. The model assumed that co-prescription of senna is more frequent in patients not experiencing successful resolution of symptoms following lactulose treatment (13%) than following PEG+E treatment (2%). In the trial patients were not allowed to take additional laxatives, so the effectiveness of adding senna to lactulose in this way would not be captured in the model but the cost of co-prescribing senna has been included in the model. Assuming no senna use in the lactulose arm reduced the cost to £87 which suggests that the cost-effectiveness is sensitive to the accuracy of this assumption.

The study was a partial economic evaluation as it did not assess the incremental cost of any benefit achieved in the form of a cost-effectiveness ratio. This may be appropriate given that the intervention was more effective than the comparator. However, the effectiveness was only

measured in terms of the probability of successful treatment rather than overall health impact. This may be misleading if adverse events have a higher impact on health than successful treatment. Adverse events were included in the analysis but from a cost perspective only. The evidence provided by this study was not directly relevant to the guideline as it considered a patient population that isn't fully representative of the population considered by this guideline. No potential areas of significant bias were identified, but the sensitivity analysis demonstrated that the magnitude of cost-saving estimated by the model was variable under the parameter ranges considered. Modelled direct health care costs were lower in the PEG+E arm despite a higher acquisition cost. As this study did not provide an estimate of the cost per QALY for PEG+E compared to lactulose, and did not consider the cost-effectiveness of either intervention compared to no laxative treatment, it was not particularly useful in determining whether recommending PEG+E or lactulose would result in the efficient use of NHS resources.

COST-EFFECTIVENESS ANALYSIS FOR LAXATIVES

This section describes the health economic analysis undertaken to inform recommendations on the use of laxatives as a long-term maintenance therapy in IBS. The general methods used in the economic analysis for all management interventions are described in detail in Chapter 5 and the model inputs and assumptions relevant to this particular intervention are described below.

The general approach was the same as for other maintenance therapies except:

- None of the trials provided an estimate of the relative risk of an improvement in global symptom score, which was the favoured outcome for determining a successful response to treatment for the economic model. An improvement in bowel habit was considered as a possible alternative definition for response, but this was also not available for any of the long-term maintenance studies. In the absence of this, a successful response was defined as no use of other laxatives.
- For sodium picosulfate and bisacodyl there was evidence for their effectiveness compared to placebo for short term use (3 days) but there was no evidence on their effectiveness compared to placebo for long-term use. In the absence of evidence on the effectiveness of long-term maintenance use, we have applied the effectiveness from the short-term trials and assumed that it would persist in the long-term. This is an extreme extrapolation beyond the available trial duration and should be considered with caution.
- PEG, sodium picosulfate and bisacodyl were included in the economic model as potential laxative treatments. We assumed that PEG is used first line as this was the only intervention with evidence of clinical effectiveness in long-term maintenance use. Sodium picosulfate and bisacodyl are assumed to be used second line in patients who do not respond to PEG.
- Lactulose was less effective than PEG 3350 (with electrolytes) (Attar 1999). GDG consensus was that people with IBS should be actively discouraged from taking Lactulose as it promotes gaseous bloating which can exacerbate IBS symptoms. It was therefore excluded from the cost-effectiveness analysis.

- The studies included in the clinical effectiveness review did not stratify results by IBS subtype, but all the studies were carried out in patients with chronic constipation. Therefore, the cost-effectiveness is estimated for patients with IBS-C. The applicability of these results to people with IBS-A was considered by the GDG as they may have intermittent periods of chronic constipation.

Modelled response rates

In the basecase scenario the response rate of 45% in the no treatment arm is taken from the Mearin (2004) cohort study. This represents the group of patients whose symptoms improve without any specific intervention. The RR of response for PEG versus placebo is 1.61; therefore the response rate in the PEG arm is 72% (=45% x 1.61), giving an absolute difference in response between the intervention and no treatment arms of 27% (=72%-45%) during the first month for PEG. The RR of bisacodyl and sodium picosulfate is 1.34 compared to placebo, so if these interventions are used first line then we would expect an absolute difference in response between intervention and no treatment of 15% (=1.34*45%-45%). The first line use of bisacodyl and sodium picosulfate has not been modelled due to a lack of longer-term data on their effectiveness compared to placebo.

In the basecase scenario the response rate for the subsequent interventions is assumed to be equal to the response rate to the first intervention. If bisacodyl and sodium picosulfate are used second line in patients who do not respond to PEG, we would expect an additional 4.2% (=15% x 28%) of the original cohort to respond to the second laxative, and an additional 3.6% (=15% x 24%) to respond to the third laxative, giving an overall response rate of 80% for laxatives. The response rate over time for the basecase is given in Figure 52. It is assumed that bisacodyl is tried first after a failure to respond to PEG as it has a lower cost than sodium picosulfate.

We have also considered an alternative scenario in which no patient in the comparator arm achieves an improvement in symptoms, but the absolute gain in response rates is maintained from the basecase (e.g. for first line PEG, we modelled a zero response to no treatment but a 27% response to PEG for this scenario).

Figure 52: Modelled response rates for laxatives (PEG followed by two switches to other laxatives for non responders) and no treatment

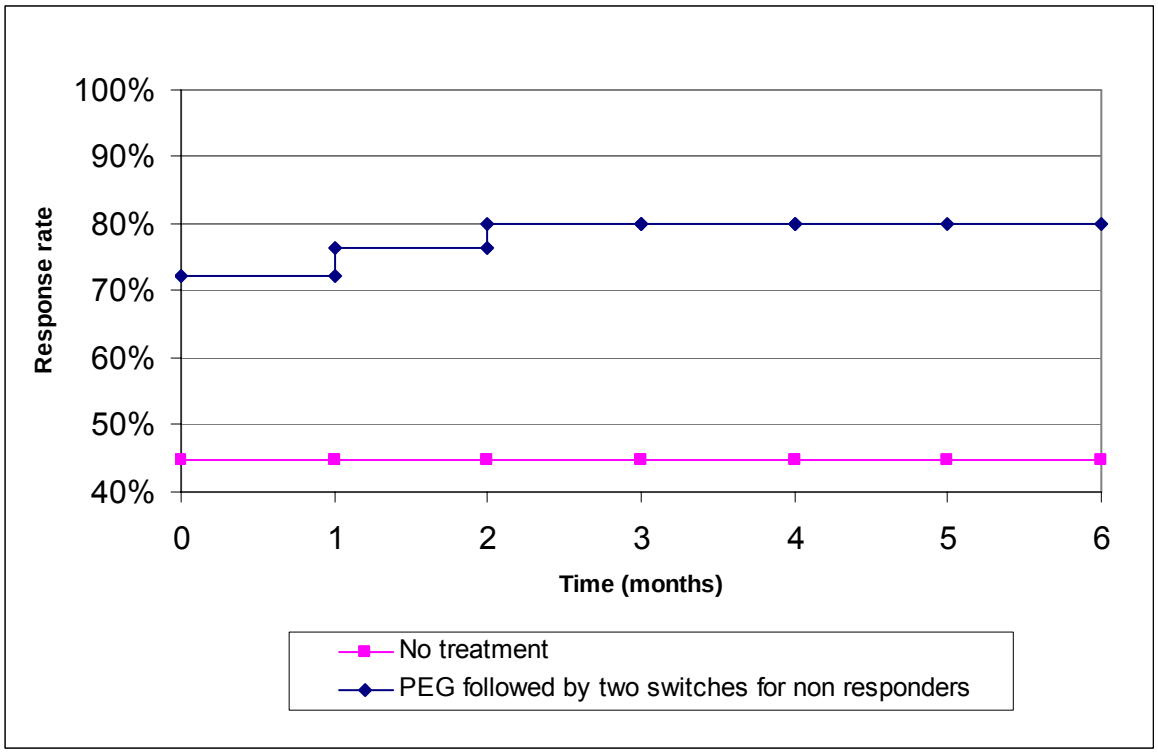


Table 1: Intervention specific parameters – laxatives

Description	**Value**		**Evidence**
RR of response for PEG vs placebo	1.61		Meta-analysis of RCT evidence for no use of other laxatives
RR of response for bisacodyl and sodium picosulfate compared to placebo	1.34		Meta-analysis of RCT evidence for improvement in bowel habit
Maximum number of switches considered	2		Limited by number of effective interventions
Drug costs			
Intervention	**Dose per day**	**Cost per month* (assuming lowest cost preparation)**	
PEG	23g (equiv to 1.8 sachets of Movicol or 2.3 sachets of Idrolax)	£12.54	
Bisacodyl	10mg	£1.43	
Sodium picosulfate	7mg	£3.94	

* British National Formulary (Joint Formulary Committee 2007)

Table 2: Incremental cost-effectiveness of allowing subsequent switches in laxative therapy

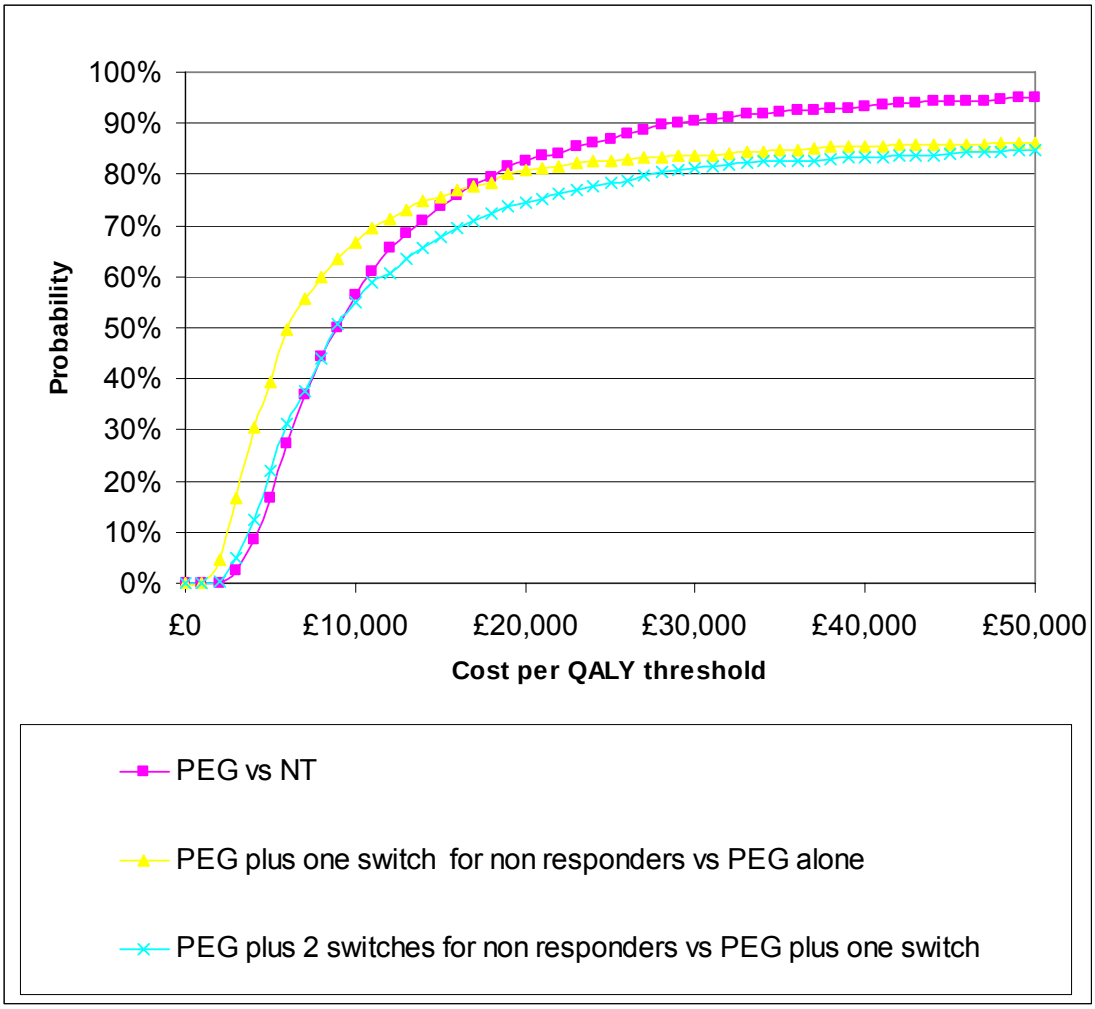
Strategy	Cost	QALY	Incremental Cost per QALY compared to previous row	Incremental cost per QALY compared to no treatment
No treatment	£0	1.60	N/A	N/A
Intervention, no switches	£7,575	2.57	£7,779	£7,779
Intervention with up to 1 switch	£8,141	2.70	£4,488	£7,401
Intervention with up to 2 switches	£8,703	2.78	£6,561	£7,341

Table 2 gives the incremental cost-effectiveness for several laxative treatment pathways in order of the benefits they achieve. It shows that whilst PEG provides additional benefit for a cost per QALY of £7,779, compared to no treatment, further benefit can be achieved by allowing non responders to PEG to switch to bisacodyl and if that is not effective to switch to sodium picosulfate. Each of these additional switches for non responders has a low cost per QALY compared to no further treatment for non-responders (£4,488 and £6,561 respectively). However, it should be noted that the cost-effectiveness of these second line laxatives is based on clinical effectiveness evidence for bisacodyl and sodium picosulfate from short term trials lasting only 3 days.

These results are an estimate of the cost-effectiveness over the first 6 months after the initiation of laxative therapy. The cost per QALY for continuing laxative therapy beyond 6 months is lower than the cost per QALY during the initial 6 months provided that treatment is reviewed every 6 months and discontinued in patients who no longer experience a therapeutic benefit, either due to lack of effectiveness or a change in their symptom profile.

The probabilistic sensitivity analysis provides an estimate of the uncertainty in the cost per QALY estimate due to uncertainty in the efficacy estimate, the probability of response in the no treatment arm and the utility gain. The CEAC in Figure 53 shows the uncertainty surrounding the cost-effectiveness of PEG, compared to no treatment and the incremental cost-effectiveness of allowing non-responders to switch to other laxatives. It shows that there is an 83% likelihood that the cost per QALY for PEG compared to no treatment is under £20K, suggesting that PEG provides health benefit at an acceptable cost in patients with IBS-C. Allowing non responders to PEG one treatment switch has an 81% probability of a being cost-effective when a £20K threshold is applied compared to no further treatment for non responders. Similarly, allowing a second treatment switch for non-responders has a 74% probability of being cost-effective.

Figure 53: CEAC for PEG with up to two switches for non responders compared to no treatment (NT)



However, it should be noted that these estimates only consider the uncertainty in cost-effectiveness due to the accuracy of several input parameters and they do not reflect general uncertainty around the assumptions made in the model. The uncertainty from these assumptions was explored in the univariate sensitivity analysis.

Univariate sensitivity results for laxatives

The results of the univariate sensitivity analysis for PEG compared to no treatment are given in Table 3. Maintaining the 27% difference in response between the two arms but reducing the response rate in the no treatment arm from 45% to zero decreased the cost per QALY to £4,896. The use of higher cost formulations increased the cost per QALY to £9,980, whilst assuming that 50% of prescriptions were over the counter reduced the cost per QALY to £4,814.

The cost per QALY is less favourable for patients who only use the medication on 25% of days as the upfront costs of initiating therapy and establishing response are constant despite lower

benefit from less frequent use. PEG compared to no treatment has a cost per QALY of £13,325 when used on 25% of days.

We carried out a threshold analysis to determine whether laxative therapy would still be cost-effective for lower gains in health related quality of life. In the basecase it was assumed that patients who respond to therapy accumulate 0.071 QALYs more per annum than patients who do not respond. For comparison, a gain of 0.135 QALYs would represent a complete remission of IBS symptoms. If the QALY gain associated with a response to therapy was reduced to 0.027 QALYs, then the cost per QALY of providing PEG compared to no treatment would be above £20,000 per QALY. The methods used in this analysis vary from the methods used for other pharmacological interventions as we were unable to estimate the response rate in terms of an improvement in global symptoms from the trial data available. Instead we assumed that patients who did not use another laxative during the trial had responded to the trial intervention. This outcome was considered a less reliable indicator of whether there had been an overall improvement in HRQoL than an improvement in global symptoms. However, the threshold analysis shows that laxatives are cost-effective even if the utility gain associated with a therapeutic response is small.

We carried out a similar univariate sensitivity analysis on the incremental cost-effectiveness of allowing non responders to switch to an alternative laxative. The incremental cost per QALY for the first and second switches was increased to £8,784 and £12,624 when assuming that patients who demonstrate no response to PEG would be half as likely to respond to another laxative. The incremental cost per QALY for each subsequent treatment switch in non-responders was higher for patients using treatments intermittently with a cost per QALY of £8,468 for the first switch and a cost per QALY of £11,536 for the second switch in patients who use laxatives on only 50% of days. When laxatives are used on only 25% of days, the incremental cost per QALY estimates for the first and second switches are £16,428 and £21,485 respectively.

If a patient also takes another medication (an antispasmodic), then this medication can be reviewed at the same time, so it may be cost-effective to provide both therapies. For example, if laxatives are prescribed with the antispasmodic and both used on 25% of days then allowing up to 2 switches of both treatments was estimated to be cost-effective with a cost per QALY of £10,107 compared to no treatment a cost per QALY of £17,393 compared to 1 switch.

Table 3: Sensitivity results for PEG compared to no treatment for 100 patients with IBS-C

Scenario	No Treatment		Intervention		Incremental
	Cost	QALY	Cost	QALY	Cost per QALY
Basecase	£0	1.60	£7,575	2.57	£7,779
No response in no treatment arm	£0	0.00	£4,767	0.97	£4,896
Response rate in no treatment arm from RCTs	£0	1.69	£7,847	2.72	£7,601
Treatment used 75% of days	£0	1.60	£6,131	2.33	£8,395
Treatment used 50% of days	£0	1.60	£4,687	2.08	£9,628
Treatment used on 25% of days	£0	1.60	£3,244	1.84	£13,325
Half of treatment obtained over the counter	£0	1.60	£4,687	2.57	£4,814
Higher cost formulations (same dose)	£0	1.60	£9,717	2.57	£9,980
High utility gain of 0.135	£0.00	3.02	£7,575	4.87	£4,109
Threshold analysis on lowest utility	A cost per QALY of £20,000 is reached when the QALY gain associated with responding to treatment lies between 0.028 and 0.027.				

GDG DISCUSSION

Many of the studies included in the laxative review may be considered to be indirect evidence as the participants were defined as having simple constipation. However the GDG considered that many of these participants may have had IBS, but the studies did not use any IBS assessment criteria and the trials were designed to treat the symptoms of constipation. General consensus is that IBS is very different from simple constipation. People with IBS cannot cope with gas and some laxatives increase gas and exacerbate IBS symptoms, lactulose in particular. IBS patients should be actively discouraged from taking lactulose. The GDG also referred to best practice of titrating the dose of laxative to optimise symptoms, using the Bristol Stool Form Scale.

EVIDENCE STATEMENTS

For this review, the evidence was assessed using the GRADE process and tables are shown in Appendix F. The following evidence statements are derived from the GRADE tables.

1. In studies for short-term symptom relief of constipation there is a moderate amount of good evidence to show a significant improvement in bowel habit for stimulant laxatives (bisacodyl

and sodium picosulphate) compared to placebo. The study population included patients with IBS.

2. There were no studies identified that used global improvement of symptoms as an outcome in longer-term maintenance treatment of constipation for PEG.

3. In studies for longer-term maintenance treatment with PEG versus placebo in people with constipation (including people with IBS) there is a:
   - Limited amount of good evidence that those taking PEG required significantly less rescue medication than those taking placebo.
   - Limited amount of good evidence showing no significant difference in pain.
   - Limited amount of good evidence showing significant reduction in bloating
   - Moderate amount of good evidence showing a large significant improvement in bowel habit.

4. There are no trials of longer term treatment that compared:
   - Lactulose versus placebo
   - Bisacodyl versus placebo
   - Sodium picosulphate versus placebo.

5. In studies for longer-term maintenance of PEG versus lactulose in people with constipation (including people with IBS) there is a:
   - Fair amount of evidence showing significant improvement in global symptoms
   - Moderate amount of good evidence that those taking PEG required significantly less rescue medication than those taking lactulose
   - Moderate amount of good evidence showing a significant improvement in stool frequency.

6. In studies for longer-term maintenance of bisacodyl versus sodium picosulphate in patients with constipation (including participants with IBS) there is a moderate amount of good evidence that there is no significant difference in stool frequency.

7. In studies for longer term maintenance of PEG + Electrolyte versus PEG-Electrolyte in people with constipation (including participants with IBS) there is a:
   - Moderate amount of good evidence to show that both are equally effective with no significant difference in pain, bloating, stool frequency, the number of people with normal stools, quality of life and adverse effects.

8. In studies for longer-term maintenance treatment with standard and maximum dose PEG in people with constipation (including people with IBS) there is a:

- Moderate amount of good evidence to show that both are equally effective with no significant difference in pain, bloating, quality of life and adverse effects
- Moderate amount of good evidence showing a significant increase in the number of people with normal stools (standard dose)
- Fair amount of good evidence showing a significant increase in the incidence of people with diarrhoea (maximum dose).

ADVERSE EFFECTS EVIDENCE STATEMENTS

1. There is limited evidence that laxatives are significantly associated with GI adverse effects (Abdominal cramps, abdominal discomfort, bloating, diarrhoea, abdominal pain, nausea).

2. There is consistent evidence that lactulose increases the risk of abdominal symptoms in people with IBS.

3. There is moderate evidence that low dose PEG is associated with fewer adverse effects compared to high dose PEG.

HEALTH ECONOMIC EVIDENCE STATEMENT

Evidence from a published model based economic evaluation comparing PEG with lactulose showed that PEG dominates lactulose by achieving a higher response to treatment rate at lower overall cost. The study was a partial economic evaluation as it did not assess the overall impact on health or provide the incremental cost of any benefit achieved in the form of a cost-effectiveness ratio. It is also considered to be indirect evidence as the population was not fully representative of the IBS population.

Evidence from a decision analytic model showed that laxatives (polyethylene glycol (PEG), bisacodyl and sodium picosulfate) are cost-effective for long-term maintenance use in individuals with IBS. The cost-effectiveness estimate is based on a clinical pathway in which response is assessed after one month and non-responders are switched to an alternative laxative with PEG used first line followed by bisacodyl and then sodium picosulfate. The cost-effectiveness analysis assumes that treatment is reviewed every 6 months to establish whether it is still relevant to the individual's symptom profile.

EVIDENCE TO RECOMMENDATIONS

The evidence from the review suggests that laxatives are clinically and cost effective in the management of constipation. However the GDG clinical opinion is that IBS is more complex than simple constipation. Some laxatives exacerbate IBS symptoms and should therefore be avoided by people with IBS. The GDG recommended the continuation of current best practice of titrating the dose of laxative to optimise symptoms, based on the Bristol Stool Form Scale.

RECOMMENDATION

Laxatives should be considered for the treatment of constipation in people with IBS, but people should be discouraged from taking lactulose.

RECOMMENDATION

People with IBS should be advised how to adjust their doses of laxative or antimotility agent according to the clinical response. The dose should be titrated according to stool consistency, with the aim of achieving a soft, well-formed stool (corresponding to Bristol Stool Form Scale type 4).

8.2 Antimotility agents

SELECTION CRITERIA

The selection criteria described in the general methodology section were used, but some were specific to the antimotility agents review and are reported below.

Types of participants

For this review, participants were required to have IBS and not to have inflammatory bowel disease or diarrhoea subsequent to surgery. This inclusion criterion was adhered to for the longer term maintenance studies, but, for short term relief of symptoms investigations, there were insufficient data for IBS patients. Therefore, for this section of the review only, the GDG extended the population, post-hoc, to include studies in patients with acute diarrhoea of any cause (including those with diarrhoea caused by infection or virus). Such studies were regarded as indirect as far as the population was concerned.

Types of studies

The GDG decided that the washout period for this review should be at least one week. Trials with shorter washout periods were not included in the analysis.

Types of intervention

Studies included the following interventions:

- Codeine phosphate
- Co-phenotrope (diphenoxylate and atropine mixture; Trade name: Lomotil®)
- Loperamide
    - Single drug: loperamide hydrochloride (Trade names: Norimode®, Imodium®)
    - Compound preparation: loperamide hydrochloride and simeticone (Trade name: Imodium® Plus)
- Morphine
    - Kaolin and Morphine mixture BP
    - Morphine preparations on sale to the public.

The following comparisons were included:

- Antimotility agent versus placebo (or nothing)
- Antimotility agent type 1 versus type 2
- Antimotility agent dose 1 versus dose 2
- Antimotility agent + another intervention versus the other intervention alone
- Antimotility agent delivery mode 1 versus delivery mode 2
- Duration of treatment 1 versus duration 2.

NB: In spite of the large placebo effect associated with IBS, comparisons with no treatment are included.

The antimotility agents review was concerned with both longer term maintenance treatment and short-term symptom relief.

For maintenance studies, the GDG had decided that there should be a minimum duration of treatment of four weeks, but on further reflection agreed to include studies of two weeks or more. Studies of shorter durations were excluded. Short-term /symptom relief studies had duration of less than one week.

Subgroup analyses

We planned to carry out subgroup analyses by type of antimotility agent, dose, mode of delivery (modified release/conventional) and duration of intervention.

SEARCH STRATEGY FOR IDENTIFICATION OF STUDIES

Searches were performed on the following core databases: MEDLINE; EMBASE; CINAHL, and; *The Cochrane Library (*1966 to current day with guidance from the GDG). Additional databases were not searched for this review. The search strategies are listed in Appendix B.

The search strategy identified 2869 possible studies. The titles and abstracts of these studies were assessed. Forty were identified to be potentially relevant to the review and these papers were retrieved in full. The reference lists for each of the retrieved studies were inspected for further potential papers but none were identified. The 18 excluded studies are listed in Appendix E, along with reasons for exclusion.

DESCRIPTION OF STUDIES INCLUDED IN THE REVIEW

There were 22 included studies, six of which had at least some patients with IBS and 16 were in an indirect population (Allison 1988; Amery 1975; Barbezat 1979; Cann 1984; Corbett 1980; Cornett 1977; Dettmer 1994; Dom 1974; Dreverman 1995; Efskind 1995; Ericsson 1990; Harford 1980; Hovdenak 1987; Jaffe 1977; Lavö 1987; Lee 1968; Lustman 1987; Palmer 1980; Pelemans and Vantrappen 1976; Taneja 2004; Tijtgat 1975; Verhaegen 1974). Seven were conducted in the UK (Allison 1988; Cann 1984; Corbett 1980; Jaffe 1977; Lee 1968; Lustman 1987 and Palmer 1980); ten in the rest of Europe, three in the USA; one in India and one in South Africa.

All studies but six had fewer than 100 patients, with seven having 20 or fewer in the intervention arm (Allison 1988; Harford 1980; Hovdenak 1987; Lavö 1987; Taneja 2004; Tijtgat 1975; Verhaegen 1974). One study included 227 patients in total but only 46 in the loperamide group and 45 in the placebo group (Ericsson 1990). The remaining studies had between 152 and 614 patients (Dom 1974). Some of the studies were of crossover design, so fewer patients are required to achieve adequate power.

Study Design

There were seven crossover studies (Allison 1988; Cann 1984; Corbett 1980; Harford 1980; Palmer 1980; Pelemans and Vantrappen 1976; Verhaegen 1974) in which participants were allocated to receive both the intervention and control treatments during the course of the study, in a random order. Four of these studies (Allison 1988; Cann 1984; Corbett 1980; Palmer 1980) had either no washout period or it was not reported, in which case this was assumed to be none. One acute study had a washout period of 12 to 24 hours (Harford 1980). One longer term study had a washout period of 2 to 7 days, and the drugs were discontinued until severe diarrhoea returned (Verhaegen 1974). The other longer term study (Pelemans and Vantrappen 1976) had a washout period of 3 to 20 days (median 7 days). As the GDG had specified a washout period of one week minimum for maintenance studies, the latter three studies were included on the basis of washout period, but those with no washout were excluded from the analysis and transferred to the excluded studies table. The remaining studies had a parallel design.

The GDG had specified a minimum treatment period of four weeks for each intervention in the maintenance studies. One study had a treatment duration of one week (Barbezat 1979); one had a duration of at least 10 days or until relapse (Tijtgat 1975); one had at least 12 days (Verhaegen 1974), one had from 14 to 49 days, median 25 days (Pelemans and Vantrappen 1976); one had three weeks (Hovdenak 1987). The GDG decided to exclude Barbezat (1979); Tijtgat (1975), and; Verhaegen (1974) on this basis, and to accept Hovdenak (1987), and; Pelemans and Vantrappen (1976). The remaining studies had durations of seven weeks (Efskind 1995), 2 months (Taneja 2004) and 13 weeks (Lavö 1987).

Thus, 15 studies were included in the analysis: thirteen parallel (Amery 1975; Cornett 1977; Dettmer 1994; Dom 1974; Dreverman 1995; Efskind 1995; Ericsson 1990; Hovdenak 1987; Jaffe 1977; Lavö 1987; Lee 1968; Lustman 1987; Taneja 2004), and two crossover (Harford 1980; Pelemans and Vantrappen 1976).

Ten studies investigated the use of anti-motility agents for acute diarrhoea (Amery 1975; Cornett 1977; Dettmer 1994; Dom 1974; Dreverman 1995; Ericsson 1990; Harford 1980; Jaffe 1977; Lee 1968; Lustman 1987). Only one of these had some patients with IBS (Harford 1980). Five studies investigated the effectiveness of anti-motility agents for the treatment chronic diarrhoea in IBS.

Three studies had more than two arms. Amery (1975) compared diphenoxylate with loperamide and placebo. Dettmer (1994) and Dreverman (1995) compared two dose of loperamide with placebo, giving a total of 21 comparisons.

Setting: seven studies were in primary care (Amery 1975; Dom 1974; Dreverman 1995; Efskind 1995; Jaffe 1977; Lee 1968; Lustman 1987); three were in secondary care (Dettmer 1994; Lavö 1987; Taneja 2004) and the others did not report the setting.

Funding: four studies (Amery 1975; Cornett 1977; Dettmer 1994; Dreverman 1995) were from Janssen Pharmaceutica (manufacturers of Imodium, i.e., loperamide) and Efskind (1995) stated that Janssen Pharmaceutica provided the drug, monitored the study and gave statistical support. Lustman (1987) did not specify funding, but the corresponding author was employed by Gold Cross Pharmaceuticals, a division of GD Searle & Co Ltd (manufacturers of Lomotil). Three studies were funded by non-industry sources (Ericsson 1990; Harford 1980; Taneja 2004) and the others did not state their funding.

Population

Four studies were in patients with IBS (Efskind 1995; Hovdenak 1987; Lavö 1987; Taneja 2004), and two studies had some patients with IBS. The acute study, Harford (1980), had 4/15 patients with IBS; and the maintenance study, Pelemans and Vantrappen (1976), had 4/23; 18 of the remaining patients in the latter study had inflammatory bowel disease. In both studies, individual patient data were reported for the IBS subgroup, but these were not stratified before randomisation and the small numbers give uncertainty and likely potential for bias. The definition of IBS varied between studies: one included patients meeting the Rome II criteria (Taneja 2004), one met criteria defined by the authors that were similar to the Rome criteria (Efskind 1995), and in the other studies, the authors stated that the patients had IBS, with no further explanation.

Most studies included patients with diarrhoea predominance, but one study (Hovednak 1987) had a mixture of types: IBS-D (16); IBS-A with pain (21); IBS-A without pain (12); IBS-C (9). None of the studies stated that any participants had IBS as result of gastrointestinal infection. The majority of studies did not state the number of participants with bloating. One study had some patients with bloating (Efskind 1995).

Most of the studies did not describe symptom severity. Two studies stated that participants had symptoms of mixed severity (Efskind 1995; Hovednak 1987), one of which excluded patients with mild symptoms (Hovednak 1987).

The remaining studies were in patients who did not have IBS and these were treated as indirect evidence. Further details are given in the included studies table.

The age range of participants across the IBS studies was 18 to 70 years, with the mean age, where given, ranging from 31 to 43 years. No study particularly identified elderly participants. The indirect studies included patients aged 9 to 95 years, with four of the studies definitely including children: Amery (1975) included patients aged 9 to 82 years, with a median age of 31

years; Cornett (1977) had an age range of 11 to 84 years, with 8% patients in the age group 10 to 19 years; Dom (1974) had a range of 14 to 95 years with a median of 35 years; and Drevermann (1995) had patients aged 16 to 75 years.

Five studies had more women than men (Efskind 1995; Harford 1980; Lavö 1987; Lee 1968; Lustman 1987); two studies had about the same number of men and women (Dettmer 1994; Pelemans and Vantrappen 1976); one study examined only men (Taneja 2004) and the other indirect studies had more men than women. One study did not report the numbers of men and women (Ericsson 1990).

Interventions

The studies varied in the type of antimotility agent used:

- No studies examined codeine phosphate
- Seven acute studies gave the patients co-phenotrope (Amery 1975; Cornett 1977; Dom 1974; Harford 1980; Jaffe 1977; Lee 1968; Lustman 1987). The Amery study stated that they gave the patients 2.5mg diphenoxylate and that the contents of the capsules were identical to Lomotil (co-phenotrope)
- Twelve studies (seven acute) gave the patients loperamide (Amery 1975; Cornett 1977; Dettmer 1994; Dom 1974; Dreverman 1995; Efskind 1995; Ericsson 1990; Hovdenak 1987; Jaffe 1977; Lavö 1987; Pelemans and Vantrappen 1976; Taneja 2004)
- One acute study examined morphine (Lee 1968 used a kaolin and morphine mixture).

Ten of the included studies used antimotility agents for acute diarrhoea (Amery 1975; Cornett 1977; Dettmer 1994; Dom 1974; Dreverman 1995; Ericsson 1990; Harford 1980; Jaffe 1977; Lee 1968; Lustman 1987).

In the maintenance studies, no study allowed rescue medication, but patients were allowed to vary the dose of study drug in three studies (Efskind 1995; Lavö 1987; Pelemans and Vantrappen 1976). A fixed dose was used in the remaining studies.

Comparisons

The included studies covered the following comparisons:

- Ten comparisons of antimotility agent versus placebo:
    - Three gave co-phenotrope for acute episodes (Amery 1975; Harford 1980; Lustman 1987)
    - Four gave loperamide for acute episodes (Amery 1975; Dettmer 1994, in a dose of 1mg or 2mg; Dreverman 1995 in a dose of 1mg or 0.5mg; Ericsson 1990 2mg)
    - Three gave loperamide for maintenance treatment (Efskind 1995; Hovdenak 1987; Lavö 1987).
- Three comparisons of different types of antimotility agent:

    - Four studies compared loperamide and diphenoxylate for acute episodes (Amery 1975; Cornett 1977; Dom 1974; Jaffe 1977)
    - One study compared loperamide and co-phenotrope for maintenance treatment (Pelemans and Vantrappen 1976)
    - One study compared co-phenotrope with kaolin-and-morphine for acute episodes (Lee 1968).
- Two acute studies compared two doses of loperamide (Dettmer 1994: 1mg versus 2mg; Dreverman 1995 1mg versus 0.5mg)
- One maintenance study compared loperamide with yoga (Taneja 2004).

METHODOLOGICAL QUALITY

The results of the quality assessment for included trials are shown in Appendix D. The method of randomisation was reported in none of the studies. Allocation concealment was reported in one study (Pelemans and Vantrappen 1976), which reported a partially adequate method in which bottles of the drug were marked with the patient's code number and contained identical capsules.

All the studies reported that the patients were blinded to the interventions except for three. Jaffe (1977) reported that the drugs were presented in their normal marketed form and as they are dissimilar in appearance and had different dose regimens, no attempt was made to blind participants or investigators. Lee (1968) did not report blinding and the treatments used were dissimilar: Lomotil-with-neomycin was used at the recommended dose of 4 tablets at the start of therapy then 2 tablets every 6 hours, while the kaolin-and-morphine mixture was used at 2 tablespoons at the start of treatment then 1 tablespoon every 6 hours. Taneja (2004) compared loperamide with yoga and this was not blinded. Only two studies reported a sample size calculation (Dettmer 1994; Ericsson 1990).

Most studies included in the review demonstrated baseline comparability of the groups, but two studies were not comparable at baseline for the age of the patients (Amery 1975 had significantly older patients in the loperamide group; Lavö 1987 had significantly younger patients in the loperamide group). The GDG did not regard these differences to be important.

Five acute diarrhoea studies reported no withdrawals (Amery 1975; Cornett 1977; Dom 1974; Jaffe 1977; Lee 1968). One of the 13 patients allocated to loperamide in the Taneja (2004) study could not attend for the final assessment but the nine treated with yoga all attended. Dettmer (1994) reported missing data for 7% (13/230) of patients. Dreverman (1995) reported missing data for 3% (8/242) of patients. Lustman (1987) reported missing data for 4% (7 of 152) of patients.

In the Ericsson (1990) acute diarrhoea study, 46 patients were allocated to the loperamide group and 45 to the placebo group. Of these, 6 and 4 patients respectively dropped out and were excluded from the efficacy analysis. In addition, those who were non-compliant with medication (13 and 14 patients respectively) were also excluded from the analysis. This led to the final numbers being 27 for each group (i.e. missing data for 41% in each group). This raises the potential for bias in this study.

Two maintenance studies reported that more than 20% of patients in at least one arm (or overall) were not analysed or were lost to follow-up (attrition bias). Efskind (1995) reported 23% (21/90) missing overall, but 8 of these did not arrive at the start of the trial (thus drop-outs related to treatment were 12/90, i.e. 13%). Pelemans and Vantrappen (1976) had 26% (6/23) missing overall for the stool frequency outcome measure, but none of the IBS patients were missing.

Two of the studies (Harford 1980; Pelemans and Vantrappen 1976) each gave individual patient data for 4 IBS patients. This was a within-trial subgroup analysis and stratification had not taken place. The GDG decided to consider the results for all patients in the Harford (1980) acute study, but decided that the Pelemans and Vantrappen (1976) maintenance study had too few IBS patients and would be misleading, so this study was not considered further.

The risk of bias was assessed for each included study and two studies were excluded from the analysis: Pelemans and Vantrappen (1976) was excluded on the basis of wrong population, and; Ericsson (1990) was considered to have too high a drop-out rate. None of the other studies were considered to be at risk of bias, although the inclusion of children in some studies was noted.

RESULTS

I. TREATMENT FOR ACUTE EPISODES OF DIARRHOEA

For the treatment of acute diarrhoea the GDG simply wished to know whether anti-motility agents were effective in stopping diarrhoea, regardless of its cause. Therefore only outcomes relating to bowel habit are reported.

A. Anti-motility agent versus placebo

Three studies gave co-phenotrope for acute episodes (Amery 1975; Harford 1980; Lustman 1987).

- Amery (1975) gave 5 mg diphenoxylate per day (1 tablet twice a day) for 24 hours
- Harford (1980) gave 10 or 20 mg per day (1 or 2 tablets 4 times a day) for 3 days.
- Lustmann (1987) gave 10 mg initially (4 tablets) then 20mg per day (2 tablets four times per day) for 3 days.

The recommended initial dose for co-phenotrope is initially 10 mg (4 tablets) then 20mg per day (2 tablets four times a day), thus the Amery (1975) study can be considered to have a low dose of diphenoxylate.

Three studies gave loperamide for acute episodes compared with placebo (Amery 1975; Dettmer 1994, 2 doses; Dreverman 1995, 2 doses).

- Amery (1975) gave 4 mg loperamide per day (1 tablet twice a day) for 24 hours
- Dreverman (1995a) gave 1mg loperamide (2 tablets) initially then up to 3.5mg (7 tablets) per day for 3 days
- Dreverman (1995b) gave 2mg loperamide (2 tablets) initially then up to 7mg (7 tablets) per day for 3 days
- Dettmer (1994a) gave loperamide in a slow release formulation, 2 mg initially (2 tablets) then up to 8 mg (8 tablets) per day for 3 days
- Dettmer (1994b) gave loperamide in a slow release formulation, 4 mg initially (2 tablets) then up to 16 mg (8 tablets) per day for 3 days.

The recommended dose is 4 mg initially (2 tablets) followed by 2 mg (1 tablet) after each loose stool for up to 5 days.

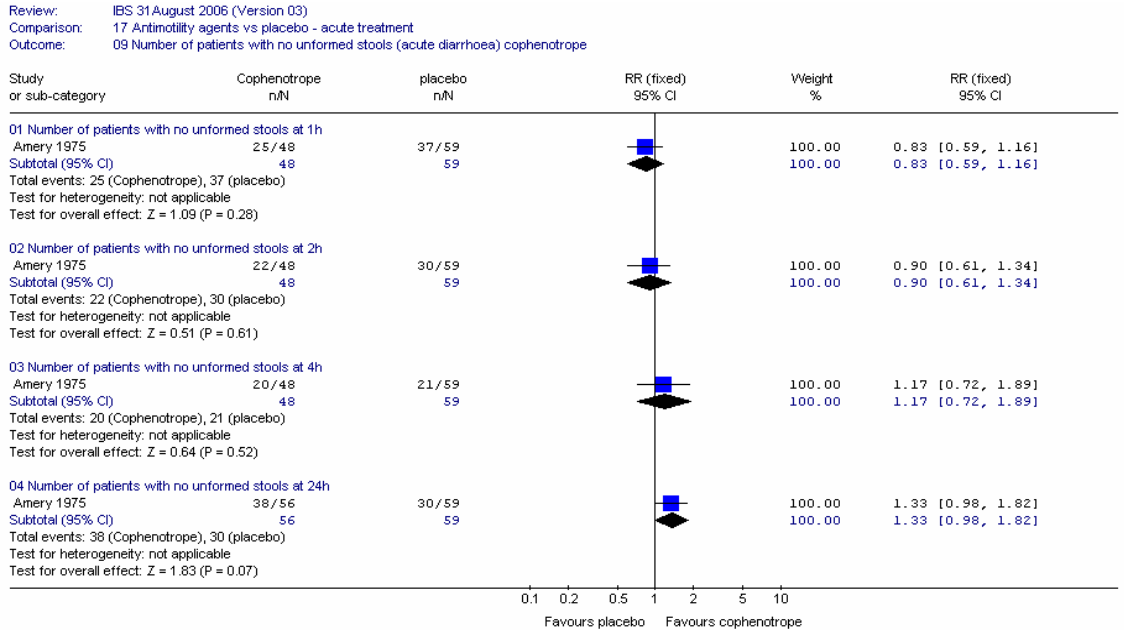
We noted that all of the loperamide studies were funded by Janssen Pharmaceutica, manufacturers of Imodium (i.e. loperamide).

A1. Co-phenotrope versus placebo

i. Number of patients with improvement in bowel habit

One study (Amery 1975) reported the number of patients without recurrence (unformed stools) after 1, 2, 4 and 24 hours. There was no significant difference between diphenoxylate and placebo at any duration.

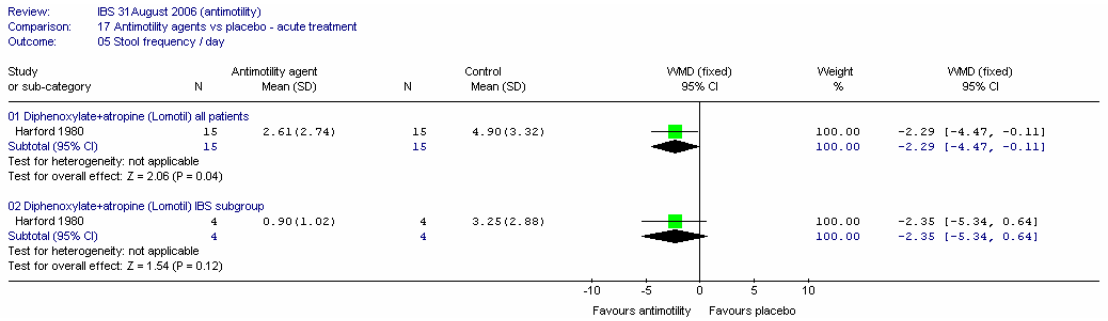
Figure 1: Acute diarrhoea – co-phenotrope



ii. Stool frequency

Harford (1980) recorded stool frequency averaged over 3 days of co-phenotrope or placebo in a crossover study in 15 patients; individual patient data were given. Results are reported for all patients and for the IBS subgroup separately. For all patients, there was a statistically significant difference in stool frequency of -2.29 stools per day (95%CI -4.47, -0.11), favouring co-phenotrope. For the IBS subgroup, the effect was not statistically significant, but the confidence interval was wide.

Figure 2: Stool frequency



Lustman (1987) reported the change in the median number of bowel actions (24 hours prior to start of therapy minus first 24 hours of treatment). This fell from 5 in each group to 3 on diphenoxylate, compared to 4 on placebo, which was a statistically significant difference (p=0.046).

iii. Time to recurrence of unformed stools

Amery (1975) also reported the median time to first recurrence of unformed stools. This was 2 hours for both diphenoxylate and placebo groups, i.e. no significant difference (p=0.48).

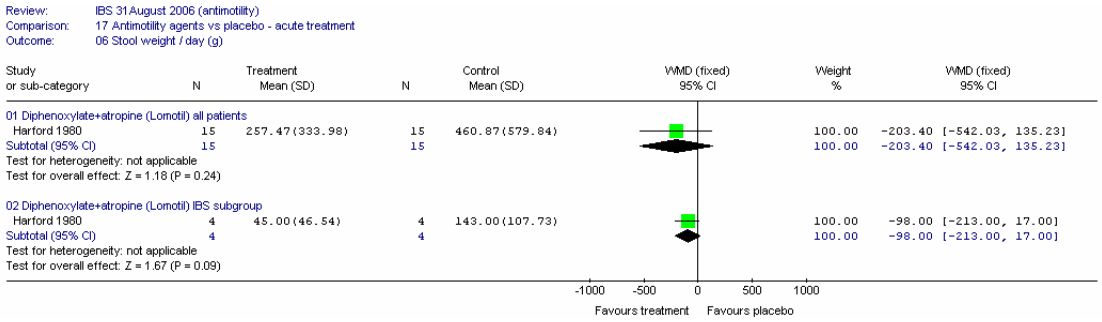
Lustman (1987) reported the median time to the last loose or watery stool, which was 25 hours on diphenoxylate compared with 30 hours for placebo (not statistically significant).

Lustman (1987) also reported the median time (hours) to the start of an interval of at least 12 hours between bowel actions: 14 hours for diphenoxylate vs. 24 hours for placebo, p=0.025.

iv. Stool weight

Harford (1980) recorded stool weight averaged over 3 days of co-phenotrope or placebo in a crossover study in 15 patients. The results are reported for all patients and for the IBS subgroup separately. The confidence interval was too wide to determine if there was a difference for all patients and there was no statistically significant difference for the IBS patients.

Figure 3: Stool weight



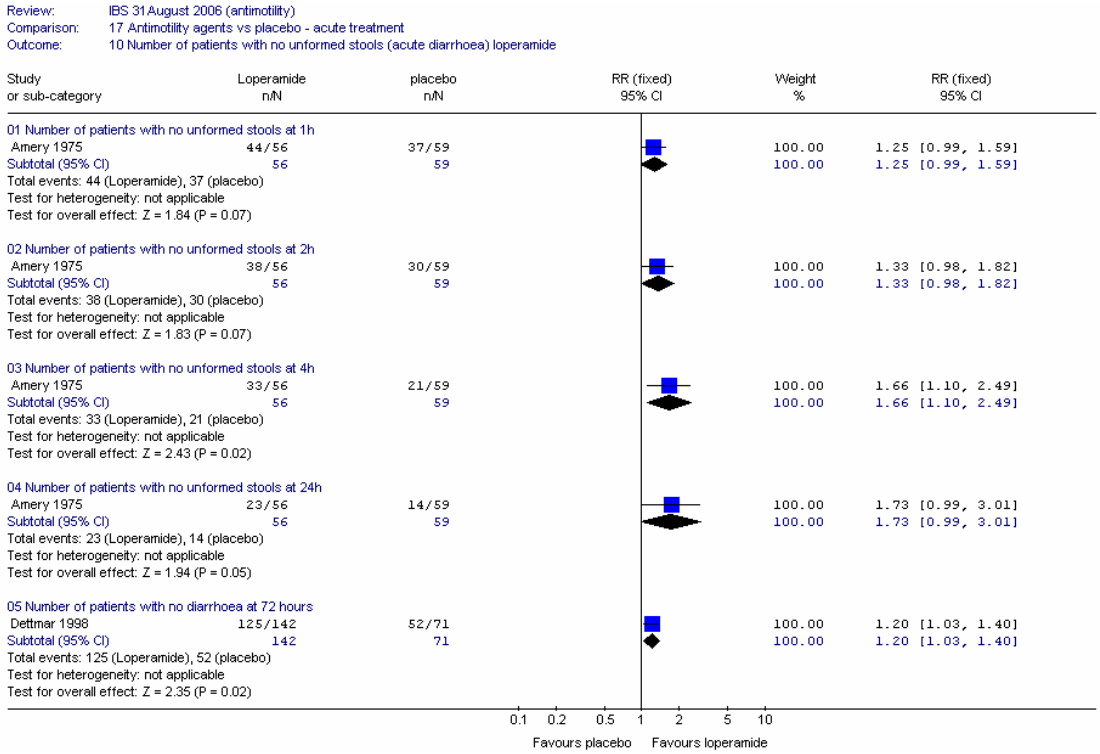
A2. Loperamide versus placebo

i. Number of patients with improvement in bowel habit

Amery (1975) reported the number of patients without recurrence (unformed stools) after 1, 2, 4 and 24 hours. Dettmer (1994) also recorded the number of patients without diarrhoea at 3 days for the two loperamide doses combined.

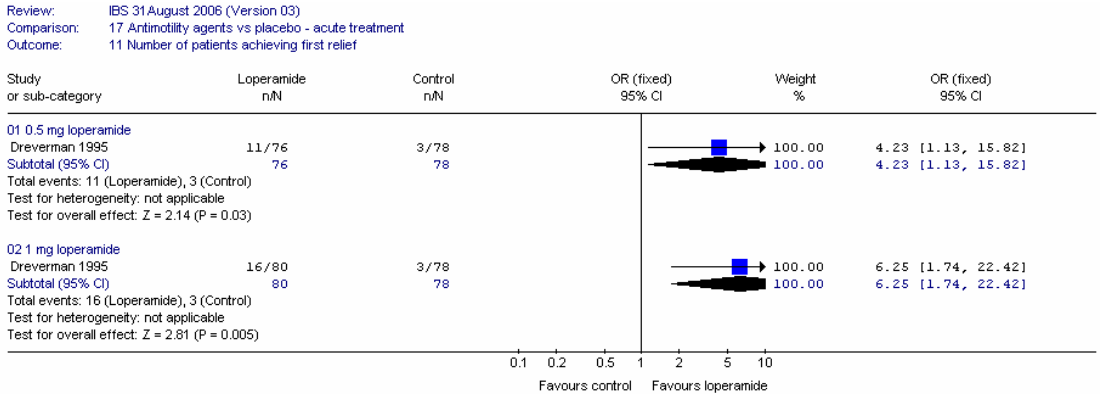
At 1 and 2 hours Amery (1975) showed no significant difference between loperamide and placebo. After 4 hours there were significantly fewer patients with unformed stools in the loperamide group compared to placebo, with a number needed to treat of 5 (95%CI 3, 17), for a control group risk of 36%. After 24 hours, loperamide showed fewer patients with unformed stools, with borderline significance, but the confidence interval was fairly wide. At 72 hours, Dettmar (1994) showed a small statistically significant difference between loperamide and placebo, with an NNT of 7 (95%CI 4, 34), for a control group risk of 73%.

Figure 4: Acute diarrhoea – loperamide



Dreverman (1995) reported the number of patients achieving first relief (the start of a 24 hour period during which no more than 1 pasty stool and no watery or loose stools were passed). There were statistically significantly more patients achieving relief for each dose of loperamide compared with placebo, but the confidence intervals are wide.

Figure 5



ii. Time taken to first relief of symptoms

Two studies reported the median time to first relief of symptoms, but different doses were used.

- 0.5 mg versus placebo

  Dreverman (1995) in 156 patients: 20 hours 15 minutes for loperamide 0.5mg versus 24

hours 50 minutes for placebo (p=0.012), i.e. statistically significantly in favour of loperamide

- 1 mg versus placebo (2 studies)
  - Dettmer (1994): 22.4 hours for loperamide 1mg versus 30 hours for placebo
  - Dreverman (1995) in 158 patients: 15 hours 30 minutes for loperamide 1mg versus 24 hours 50 minutes for placebo (p=0.003), i.e. highly statistically significant, in favour of loperamide
- 2 mg versus placebo
  - Dettmer (1994): 22.1 hours for loperamide 1mg versus 30 hours for placebo.

In Dreverman (1995), the median time to complete relief of symptoms was 26 hours 30 minutes for loperamide 1mg; 25 hours 40 minutes for loperamide 0.5mg; and 34 hours 15 minutes for placebo (p=0.041 for 0.5 mg and 0.044 for 1mg).

iii. Time to first recurrence

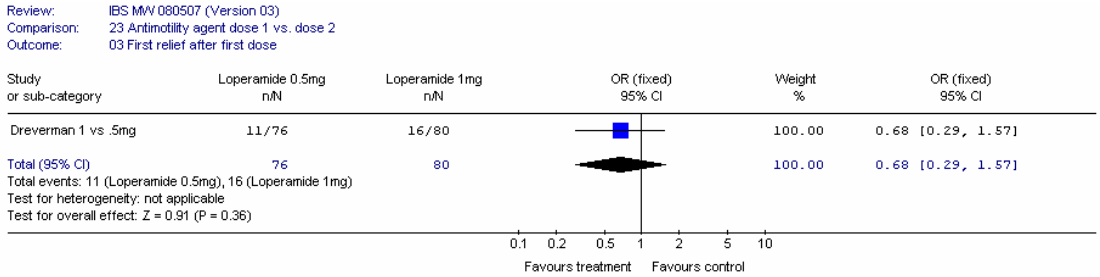
Amery (1975) also reported the median time to first recurrence of unformed stools. For the loperamide and placebo groups, this was 24, and 2 hours respectively. The p value for the difference between loperamide and placebo was p=0.016, i.e. statistically significant.

B. Anti-motility agent dose 1 versus dose 2

i. Number of patients with improvement in bowel habit

Dreverman (1995) reported the number of patients achieving first relief. There was no significant difference between the doses and the confidence interval was fairly wide.

Figure 6



ii. Median time to first relief of symptoms

- 0.5 mg versus 1 mg
  Dreverman (1995): 20 hours 15 minutes for loperamide 0.5mg versus 15 hours 30 minutes for loperamide 1mg
- Dettmer (1994): 22.4 hours for loperamide 1mg versus 22.1 hours for loperamide

In Dettmar (1994), the median time to complete relief of symptoms was 27.55 hours for loperamide 1mg and 25.00 hours for loperamide 2mg, with no significant difference between dose groups.

C. Anti-motility agent type 1 versus type 2

C1. Co-phenotrope versus loperamide

Four studies compared co-phenotrope and loperamide for acute episodes (indirect population) (Amery 1975; Cornett 1977; Dom 1974; Jaffe 1977). Although different doses were compared across studies, the proportions of drugs were the same.

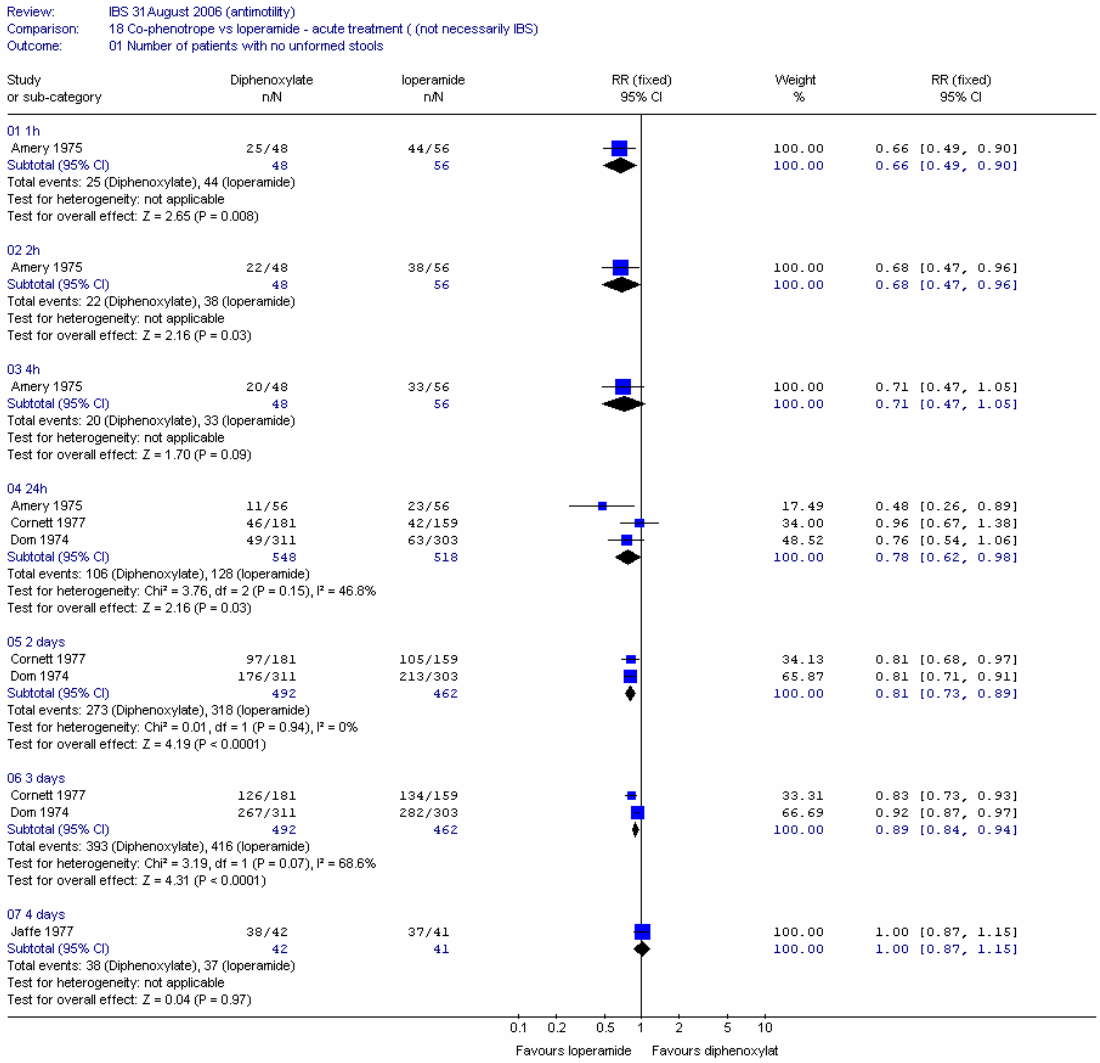
- Amery (1975): 5 mg diphenoxylate per day (1 tablet twice a day) versus loperamide 4 mg (2 mg twice a day) for 24 hours.
- Cornett (1977): initially 5mg (2 capsules) co-phenotrope then up to 20 mg per day versus 4 mg (2 capsules) loperamide initially, then up to 16 mg per day
- Dom (1974): initially 5 mg (2 capsules) co-phenotrope then up to 25 mg per day versus 4 mg loperamide intitially (2 capsules) then up to 20 mg per day
- Jaffe (1977): initially 10 mg (4 capsules) co-phenotrope then 20 mg per day (2 capsules x 4) versus 4 mg (2 capsules) loperamide initially, then up to 16 mg per day.

We noted that Amery (1975) and Cornett (1977) were funded by Janssen Pharmaceutica, manufacturers of Imodium (i.e. loperamide).

i. Number of patients with improvement in bowel habit

Three studies reported the number of patients with no unformed stools at different durations: Amery (1975) reported the number of patients without recurrence (no unformed stools) after 1, 2, 4 and 24 hours; Dom (1974) recorded the same outcome after 24 hours and 2 and 3 days; Cornett (1977) recorded the number of patients with unformed stools, from which we calculated the number with no unformed stools after 24 hours and 2 and 3 days. Jaffe (1977) reported the number of patients not reaching a 'cure' after 4 days (figure 10). At 1 and 2 hours there were statistically significantly more patients who were diarrhoea free for the loperamide group compared to the diphenoxylate. NNTs are 4 (95%CI 3, 12) and 5 (9%CI 3, 34). There was no significant difference at 4 hours. At 24 hours, meta-analysis of three studies showed statistically significantly more patients had no unformed stools for the loperamide group; RR 0.78 (95%CI 0.62, 0.98); with some heterogeneity (I^2=47%, p=0.15). The NNT was 20 (95%CI 10, 100) for a control group rate of 21 to 41%. At 2 and 3 days there was still a statistically significant effect favouring loperamide, but there was significant heterogeneity for the 3 day meta-analysis. We note, however, that some of these trials were industry sponsored.

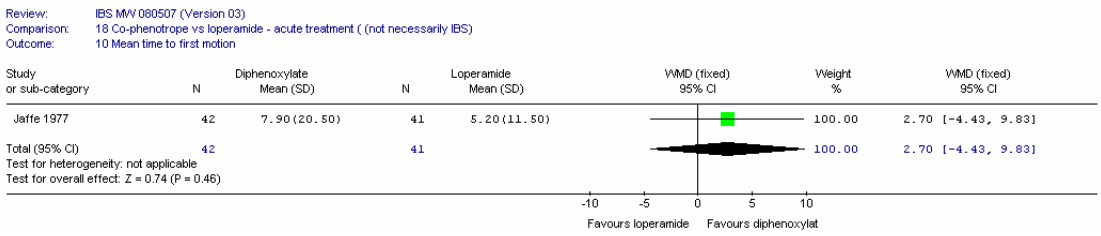
Figure 7: Number of patients with no unformed stools

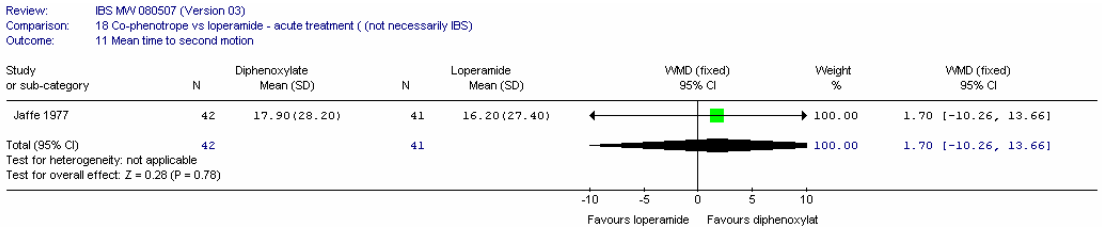


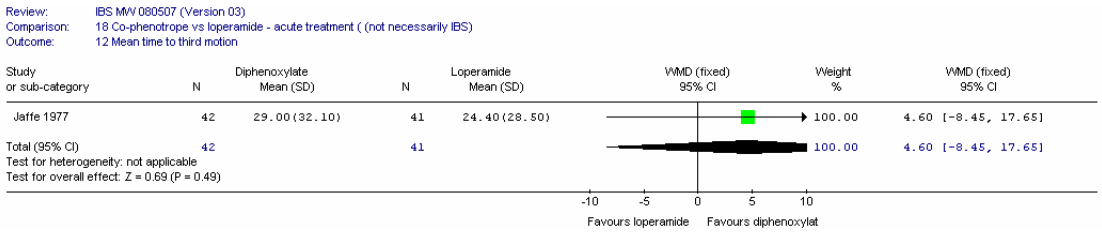
ii. Time taken to first stools

Jaffe (1977) reported the mean time to the 1st, 2nd, and 3rd motion. In all cases the confidence intervals were wide.

Figure 8





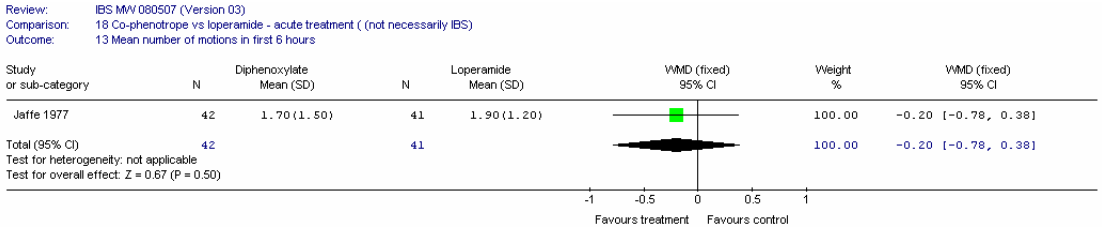


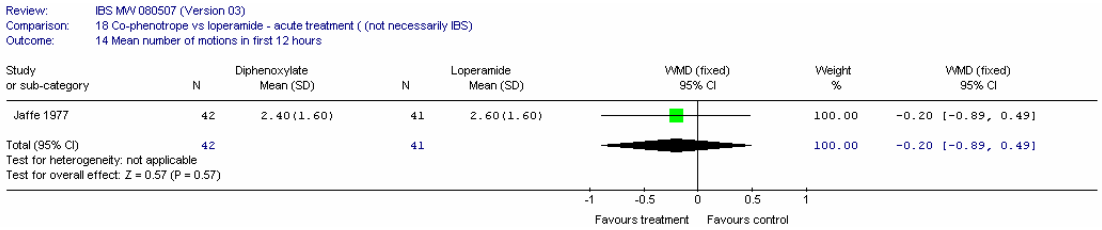
Amery (1975) reported the median time to first recurrence of unformed stools. For the loperamide and diphenoxylate groups, this was 24 and 2 hours respectively. This was a statistically significant difference (p=0.024), favouring loperamide. We note, however, that this was an industry funded study.

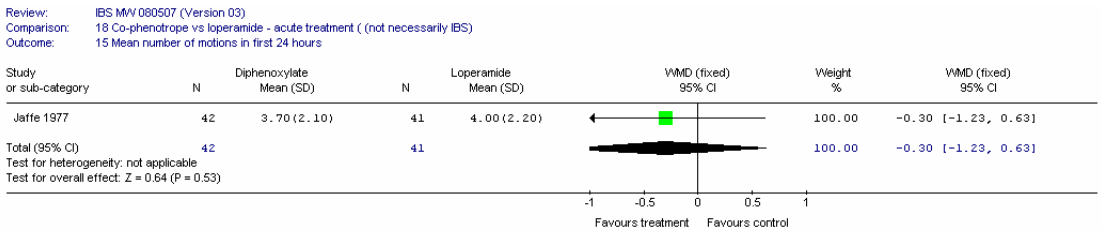
iii. Stool frequency

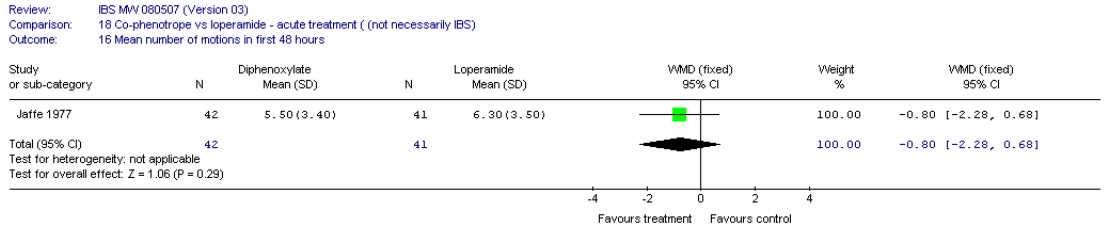
Jaffe (1977) reported the stool frequency in the first 6 hours; first 12 hours; first 24 hours; and first 48 hours following the first dose of the medication. In all cases the confidence intervals were wide, so conclusions were not drawn.

Figure 9









Cornett (1977) also reported the frequency of unformed stools over 72 hours. From a mean of 9.14 unformed stools before treatment, patients on diphenoxylate reduced to 5.47 (a fall of 3.67) while those on loperamide fell from 8.75 to 4.38 (a fall of 4.37). No standard deviations were given.

Dom (1974) reported the change in the mean number of unformed stools in a 72 hour period (from 8.06 before treatment with diphenoxylate and 8.02 in the loperamide group to 3.68 and 2.65 respectively, i.e. a fall of 4.38 and 5.37 respectively, this was statistically significantly in favour of loperamide (p=0.011).

iv. Time to cure

Jaffe (1977) reported the mean time to cure. There was a wide confidence interval so conclusions were not drawn.

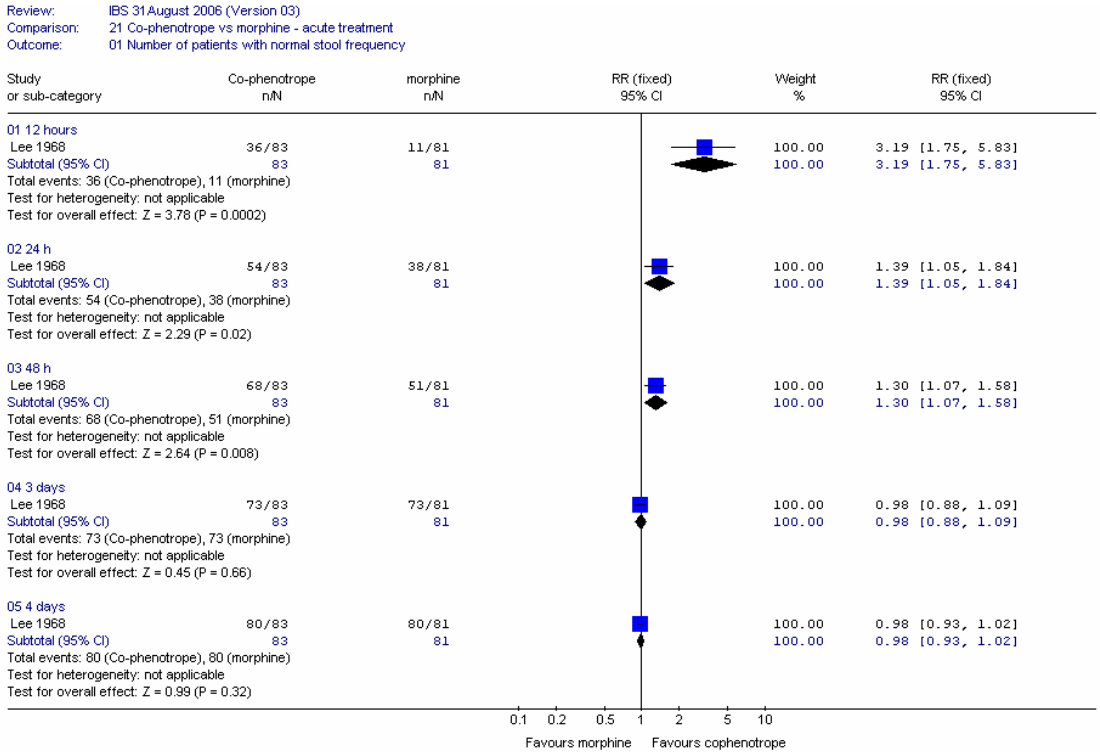
Figure 10

C2. Co-phenotrope versus morphine

i. Number of patients with normal stool frequency

One study (Lee 1968) compared cophenotrope-with-neomycin to kaolin-and-morphine. This study reported the number of patients with abnormal stool frequency after 12 hours, 24 hours, 2 days, 3 days and 4 days. We have reported the number of patients with normal stool frequency. There was a statistically significant difference favouring co-phenotrope at durations up to 48 hours. At 12 hours the NNT was 4 (95%CI 3, 6), for a control group risk of 14%.

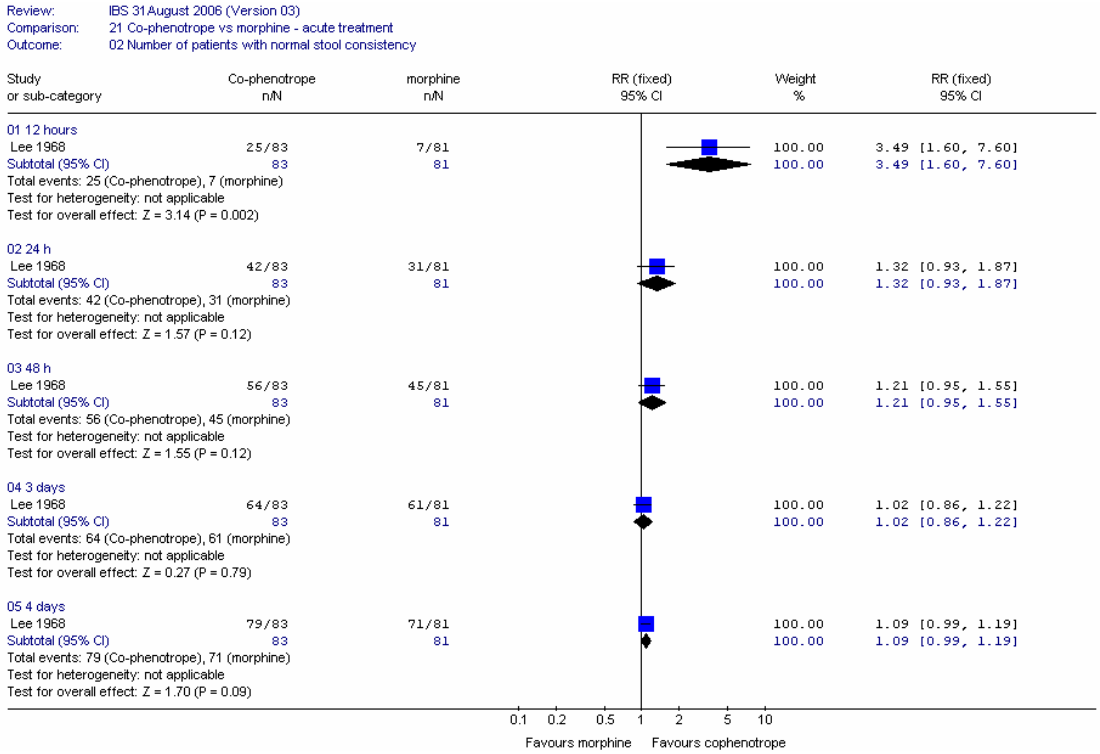
Figure 11



ii. Number of patients with normal stool consistency

One study (Lee 1968) compared cophenotrope-with-neomycin to kaolin-and-morphine. This study reported the number of patients with abnormal stool consistency after 12 hours, 24 hours, 2 days, 3 days and 4 days. We have reported this as the number of patients with normal stool consistency. There was a statistically significant effect, favouring co-phenotrope at 12 hours (RR 3.49 (95%CI 1.60, 7.60); NNT 5 (95%CI 4, 10), for a control group risk of 9%. Otherwise there was no significant difference between interventions.

Figure 12



II. MAINTENANCE TREATMENT FOR CHRONIC DIARRHOEA

A. Antimotility agent versus placebo

Three studies gave loperamide for maintenance treatment (Efskind 1995; Hovdenak 1987; Lavö 1987). All were in patients with IBS, although Hovdenak (1987) stated that the patients had different types of IBS, including IBS-C. Subgroup analyses were presented, but these did not constitute stratification before randomisation. This study also had a duration of 3 weeks, but the GDG agreed that this was acceptable. We noted that Efskind (1995) was industry supported (by Janssen Pharmaceutica, the manufacturers of loperamide).

The dose in Hovdenak (1987) was fixed at 4 mg at night, whilst the patients were able to adjust the dose in the other two studies. Both started the patients on 2 mg at night, which was increased to 6 mg (Efskind 1995) or 8 mg (Lavö 1987) as required.

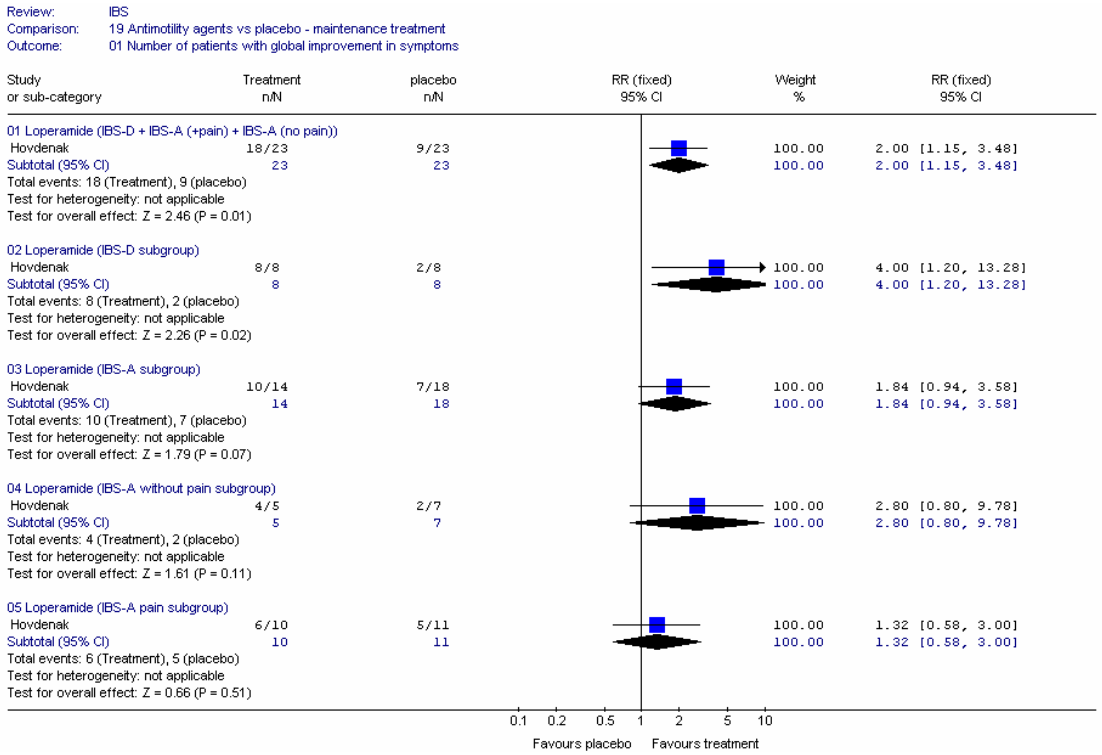
1. Global symptoms

a) Number of patients with improvement in global symptoms

One study (Hovdenak 1987) reported the number of patients with improvement in global symptoms after 3 weeks. The study reported results for three of the different IBS subgroups (IBS-C results were not reported). The exclusion of the IBS-C results breaks the randomisation, so these are post-hoc subgroups, but still gives some information. We have grouped together the results for IBS-D, IBS-A (with pain), IBS-A (without pain), and the separate subgroups. There was a statistically significant improvement in symptom score for

the 3-type IBS group and for the IBD-D group alone, although the confidence interval for the latter was wide. The relative risks were 2.00 (95%CI 1.15, 3.48) and 4.00 (1.20, 13.28) respectively. These corresponded to a number needed to treat of 3 (95%CI 2, 8) and 2 (95%CI 1, 3), for control group rates of 39% and 25% respectively.

Figure 13



b) Global symptom improvement score

One study (Lavö 1987) reported a subjective overall response for the whole 13 week study period, which was said to statistically significantly favour loperamide ($p<0.03$).

2. Individual symptoms

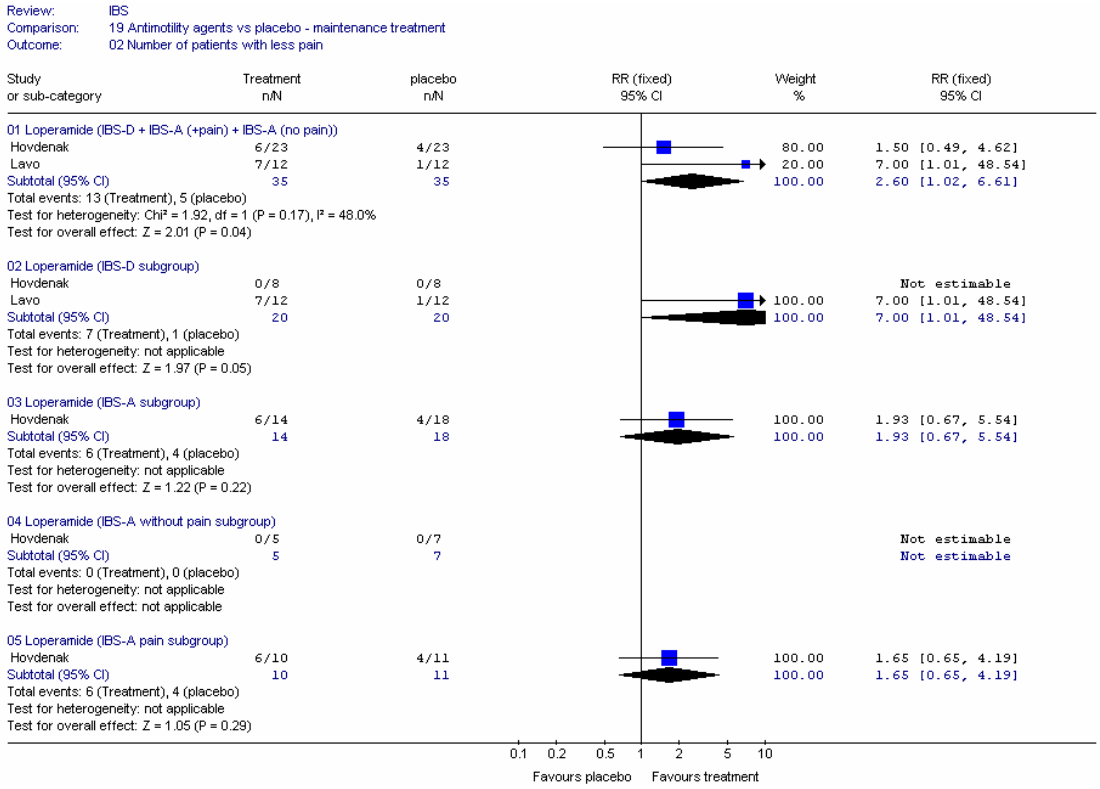
a) Pain

i. Number of patients with less pain

Two studies reported the number of patients with less pain, one (Hovdenak 1987) after 3 weeks in a range of different IBS subgroups; and the other (Lavö 1987) after 13 weeks in patients with IBS-D only. For the former study we grouped together the results for IBS-D, IBS-A (with pain), IBS-A (without pain) and also reported these separately.

The confidence intervals were wide for each study. Meta-analysis of the 3-type IBS group with the Lavö study, in 70 patients gave a statistically significant difference between interventions, favouring loperamide; RR 2.60 (95%CI 1.02, 6.61) but there was some heterogeneity (I^2=48%, p=0.17). The NNT was 5 (95%CI 3, 25), for a control group rate of 8 to 17%.

Figure 14: Number of patients with less pain

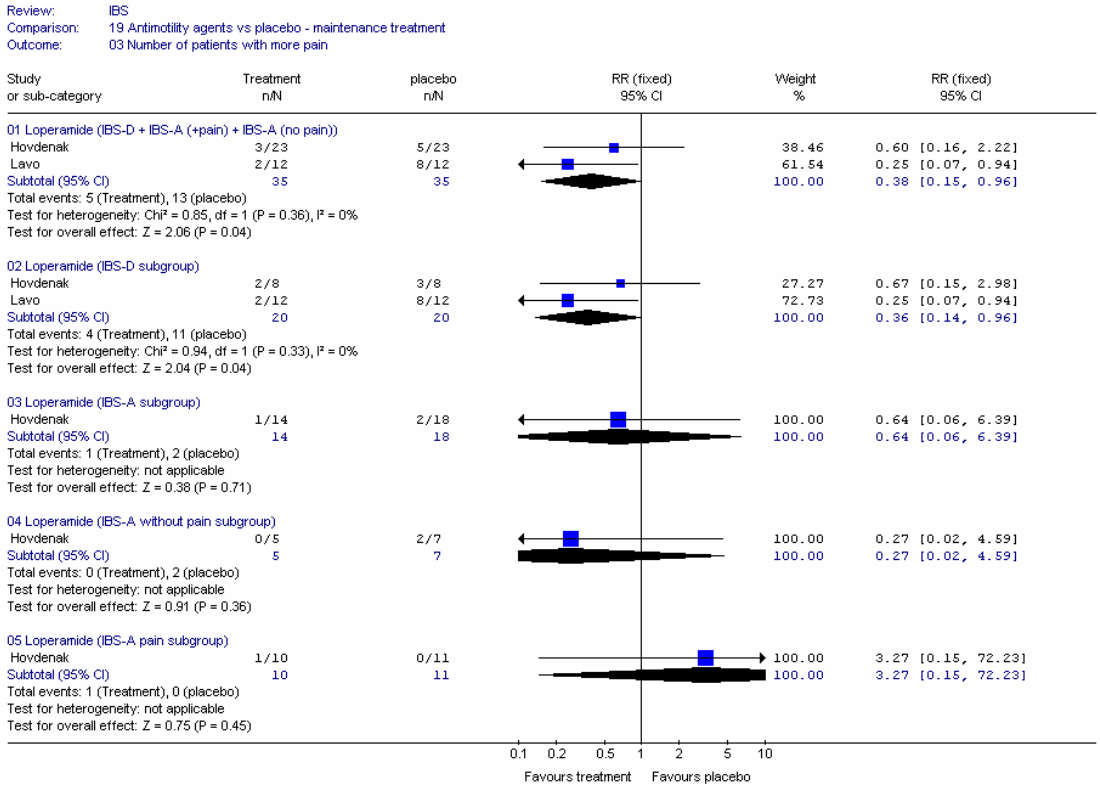


ii. Number of patients with increased pain

Two studies reported the number of patients with more pain, one (Hovdenak 1987) after 3 weeks in a range of different IBS subgroups; and the other (Lavö 1987) after 13 weeks in patients with IBS-D only. For the former study we grouped together the results for IBS-D, IBS-A (with pain), IBS-A (without pain) and also reported these separately.

The confidence intervals were wide for each study. Meta-analysis of the 3-type IBS group with the Lavö (1987) study, in 70 patients, gave a statistically significant difference between interventions, favouring loperamide; RR 0.38 (95%CI 0.15, 0.96) and there was no heterogeneity (I^2=0%), although the confidence interval was wide. The NNT was 5 (95%CI 3, 25), for a control group risk of 22 to 67%. For the meta-analysis of 40 patients with IBS-D, the difference was still statistically significant with no heterogeneity; RR 0.36 (95%CI 0.14, 0.96), i.e. 3 times more risk of pain for the placebo group (Figure 14). The NNT was 3 (95%CI 2, 13) for a control group risk of 38 to 67%, but the confidence interval was wide.

Figure 15: Number of patients with more pain



iii. Number of days with pain

One study (Hovdenak 1987) recorded the number of days with pain over 3 weeks. In the subgroup of IBS-A with pain, there was a statistically significant mean difference of 6.1 days between loperamide and placebo ($p<0.01$), favouring the former.

iv) Pain score

One study (Efskind 1996) in 69 patients reported no significant difference between interventions in the change from baseline in abdominal pain measured on a visual analogue scale. This was the case for both their 2 week dose adjustment period and for 5 weeks of fixed dose loperamide or placebo. However, the study found significantly more pain at night for the loperamide group ($p<0.05$ for both periods). In contrast, another study in 21 patients (Lavö 1987) found a statistically significant difference in pain score, favouring loperamide ($p<0.05$).

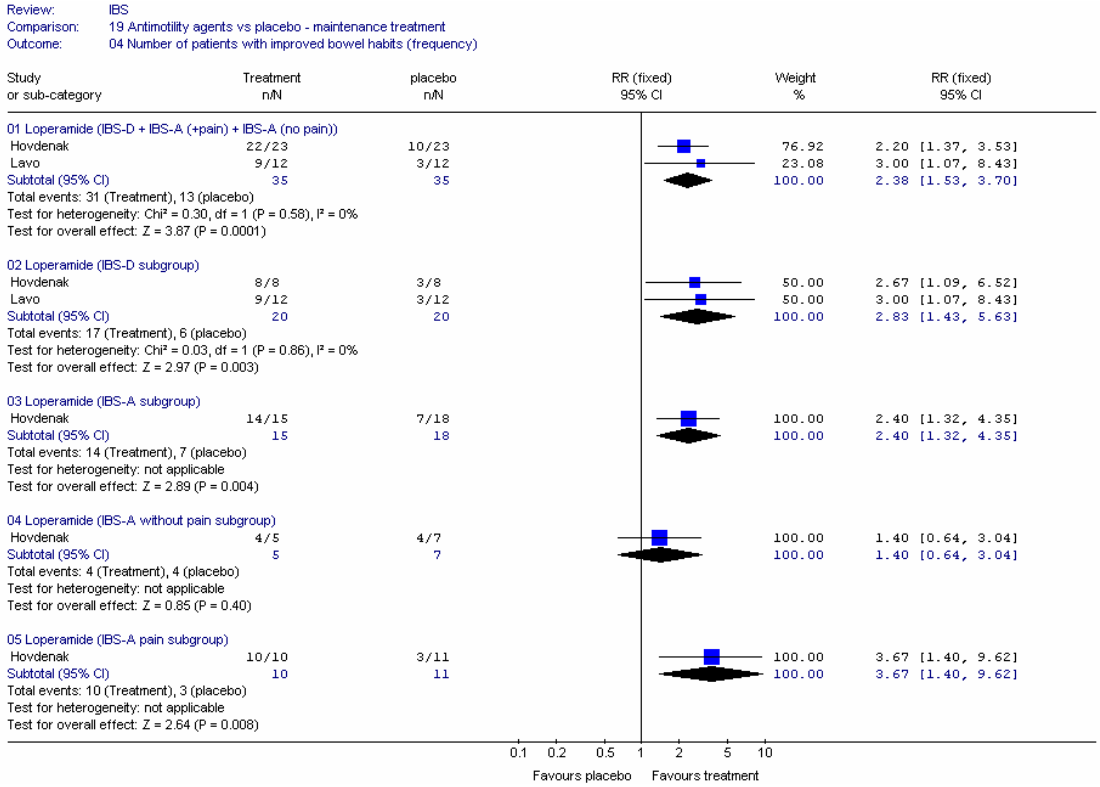
b) Bowel habit

i. Number of patients with improved bowel habit (frequency)

Two studies reported the number of patients with improved stool frequency, one (Hovdenak 1987) after 3 weeks in different IBS subgroups; and the other (Lavö 1987) after 13 weeks in patients with IBS-D only. For the former study we grouped together the results for IBS-D, IBS-A (with pain), IBS-A (without pain) and also reported these separately.

Meta-analysis of the 3-type IBS group with the Lavö study, in 70 patients gave a statistically significant difference between interventions, favouring loperamide; RR 2.38 (95%CI 1.53, 3.70) and there was no heterogeneity (I^2=0%). This corresponded to an NNT of 2 (95%CI 2, 4) for a control group risk of 25-43%. For the meta-analysis of 40 patients with IBS-D, the difference was still statistically significant with no heterogeneity; RR 2.83 (95%CI 1.43, 5.63). This corresponded to a number needed to treat of 2 (95%CI 2, 4) for a control group risk of 25-38% (figure 15). Statistically significant improvements were also achieved for the IBS-A group, which had an NNT of 2 (95%CI 2, 4), for a control group risk of 45%. Confidence intervals for these meta-analyses were fairly wide.

Figure 16: Improvement in stool frequency

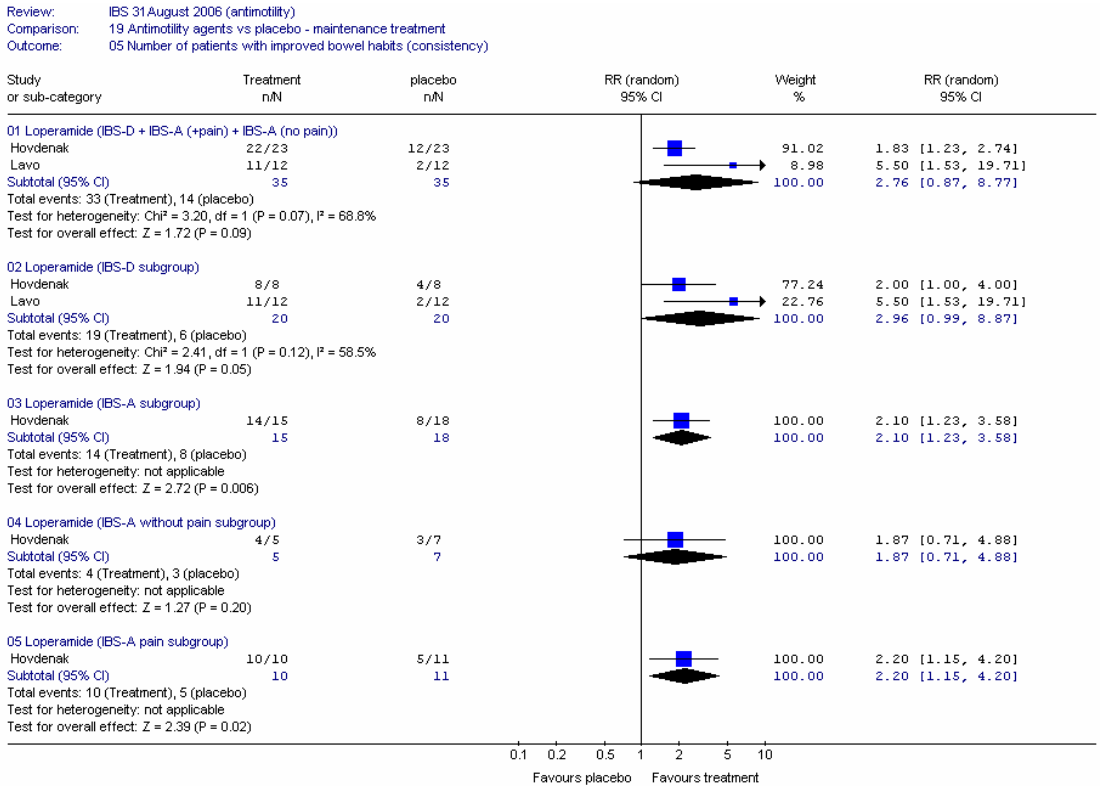


ii. Number of patients with improved bowel habit (consistency)

The same two studies reported the number of patients with improved stool consistency (Hovdenak 1987; Lavö 1987). Meta-analysis of the 3-type IBS group with the Lavö (1987) study, in 70 patients gave a statistically significant difference between interventions, favouring loperamide; but there was significant heterogeneity (I^2=69%; p=0.07). This heterogeneity may possibly be explained by differences in the study duration or the intervention dose, both of which were higher for the Lavö (1987) study. For the meta-analysis of 40 patients with IBS-D, the difference was still statistically significant with some heterogeneity (I^2=59%; p=0.12). Random effects analysis showed wide confidence intervals and neither analysis was statistically significant. Statistically significant improvements were also achieved for the

combined IBS-A group; RR: 2.10 (95%CI 1.23, 3.58), which corresponded to an NNT of 3 (95%CI 2, 5) for a control group risk of 44%.

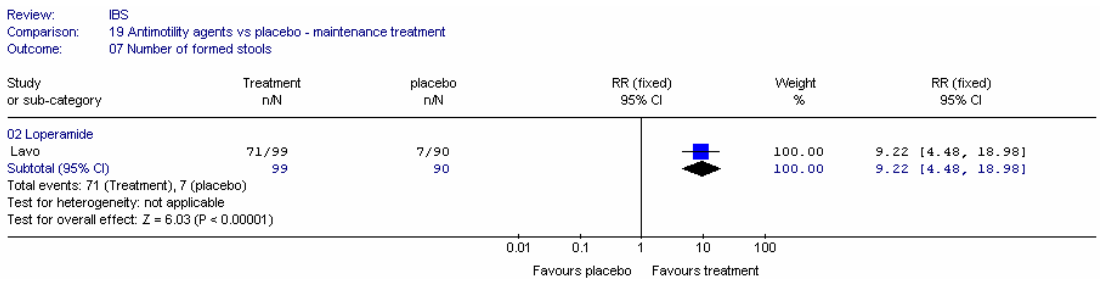
Figure 17: Improvement in stool consistency



iii. Stool scores

Two studies (Efskind 1996 (n=69) and Lavö 1987 (n=21)) reported a stool score measure for both consistency and frequency. Each found a statistically significant improvement in stool consistency ($p<0.002$ and $p<0.001$) respectively, favouring loperamide. Efskind (1996) also found a statistically significant difference over 7 weeks for frequency ($p<0.05$) but Lavö (1987) found no significant difference. Lavö (1987) found a highly significant difference in the number of formed stools, favouring the loperamide group.

Figure 18: Number of formed stools

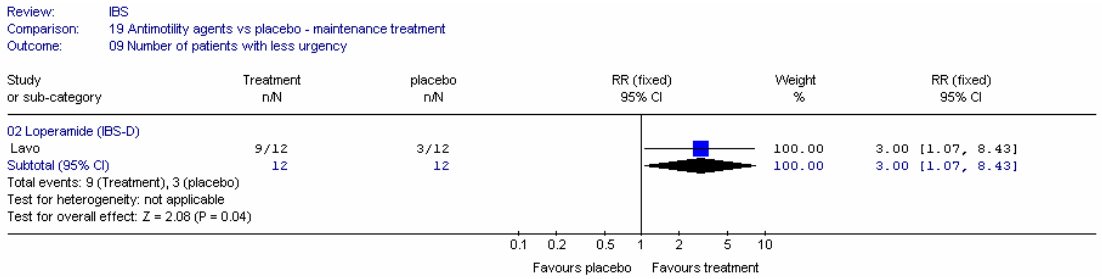


iv. Number of patients with improvement in urgency

One study (Lavö 1987) in 21 patients reported the number of patients with less urgency and found this to be significantly greater for the loperamide group, although the confidence interval

was wide; RR 3.00 (95%CI 1.07, 8.43). This corresponds to an NNT of 2 (95%CI 2, 7), for a control group rate of 25%.

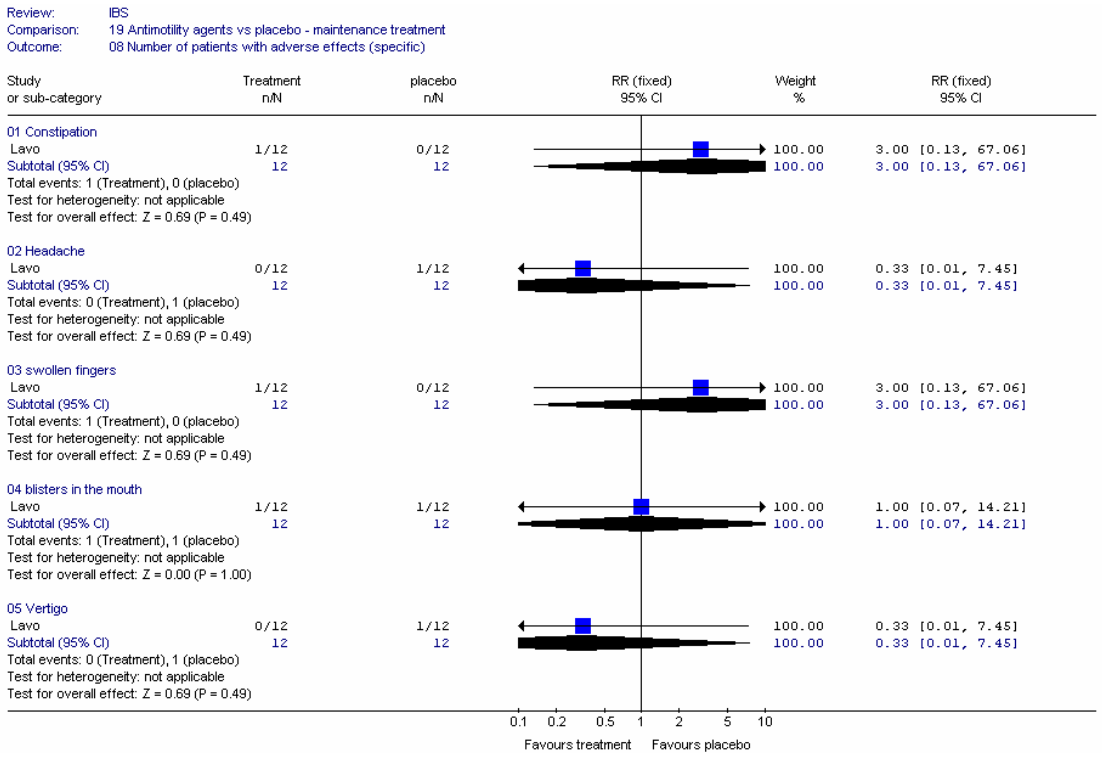
Figure 19: Number of patients with less urgency



3. Adverse effects

Only one small study in 24 patients reported the number of patients with adverse effects (Lavö 1987). In all cases there are very wide confidence intervals and conclusions cannot be drawn.

Figure 20: Adverse effects



B. Anti-motility agent type 1 versus Anti-motility agent type 2

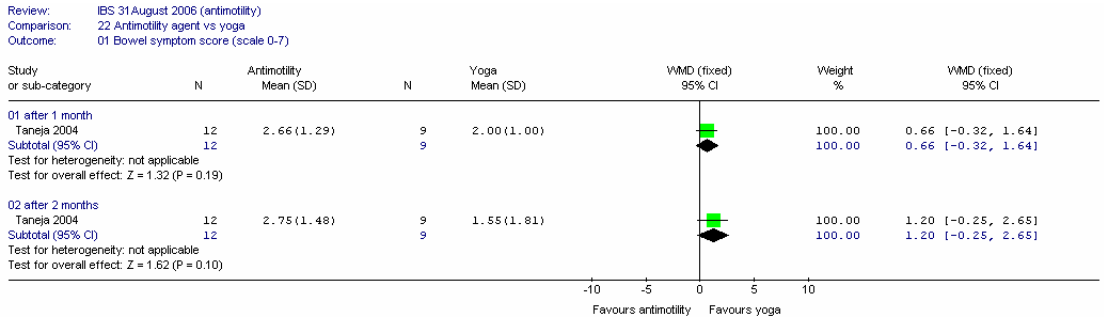
One study compared different types of anti-motility agent: Pelemans and Vantrappen (1976) compared co-phenotrope and loperamide for 14 to 49 days in a crossover trial in 23 patients. Only 4 of the patients had IBS, 18 of the rest had inflammatory bowel disease and the GDG considered this population to be too indirect to be useful, even though this was the only maintenance study considering co-phenotrope.

C. Antimotility agent versus yoga

1. Bowel symptom score

Taneja (2004) reported bowel symptom scores 1 and 2 months after starting either loperamide or yoga. Patients were asked the following questions: Is the frequency of stools >3 times per day? Is the frequency of stools <3 times per week? Are the stools lumpy or hard? Is there straining? Are the stools loose or watery? Is there urgency to pass the stools? Are the stools mucoid? For each symptom, if present >25% of the time, a positive answer scored 1 and a negative answer 0, so the range is 0-7. Both groups reduced their scores from baseline (loperamide 4.08 (SD 0.9); yoga 3.77 (SD 1.2)), but there was no significant difference between the groups.

Figure 21: Bowel symptom score



Adverse Effects

Two RCTs with adverse effects data were identified (Lavo 1987; Cann 1984). One was a crossover trial which should be treated with caution (Cann 1984). No clear trend could be identified from these two studies but abdominal cramps, dizziness, drowsiness, and skin reactions including urticaria; paralytic ileus and abdominal bloating have been reported (BNF 2007).

ECONOMIC LITERATURE FOR ANTIMOTILITY AGENTS

No relevant health economic analyses were identified on the cost-effectiveness of antimotility agents in the treatment of IBS.

COST-EFFECTIVENESS ANALYSIS FOR ANTIMOTILITY AGENTS

This section describes the health economic analysis undertaken to inform recommendations on the use of antimotility agents as a long-term maintenance therapy in IBS. The general methods used in the economic analysis for all management interventions are described in detail in Chapter 5 and the model inputs and assumptions relevant to this particular intervention are described below.

- Loperamide was the only intervention considered by the economic model as it was the only intervention which had evidence of clinical effectiveness for longer-term maintenance use.

- Separate efficacy estimates were available for subgroups of patients with IBS-D and patients with IBS-A with pain or IBS-A without pain. Loperamide was statistically significantly better than placebo in achieving an improvement in global symptoms for all three subgroups combined but was also statistically significantly better for the IBS-D subgroup but not for the IBS-A subgroups when considered separately. However, the confidence intervals for the subgroups were wide due to the small number of patients in each subgroup. The combined effectiveness estimate for IBS-D and IBS-A (with and without pain) was used in the basecase.

Modelled response rates

In the basecase scenario the response rate of 45% in the no treatment arm is taken from the Mearin (2004) cohort study. This represents the group of patients for whom we would expect an improvement in symptoms without any specific intervention. The RR of response for antimotility vs placebo is 2.00; therefore the response rate in the intervention arm is 90% (=45% x 2.00) giving an absolute difference in response between the intervention and no treatment arms of 45% (=90%-45%) during the 1st month.

We have also considered an alternative scenario in which no patient in the comparator arm achieves an improvement in symptoms but there is still a 45% chance of response for the intervention arm.

Table 1: Intervention specific parameters – anti-motility agents

Description	**Value**		**Evidence**
RR of response for intervention vs placebo	2.00		Meta-analysis of RCT evidence for improvement in global symptoms
Maximum number of switches considered	0		Limited by number of effective interventions
Drug costs			
Intervention	**Dose per day**	**Cost per month* (assuming lowest cost preparation)**	
Loperamide	4mg	£2.29	

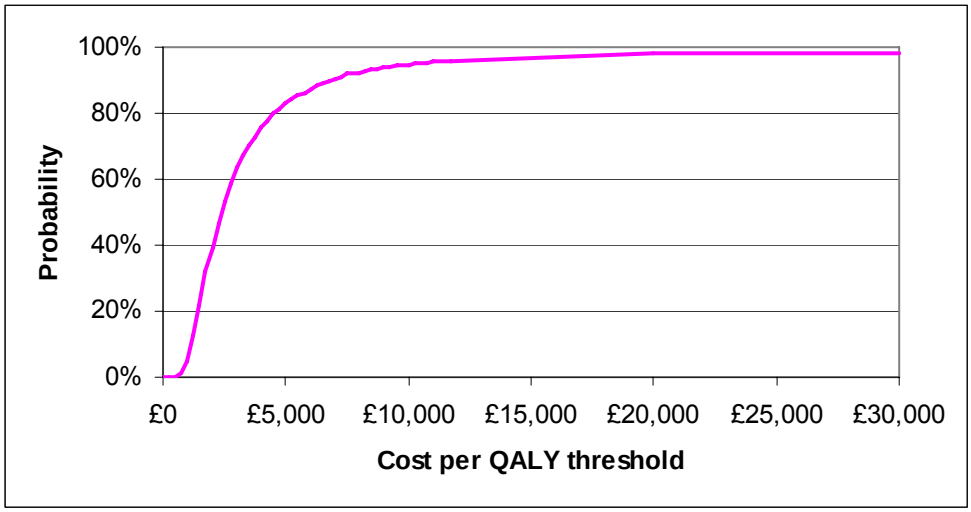
* British National Formulary (Joint Formulary Committee 2007)

In the basecase analysis, treatment with loperamide for 100 patients with IBS-D or IBS-A results in an additional 1.60 QALYs but costs an additional £3,055 over a 6 month time frame, compared to no treatment, giving a cost per QALY of £1,914. The basecase analysis assumes that the intervention is used on a daily basis, meaning this estimate may be more relevant to patients with IBS-D. The cost-effectiveness of using loperamide on 25% to 75% of days is considered in the sensitivity analysis, and this estimate may be more relevant to patients with IBS-A whose primary symptom may vary from constipation to diarrhoea.

These results are an estimate of the cost-effectiveness over the first 6 months after initiating treatment with loperamide. The cost per QALY for continuing treatment with loperamide beyond 6 months is lower than the cost per QALY during the initial 6 months provided that treatment is reviewed every 6 months and discontinued in patients who no longer experience a therapeutic benefit, either due to lack of effectiveness or a change in their symptom profile.

The probabilistic sensitivity analysis considered the uncertainty in the basecase estimate of cost-effectiveness due to uncertainty in the parameters used to estimate the cost-effectiveness. The CEAC presented in Figure 22 shows the probability that the cost per QALY for loperamide compared to no treatment is under various cost per QALY thresholds. For example, it shows that there is an 83% probability that loperamide has a cost per QALY of under £5,000 compared to no treatment and a 98% probability that it has a cost per QALY under £20,000. However, it should be noted that these estimates only consider the uncertainty in cost-effectiveness due to the accuracy of several input parameters and they do not reflect general uncertainty around the assumptions made in the model. The uncertainty from these assumptions was explored in the univariate sensitivity analysis.

Figure 22. Cost-effectiveness acceptability curve for loperamide compared to no treatment



Univariate sensitivity analysis

Maintaining the 45% difference in response between the two arms but reducing the response rate in the no treatment arm from 45% to zero marginally decreased the cost per QALY to £1,593.

We carried out a threshold analysis to determine whether antimotility therapy is still cost-effective for lower gains in health related quality of life. In the basecase it is assumed that patients who respond to therapy accumulate 0.071 QALYs more per annum than patients who do not respond. For comparison, a gain of 0.135 QALYs would represent a complete remission

of IBS symptoms. If the QALY gain associated with a response to therapy was reduced to 0.006 QALYs, then the cost per QALY of providing antimotility therapy would be above £20,000 per QALY.

The basecase analysis assumes that the lowest cost preparation is prescribed. If, the highest cost preparation (Imodium syrup) is prescribed at the same dose, then the cost per QALY is increased to £3,173. If the dose is increased to the maximum dose of 16mg per day, which is double the highest dose used in the maintenance therapy trials, and the highest cost preparation is prescribed, then the monthly cost of loperamide rises to £23.85, but the cost per QALY is still well below £20,000 per QALY at £9,311.

If a patient takes a therapy on an as needed basis, it is assumed that they take the therapy on days when their quality of life is significantly affected by their IBS symptoms but not on days when their symptoms are less severe. They only accrue QALY benefits and drug costs on the days they take the therapy. However, it is still necessary to assess all patients for response after 1 month of initiating therapy. This means that it is less cost-effective to initiate therapy in patients who use the therapy on fewer days as the monitoring costs are just as high but the benefits are lower. This is shown by the cost per QALY of £5,297 for patients who take the therapy on 25% on days.

Table 2: Sensitivity results for loperamide compared to no treatment for 100 patients with IBS-D or IBS-A

Scenario	No Treatment		Intervention		Incremental
	Cost	QALY	Cost	QALY	Cost per QALY
Basecase	£0	1.60	£3,055	3.19	£1,914
No response in no treatment arm	£0	0	£2,542	1.60	£1,593
Response rate in no treatment arm from RCTs	£0	1.69	£3,117	3.38	£1,842
Treatment used 75% of days	£0	1.60	£2,741	2.79	£2,290
Treatment used 50% of days	£0	1.60	£2,428	2.39	£3,042
Treatment used on 25% of days	£0	1.60	£2,114	2.00	£5,297
Half of treatment obtained over the counter	£0	1.60	£2,428	3.19	£1,521
Higher cost formulations (same dose)	£0	1.60	£5,066	3.19	£3,173
High utility gain of 0.135	£0	3.02	£3,055	6.04	£1,011
Threshold analysis on lowest utility	A cost per QALY of £20,000 is reached when the QALY gain associated with responding to treatment lies between 0.006 and 0.007				

EVIDENCE STATEMENTS

For this review, the evidence was assessed using the GRADE process and tables are shown in Appendix F. The following evidence statements are derived from the GRADE tables.

1. In studies for short-term symptom relief of diarrhoea (including people with IBS) for loperamide versus placebo there is fair evidence showing a significant number of patients without unformed stools.

2. In studies for short-term symptom relief of diarrhoea (including people with IBS) for co-phenotrope (lomotil) compared with placebo there is:
   - Limited evidence showing significant improvement in stool frequency
   - Fair evidence showing no significant difference in the number of patients without unformed stools

3. In studies for short-term symptom relief of diarrhoea (including people with IBS) for loperamide versus co-phenotrope (lomotil) there is:
    - Fair evidence showing a significant improvement in the number of patients without unformed stools.
    - Good evidence to show a significant improvement in stool score.

4. In studies for short-term symptom relief of diarrhoea (including participants with IBS) for co-phenotrope (lomotil) compared with Kaolin and Morphine there is fair evidence showing a significant improvement in stool consistency for co-phenotrope.

5. In studies for longer-term maintenance treatment of diarrhoea (including participants with IBS) for loperamide versus placebo there is:
    - Limited amount of fair quality evidence showing a highly significant improvement in global symptoms
    - Limited evidence showing significant improvement in pain and bowel habit.

6. In studies for longer-term maintenance treatment of diarrhoea (including people with IBS) for loperamide versus yoga there is a limited amount of weak evidence showing no significant difference in bowel score.

7. There is no clear evidence on adverse effects for antimotility agents.

HEALTH ECONOMIC STATEMENT

Evidence from a decision analytic model showed that loperamide is cost-effective as a long-term maintenance therapy for individuals with diarrhoea provided that response is assessed after the first month and every 6 months thereafter and treatment is discontinued in individuals for which it provides no therapeutic benefit.

GDG DISCUSSION

The GDG noted that, despite the small number of trials, loperamide is widely used and accepted as clinically effective for the treatment of diarrhoea in people with IBS. The GDG noted that it was good practice to titrate the dose of loperamide, according to symptom response, with the aim of achieving a well formed stool (Bristol Stool Form Scale type 4). In certain situations the daily dose of loperamide required may exceed 16 mg, and the GDG noted that this is an out of licence dose.

EVIDENCE TO RECOMMENDATIONS

The GDG took into consideration the clinical and cost effective evidence and their experience of the widespread use of loperamide. They noted the lack of evidence about adverse effects, but

did not consider this to be a significant factor in practice. The GDG wished to encourage primary care clinicians to advise people with IBS of the need to titrate doses and the method of doing so.

RECOMMENDATION

Loperamide should be the first choice of antimotility agent for diarrhoea in people with IBS[2].

RECOMMENDATION

People with IBS should be advised how to adjust their doses of laxative or antimotility agent according to the clinical response. The dose should be titrated according to the stool consistency, with the aim of achieving a soft, well-formed stool (corresponding to Bristol Stool Form Scale type 4).

[2] In certain situations the daily dose of loperamide required may exceed 16 mg, which at the time of publication (February 2008) was an out of licence dose. Informed consent should be obtained and documented.

8.3 Antispasmodics

SELECTION CRITERIA

The selection criteria described in the general methodology section were used, but some were specific to the antispasmodics review and are reported below.

Types of studies

The GDG decided that the washout period for this review should be at least one week. Trials with shorter washout periods were not included in the analysis.

Types of intervention

Studies were to include the following interventions:

- Anti-muscarinic agents:
    - Atropine (synonyms: hyoscyamine)
    - Dicycloverine (synonyms: dicyclomine, diethylaminocarbethoxybicyclohexyl hydrochloride; trade name: Merbentyl®)
    - Hyoscine (synonyms: scopolamine; trade name: Buscopan®)
    - Propantheline (Trade name: Pro-Banthine®).
- Direct-action smooth muscle relaxants:
    - Alverine (Trade name: Spasmonal®)
    - Mebeverine: includes modified release and conventional drug delivery (Trade name: Colofac®)
    - Peppermint oil: includes modified release and enteric coated (Trade names: Colpermin®; Mintec®).

Studies with interventions not available in the UK were included in the review. These studies were listed, but not included in the sections on analysis or characteristics of studies.

The following comparisons were included

- Antispasmodic versus placebo (or nothing)
- Antispasmodic type 1 versus type 2
- Antispasmodic dose 1 versus dose 2
- Antispasmodic + another intervention versus the other intervention alone
- Antispasmodic modified release versus conventional delivery
- Duration of treatment 1 versus duration 2.

NB: In spite of the large placebo effect associated with IBS, comparisons with no treatment were included.

The antispasmodics review was concerned with both longer term maintenance treatment and short term symptom relief.

The GDG decided that there should be a minimum duration of treatment of four weeks for maintenance in this review. Studies of shorter durations were included but dealt with in sensitivity analyses.

Subgroup analyses

We planned to carry out subgroup analyses by type of antispasmodic (antimuscarinic and direct-acting smooth muscle relaxants); dose; mode of delivery (modified release/ conventional), and; duration of intervention.

Search strategy for identification of studies

The initial search identified a Cochrane Review (Quartero 2005, *Bulking agents, antispasmodic and antidepressant medication for the treatment of irritable bowel syndrome*). Searches were partly based on the terms in this review. Searches were performed on the following core databases: MEDLINE, EMBASE, CINAHL and *The Cochrane Library* (1966 to current day with guidance from the GDG). Additional databases were not searched for this review. The search strategies are listed in Appendix B.

The titles and abstracts identified by the search strategy were assessed. One-hundred and three were identified as being potentially relevant to the review and these papers were retrieved in full. Twenty-three studies met the inclusion criteria for the review. The reference lists for each of the retrieved studies were inspected for further potential papers, but none were identified. The 80 excluded studies are listed in Appendix E, along with the reasons for exclusion

DESCRIPTION OF STUDIES INCLUDED IN THE REVIEW

The Cochrane review recently published on this topic did not cover all the comparisons required for the guideline, as only comparisons with placebo were included. The interventions in the Cochrane Review also extended to drugs not licensed for use in the UK, and the subdivision by types of antispasmodic was different from that determined by the GDG. In addition, crossover trials were excluded from the Cochrane review unless first-period only results were given. We also did not agree with some of the other inclusions/exclusions. A simple update of the Cochrane review was therefore not appropriate to the needs of the guideline and the review was instead used mainly as a reference. Studies excluded from the Cochrane review as non-placebo comparisons or crossover trials were assessed for inclusion in the guideline review.

This review relates only to those studies using interventions licensed for use in the UK. The following 38 studies were therefore eliminated from the review:

- Cimetropium bromide (Centonze 1988; Dobrilla 1990; Passaretti 1989; Piai 1985; Piai 1987)
- Fenoverine (Galeone 1992)
- Octatropine methylbromide (Barbara 1979)

- Octilonium bromide (Baldi 1992; Capurso 1984; Capurso 1992a; D'Arienzo 1980; Defrance 1991; Ferrari 1986)
- Otilonium bromide (Baldi 1982; Baldi 1991; Battaglia 1998; Evangelista 1999; Glende 2002)
- Pinaverium bromide (Awad 1997; Corazza 1983; Delmont 1981; Dubarry 1977; Galeone 1986; Levy 1977; Lu 2000; Virat 1987)
- Prifinium bromide (Piai 1979; Sasaki 1985)
- Propinox (Pulpeiro 2000)
- Rociverine (Ghidini 1986)
- Secoverine (Ehsanullah 1985)
- Syntropium bromide (Galeone 1990)
- Trimebutine (Dumitrascu 2000; Ghidini 1986; Luttecke 1980; Moshal 1979; Schaffstein 1990; Schang 1993)
- Zamifenacin (Houghton 1997)

There were 23 included studies remaining. Nine were conducted in the UK (Dew 1984; Evans 1998; Flavell Matts 1967; Gilbody 2000; GP research group; Mitchell 2002; Nash 1986; Prout 1983; Ritchie 1979); eight in the rest of Europe, one in the USA, three in Australia and New Zealand, one in India, and one in Taiwan.

Generally, we excluded reports of studies if they were not in English, however, some studies translated and included in the Cochrane review were exceptions to this (Berthelot 1981; Czalbert 1990; Lech 1988; Schafer 1990). We had some reservations about doing this because of a difference of opinion with the Cochrane review on the eligibility of one of the English-language studies (Fielding 1980) due to the absence of reporting randomisation, but the study was included in the Cochrane review. However, we decided to include all the non-English language studies in the Cochrane review on the basis of trust. There was only one paper (Czalbert 1990) for which we were unable to verify that the patients were randomised to treatments, and we decided to include this and carry out a sensitivity analysis.

The majority of studies (17/23) had fewer than 100 patients, with six having 20 or fewer in the intervention arm (Carling 1989; Czalbert 1990; Evans 1998; Lech 1988; Ritchie 1979; Tasman-Jones 1973). Six studies had more than 100 patients in total and one had 712 patients (Schafer 1990). Some of the studies were of crossover design, so fewer patients are required to achieve adequate power.

Study Design

Setting: The majority of studies took place in secondary care; two studies were in primary care (Gilbody 2000; GP research group); five studies did not report the setting or it was not possible to determine it because the report was not in English (Berthelot 1981; Czalbert 1990; Evans 1998; Flavell Matts 1967; Schafer 1990).

There were ten crossover studies (Dew 1984; Evans 1998; Flavell Matts 1967; GP research group; Hennessy 1975; Lawson 1988; Nash 1986; Prout 1983; Tasman-Jones 1973; van Outryve 1995) in which participants were allocated to receive both the intervention and control treatments during the course of the study, in a random order. All of these studies had either no 'washout period' or it was not reported, in which case this was assumed to be none. As the GDG had specified a washout period of one week minimum, all these studies were eliminated from the analysis. One additional crossover study (Carling 1989) reported first period results for the global improvement of symptoms outcome, so these data were combined with those from parallel design studies.

The remaining 12 studies had a parallel design (Berthelot 1981; Czalbert 1990; Gilbody 2000; Inauen 1994; Kruis 1986; Lech 1988; Liu 1997; Mitchell 2002; Nigam 1984; Page 1981; Richie 1979; Schafer 1990).
Thirteen studies were therefore included in the analysis (12 parallel and one crossover trial, first period only).

Two studies had more than two arms: Schafer (1990) compared hyoscine plus paracetamol and hyoscine alone with placebo; Carling (1989) compared peppermint oil with hyoscamine and placebo; Ritchie (1979) compared hyoscine with placebo, and hyoscine+lorazepam with lorazepam alone. There were thus 17 comparisons in the antispasmodics review.

The rest of the description of studies will focus on these studies/comparisons.

Population
The definition of IBS varied between studies: one used the Rome I criteria (Mitchell 2002); one used the Rome II criteria (Gilbody 2000); three met criteria defined by the authors that were similar to the above (Inauen 1994; Nigam 1984; Page 1981). In seven comparisons, the authors stated that the patients had IBS, with no further explanation (Berthelot 1981; Czalbert 1990; Liu 1997; 2 x Ritchie 1979; 2 x Schafer 1990). The remaining five comparisons (3 x Carling 1989; Kruis 1986; Lech 1988) did not use a formal definition but described a range of symptoms consistent with IBS.

Most studies included a combination of IBS types, one study specified constipation (Page 1981); one study (Carling 1989) included only patients with IBS-C and IBS-A; and eight were unclear (Berthelot 1981; Czalbert 1990; Gilbody 2000; Lech 1988; Liu 1997; Nigam 1984; 2 x Ritchie 1979).

None of the studies stated that any participants had IBS as result of gastrointestinal infection.

The majority of studies did not state the number of participants with bloating. Four studies had some patients with bloating (Czalbert 1990; Inauen 1994; Kruis 1986; Liu 1997). Three comparisons (3 x Carling 1989) stated that all patients had bloating.

Most of the studies did not describe symptom severity. Two studies stated that participants had symptoms of mixed severity (Inauen 1994; Mitchell 2002).

The age range of participants across studies was 16 to 79 years, with the mean age (where given) ranging from 34.5 to 48 years (Czalbert 1990). None of the studies particularly identified elderly participants.

Most studies had more women than men; two studies had more men than women (Liu 1997; Nigam 1984).

Interventions

The studies varied in the type of antispasmodic used:

- Eight comparisons used anti-muscarinics:
    - One dicyclomine bromide (Page 1981)
    - Two hyoscamine (2 x Carling 1989)
    - Three hyoscine (Nigam 1984; Schafer 1990; Ritchie 1979)
    - One hyoscine plus paracetamol (Schafer 1990)
    - One hyoscine plus diazepam (Ritchie 1979).
- Nine had direct-action smooth muscle relaxants:
    - One alverine (Mitchell 2002)
    - Four mebeverine (Berthelot 1981; Kruis 1986; Gilbody 2000; Inauen 1994 (the last two were also modified release)
    - Four peppermint oil (Carling 1989; Czalbert 1990; Lech 1988; Liu 1997).

None of the included studies used antispasmodics for short-term symptom relief. The duration ranged from two weeks to 16 weeks (Kruis 1986). The most common durations were 12 weeks (four studies), four weeks (four studies) and two weeks (four studies). Studies of less than 4 weeks duration were considered in sensitivity analyses because the GDG preferred a minimum of four weeks duration. This meant the following: two weeks – four studies (3 x Carling 1989; Page 1981); three weeks – one study (Inauen 1994).

Comparisons

The included studies covered the following comparisons (we have indicated with an asterisk the studies with less than 4 weeks duration):

- 13 comparisons of antispasmodics versus placebo:

    - Five gave anti-muscarinics (Carling 1989*; Nigam 1984; Page 1981*; Richie 1979; Schafer 1990)
    - Seven gave direct-action smooth muscle relaxants (Berthelot 1981; Carling 1989*; Czalbert 1990; Kruis 1986; Lech 1988; Liu 1997; Mitchell 2002)
- One study (Ritchie 1979) compared antispasmodic plus diazepam versus diazepam alone
- One study (Schafer 1990) compared antispasmodic plus paracetamol versus paracetamol alone
- One study compared different classes of antispasmodic:
    - One compared an anti-muscarinic with a smooth muscle relaxant (Carling 1989*)
- Two studies compared different types of antispasmodic in the same class (smooth muscle relaxant):
    - Two studies (Gilbody 2000; Inauen 1994*) compared mebeverine modified release (200 g bid) with mebeverine conventional (135g tid).

Methodological Quality

The results of the quality assessment for included trials are shown in Appendix D.

The method of randomisation was reported in none of the studies. Allocation concealment was reported in one study (Ritchie 1979), which reported an adequate method, in which the drugs were issued in random order by the pharmacist. All but two of the studies reported that the patients were blinded to the interventions. One stated that the patients were not blinded (Inauen 1994). One study (Czalbert 1990) was unclear about patient blinding. Only one study (Mitchell 2002) described an *a-priori* power calculation. Several studies included in the review demonstrated baseline comparability of the groups, but 11 did not give baseline characteristics or were in non-English languages (Berthelot 1981; Lech 1988; Nigam 1984; Ritchie 1979; Schafer 1990). One study was not comparable at baseline (Liu 1997) for the severity of stool frequency (more severe for Colpermin). Three studies reported no withdrawals (Czalbert 1990; Nigam 1984; Ritchie 1979). One study (Page 1981) reported that more than 20% of patients in at least one arm (or overall) were not analysed or were lost to follow-up (attrition bias): 33% in the intervention group and 39% in the placebo group.

The GDG preferred a minimum intervention period of four weeks as this was felt to be clinically significant relative to potential effect. This meant the following were treated with caution: two weeks: Carling (1989); Inauen (1994); Page (1981).

The risk of bias was assessed for each included study and no studies were excluded from the analysis. Four studies were assessed as being at higher risk of bias: Page (1981) (attrition bias and duration less than four weeks); Inauen (1994) (patients not blinded and duration less than four weeks); Liu 1997 (lack of baseline comparability), and; Carling (1989) (duration less than 4

weeks). All these studies were treated with caution and sensitivity analyses were carried out. This was also done for Czalbert as discussed earlier.

RESULTS

A. Antispasmodics versus Placebo

There were 12 studies included in the analysis that compared antispasmodics with placebo, and a further two studies that compared antispasmodics + another intervention versus that other intervention alone. The GDG decided that it was inappropriate to combine the two types of comparison, even though each could be considered to be a comparison of antispasmodics versus placebo. The GDG's view was that the drugs could interact and their effects would not simply be additive.

One of the studies was in patients with constipation-predominant IBS (Page 1981); eight did not specify the type of IBS and the remainder had patients of mixed IBS-type. Therefore the studies were not stratified by IBS type. Similarly, there was too little information to separate by severity, post-infective cause or bloating status. Only one study (Mitchell 2002) reported using established criteria to diagnose IBS (Rome I).

Where outcomes were measured at different times during the study, we took the end-study results unless there were significant numbers of withdrawals or problems with compliance. Therefore, for the Kruis (1986) study we took the values at four weeks.

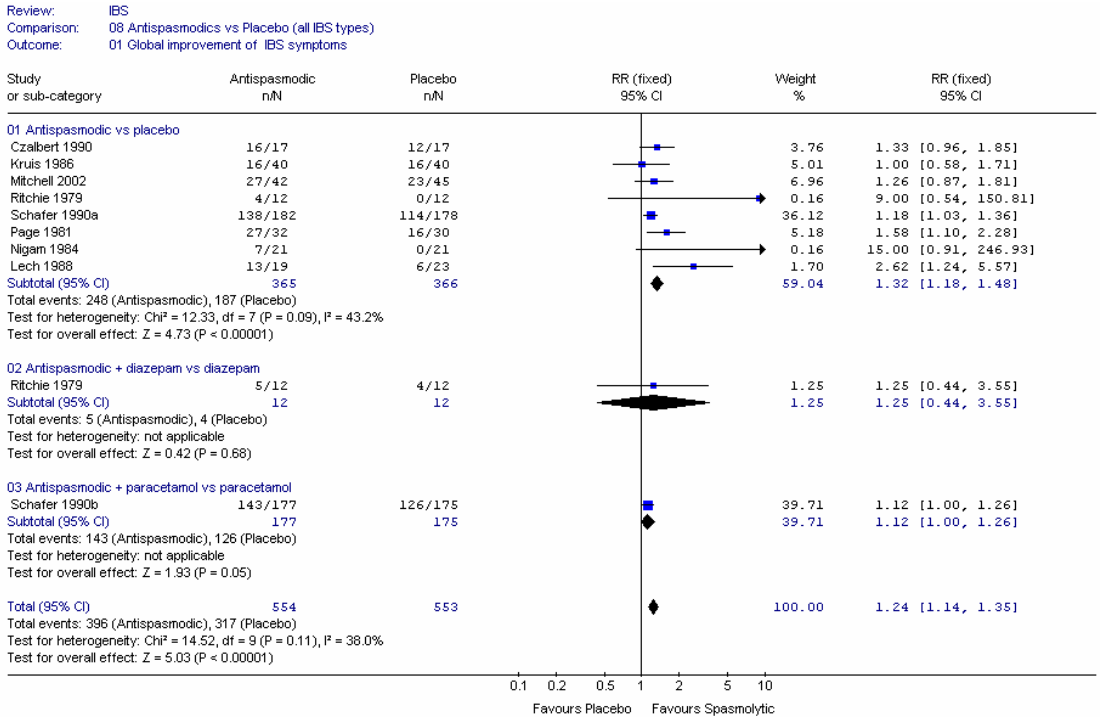
1. Global symptoms

a) Number of patients with improvement in global symptoms

Eight studies with 731 patients reported this outcome for the comparison antispasmodics versus placebo. As described in the general section, patient assessments of improvement were combined with symptom score related methods (unlike the Cochrane review). Overall the relative risk was 1.32 (95%CI 1.18, 1.48), i.e. statistically significant, favouring antispasmodics. There was some heterogeneity, but it was not significant (p=0.09; I^2=43%). The sensitivity analysis without Page (1981) made little difference to the summary statistics.

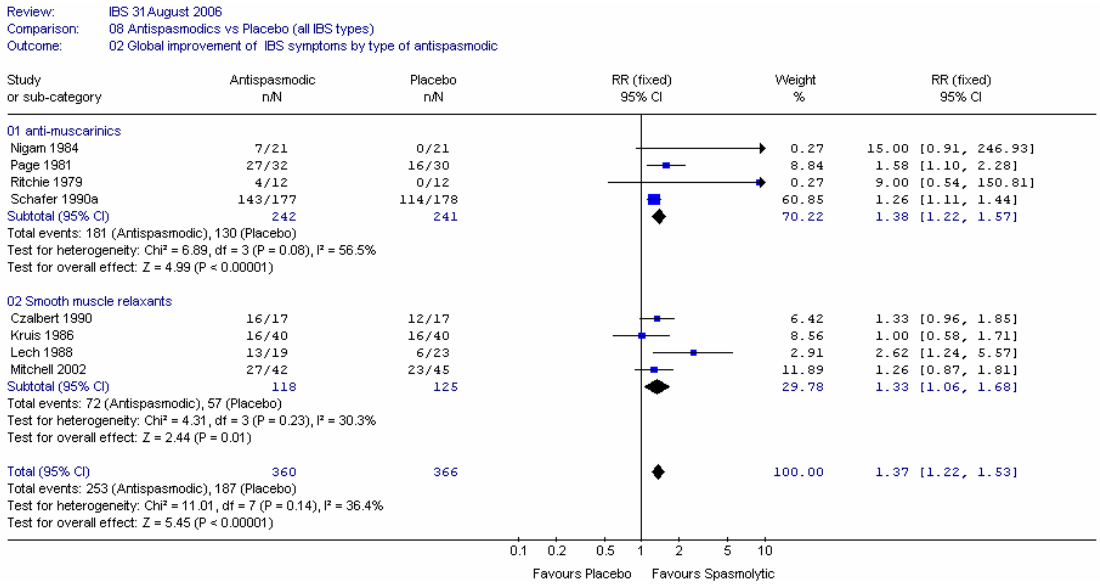
The full meta-analysis corresponded to a number needed to treat (NNT) of 6 (95%CI 5, 10), for a placebo group rate of 0 to 71%. This meant that clinicians needed to treat 6 patients to get additional benefit in relief of symptoms for one patient. Typically this is viewed as a low NNT.

Figure 1



Subgroup analysis into anti-muscarinic agents and direct-acting smooth muscle relaxants, for all antispasmodics-placebo comparisons (Figure 2) suggested there was little difference between classes of antispasmodics, although there was some heterogeneity (I2=57%, p=0.08) for the anti-muscarinics group. The RR for the random effects model was 1.51 (95%CI 1.00, 2.28), i.e. this result was sensitive to the method of analysis.

Figure 2



We noted that three of these studies were in hyoscine and the remaining one (Page 1981) was in dicyclomine bromide. Page (1981) had over 30% missing data and was only two weeks

in duration. In its absence there was little difference to the fixed effects result, but a substantial difference to the random effects model.

b) Global symptom score (mean)

This outcome was recorded by one study (Carling 1989), which compared the change in symptom score (before and after intervention) for peppermint oil and hyoscamine (atropine) compared with placebo. This was a crossover study that reported first period results. The study reported p values for the difference:

- Peppermint oil versus placebo: mean difference for change score was -11.8 (on a scale of 105 for a week); p=0.063 (i.e. statistically significant).
- Atropine versus placebo: mean difference for change score was -1.0 (on a scale of 105 for a week); p=0.46 (i.e. not statistically significant).

2. Individual symptoms

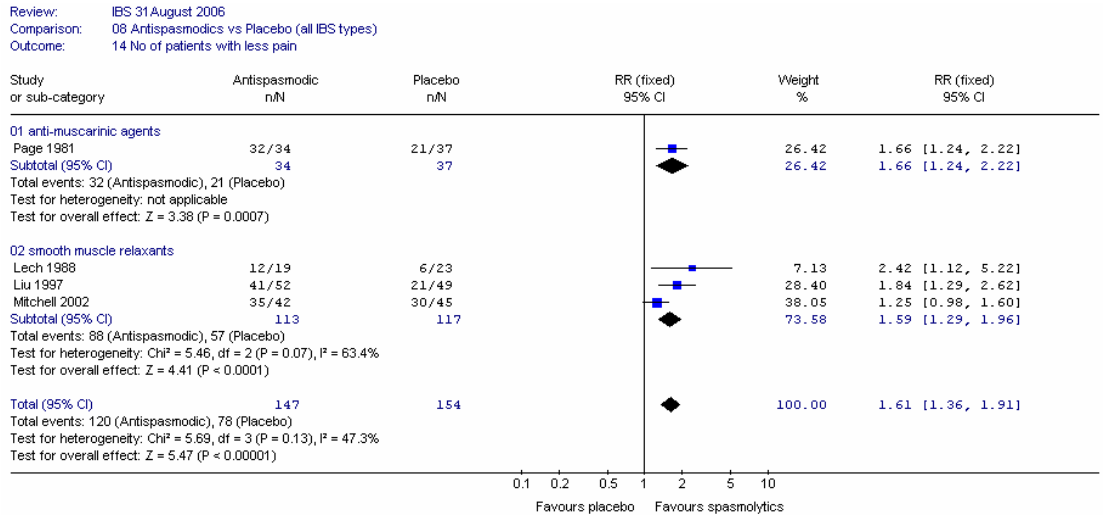
a) Pain

The following studies measured pain:

i. Number of patients with no pain: one study (Liu 1997)
ii. Number of patients with less pain: four studies (Lech 1988; Liu 1997; Mitchell 2002; Page 1981 (physician assessed)). The Kruis (1986) study was not included because of poor compliance – 4 week results were not reported for this outcome.
iii. Pain score (change): one study (Berthelot 1981).

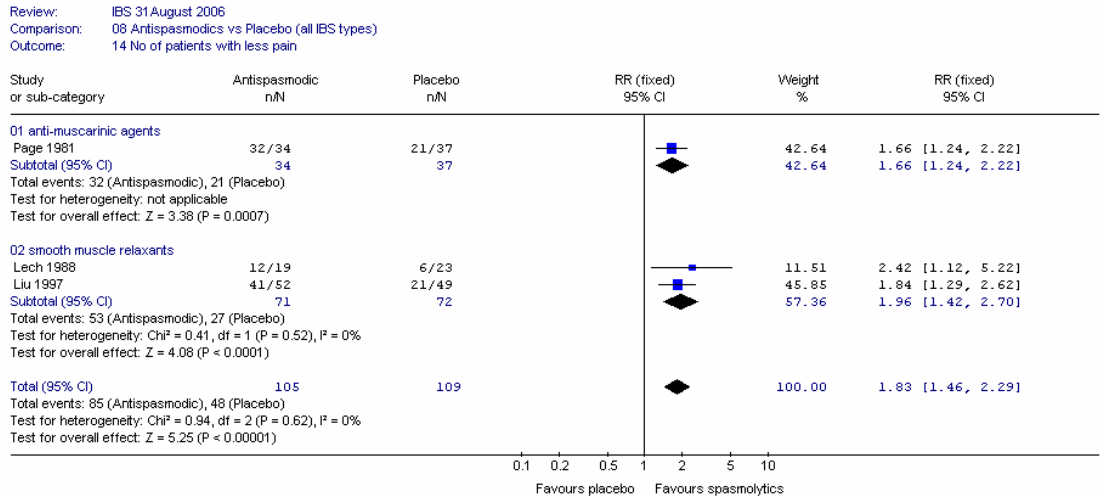
Figure 3 shows the number of patients with less pain. There was a statistically significant increase in the number with less pain, favouring antispasmodics. However, there was also significant heterogeneity within the smooth muscle relaxants group (p=0.07, I^2=63%). This was possibly a drug specific effect: Lech (1988) and Liu (1997) gave peppermint oil and Mitchell (2002) gave alverine citrate. However, the duration of Mitchell (2002) was also longer (12 weeks versus 4 weeks).

Figure 3



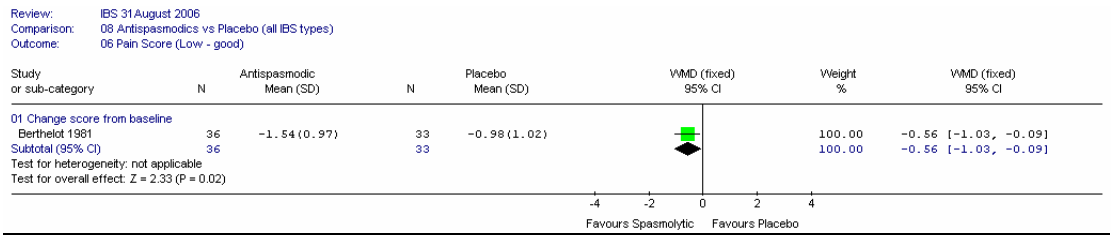
A sensitivity analysis without Mitchell (2002) shows that this was responsible for the heterogeneity, but it was not clear why. It was interesting to note that this study was the only one that carried out a power calculation.

Figure 4: Sensitivity analysis



The one study (Berthelot 1981) recording a pain score showed a statistically significant decrease in pain score, favouring the antispasmodic (figure 5). The mean difference was -0.56 (95%CI -1.03, -0.09) on a scale of 1 to 4.

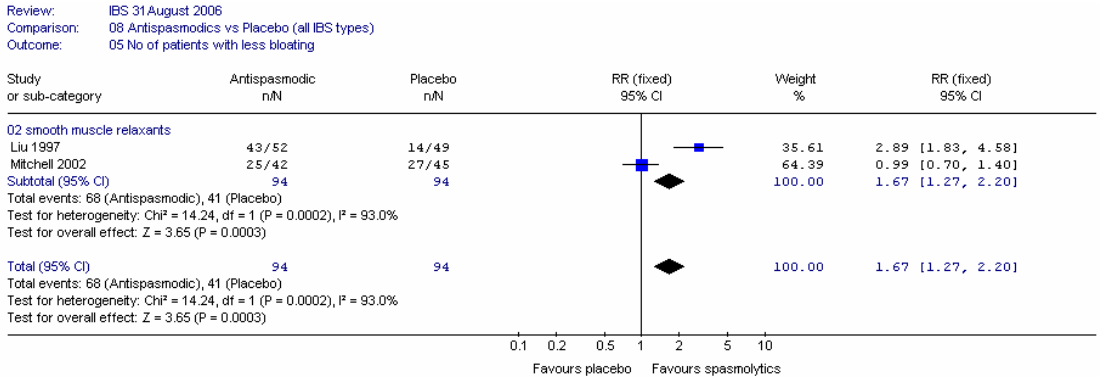
Figure 5



b) Bloating

Only two studies (Liu 1997 and Mitchell 2002) reported the number of patients with less bloating (Figure 6). Meta-analysis showed a high degree of heterogeneity between studies (p=0.0002, I^2=93%). It was not clear why these studies were so different, but see the discussion above regarding the pain outcome.

Figure 6

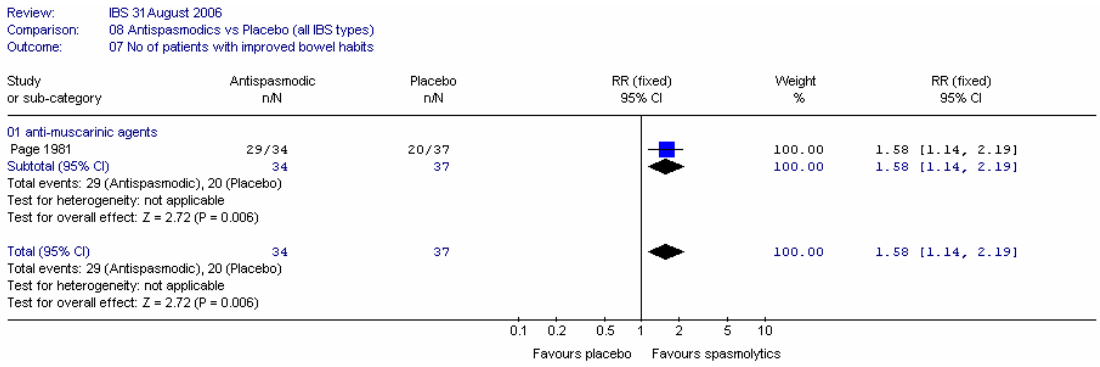


c) Bowel habits

i. Number of patients with improved bowel habits

One study (Page 1981), with 71 patients and attrition bias, recorded the number of patients with improved bowel habits (figure 7). There was a statistically significant improvement with the antispasmodic.

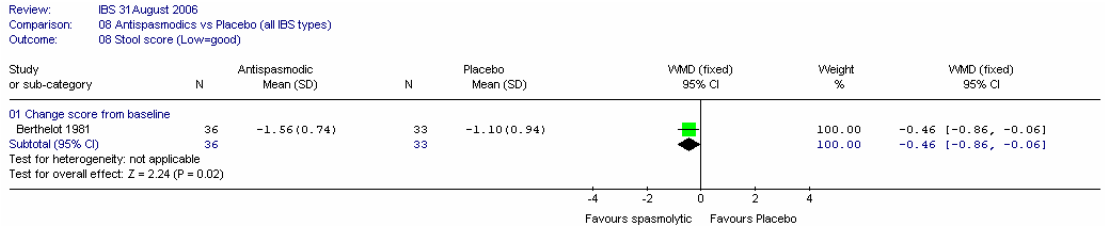
Figure 7



ii. Stool score

One study reported a stool score (Berthelot 1981) on a scale of 1-4. There was a statistically significant difference between antispasmodic and placebo, favouring the former.

Figure 8



3. Adverse effects

Three studies (four comparisons) reported the number of patients with adverse effects. These were grouped by antispasmodic. In all cases there were wide confidence intervals, but it appeared that there were significantly more side effects for both atropine and dicyclomine bromide than placebo (Figure 9). In particular, the statistically significant effect of atropine was manifested as dry mouth and blurred vision, but the confidence intervals were very wide, as demonstrated in figure 10.

Figure 9

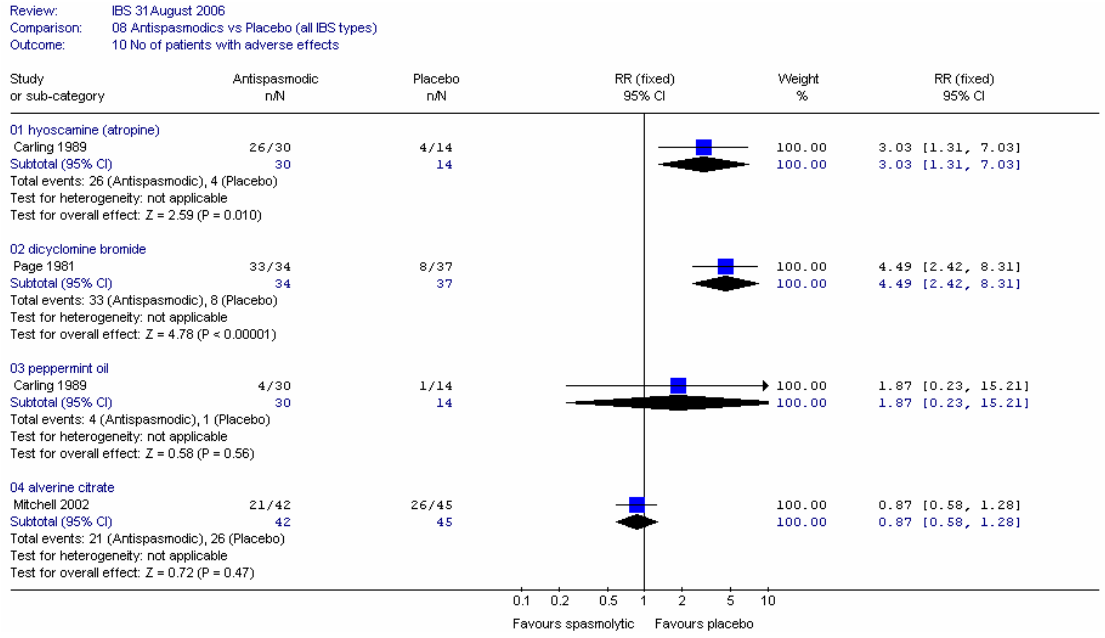
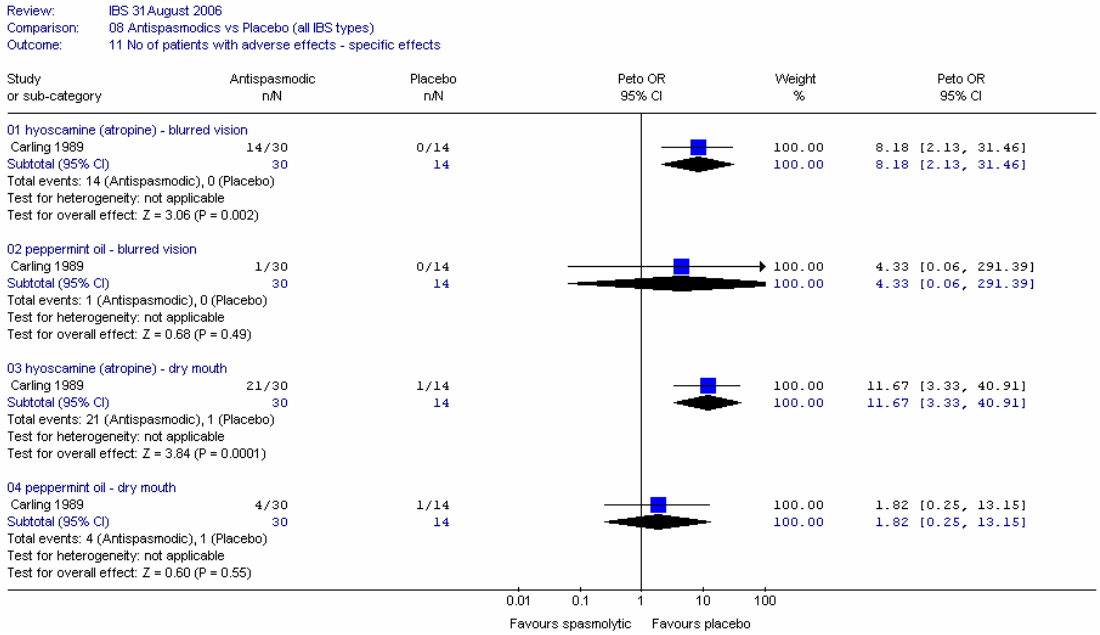


Figure 10: Specific side effects



B. Antispasmodic type 1 versus Antispasmodic type 2

One study compared different types of antispasmodic: Carling (1989) compared hyoscamine (atropine) with peppermint oil (smooth muscle relaxant).

1. Global outcomes

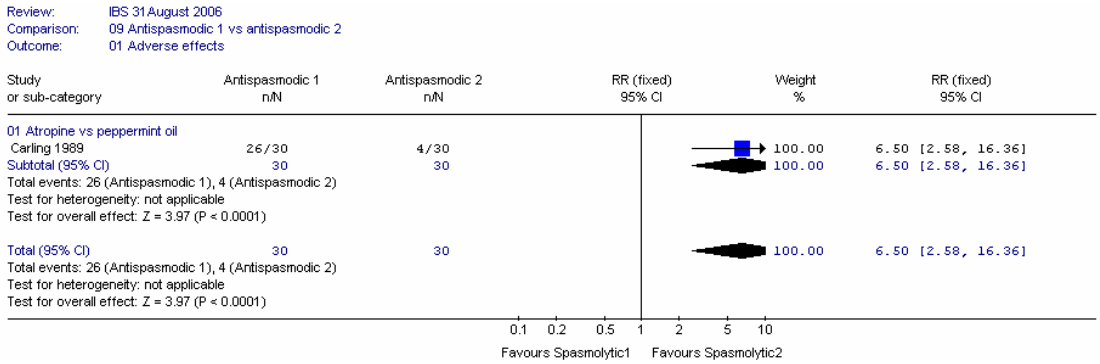
a) Global symptom score

The study did not record standard deviations or p-values.

2. Adverse effects

The study showed a statistically significant increase in side effects for atropine compared with peppermint oil, although the confidence interval was wide.

Figure 11



C. Comparison of antispasmodics in the same class

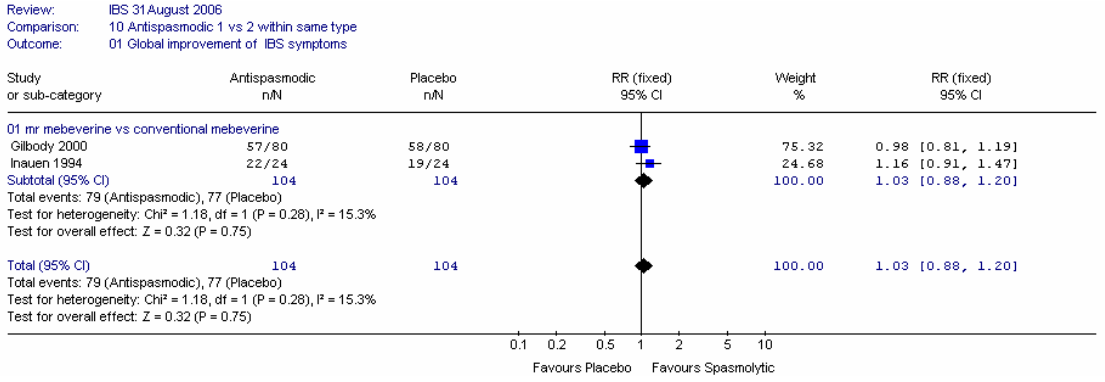
Two studies (Gilbody 2000; Inauen 1994) compared modified release mebeverine twice daily (total 400 mg) with conventional mebeverine three times daily (total 405 mg). The two studies had different durations: Gilbody (2000) had duration of eight weeks, and; Inauen (1994) had duration of three weeks. Gilbody (2000) was also carried out in general practice.

1. Global improvement of symptoms

a) Number of patients with improved symptoms

There appeared to be little difference between the two formulations (figure 12).

Figure 12

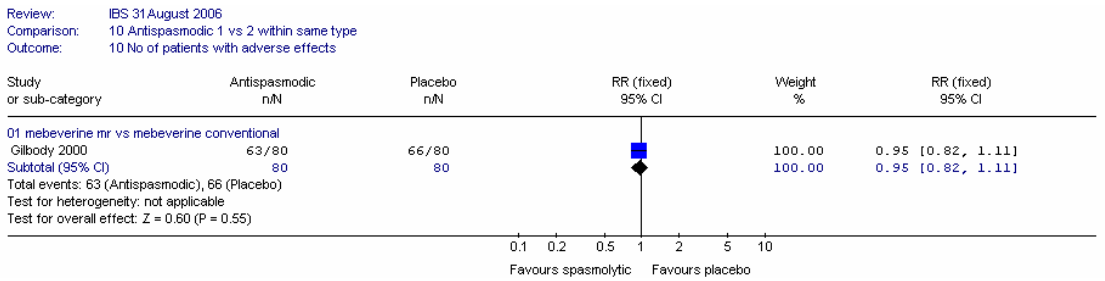


2. Adverse effects

a) Pain

One study in general practice (Gilbody 2000) showed little difference between the interventions for the number of patients with adverse effects, although it was noted that the number of adverse effects was high in both groups and the study said this included symptoms associated with IBS (pain and diarrhoea).

Figure 13



Adverse Effects

An adverse effects review has been carried out and is reported in section 8.5.1. There were six included RCTs in the review of adverse effects of antispasmodics (Grillage 1990; Gilbody 2000; Schaffstein 1990; Mitchell 2002; Liu 1997; Van Outryve 1995). The interventions and comparators were extremely varied, as was the reporting of adverse effects outcomes. In view

of this, no meta-analysis was performed. Dry mouth, drowsiness, dizziness and constipation were the most common complaints reported amongst people taking antispasmodics.

One of the limitations of the adverse effects review was that many of the adverse outcomes of interest were very similar to the symptoms of the IBS itself. For instance, antispasmodics were associated with drowsiness and constipation, both of which are commonly seen in people with untreated IBS. This made it difficult for the investigators to differentiate between the progress of the condition and the harmful effects of the drug.

ECONOMIC LITERATURE FOR ANTISPASMODICS

No relevant health economic analyses were identified on the cost-effectiveness of antispasmodic therapy in the treatment of IBS.

COST-EFFECTIVENESS ANALYSIS FOR ANTISPASMODICS

This section describes the health economic analysis undertaken to inform recommendations on the use of antispasmodics as a long-term maintenance therapy in IBS. The general methods used in the economic analysis for all management interventions are described in detail in Chapter 5 and the model inputs and assumptions relevant to this particular intervention are described below.

- The following interventions were treated as a class of interventions with the same clinical effectiveness as there was insufficient evidence to demonstrate a significant difference in effectiveness between them; hyoscine, mebeverine (standard and slow release), peppermint oil, dicycloverine (dicylcomine), alverine.
- There was insufficient evidence to demonstrate that atropine (hyoscamine) was more effective than placebo. Therefore, the cost-effectiveness of atropine was not estimated.
- The studies included in the clinical effectiveness review did not stratify results by IBS subtype, so it was not possible to estimate the effectiveness for each of the subtypes separately. Therefore, it was assumed that antispasmodics are equally effective in all subtypes.

Modelled response rates

In the basecase scenario the response rate of 45% in the no treatment arm is taken from the Mearin (2004) cohort study. This represents the group of patients for whom we would expect an improvement in symptoms without any specific intervention. The RR of response for antispasmodics versus placebo is 1.32; therefore the response rate in the intervention arm is 59% (=45% x 1.32), giving an absolute difference in response between the intervention and no treatment arms of 14% (=59%-45%) during the 1st month. In the basecase scenario the response rate for the subsequent interventions is assumed to be equal to the response rate for the first intervention. Therefore an additional 14% of those who do not respond to the first

intervention achieve a therapeutic response to the second intervention, increasing the overall response rate to 65% (=59%+14%*[1-59%]) after the second month. The response rate over time for the basecase is given in Figure 14.

We have also considered an alternative scenario in which no patient in the comparator arm achieves an improvement in symptoms but there is still a 14% chance of response for the intervention arm.

Figure 14: Modelled response rate for antispasmodic therapy, when allowing up to 4 switches of antispasmodic therapy, and no treatment

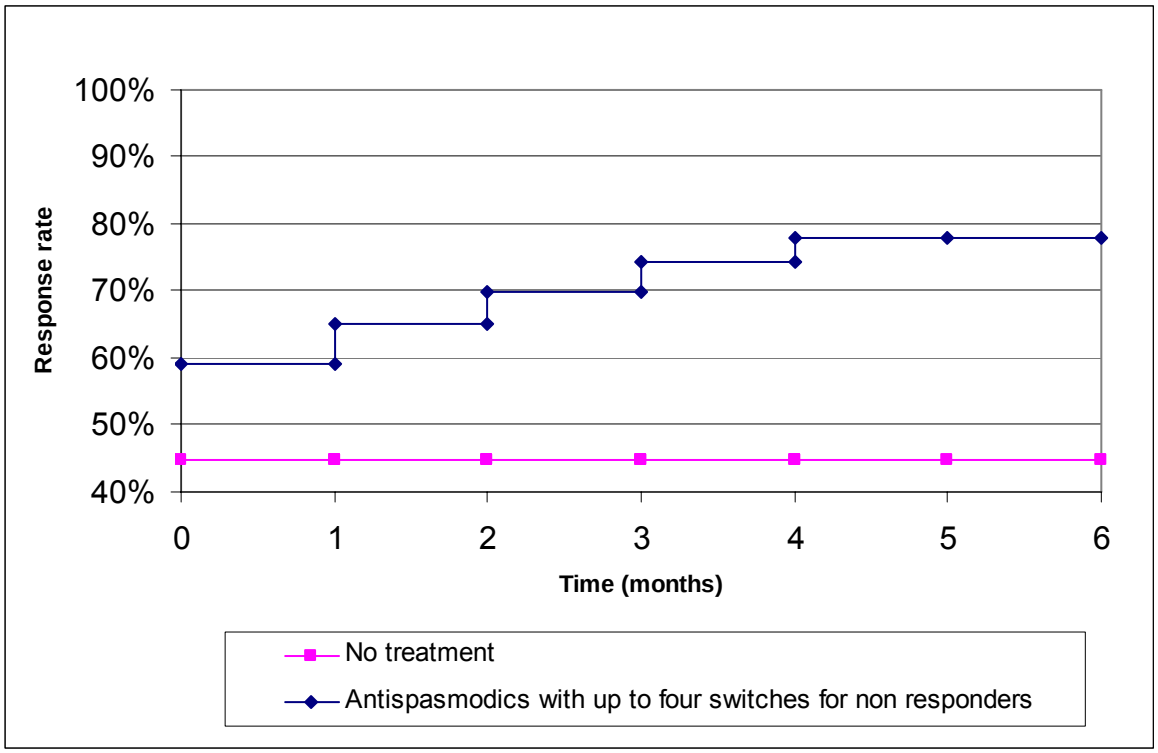


Table 1: Intervention specific parameters – antispasmodics

Description	Value		Evidence
RR of response for intervention vs placebo	1.32 (1.18 – 1.48)		Meta-analysis of RCT evidence for improvement in global symptoms
Maximum number of switches considered	4		Limited by number of effective interventions
Drug costs			
Intervention	**Dose per day**	**Cost per month* (assuming lowest cost preparation)**	
Hyoscine	30mg	£4.22	
Mebeverine	400mg	£6.76	
Peppermint oil	0.6ml	£7.65	
Alverine	360mg	£20.99	
Dicyclomine hydrochloride	160mg	£24.54	

* British National Formulary (Joint Formulary Committee 2007)

Results

Table 2: Incremental cost-effectiveness of allowing subsequent switches in antispasmodic therapy

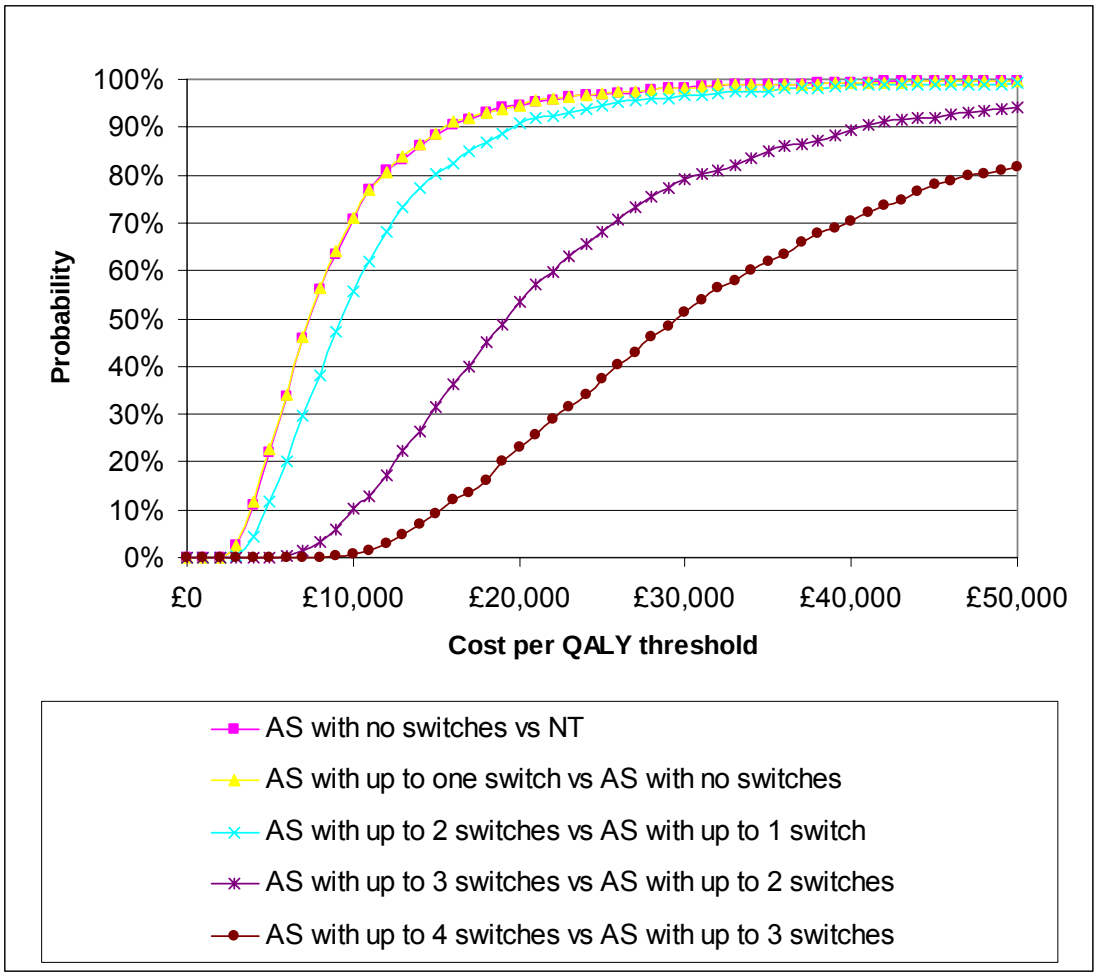
Strategy	Cost	QALY	Incremental Cost per QALY compared to previous row	Incremental cost per QALY compared to no treatment
No treatment	£0.00	1.60	N/A	N/A
Intervention, no switches	£3,469	2.11	£6,792	£6,792
Intervention with up to 1 switch	£4,640	2.28	£6,728	£6,775
Intervention with up to 2 switches	£5,654	2.40	£8,497	£7,031
Intervention with up to 3 switches	£7,005	2.48	£17,620	£7,952
Intervention with up to 4 switches	£8,189	2.52	£27,047	£8,857

Table 2 gives the incremental cost-effectiveness for several treatment pathways with different numbers of therapy switches included. These results demonstrate that although a treatment pathway which allows up to 4 switches had a cost per QALY under £20,000 compared to no treatment, the incremental cost-effectiveness compared to a pathway which allows up to 3 switches was greater than £20,000. Therefore, at a willingness to pay threshold of £20,000 per QALY, it would only be cost-effective to allow up to 3 switches as the additional switch would not provide sufficient additional benefit.

These results are an estimate of the cost-effectiveness over the first 6 months after the initiation of antispasmodic therapy. The cost per QALY for continuing antispasmodic therapy beyond 6 months is lower than the cost per QALY during the initial 6 months provided that treatment is reviewed every 6 months and discontinued in patients who no longer experience a therapeutic benefit, either due to lack of effectiveness or a change in their symptom profile.

The probabilistic sensitivity analysis provided an estimate of the uncertainty in the cost per QALY estimate due to uncertainty in the efficacy estimate, the probability of response in the no treatment arm and the utility gain. The CEAC in Figure 15 shows the uncertainty surrounding the relative cost-effectiveness of allowing each additional switch in therapy. For example, the first curve on the left of Figure 15 shows that it is highly likely that using a first antispasmodic therapy would be cost-effective compared to no treatment as the probability of the cost per QALY being under a £20K threshold is over 90%. The second curve from the left is very close to the first and it shows that it is highly likely that allowing patients to switch once to an alternative antispasmodic therapy would be cost-effective compared to no further antispasmodic therapy for those who do not respond to the first. Similarly, the second switch is also highly likely to be cost-effective as it has a 91% probability of being under £20K. However, once the third switch of therapy is considered, it is only fairly likely to be cost-effective as there is a 53% likelihood that the true cost per QALY is under £20K and a 79% likelihood that it is under £30K. Providing four switches is fairly unlikely to be cost-effective compared to 3 switches as the cost per QALY has a 23% probability of being under £20K and a 51% probability of being under £30K. However, it should be noted that these estimates only consider the uncertainty in cost-effectiveness due to the accuracy of several input parameters and they do not reflect general uncertainty around the assumptions made in the model. The uncertainty from these assumptions was explored in the univariate sensitivity analysis.

Figure 15: Cost-effectiveness acceptability curves for antispasmodics (AS) compared to no treatment (NT) and for each additional switch of antispasmodic for non responders (AS)



Univariate sensitivity results for up to three switches

The results in Table 3 show that initiating treatment with an antispasmodic and allowing up to three switches in therapy for non-responders had a cost per QALY of £7,952 compared to no treatment. When the response rate in the no treatment arm was taken from the average response rate in the RCTs of pharmacological interventions (47%), rather than from the cohort study (45%), the cost per QALY was very similar at £7,539. Maintaining the 14% difference in response between the two arms but reducing the response rate in the no treatment arm from 45% to zero marginally decreased the cost per QALY to £7,772. Reducing the response rate for subsequent antispasmodics, in patients who have not responded to initial therapy, by 50% significantly increased the cost per QALY for each subsequent switch of therapy, such that only 2 rather than 3 switches of therapy could be provided for a cost per QALY under £20,000. However, the cost per QALY for 3 switches compared to no treatment was only moderately increased to £10,003 per QALY and even when the response rate for subsequent therapy was

set to zero, the cost per QALY for antispasmodic therapy with up to 3 switches remained under £20,000 when compared to no treatment.

We carried out a threshold analysis to determine whether antispasmodic therapy would still be cost-effective for lower gains in health related quality of life. In the basecase it was assumed that patients who respond to therapy accumulate 0.071 QALYs more per annum than patients who do not respond. For comparison, a gain of 0.135 QALYs would represent a complete remission of IBS symptoms. When the QALY gain associated with a response to therapy was reduced to 0.028 QALYs, the cost per QALY of providing antispasmodic therapy with up to 3 switches was estimated to be above £20,000 per QALY compared to no treatment.

If a patient takes a therapy on an as needed basis, it would be reasonable to assume that they take the therapy on days when their quality of life is significantly affected by their IBS symptoms but not on days when their symptoms are less severe. It has therefore been assumed in the model that they only accrue QALY benefits and drug costs on the days they take the therapy. However, it is still necessary to assess all patients for response after 1 month of initiating therapy. This means that it would be less cost-effective to initiate therapy in patients who use the therapy on fewer days, as the monitoring costs are just as high but the benefits are lower. This is shown by the estimated cost per QALY of £20,578 for patients who take the therapy on 25% on days. However, a more detailed look at the results for these patients (data not tabled) shows that up to 1 switch of therapy could be provided for a cost per QALY of £19,414 with a 45% likelihood of being under £20,000 per QALY and a 73% likelihood of being under £30K per QALY. So, cost-effective treatment strategies may be available for patients who do not experience severe symptoms as frequently.

If a patient also takes another medication (such as a laxative or anti-motility agent), then these medications can be reviewed at the same time, so it may be cost-effective to provide both therapies. For example, if laxatives are prescribed with the antispasmodic and both used on 25% of days then allowing up to 2 switches of both treatments was estimated to be cost-effective with a cost per QALY of £10,107 compared to no treatment a cost per QALY of £17,393 compared to 1 switch.

Table 3: Sensitivity results for antispasmodic therapy with up to 3 switches compared to no treatment for 100 patients with IBS (all subtypes)

Scenario	No Treatment		Intervention		Incremental
	Cost	QALY	Cost	QALY	Cost per QALY
Basecase	£0	1.60	£7,005	2.48	£7,952
No response in no treatment arm	£0	0.00	£9,931	1.29	£7,722
Response rate in no treatment arm from RCTs	£0	1.69	£6,736	2.59	£7,539
Response to subsequent treatment half as likely as response to first	£0	1.60	£7,077	2.30	£10,003
Response to subsequent treatment zero	£0	1.60	£7,125	2.11	£13,949
Treatment used 75% of days	£0	1.60	£6,180	2.26	£9,355
Treatment used 50% of days	£0	1.60	£5,356	2.04	£12,161
Treatment used on 25% of days	£0	1.60	£4,532	1.82	£20,578
Half of treatments obtained over the counter	£0	1.60	£5,356	2.48	£6,080
Higher cost formulations (same dose)	£0	1.60	£7,298	2.48	£8,285
High utility gain of 0.135	£0.00	3.02	£7,005	4.69	£4,200
Threshold analysis on lowest utility	A cost per QALY of £20,000 is reached when the QALY gain associated with responding to treatment lies between 0.028 and 0.029.				

GDG DISCUSSION

The GDG consensus was that antispasmodics should be used as first line therapy alongside dietary and lifestyle advice for people with IBS, particularly those with pain occurring as spasm. Antispasmodics should be taken as needed.

EVIDENCE STATEMENTS

For this review, the evidence was assessed using the GRADE process and tables are shown in Appendix F. The following evidence statements are derived from the GRADE tables.

1. There is a fair amount of good quality evidence showing significant improvement in symptoms for antispasmodics, in general, and smooth muscle relaxants, in particular, when compared to placebo.

2. There is a fair amount of evidence showing significant global improvement in symptoms for antimuscarinic agents compared with placebo.

3. Sub-group analysis suggests there is little difference in the effect of antimuscarinic agents and smooth muscle relaxants for global improvement of symptoms.

4. There is a moderate amount of good quality evidence showing a significant reduction in pain and an improvement in bowel habit for antispasmodics compared with placebo.

5. There is a moderate amount of good quality evidence showing that conventional and modified release mebeverine were equally effective.

ADVERSE EFFECTS EVIDENCE STATEMENT

There is limited evidence that antispasmodics are associated with dry mouth, dizziness and drowsiness.

HEALTH ECONOMIC STATEMENT

Evidence from a decision analytic model showed that antispasmodics (hyoscine, mebeverine, peppermint oil, dicycloverine, alverine) are cost-effective for long-term maintenance use in individuals with IBS. The cost-effectiveness estimate is based on a clinical pathway in which response is assessed after one month and non-responders are switched to an alternative antispasmodic with the lower cost antispasmodics used before higher cost antispasmodics. The analysis assumes that the response to each subsequent therapy is independent of the response to previous antispasmodics. Trying a further antispasmodic is unlikely to be cost-effective in individuals who have not responded to four previous antispasmodics. The cost-effectiveness analysis assumes that treatment is reviewed every 6 months to establish whether antispasmodic therapy is still relevant to the individual's symptom profile.

EVIDENCE TO RECOMMENDATIONS

The GDG took into consideration the clinical and cost effective evidence. They noted the limited evidence about adverse effects, but did not consider this to be a significant factor in practice. The GDG wished to encourage primary care clinicians to give antispasmodics as a first line therapy alongside dietary and lifestyle advice.

RECOMMENDATION

Healthcare professionals should consider prescribing antispasmodic agents for people with IBS. These should be taken as required, alongside dietary and lifestyle advice.

8.4 Antidepressants

SELECTION CRITERIA

The selection criteria described in the general methodology section were used, but some criteria specific to the antidepressants review are reported below.

Types of patients

For this review, patients were required to have IBS and not to have inflammatory bowel disease or major psychiatric disorders.

Types of studies

Studies that investigated drugs not listed in the BNF were excluded. These included: Amineptine; Amoxapine; Desipramine, and; Pirenzepine.

The GDG decided that crossover studies were acceptable and that the washout period for this review should be at least one week. Trials with shorter washout periods were not included in the analysis.

Types of intervention

Studies included the following interventions:

Tricyclics and related antidepressants:

- Amitriptyline (Triptafen®, Triptafen-M® (with perphenazine)
- Clomipramine (Anafranil®)
- Dosulephin (Prothiaden®)
- Doxepin (Sinepin®)
- Imipramine
- Lofepramine (Feprapax®, Lomont®, Gamanil®)
- Nortriptyline (Allegron®)
- Trimipramine(Surmontil®)
- Mianserin
- Trazodone (Molipaxin®).

Selective serotonin re-uptake inhibitors (SSRIs):

- Citalopram (Cipramil®)
- Escitalopram (Cipralex®)
- Fluoxetine (Prozac®)
- Fluvoxamine (Faverin®)
- Paroxetine (Seroxat®)

- Sertraline (Lustral®).

Monoamine oxidase inhibitors (MAOIs):

- Phenelzine (Nardil®)
- Isocarboxazid
- Tranylcypromine.

Reversible MAOIs:

- Moclobemide (Manerix®).

Others:

- Duloxetine (Cymbalta®)
- Flupentixol (Fluanxol®)
- Mirtazapine (Zispin Soltab®)
- Reboxetine (Edronax®)
- L-Tryptophan (Optimax®).

The following comparisons were included:

- Antidepressant versus placebo (or nothing)
- Antidepressant type 1 versus Antidepressant type 2
- Antidepressant dose 1 versus Antidepressant dose 2
- Antidepressant versus other interventions.

NB: In spite of the large placebo effect associated with IBS, comparisons with no treatment were included.

The antidepressants review was concerned with medium and longer term symptom relief. Medium term treatment was defined as three months and long term as between six months and one year.

Subgroup analyses

We planned to carry out subgroup analyses by type of antidepressant; dose; mode of delivery, and; duration of intervention.

Search strategy for identification of studies

Searches were performed on the following core databases: MEDLINE; EMBASE; CINAHL, and; *The Cochrane Library* (1966 to current day with guidance from the GDG). Additional databases were not searched for this review. The search strategies are listed in Appendix B.

The search strategy identified 1458 studies. The titles and abstracts of these studies were assessed. Thirty were identified to be potentially relevant to the review and these papers were retrieved in full. The reference lists for each of the retrieved studies were inspected for further potential papers, but none were identified. The 17 excluded studies are listed in the Appendix, along with reasons for exclusion. The remaining 13 studies were included (Boerner 1988; Creed 2003; Kuiken 2003; Myren 1982; Myren 1984; Rajagopalan 1998; Schrivastava 1984; Steinhart 1982; Tabas 2004; Tanum and Malt 1996; Tripathi 1983; Vij 1991; Quartero 2007). One of these studies was a Cochrane review (Quartero 2007). The Myren (1982) study did not state that it was randomised although it was double blind. Since this study was included in the Cochrane review (under the name of Block (1983), which is an identical paper in Norwegian) we included it too, but treated it with caution.

DESCRIPTION OF STUDIES INCLUDED IN THE REVIEW

One Cochrane review was identified (Quartero 2007) and this guideline review is an update, with revision to make it appropriate to the UK. This mainly involved elimination of one of the included studies (Heefner 1978) because the antidepressant, desipramine, is not in the BNF. Therefore the analysis for the guideline review was based on six studies included in the Cochrane review (Boerner 1988; Myren 1982; Myren 1984; Rajagopalan 1998; Shrivastava 1984; Vij 1991) and six additional studies (Creed 2003; Kuiken 2003; Steinhart 1982; Tabas 2004; Tanum and Malt 1996; Tripathi 1983). Tripathi (1983) and Shrivastava (1984) were two reports of a single trial, i.e. there were 11 included studies.

One study was conducted in the UK (Creed 2003); one was conducted in Germany (Boerner 1988); one in The Netherlands; three in Norway (Myren 1982; Myren 1984; Tanum and Malt 1996): three in India (Rajagopalan 1998; Tripathi 1983; Vij 1991) and the remaining two in the United States (Steinhart 1982; Tabas 2004).

Eight studies had fewer than 100 patients (Myren 1982; Boerner 1988; Kuiken 2003; Steinhart 1982; Rajagopalan 1998; Tripathi 1983; Tabas 2004; Tanum and Malt 1996). Two studies had fewer than 20 patients in the intervention arm (Kuiken 2003; Steinhart 1982).The latter was a crossover design so fewer patients were required to achieve adequate power. Creed (2003) had 257 patients and Myren (1984) had 258.

Study Design

Setting: The majority of studies took place in secondary care, one of which treated inpatients (Tripathi 1983); one was stated to take place in primary care in a later paper (Myren 1982); three included patients from both primary and secondary care settings (Boerner 1988; Myren 1984; Tabas 2004) and one study (Steinhart 1982) did not report the setting.

Funding: three studies received some funding from industry: Kuiken (2003) was sponsored by Eli Lilly (manufacturers of fluoxetine); Tripathi (1983) received the study medication and placebo from May & Baker India Ltd. (manufacturers of trimipramine); Steinhart (1982) received the study medication and placebo from Merck Sharp & Dohme. Six studies (Myren 1982; Myren 1984; Rajagopalan 1998; Vij 1991; Boerner 1988) did not state source of funding. The remaining studies were funded by non-industry sources (Tabas 2004; Tanum and Malt 1996; Creed 2003).

Population

The age range of patients across the IBS studies was 13 to 75 years, with the mean age, where given, ranging from 35 to 41 years. The study with a lower age of 13 was Tripathi (1983); in this study the range was 13 to 60 years, with a mean of 37. The GDG did not consider this level of children to be important. No study particularly identified elderly patients.

Five studies had more women than men (Creed 2003; Myren 1982; Steinhart 1982; Tabas 2004; Tanum and Malt 1996); three studies had about the same number of men and women (Kuiken 2003; Rajagopalan 1998; Myren 1984) and two studies did not give the proportions of patients by gender (Boerner 1988; Tripathi 1983).

Six studies identified the type of IBS as mixed (Boerner 1988; Creed 2003; Kuiken 2003; Steinhart 1982; Tabas 2004; Vij 1991). The remaining studies gave no information regarding type of IBS. In Tanum and Malt (1996) only 60% of the patients had IBS; the rest had non ulcer dyspepsia (NUD). The authors reported that there was no *significant* difference in response between IBS and NUD patients, although there was a trend towards a slightly better response in the NUD patients.

Two studies stated that the patients had severe IBS (Creed 2003; Steinhart 1981); one study had mixed severity patients (Vij 1991). Creed (2003) was stratified by pain level before randomisation. Tabas (2004) also selected patients who were non-responders to placebo.

Four studies reported the inclusion of refractory IBS patients: Creed (2003) included patients that had failed to respond to usual treatment and had a median duration of IBS of eight years; Kuiken (2003) stated that the patients had all been treated unsuccessfully previously. Steinhart (1981) reported a mean duration of IBS of 5 years and stated that all patients had received antispasmodics previously; Tabas (2004) included patients who had failed to respond to a high fibre diet.

Three studies reported a long duration of IBS: Tanum and Malt (1996) had a mean duration of symptoms of about 8 years; Rajagopalan (1998) had a mean duration of about 4 years; Kuiken (2003) had a mean duration of symptoms of 5.9 years.

One study implied that some of the patients did not have refractory IBS: in Myren (1984), 45 to 61% were not taking other drugs before the study started, and the other studies did not report previous treatments.

Five studies stated that the patients had some depression: Tabas (2004) reported that 27/81 (33%) had a score greater than 10 on the Beck Depression Inventory (although major psychiatric illnesses were excluded); Creed (2003) reported that 47% had anxiety or depression; Steinhart (1981) stated that 57% had depression and 79% anxiety; Vij (1991) had 57% with psychiatric co-morbidities; Boerner (1988) reported that some patients had depression (mid point on the Hamilton depression scale). Kuiken (2003) excluded patients with depression.

One study stated that all the patients had anxiety (Tripathi 1983). Three studies reported that the patients did not have psychiatric disorders: Rajagopalan (1998) stated that patients had no major medical or psychiatric illnesses; Tanum and Malt (1986) excluded patients with schizophrenia, anxiety or depression, and; Myren (1982) and Myren (1984) both showed low scores on depression and anxiety scales.

Interventions

The interventions included:

- Tricyclic Amitriptyline up to 75mg for 3 months (Rajagopalan 1998) and 50mg for 1 month (Steinhart 1982) – c.f. BNF levels for depression treatment: initially 75mg, increasing to 150 to 200mg
- Tricyclic Trimipramine 30 to 50mg for 4 to 6 weeks in three studies (Myren 1982; Myren 1984; Tripathi 1983) – c.f. BNF levels for depression: initially 50-75mg, then 150 to 300mg
- Tricyclic Doxepin 50mg for 8 weeks (Boerner 1988) and 75mg for 6 weeks (Vij 1991) – c.f. BNF levels for depression: initially 75mg, then 30 to 300mg
- Tricyclic-related Mianserin 30 mg initially, then up to 120mg for weeks 2 to 7, then tapered in week 8 – c.f. BNF levels for depression: 30 to 40mg initially; usual dose 30 to 90mg
- SSRI Paroxetine 20mg per day for 3 months (Creed 2003) and up to 40mg for 3 months; 23% 10mg; 43% 20mg; 33% 40mg (Tabas 2004) – c.f. BNF levels for depression: initially 20mg, then up to 50mg
- SSRI Fluoxetine 20mg per day for 6 weeks – c.f. BNF levels for major depression: 20mg once daily increased after 3 weeks if necessary, usual dose 20 to 60mg.

Comparisons

The majority of comparisons were of antidepressants versus placebo. One study (Creed 2003) compared antidepressants with usual care. One study compared different doses of antidepressants (Myren 1984).

Antidepressant versus placebo

- Tricyclics versus placebo:
  - Trimepramine (Myren 1982; Myren 1984; Tripathi 1983)
  - Amitriptyline (Rajagopalan 1998; Steinhart 1982)
  - Doxepin (Boerner 1988; Vij 1991)
  - Mianserin (Tanum and Malt 1996).

- SSRI versus placebo:
  - Paroxetine (Tabas 2004) included high fibre diet (>25g daily) in both the treatment and placebo groups (NB. these patients had already been identified as non-responders to high fibre)
  - Fluoxetine (Kuiken 2003).

Antidepressant versus usual care

- SSRI versus usual care:
  - Paroxetine (Creed 2003) versus 'routine care' by gastroenterologist and GP including antispasmodics, laxatives, antidiarrhoeal medication or additional analgesics.

Antidepressant versus psychotherapy (this is covered in the psychotherapy review)

- Paroxetine versus psychotherapy (Creed 2003).

It was decided to combine the SSRI studies with comparators of placebo and usual care using subgroup analyses.

METHODOLOGICAL QUALITY

The results of the quality assessment for included trials are shown in Appendix D.

The method of randomisation was adequate in four of the studies: three used computer generated random numbers (Creed 2003; Kuiken 2003; Tabas 2004) and the other used a random number table (Vij 1991). Myren (1982) did not state that the study was randomised, but stated that the study was double blinded; we included this study because it was stated to be an RCT in the Cochrane review. The remaining studies did not state the method of randomisation. Allocation concealment was reported in four studies (Creed 2003; Myren 1982; Tabas 2004). Creed (2003) and Kuiken (2003) reported that an independent third party carried out the randomisation; Tabas (2004) reported that identical capsules were sealed in sequentially numbered identical boxes.

The majority of studies reported that the patients were blinded to the interventions, with the exception of Creed (2003), in which blinding was not possible due to the nature of the comparisons. However, the outcome assessors were blinded in this study.

Three studies reported a sample size calculation (Creed 2003; Kuiken 2003; Tabas 2004), but Kuiken (2003) was powered for a different primary outcome (rectal sensitivity) and was underpowered for symptoms. The remaining studies gave no details of an *a priori* sample size calculation (Boerner 1988; Myren 1982; Myren 1984; Rajagopalan 1998; Tripathi 1983; Steinhart 1982; Tanum and Malt 1996; Vij 1991).

The majority of studies included in the review demonstrated baseline comparability of the groups, apart from Myren (1982) which was not comparable at baseline for vomiting, but levels of this were low in both groups (0.5 and 0.1 on 10cm VAS), and; Rajagopalan (1998) which was not comparable on stool type, with the antidepressant group having looser stools. In two studies there were no details of baseline characteristics (Tripathi 1983; Boerner 1988).

Only one study had total missing data of more than 20% (Rajagopalan 1998), comprising 9/20 in each group (45%). Those who dropped out had a significantly shorter duration of symptoms at recruitment, but otherwise there was no difference between completers and dropouts. Two studies had no missing data (Tripathi 1983; Myren 1982). Four reported missing data of less than 20% (Kuiken 2003; Tanum and Malt 1996; Tabas 2004; Vij 1991). However, there were 24% missing data in each arm of Vij (1991) for the outcome of pain. Myren (1984) and Steinhart (1982) provided no information regarding the number of drop outs.

In Creed (2003) there were missing data, 16% (14/86) in the paroxetine group; 14% (12/85) psychotherapy. 0% in the routine care group did not start the trial. A further 29/86 (34%) in the paroxetine group and 14/85 (16%) in the psychotherapy arm discontinued treatment, but these patients still appear to have been followed. Overall, loss to follow-up at three months was 12/86 (14%) for paroxetine, 11/85 (13%) psychotherapy and 7/86 (8%) usual care arm. At 15 months the authors contacted more of the patients. The authors reported that there were no significant differences at baseline between those who did and did not complete the treatments. For the 3 month pain score and SF36 outcome measures respectively, the patients included in the analysis were 74 and 59 (69%) paroxetine; 74 and 58 (68%) psychotherapy and 79 and 63 (73%) usual care, but some of these patients had discontinued treatment. We decided to include the results from this study, with some reservations, especially about the paroxetine arm and about the SF36 results. The study also recorded the number of patients with an improvement in global symptoms, based on the results from 74, 74 and 80 patients respectively. The GDG decided that this outcome was more representative because patients that dropped out due to side effects would not have rated their global symptoms as improved. The follow-up period in Creed (2003) allowed the patients to have paroxetine in all arms: 42% in paroxetine group, 19% in psychotherapy and 22% in the usual care group, i.e. the follow-up period should be considered to be partly confounded. Therefore we did not report the results for the follow-up period for the comparison paroxetine versus placebo.

Overall, we considered that Rajagopalan (1998) was at high risk of bias because of the extent and nature of the missing data and the baseline differences, and we decided not to include the results from this study in the analysis. Three other studies were treated with caution: Myren (1982), which was not stated to be randomised; Creed (2003) which had missing data and non compliance for pain and SF36; and some confounding in the follow up period; and Vij (1991), which had 24% missing data in each arm for the pain outcome. We examined the latter three studies with sensitivity analyses.

RESULTS

A. Antidepressants versus placebo or usual care

1. Global symptoms

a) Number of patients with global improvement of symptoms (pain, bloating and bowel habit)

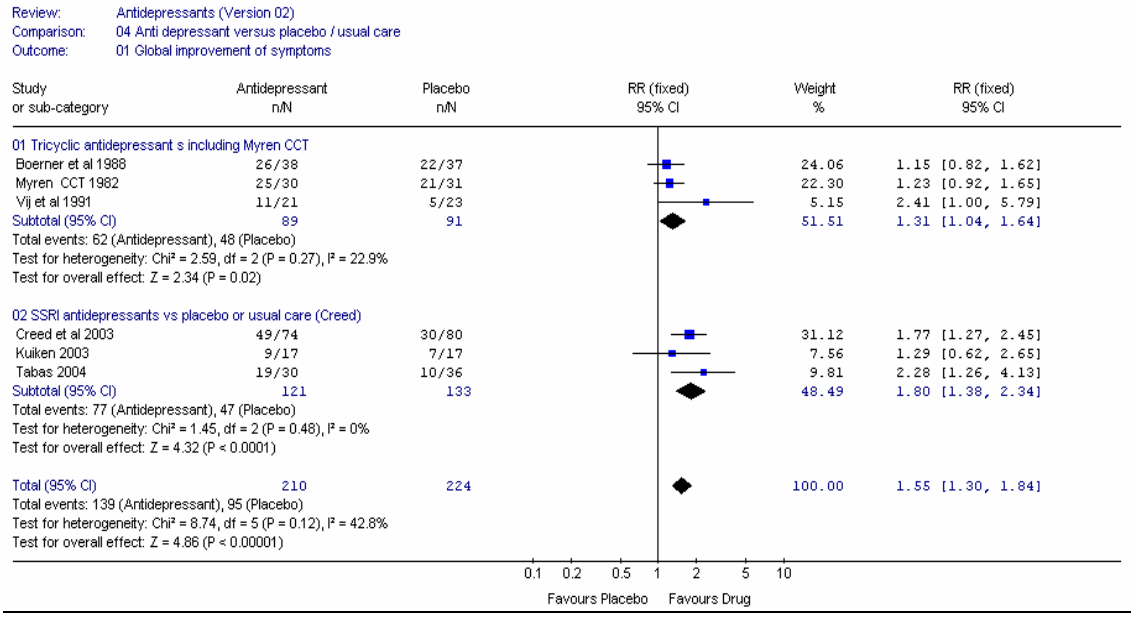
Six studies, in 434 patients, reported the number of patients with improvement in global symptoms (Boerner 1988; Creed 2003; Kuiken 2003; Tabas 2004; Myren 1982; Vij 1991). The studies were combined in a meta-analysis, but as separate subgroups by type of antidepressant. The controlled trial (Myren 1982) was included in the tricyclics subgroup and examined in a sensitivity analysis. The comparisons of paroxetine with placebo and with usual care were also considered in sensitivity analyses. 'Usual care' was defined as patients receiving IBS treatment that was deemed appropriate by either their gastroenterologist consultant or general practitioner.

The difference between the antidepressants and placebo was statistically significant overall and for each subgroup. Within subgroups there was no heterogeneity, but between groups there was some (I^2=42%, p=0.12). The overall relative risk (RR) for the meta-analysis of 434 patients was 1.55 (95%CI 1.30, 1.84), which corresponded to a number needed to treat of 5 (95%CI 4, 7), for a control group rate of 22 to 68%.

For the tricyclic subgroup (n=180) the number with global improvement of symptoms was statistically significantly higher for the antidepressant group; RR 1.31 (95%CI 1.04, 1.64), which gave an NNT of 6 (95%CI 4, 34), for a control group rate of 22-68%. In the absence of the Myren (1982) study, which was not stated to be randomised, the RR for this group was 1.37 (95%CI 0.99 1.91), i.e. no longer significant and with some heterogeneity (I^2=62%, p=0.11).

For the meta-analysis of the three SSRI studies (n=254), there was a significant difference favouring antidepressant, RR 1.80 (95%CI 1.38, 2.34), with no heterogeneity (I^2=0%, p=0.48). This corresponded to an NNT of 4 (95%CI 3, 7), for a control group rate of 28-41%. In the absence of the Creed (2003) study the effect was slightly bigger (RR 1.85 (95%CI 1.17, 2.91). We decided to use the results in Figure 1 in the health economic modelling.

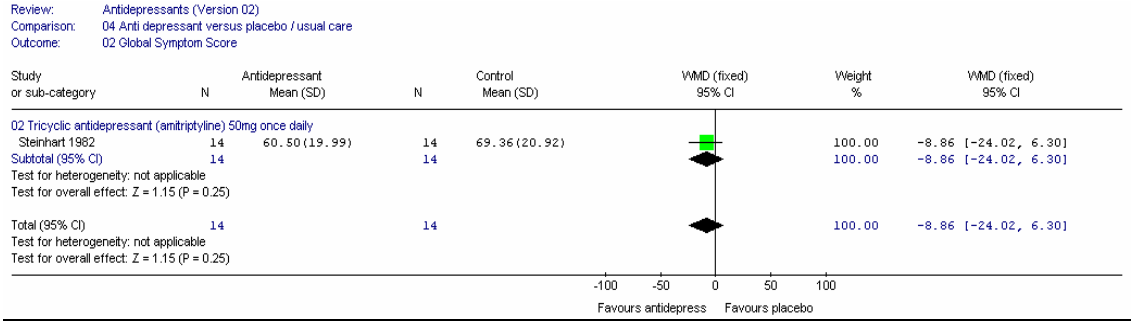
Figure 1



b) Global symptom score

One study with 28 patients reported the global symptom score, but no details of the scale were given. There was no significant difference between interventions.

Figure 2



2. Individual symptoms

a) Pain

i. Number of patients with less pain

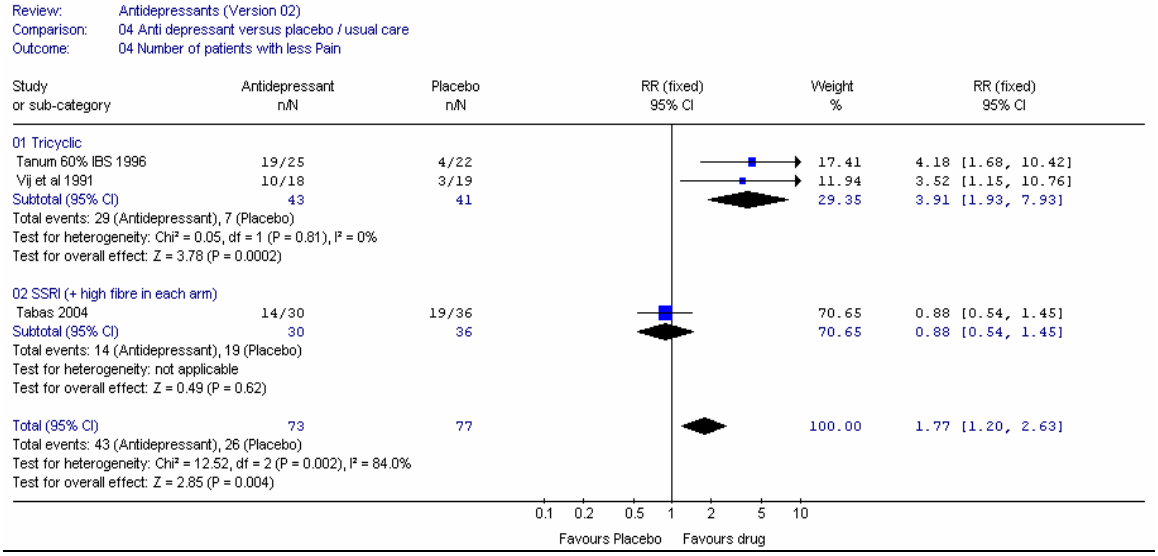
Three studies reported this outcome. Two were tricyclics versus placebo (Vij 1991; Tanum and Malt 1996) and the other was an SSRI versus placebo (Tabas 2004). These were included as subgroups in a meta-analysis in 150 patients. Overall there was significant heterogeneity (I^2=84%, p=0.004), which is attributed to the type of antidepressant.

There was a large significant difference in favour of tricyclics compared to placebo in the number of patients with reduced pain; RR 3.91 (95%CI 1.93, 7.93), with no heterogeneity (I^2=0%, p=0.81), although the confidence interval was fairly wide. This corresponded to an NNT of 2 (95%CI 2, 4), for a placebo group rate of 16-18%. We noted that this analysis

included Tanum and Malt (1996) which had only 60% of patients with IBS, and; Vij (1991) which had 24% missing data in each arm.

There was no significant difference between the SSRI and placebo in one study in 66 patients (Tabas 2004); RR 0.88 (95%CI 0.54, 1.45).

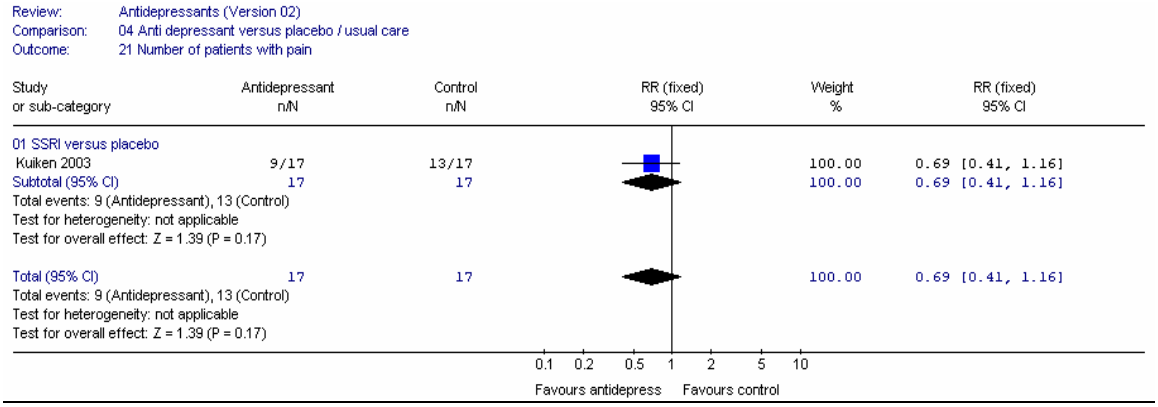
Figure 3



ii. Number of patients with pain

One study in 34 non-depressed patients (Kuiken 2003) reported the number of patients with 'significant pain'. There was no statistically significant difference between interventions, although the confidence interval was fairly wide.

Figure 4

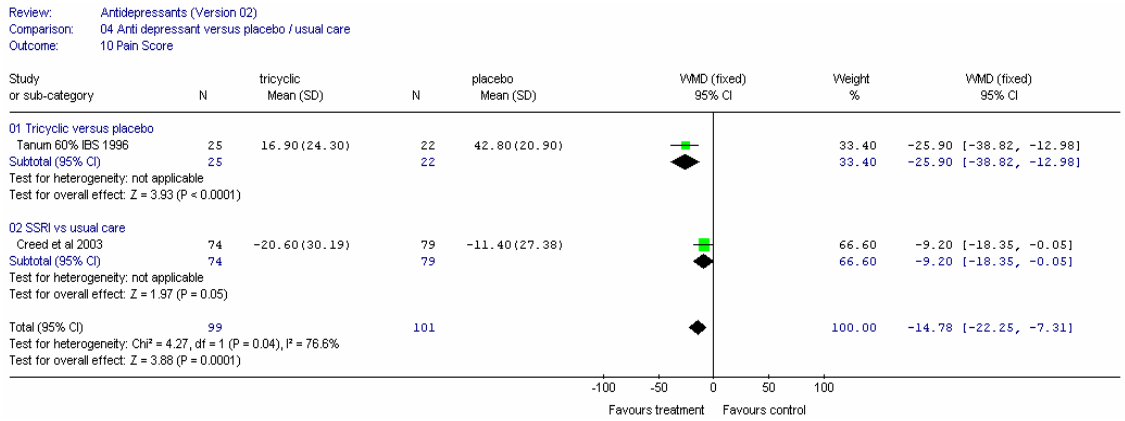


iii. Pain score

Four studies (Creed 2003; Tanum and Malt 1996; Myren 1982; Myren 1984) reported a type of pain score, all appeared to use a VAS of 100 mm or 10cm. Myren (1982) recorded an abdominal obstruction discomfort measurement, which the GDG decided was a different

outcome to pain. Myren (1984) gave means and p values only. We decided to combine the first two studies in a meta-analysis by subgroup (Creed 2003 compared an SSRI with usual care). We also noted that Tanum and Malt (1996) had only 60% of patients with IBS.

Figure 5



At the end of treatment, meta-analysis showed significant heterogeneity (I^2=77%, p=0.04), with different effect sizes being found for the two studies. This may be an effect of type of antidepressant, type of comparator, severity of IBS, or it may be that Tanum and Malt (1996) overestimated the effect because there were only 60% of patients with IBS. Individually, there was a statistically significant difference for the Tanum and Malt (1996) study (tricyclic versus placebo in 60% IBS): mean difference -25.90 (95%CI -38.82, -12.98) and for the Creed (2003) study: mean difference -9.20 (95%CI -18.35, -0.05).

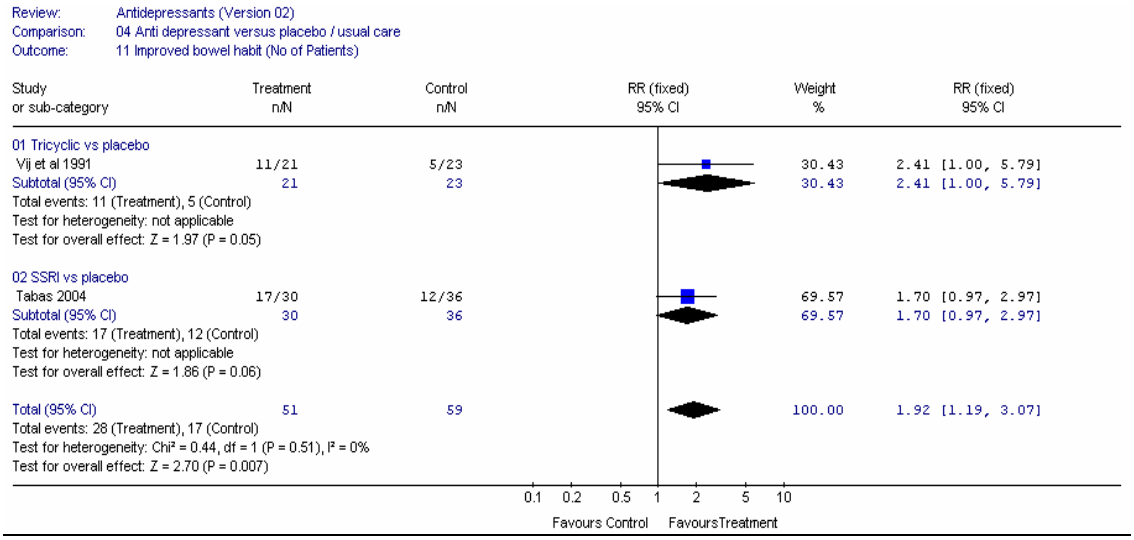
Boerner (1988) compared a tricyclic with placebo, and recorded the *median* improvement in pain on a scale of 0 to 4. There was a difference in median change score of 0.3 units, in favour of the tricyclic antidepressant, which was reported to be statistically significant at the level of p<0.05.

b) Bowel habit

i. Number of patients with improvement in bowel habit

Meta-analysis of two studies in 110 patients showed a statistically significant increase in the number of patients with improvement in bowel habit; RR 1.92 (95%CI 1.19, 3.07), with no heterogeneity between the tricyclics and SSRI subgroups (I^2=0; p=0.51) corresponding to an NNT of 4 (95%CI 3, 13). The confidence interval was fairly wide. The results for individual classes of antidepressant were not statistically significant, although the antidepressant was favoured; Vij (1991) (tricyclics) had a wide confidence interval and Tabas (2004) (SSRI) was fairly wide.

Figure 6



c) Bloating

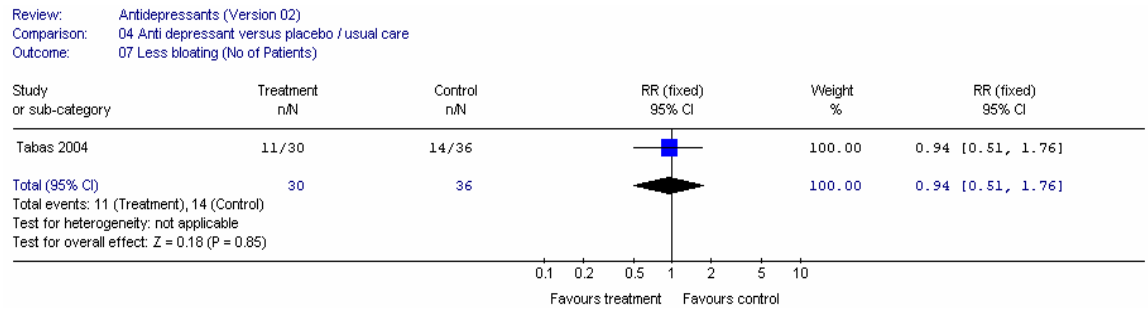
i. Number of patients with less bloating

Two studies recorded the number of patients with less bloating, one a tricyclic (Boerner 1998) and the other using an SSRI (Tabas 2004), both compared with placebo. Meta-analysis could not be carried out because Boerner (1998) reported the median.

Boerner (1988) recorded the median improvement in the feeling of fullness on a scale of 0 to 4. There was a difference in median change score of 0.23 units, in favour of the tricyclic, but this was reported to be not statistically significant.

Tabas (2004), comparing SSRI with placebo, did not demonstrate a significant effect on the number of patients with less bloating, but the confidence interval was fairly wide so this conclusion was uncertain.

Figure 7

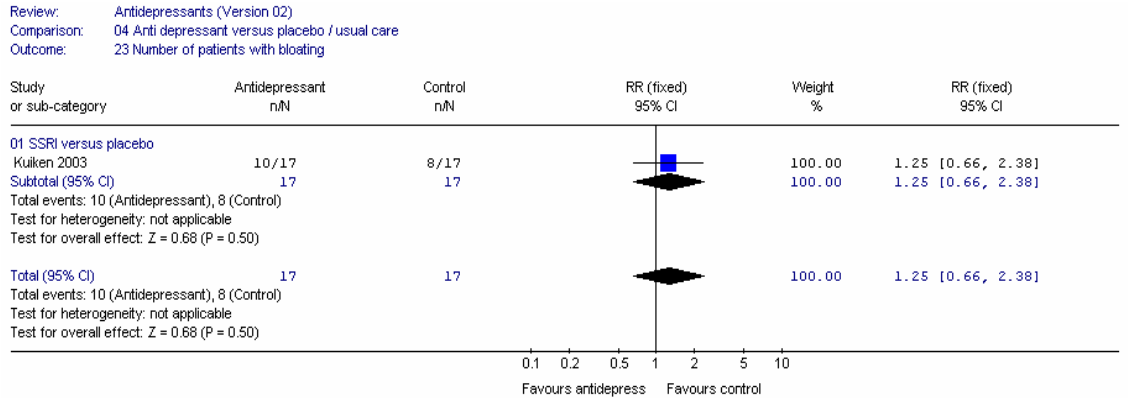


ii. Number of patients with bloating

One study (Kuiken 2003) reported the number of patients with bloating in 34 non-depressed patients. There was no significant difference between the SSRI and placebo, although the confidence interval was fairly wide. We note that the study was sponsored by Eli Lilly

(manufacturers of fluoxetine).

Figure 8

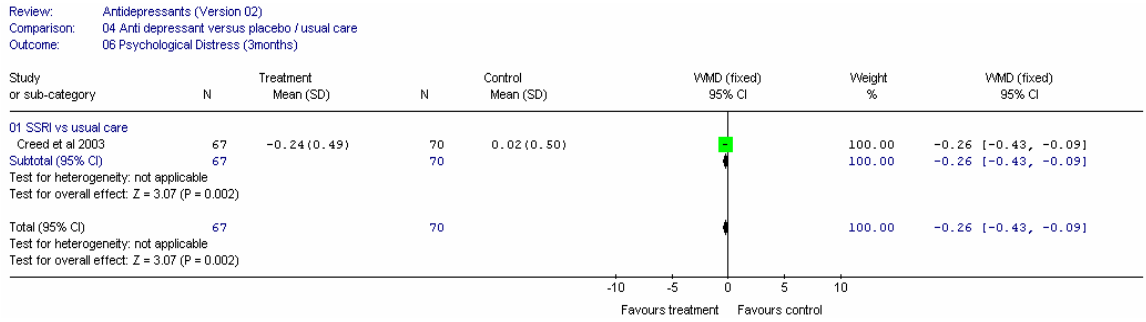


3. Mental health

a) Psychological Distress

This was measured by the SCL-90 global severity index (90 item, 5 point rating scale; range 90 to 450, high = bad). There was a small, statistically significant difference between SSRI (paroxetine) and usual care at 3 months, WMD: -0.28 (95%CI -0.43, -0.09), favouring the antidepressant.

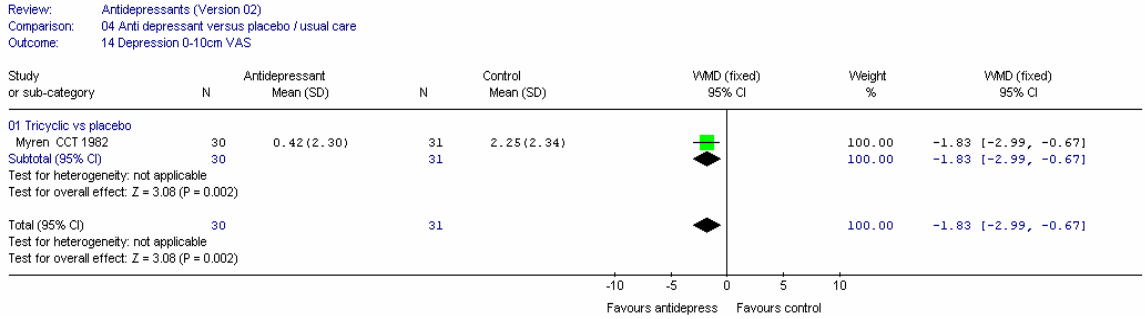
Figure 9



b) Depression score

One study (Myren 1982, CCT) recorded depression on a VAS of 0-10cm for tricyclics versus placebo, in which a high score indicated increased depression. There was statistically significantly less depression for the patients taking antidepressants. We noted that this study, at baseline, showed low scores on depression and anxiety scales.

Figure 10



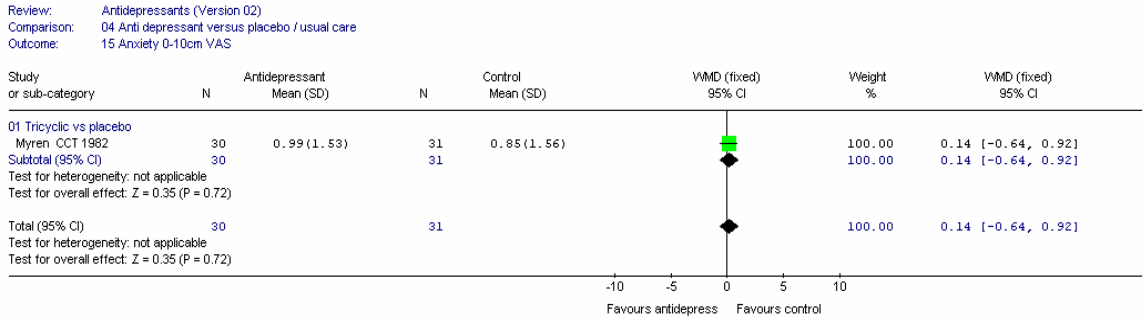
c) Anxiety

Two studies reported anxiety; one (Myren 1982, CCT) compared tricyclics versus placebo on a VAS of 0 to 10 and the other (Tabas 2004) reported the number of patients with anxiety for the comparison SSRI with placebo. The former study, at baseline, showed low scores on depression and anxiety scales, and the latter reported that 27/81 (33%) had a score greater than 10 on the Beck Depression Inventory.

i. Anxiety score

There was no significant difference in the degree of anxiety.

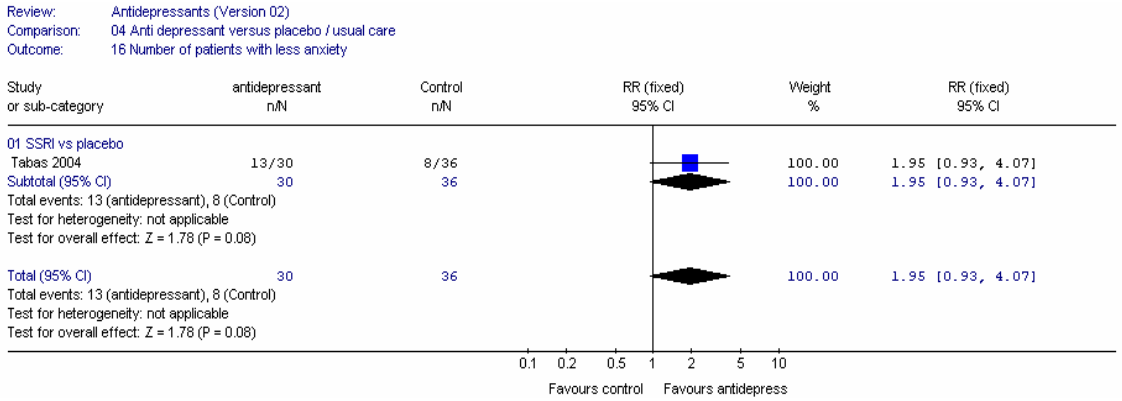
Figure 11



ii. Number of patients with anxiety

The confidence interval was wide and the result was not statistically significant.

Figure 12



4. Quality of life

Two studies reported quality of life measures, both for SSRIs (Creed 2003; Tabas 2004).

a) IBS-QoL

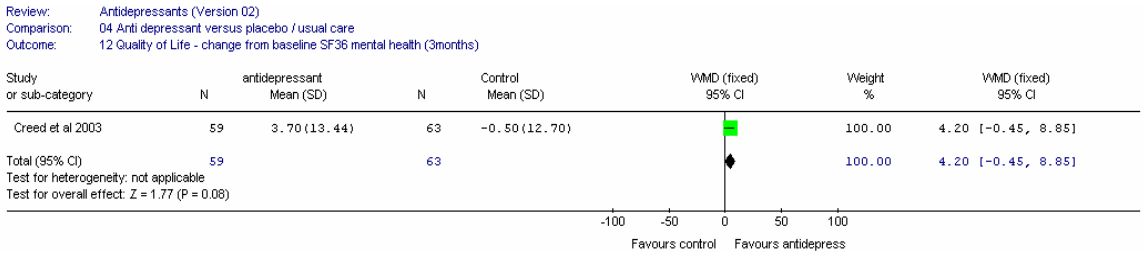
One study (Tabas 2004) comparing SSRI and placebo examined the change compared with baseline in three components of IBS-QoL: food avoidance; work function; social function. Tabas (2004) found the following differences for SSRI versus placebo:

- Food avoidance subscale – improvement of 12.7%; p value = 0.03 (statistically significant)
- Work function subscale – improvement of 2.1%; p value = 0.08 (not significant)
- Social function subscale – improvement of 13.4%; p value = 0.76 (not significant).

b) Change in SF36 Mental component score at 3 months

There was no significant difference in the mental health quality of life SF-36 score (scale 0 to 100, high=good) at 3 months between SSRI (paroxetine) and usual care, although there were 29% who discontinued treatment and 32% loss to follow up in the paroxetine arm. This conclusion does not agree with the p values reported in Creed (2003) (p=0.007).

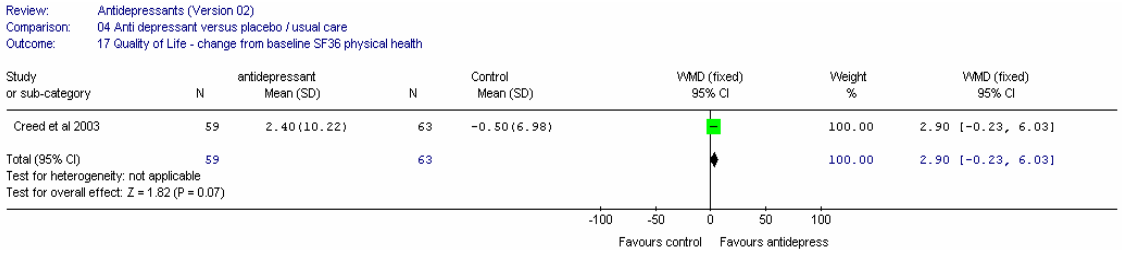
Figure 13



c) Change in SF36 physical health score at 3 months

The change in the physical health component also showed no significant difference at 3 months. This did not agree with the p value reported in Creed (2003) (p=0.24).

Figure 14



B. Comparison of different doses of Tricyclic antidepressant

One study (Myren 1984) compared different doses of Trimipramine in 428 participants.

1. Global symptoms

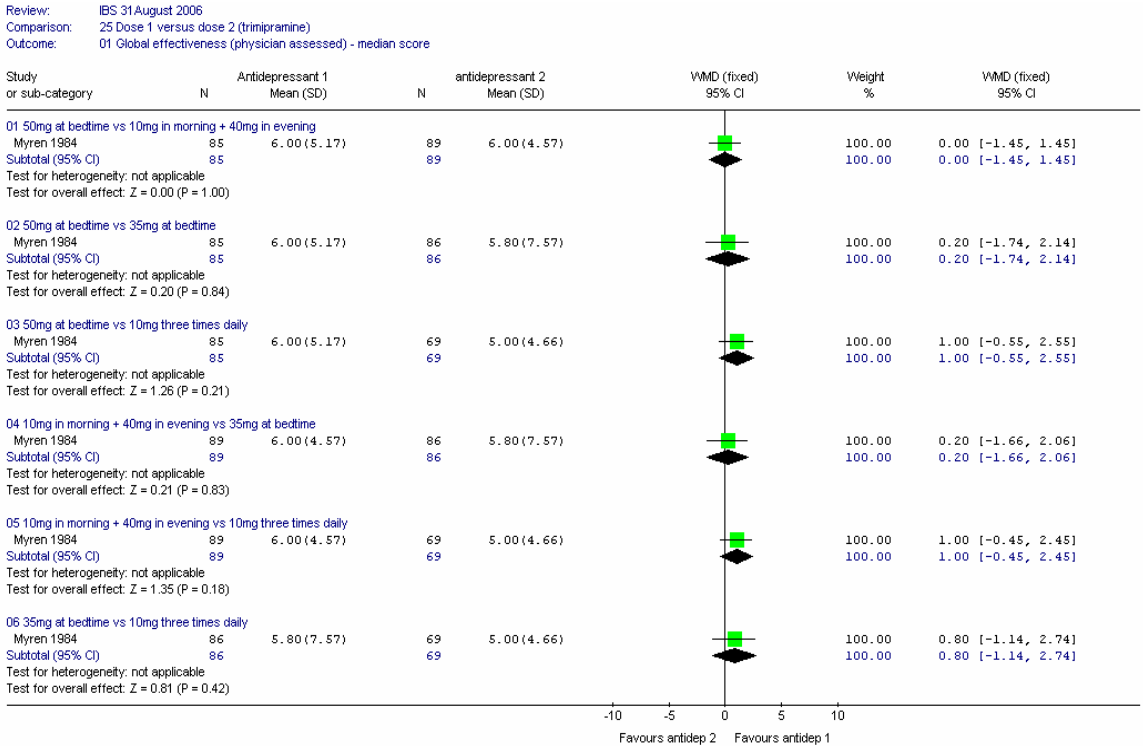
The study reported the 'total effect of treatments' in the opinion of the physicians. Medians with their 95% confidence intervals were reported for each group. We used this to calculate the standard deviation, which we used with the median value to compare groups. *Figure 16* shows there was no significant difference between any of the doses.

2. Individual symptoms

a) Number of patients with abdominal pain

The study reported a statistically significant reduction in pain in patients that were given 50mg per day either as a single dose or in two divided doses ($p < 0.01$). Patients taking 35mg in a single dose had significantly less pain than placebo ($p< 0.05$), and for patients taking 30mg per day in three divided doses there was stated to be no difference between the drug and placebo ($p= 0.10$).

Figure 15



ADVERSE EFFECTS

The evidence on adverse effects of tricyclics and SSRIs is provided in the adverse effects review (section 8.5.2).

ECONOMIC LITERATURE FOR TRICYCLICS AND SSRIS

One relevant health economic analysis was identified on the cost-effectiveness of SSRIs in the treatment of IBS (Creed 2003), but none were identified which considered the cost-effectiveness of tricyclics. Creed (2003) was a trial based economic evaluation conducted in the UK which recruited patients from secondary and tertiary care with severe IBS. This study aimed to assess whether an SSRI (paroxetine) would be superior to usual care in reducing abdominal pain and improving quality of life and whether these improvements could be achieved at no additional cost due to treatment costs being offset by reduced health care costs. (It also included a comparison of psychotherapy with usual care). The patient population considered were secondary and tertiary care patients with severe IBS who had not responded to usual treatment. The included patients had a mean duration of IBS of 8 years. This study was considered to be relevant to patients with refractory IBS only. The SSRI intervention consisted of 20mg of paroxetine daily for 3 months which was prescribed and monitored either by the patient's gastroenterologist or their GP. After three months, patients in the SSRI arm returned to their GP and received usual care for one year during which time they were followed-up. In the comparator arm patients received usual care from either their gastroenterologist or their GP for the three month treatment period and the following year of follow-up. The primary outcome was abdominal pain measured on a VAS of severity with secondary outcomes considering days with

pain, overall change in symptoms and HRQofL measured by the SF-36. Direct costs of health care and intervention costs were recorded.

The number of people with an improvement in global symptoms was significantly higher for SSRI at the end of treatment compared to usual care. The clinical outcomes from this trial have been summarised in detail in the clinical effectiveness review. Direct health care costs were not significantly increased for SSRI compared to usual care during the intervention period or the following year. However, the results for the follow-up period may have been partially confounded as patients in the usual care arm were also allowed SSRIs.

This study was a partial economic evaluation as it did not assess the incremental cost of any benefit achieved in the form of a cost-effectiveness ratio. The evidence provided by this study was considered to be indirect as the patients were recruited from secondary and tertiary care and costs may differ for refractory patients managed in primary care. No potential areas of significant bias were identified but the results for the follow-up year were considered to be partly confounded by the use of SSRIs in the comparator arm during follow-up. Direct health care costs were not significantly increased by SSRIs during the intervention period. However, the study was powered to detect a specific change in clinical rather than cost outcomes. As this study did not provide an estimate of the cost per QALY for SSRIs compared to usual care, it was not particularly useful in determining whether recommending SSRIs for use in the NHS would result in the efficient use of NHS resources.

COST-EFFECTIVENESS ANALYSIS FOR TRICYCLICS AND SSRIS

This section describes the health economic analysis undertaken to inform recommendations on the use of tricyclics and SSRIs as long-term maintenance therapies in IBS. The general methods used in the economic analysis for all management interventions are described in detail in Chapter 5 and the model inputs and assumptions relevant to this particular intervention are described below.

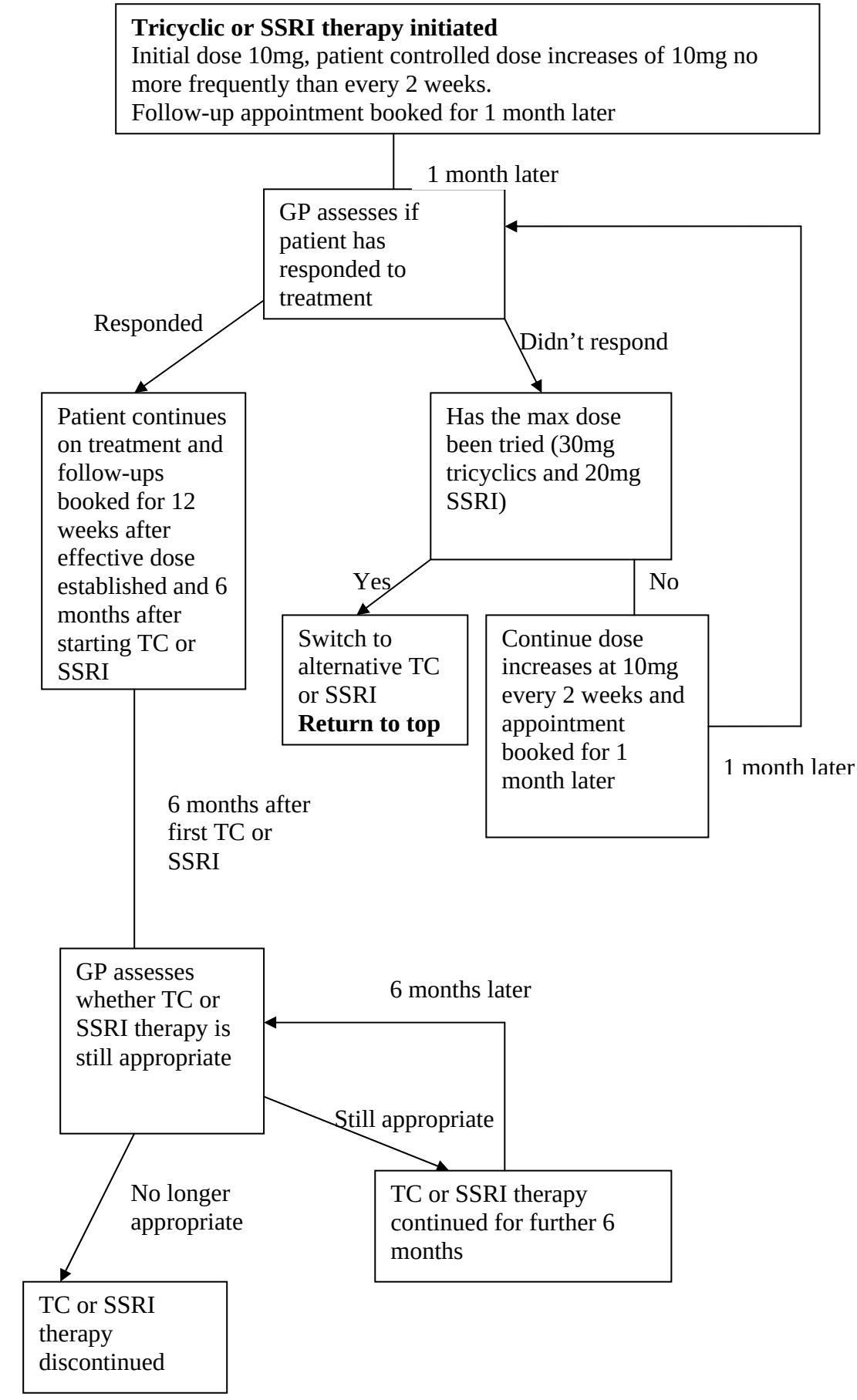
The general approach is the same as for other maintenance therapies except that the clinical pathway has been modified to allow for gradual dose increases and an additional follow-up appointment at 12 weeks. The clinical pathway was modified as follows:

- Treatment is initiated at 10mg with dose increases of 10mg no more frequently than every 2 weeks. Patients are encouraged to increase the dose until an effective dose has been established or side-effects become problematic up to a maximum dose of 30mg for tricyclics and 20 mg for SSRIs. (Alternative maximum doses of 50mg for tricyclics and 40mg for SSRIs are considered in a sensitivity analysis).
- Follow-up appointments are required every month until an effective dose has been established and a further follow-up appointment is required 12 weeks after that point. The usual 6 monthly review is carried out as for other pharmacological interventions. A sensitivity

analysis in which follow-up appointments are twice as frequent was considered in order to estimate whether monitoring patients more intensively would have a significant impact on cost-effectiveness.

- Patients who do not respond to the maximum dose are switched to an alternative tricyclic or SSRI. An incremental analysis was carried out to determine whether allowing patients who do not respond to switch to a second treatment, provides sufficient additional benefit to be cost-effective given the additional costs.
- The model assumes that the response seen in the clinical trial is gradually achieved over the range of doses considered, even if the maximum dose considered is not as high as the trial dose. For example, the RCT for tricyclics versus placebo used a range of doses from 30 to 75mg, compared to the maximum dose of 30mg used in the basecase model. In the economic model, we assumed that equal numbers of patients respond to the 10mg, 20mg and 30mg doses with the total number of responders equal to that predicted by applying the RR from the RCTs to the response rate in the no treatment arm. Sensitivity analyses were carried out assuming all patients respond to the lowest or highest dose.

Figure 16: Patient pathway for Tricyclics (TC) and SSRIs



The following assumptions have been made regarding the effectiveness of tricyclics and SSRIs based on the clinical effectiveness review:

- The following tricyclics were treated as a class of interventions with the same clinical effectiveness as there was insufficient evidence to demonstrate a significant difference in effectiveness between them: trimipramine, amitriptyline, doxepin.
- There was evidence that there is no difference in the effectiveness of tricyclics for doses above 30mg compared to 30mg (Myren 1984), so this was the maximum dose modelled in the basecase. A more conservative assumption in which doses of 50mg are required to achieve the effectiveness seen in the RCTs have been considered in a sensitivity analysis.
- The following SSRIs were treated as a class of interventions with the same clinical effectiveness as there was insufficient evidence to demonstrate a significant difference in effectiveness between them: fluoxetine, paroxetine. A maximum dose of 20mg was modelled in the basecase as this was the most commonly prescribed dose in the trials, but a sensitivity analysis was carried out on doses of up to 40mg using the dose distribution from Tabas (2004).
- The studies included in the clinical effectiveness review did not stratify results by IBS subtype, so it was not possible to estimate the effectiveness for each of the subtypes separately. Therefore, it was assumed that these interventions are equally effective across all IBS subtypes.

Modelled response rates

Figures 18 to 23 below give the modelled response rates for six different strategies for prescribing tricyclics and SSRIs for the management of chronic pain in IBS.

1. Tricyclic up to 30mg
2. Tricyclic up to 30mg followed by second tricyclic up to 30mg
3. Tricyclic up to 30mg followed by SSRI up to 20mg
4. SSRI up to 20mg
5. SSRI up to 20mg followed by tricyclic
6. SSRI up to 20mg followed by second SSRI up to 20mg

The RR of response for SSRIs versus placebo (or usual care) was much higher than the RR of response for tricyclics versus placebo (see Table 1) giving much larger increases in the number responding at each dose. However, as there was no head-to-head comparison of SSRIs and tricyclics, it was not possible to tell whether the apparent superiority of SSRIs is simply because they have been tested in a population that is more likely to respond to a pharmacological intervention. Indirect comparisons between SSRIs and tricyclics should be interpreted with caution due to the potential for bias.

Figure 17: Response rates for a tricyclic (up to 30mg) compared to no treatment

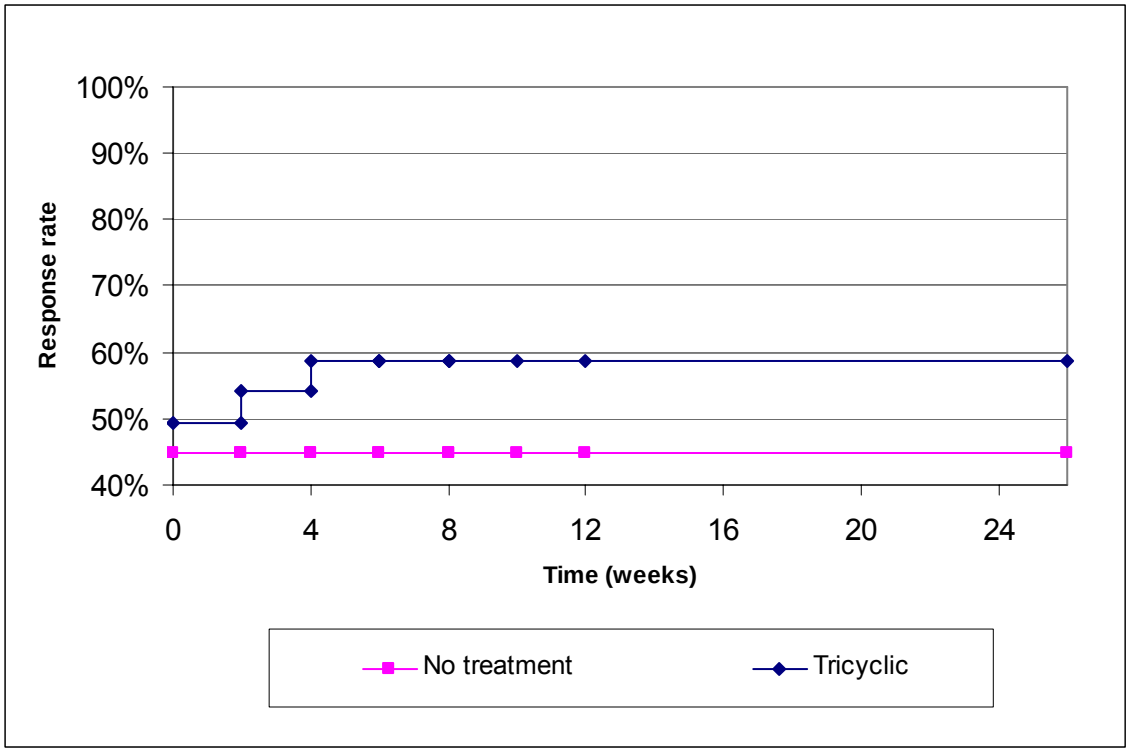


Figure 18: Response rates for a tricyclic up to 30mg followed by second tricyclic up to 30mg in non-responders compared to no treatment

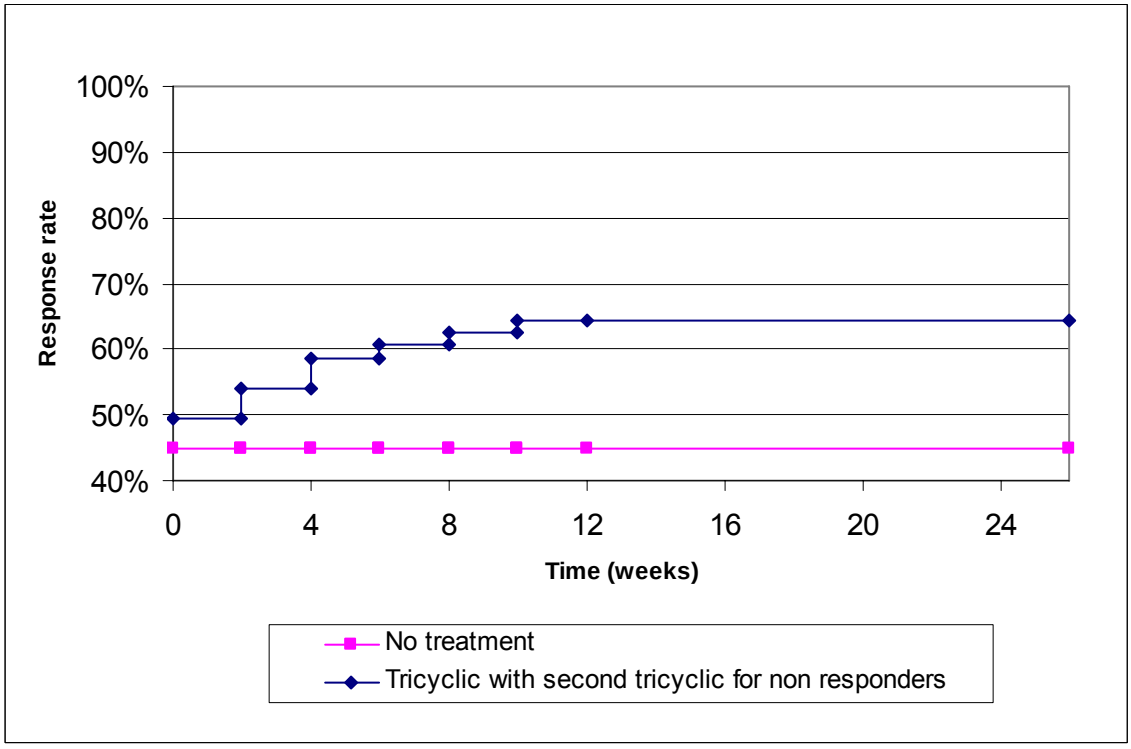


Figure 19: Response rates for a tricyclic up to 30mg followed by an SSRI up to 20mg in non-responders compared to no treatment

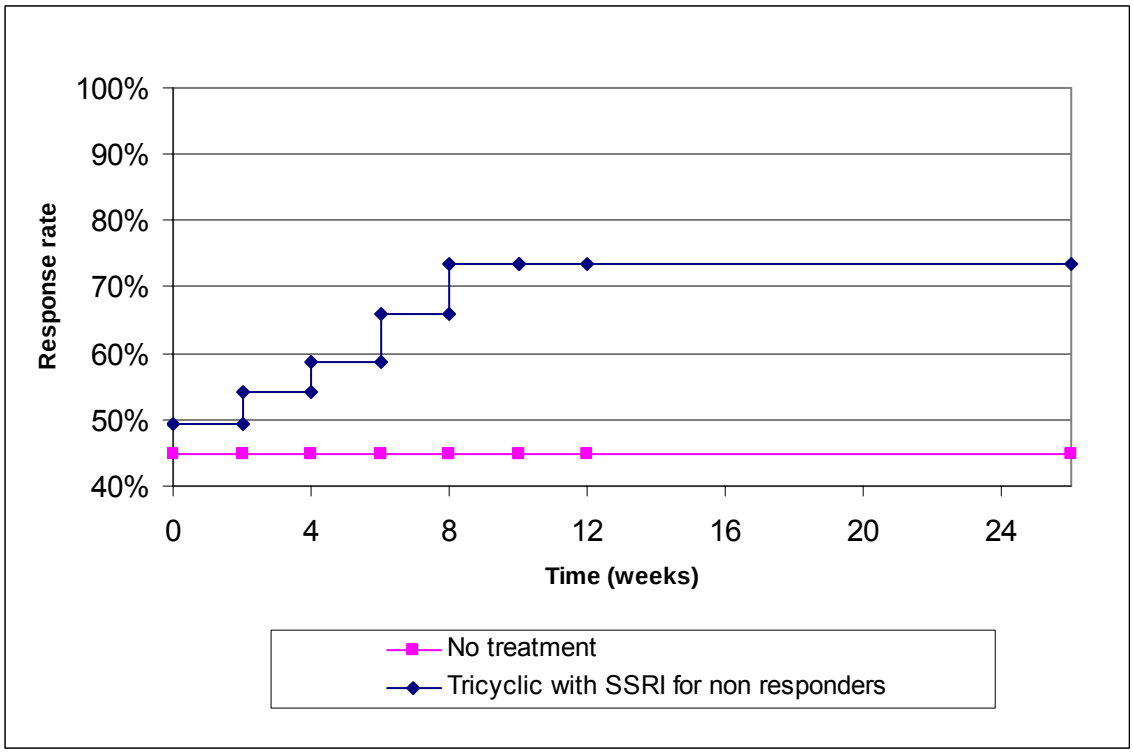


Figure 20: Response rates for an SSRI up to 20mg compared to no treatment

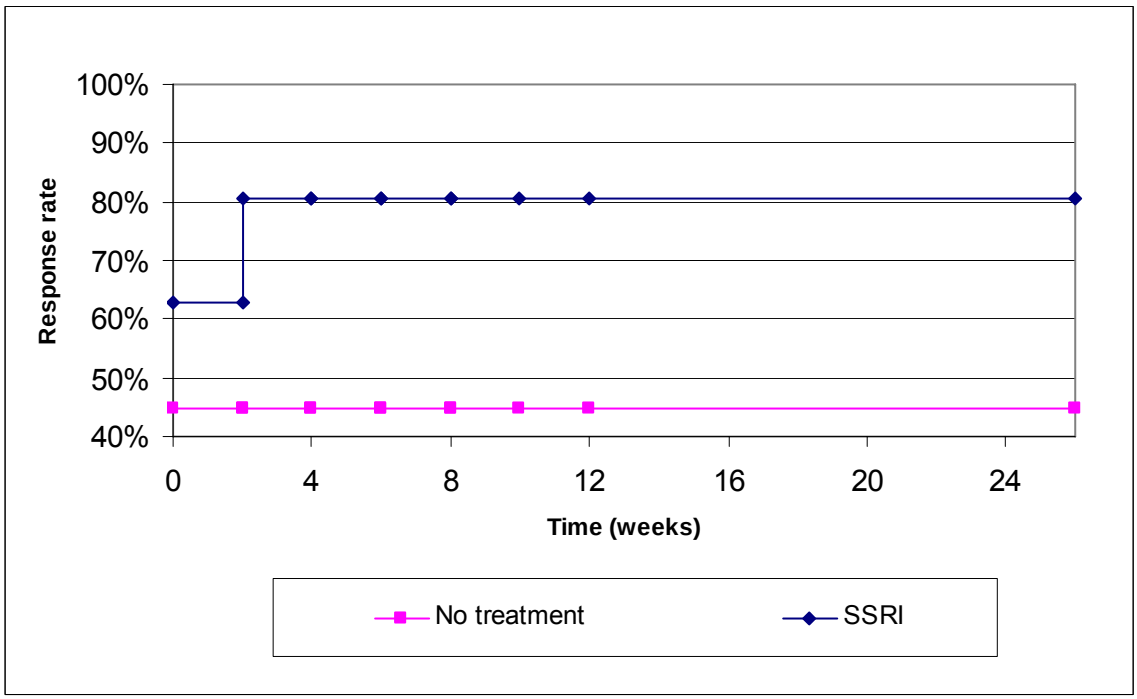


Figure 21: Response rates for an SSRI up to 20mg followed by a tricyclic up to 30mg in non-responders compared to no treatment

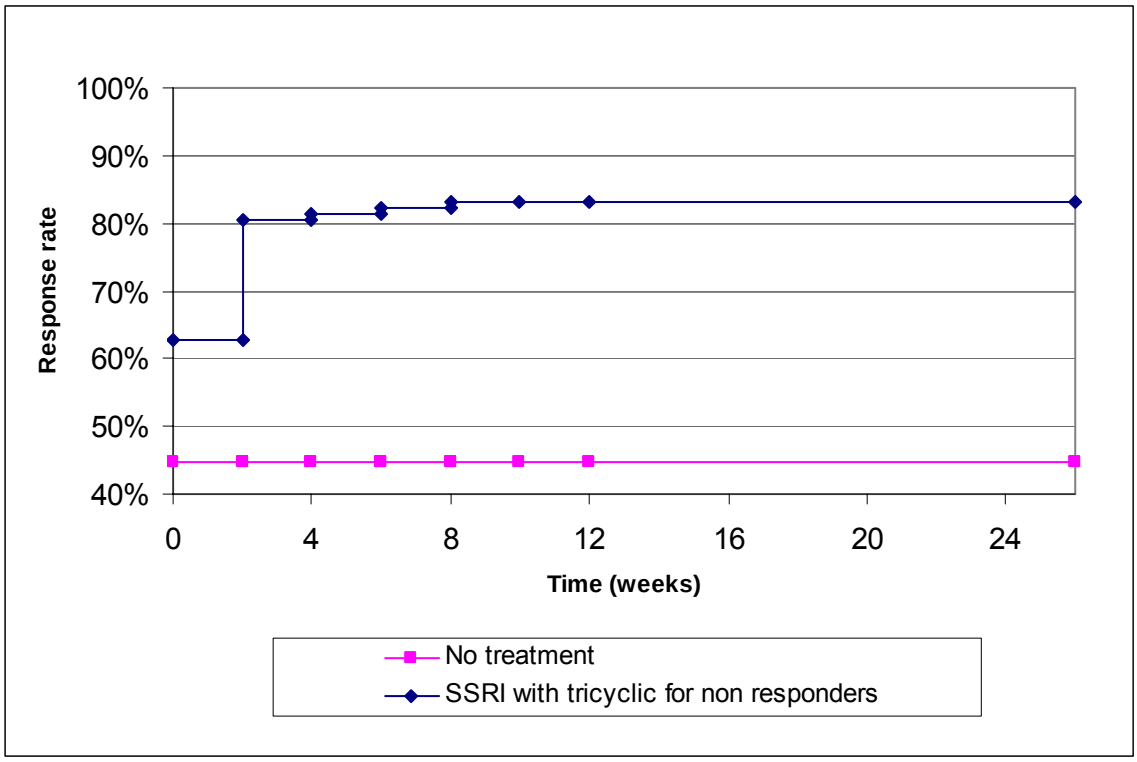
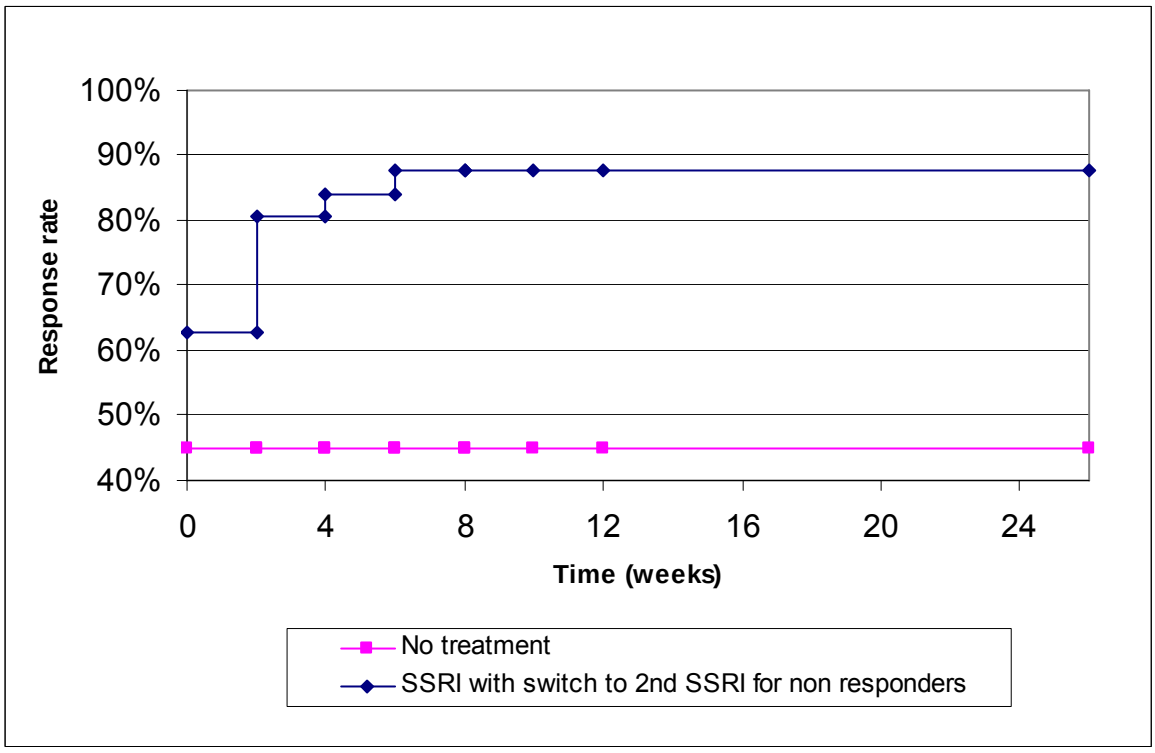


Figure 22: Response rates for an SSRI (up to 20mg) followed by a second SSRI in non-responders compared to no treatment



Amitriptyline tablets were the lowest cost tricyclic at doses of 10mg to 20mg. Doxepin had a lower cost per 10mg but the smallest tablet size is 50mg, so it was not considered practical to assume that doxepin is commonly prescribed at a doses of 10 to 30mg per day. It was assumed in the model that 10mg amitriptyline tablets (non-proprietary) are prescribed as the first line tricyclic, with trimipramine (Surmontil®) prescribed second line. The highest cost tricyclic was amitriptyline solution (non-proprietary) at £5.03 per month for a dose of 10mg per day, so this preparation was used in the high drug cost sensitivity analysis.

Of the two SSRIs considered, the lowest cost preparation is fluoxetine (non-proprietary) and it was assumed that this is prescribed first line, with the lowest cost paroxetine preparation (non-proprietary) prescribed second line. A sensitivity analysis was carried out assuming that the highest cost preparation is prescribed (Branded liquid preparations of fluoxetine and paroxetine at £14.40 and £9.62 per month respectively).

Table 1: Intervention specific parameters – Tricyclics

Description	**Value**		**Evidence**
RR of response for TCA vs placebo	1.31		Meta-analysis of RCT evidence for improvement in global symptoms
Maximum number of switches considered	1 to second tricyclic or SSRI		Assumption based
Drug costs			
Intervention	**Dose per day**	**Cost per month*(assuming lowest cost preparation)**	
Amitriptyline	10mg to 30mg	£1.43 to £4.30	
Doxepin		£1.24 to £3.72	not avail under 50mg
Trimipramine		£3.87 to £11.61	

* British National Formulary (Joint Formulary Committee 2007)

Table 2: Intervention specific parameters – SSRIs

Description	**Value**		**Evidence**
RR of response for TCA vs placebo	1.80		Meta-analysis of RCT evidence for improvement in global symptoms
Maximum number of switches considered	1 to Tricyclic or second SSRI		Assumption based
Drug costs			
Intervention	**Dose per day**	**Cost per month*(assuming lowest cost preparation)**	
Fluoxetine	10mg to 20mg	£0.75 to £1.50	
Paroxetine	10mg to 20mg	£3.05 to £6.10	

* British National Formulary (Joint Formulary Committee 2007)

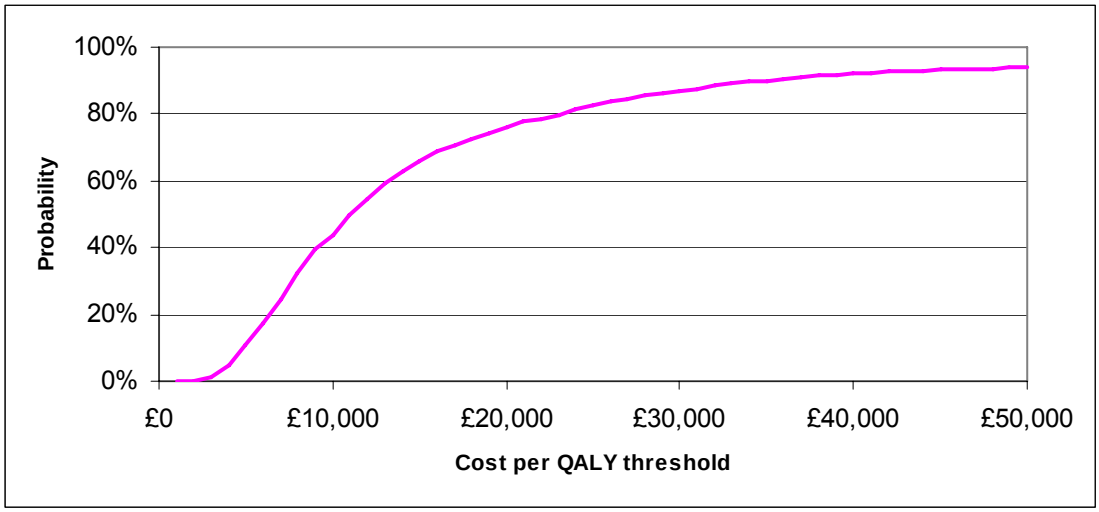
RESULTS

Tricyclic up to 30mg but no further treatment if no response

A strategy of using up to 30mg of tricyclic is estimated to provide 0.46 additional QALYs (difference between QALYs gained for intervention and no treatment), at a cost of £4,459, compared to no treatment for a cohort of 100 patients over a 6 month period, provided treatment is not continued in those who do not respond to a dose of 30mg. This strategy has a cost per QALY of £9,762, compared to no treatment, in the first 6 months after initiating treatment. Treatment can be continued in the next 6 months for a cost per QALY of £3,395 provided that treatment is reviewed every 6 months and discontinued in patients who no longer experience a therapeutic benefit, either due to lack of effectiveness or a change in their symptom profile.

The probabilistic sensitivity analysis estimates the uncertainty in the cost-effectiveness due to uncertainty surrounding the efficacy estimate, the utility gain, and the response rate in the no treatment arm. The results of this analysis are presented in Figure 24 as a CEAC, which shows the probability of the cost per QALY falling under various thresholds. The CEAC shows that a strategy of prescribing up to 30mg of tricyclic has a 76% probability of being under £20K compared to no treatment over a 6 month timeframe.

Figure 23: CEAC for up to 30mg of tricyclic compared to no treatment



Univariate sensitivity results for up to 30mg of tricyclics

The basecase cost-effectiveness estimates assume that an equal number of patients respond to the 10mg, 20mg and 30mg doses. However, if we assume that patients only respond after reaching the 30mg dose, then the cost per QALY is higher at £11,296. If patients are allowed to increase their dose up to 50mg in order to achieve a response and we assume that no patient responds to a lower dose then the cost per QALY is significantly higher at £17,937.

If the highest cost preparation is prescribed instead of the lowest cost preparation, then the cost per QALY is increased to £14,022. If the GP follow-up is twice as frequent as modelled in the

pathway (i.e. every two weeks until an effective dose is established instead of every four weeks and two follow-up appointments in the next 12 weeks instead of one), then the cost per QALY is increased to £17,826. These sensitivity analyses suggest that using tricyclics at doses of up to 30mg is likely to be cost-effective compared to no treatment, even if the costs of care are higher than estimated in the modelled care pathway.

The threshold analysis on the utility gain associated with an improvement in global symptoms shows that the cost per QALY would be over £20,000 if the utility gain is less than 0.035. For comparison, we used a utility gain of 0.071 in the basecase and a utility gain of 0.135 would be equivalent to a complete resolution of IBS symptoms.

Table 3: Results for up to 30mg tricyclic (amitriptyline) with no switches compared to no treatment in a cohort of 100 patients with IBS (all subtypes)

Scenario	No Treatment		Intervention		Incremental
	Cost	QALY	Cost	QALY	Cost per QALY
Basecase	0	1.60	4,459	2.05	9,762
No response in no treatment arm	0	0	4,252	0.46	9,308
Response rate in no treatment arm from RCTs	0	1.69	4,487	2.18	9,266
None respond until 30mg dose	0	1.60	4,730	2.01	11,296
Gradual response up to 50mg	0	1.60	5,661	2.01	13,521
None respond until 50mg	0	1.60	6,145	1.94	17,937
Higher cost formulation (liq)	0	1.60	6,405	2.05	14,022
Follow-up twice as freq	0	1.60	£8,143	2.05	17,826
High utility gain of 0.135	0	3.02	4,459	3.89	5,156
Threshold analysis on lowest utility	A cost per QALY of £20,000 is reached when the QALY gain associated with responding to treatment lies between 0.034 and 0.035.				

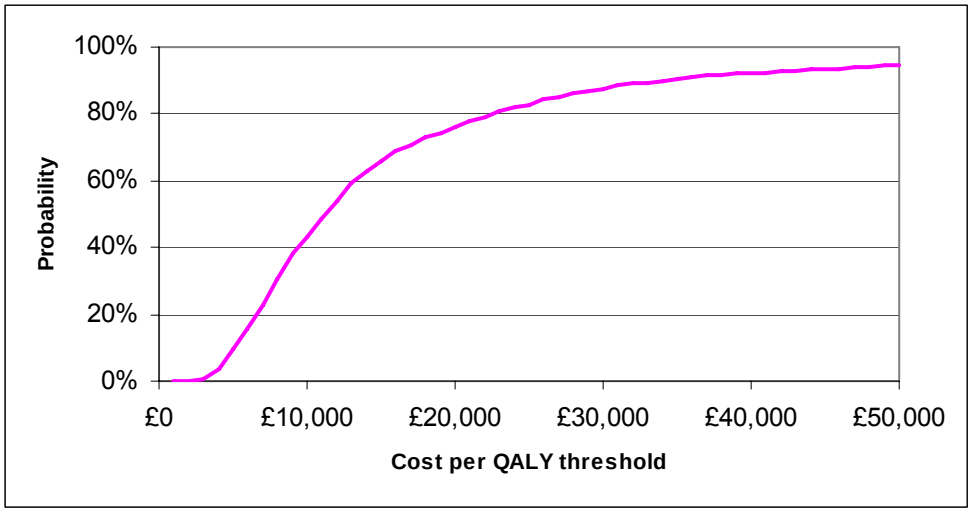
Tricyclic up to 30mg with switch to a second tricyclic if no response to first

If patients who do not respond to 30mg of tricyclic are allowed to switch to a second tricyclic drug, and we assume that the second tricyclic is just as likely to be effective, then the cost rises to £5,858 per 100 patients over the first 6 months, but the total QALY gain is increased to 0.60. The cost per QALY of treating patients with up to two tricyclics to gain a response is £9,789 per QALY compared to no treatment, and £9,873 compared to stopping treatment after the first

tricyclic. Even if the chance of response to the second tricyclic is half the chance of response to the first, the cost per QALY is £10,912 compared to no treatment and £18,324 compared to stopping after a failure on the first tricyclic.

A probabilistic sensitivity analysis was carried out on the cost-effectiveness of allowing non-responders to switch to a second tricyclic compared to no further tricyclic therapy for those who do not respond to the first tricyclic. The CEAC in Figure 25 shows that a strategy of prescribing up to 30mg of tricyclic with a switch to a second tricyclic for non-responders has an 87% likelihood of being under £20K compared to no further treatment for non-responders to 30mg of tricyclic.

Figure 24: CEAC for up to 30mg a tricyclic with switch to a second tricyclic if no response compared to up to 30mg tricyclic without switch for non-responders



Tricyclic up to 30mg followed by an SSRI if no response to tricyclic

If patients who do not respond to 30mg of tricyclic are allowed to switch to an SSRI (up to 20mg), and we assume that the SSRI effectiveness is independent of the response to the tricyclic, then the cost rises to £5,648 per 100 patients over the first 6 months, but the total QALY gain is increased to 0.84. The cost per QALY of treating patients with a tricyclic at doses of up to 30mg followed by an SSRI of up to 20mg is £6,703 per QALY compared to no treatment, and £3,080 compared to stopping after the tricyclic. Even if the chance of response to the SSRI is half the chance of response seen in the SSRI trials, then the cost per QALY is £8,450 compared to no treatment and £5,342 compared to stopping after a failure on the tricyclic.

A probabilistic sensitivity analysis was carried out on the cost-effectiveness of allowing non-responders to switch to a SSRI compared to no further SSRI therapy for those who do not respond to the first tricyclic. The CEAC in Figure 26 shows that a strategy of prescribing up to

30mg of tricyclic with a switch to an SSRI for non-responders has a 95% likelihood of being under £10K compared to no further treatment for non-responders to 30mg of tricyclic.

Figure 25: CEAC for up to 30mg of tricyclic with switch to an SSRI if no response compared to up to 30mg of tricyclic without switch for non-responders

SSRI up to 20mg but no further treatment if no response

A strategy of using up to 20mg of SSRI is estimated to provide 1.23 additional QALYs, at a cost of £3,708, compared to no treatment for a cohort of 100 patients over a 6 month period, provided treatment is not continued in those who do not respond to a dose of 20mg. This strategy has a cost per QALY of £3,020 compared to no treatment, in the first 6 months after initiating treatment. Treatment can be continued in the next 6 months for a cost per QALY of £1,483 provided that treatment is reviewed every 6 months and discontinued in patients who no longer experience a therapeutic benefit, either due to lack of effectiveness or a change in their symptom profile.

These estimates assume that an equal number of patients respond to the 10mg and 20mg doses. However, if we assume that patients only respond after reaching the 20mg dose, then the cost per QALY is higher at £3,209. If patients are allowed to increase their dose up to 40mg in order to achieve a response, then the cost per QALY is significantly higher at £3,790 when using the dose distribution from Tabas (2004). However, if no patient responds until a dose of 40mg is reached then the cost per QALY is higher still at £4,698.

If the highest cost preparation is prescribed instead of the lowest cost preparation, then the cost per QALY is increased to £9,799. If the GP follow up is twice as frequent as modelled in the pathway (i.e every two weeks until an effective dose is established instead of every four weeks and two follow-up appointments in the next 12 weeks instead of one), then the cost per QALY is increased to £5,667. These sensitivity analyses suggest that using SSRIs at doses of up to

20mg is likely to be cost-effective compared to no treatment, even if the costs of care are higher than estimated in the modelled care pathway.

The threshold analysis on the utility gain associated with an improvement in global symptoms shows that the cost per QALY would be over £20,000 if the utility gain is less than 0.011. For comparison, we have used a utility gain of 0.071 in the basecase and a utility gain of 0.135 would be equivalent to a complete resolution of IBS symptoms.

Table 4: Results for up to 20mg SSRI (fluoxetine) with no switches compared to no treatment in a cohort of 100 patients with IBS (all subtypes)

Scenario	No Treatment		Intervention		Incremental
	Cost	QALY	Cost	QALY	Cost per QALY
Basecase	0	1.60	3,708	2.82	3,020
No response in no treatment arm	0	0	2,747	1.23	2,237
Response rate in no treatment arm from RCTs	0	1.69	3,817	2.99	2,932
None respond until 20mg dose	0	1.60	3,783	2.78	3,209
Gradual response up to 40mg	0	1.60	4,430	2.77	3,790
None respond until 40mg	0	1.60	5,076	2.68	4,698
Higher cost formulation (liq)	0	1.60	12,032	2.82	9,799
Follow-up twice as freq	0	1.60	6,959	2.82	5,667
High utility gain of 0.135	0	3.02	3,708	5.35	1,595
Threshold analysis on lowest utility	A cost per QALY of £20,000 is reached when the QALY gain associated with responding to treatment lies between 0.010 and 0.011.				

A probabilistic sensitivity analysis was carried out on the cost-effectiveness of treatment with an SSRI (up to 20mg) compared to no treatment. The CEAC in Figure 27 shows the probability of the cost per QALY falling under various thresholds. The CEAC shows that a strategy of prescribing up to 20mg of SSRI has a 95% likelihood of being under £10K compared to no treatment over a 6 month timeframe.

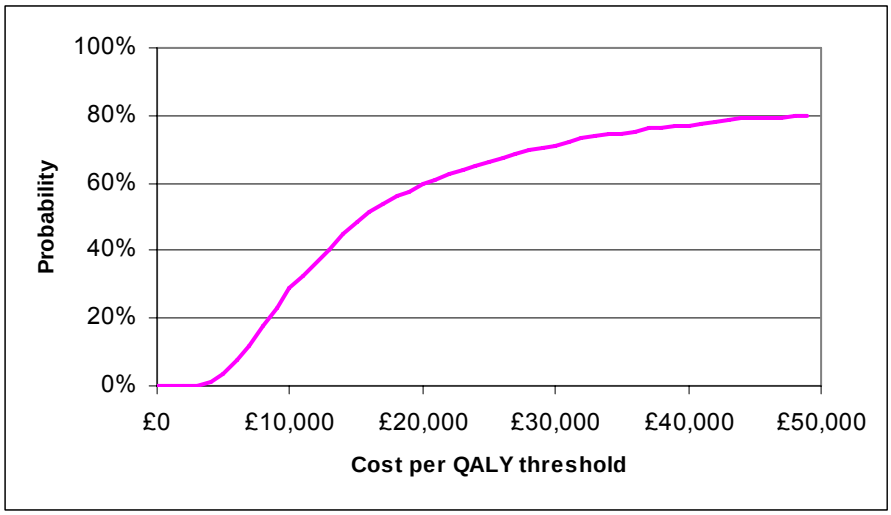
Figure 26: CEAC for SSRI up to 20mg (with no switching for non-responders) compared to no treatment

SSRI up to 20mg with switching to a tricyclic (up to 30mg) if no response to SSRI

If patients who do not respond to 20mg of SSRI are allowed to switch to a tricyclic drug (up to 30mg), and we assume that the tricyclic effectiveness is independent of the response to the SSRI, then the cost rises to £4,526 per 100 patients over the first 6 months, but the total QALY gain is increased to 1.30. The cost per QALY of allowing patients to try an SSRI followed by a tricyclic is £3,477 per QALY compared to no treatment, and £11,073 compared to stopping after the SSRI. Even if the chance of response to the tricyclic in patients who haven't responded to an SSRI is half the chance of response seen in the tricyclic trials, the cost per QALY is £3562 compared to no treatment and £21,574 compared to stopping after a failure on the first tricyclic. If the frequency of follow-up is twice that estimated in the basecase pathway, then the cost per QALY for treatment with an SSRI, followed by a TCA in non responders, is £6,523 compared to no treatment and £20,750 compared to stopping treatment after the SSRI.

A probabilistic sensitivity analysis was carried out on the cost-effectiveness of allowing non-responders to switch to a tricyclic compared to no further tricyclic therapy for those who do not respond to the SSRI. The CEAC in Figure 28 shows that a strategy of prescribing up to 20mg of SSRI with a switch to a tricyclic for non-responders has a 59.6% probability of being under £20K compared to no further treatment for non-responders to 20mg of SSRI. In the probabilistic analysis, there is a 12.8% probability that all of the patients respond to the first SSRI resulting in no further benefit to be gained by switching patients to a second SSRI. In drawing the CEAC we have assumed that the cost per QALY of allowing patients to switch would be above any reasonable threshold when no benefit can be achieved for that switch.

Figure 27: CEAC for up to 20mg of SSRI with switch to tricyclic if no response compared to up to 20mg SSRI without switch for non-responders



SSRI up to 20mg with a second SSRI (up to 20mg) if no response to first SSRI

If patients who do not respond to 20mg of SSRI are allowed to switch to a second SSRI (up to 20mg), and we assume that the effectiveness of the second SSRI is independent of the response to the first SSRI, then the cost rises to £4,677 per 100 patients over the first 6 months, but the total QALY gain is increased to 1.43. The cost per QALY of allowing patients to try an SSRI followed by a tricyclic is £3,275 per QALY compared to no treatment, and £4,843 compared to stopping after the first SSRI. Even if the chance of response to the second SSRI in patients who haven't responded to the first SSRI is half the chance of response seen in the SSRI trials, the cost per QALY is £3,361 compared to no treatment and £7,544 compared to stopping after a failure on the first SSRI.

A probabilistic sensitivity analysis was carried out on the cost-effectiveness of allowing non-responders to switch to a second SSRI compared to no further SSRI therapy for those who do not respond to the first SSRI. The CEAC in Figure 29 shows that a strategy of prescribing up to 20mg of SSRI with a switch to a second SSRI for non-responders has a 75% likelihood of being under £10K compared to no further treatment for non-responders to 20mg of SSRI. Again, there is a 12.8% probability that all of the patients respond to the first SSRI resulting in no further benefit to be gained by switching patients to a second SSRI. In drawing the CEAC we have assumed that the cost per QALY of allowing patients to switch would be above any reasonable threshold when there is no benefit can be achieved for that switch.

Figure 28: CEAC for up to 20mg SSRI with switch to a second SSRI if no response compared to up to 20mg SSRI without switch for non-responders

Indirect comparison of tricyclics and SSRIs

The results presented above (see Tables 3 and 4) for tricyclics compared to no treatment and SSRIs compared to no treatment, suggest that SSRIs are more cost-effective than tricyclics as they have a larger QALY gain and lower cost compared to usual care. However, as discussed earlier, this conclusion should be treated with caution as it is based on an indirect comparison and these have a high potential for bias.

EVIDENCE STATEMENTS

For this review, the evidence was assessed using the GRADE process and tables are shown in Appendix F. The following evidence statements are derived from the GRADE tables.

1. There is a moderate amount of good quality evidence, mainly in patients with refractory IBS and with some depression, showing a significant global improvement in symptoms for both tricyclics and SSRIs when compared with placebo.

2. There is limited evidence to show:
   - A significant reduction in pain and bloating for tricyclics when compared with placebo.
   - A borderline improvement in bowel habit for tricyclics when compared with placebo.

3. There is a moderate amount of good quality evidence showing show no significant improvement in global symptoms for 50mg tricyclics (Trimipramine) compared with 30mg.

4. The evidence is inconclusive as to whether there is an improvement in pain for SSRIs compared with placebo.

5. There is a moderate amount of good quality evidence to show there is no significant reduction in bloating or improvement in bowel habit for SSRIs when compared with placebo.

6. There is a moderate amount of weak evidence to show there is no significant improvement in quality of life for SSRIs when compared with usual care.

7. There is a moderate amount of good quality evidence to show there are significantly more patients discontinuing treatment with SSRIs compared with usual care.

ADVERSE EFFECTS EVIDENCE STATEMENTS (BASED ON NICE CLINICAL GUIDELINE 23 'DEPRESSION')

8. Patients started on antidepressants who are not considered to be at increased risk of suicide should normally be seen after 4 weeks. Thereafter they should be seen on an appropriate and regular basis.

9. In patients in primary care, there is insufficient evidence to determine whether there is a clinically significant difference between other antidepressants and amitriptyline (TCA) on reducing the likelihood of leaving treatment early either for any reason or due to side effects.

10. There is good evidence in trials of eight weeks and longer, that there is no clinically significant difference between SSRIs and placebo on reducing the likelihood of leaving treatment early. This is not consistent when analysing the reasons for leaving treatment, which demonstrate a clinically significant difference favouring placebo over SSRIs in relation to leaving the treatment early due to side effects.

HEALTH ECONOMIC STATEMENT

Evidence from a decision analytic model showed that low dose tricyclics and SSRIs (trimipramine, amitriptyline, doxepin, paroxetine, fluoxetine) are cost-effective for long-term maintenance use in individuals with IBS. The cost-effectiveness estimate is based on a clinical pathway in which dose is increased gradually and response is assessed every four weeks until an effective dose is established or the maximum dose is reached. Trying a second tricyclic or SSRI in an individual who has not responded to a previous tricyclic or SSRI is also likely to be cost-effective when assuming that response to the second treatment is independent of a lack of response to the first. The cost-effectiveness analysis assumes that treatment is reviewed every 6 months to establish whether it is still relevant to the individual's symptom profile.

EVIDENCE TO RECOMMENDATIONS

There is evidence from the clinical and cost effectiveness that tricyclics and SSRIs are effective in the symptom management of IBS. The GDG also took into consideration the reported adverse effects of tricyclics and SSRIs, but noted that the doses used for the management of IBS are

similar to those used in the treatment of chronic pain and are thus much lower than starting doses used for the management of depression. The GDG was concerned that primary care clinicians consider the side effects when prescribing tricyclics and SSRIs. Although the reported side effects of tricyclics are more common (at higher doses) than SSRIs, the GDG reported that, in primary care, tricyclics are used in preference to SSRIs in low doses. Therefore the GDG advised that Tricyclics and SSRIs should be prescribed as second line treatment, starting with Tricyclics, and moving on to SSRIs only when the former had been shown to be ineffective.

RECOMMENDATION

Healthcare professionals should consider tricyclic antidepressants (TCAs)* as second-line treatment for people with IBS if laxatives, loperamide or antispasmodics have not helped. TCAs are primarily used for treatment of depression but are only recommended here for their analgesic effect. Treatment should be started at a low dose (5–10 mg equivalent of amitriptyline), which should be taken once at night and reviewed regularly. The dose may be increased, but does not usually need to exceed 30 mg.

* At the time of publication (February 2008) TCAs did not have UK marketing authorisation for the indications described. Informed consent should be obtained and documented.

RECOMMENDATION

Selective serotonin reuptake inhibitors (SSRIs) should be considered for people with IBS only if TCAs have been shown to be ineffective.

** At the time of publication (February 2008) SSRIs did not have UK marketing authorisation for the indication described. Informed consent should be obtained and documented.

RECOMMENDATION

Healthcare professionals should take into account the possible side effects when prescribing TCAs or SSRIs***. After prescribing either of these drugs for the first time at low doses for the treatment of pain or discomfort in IBS, the person should be followed up after 4 weeks and then at 6–12 monthly intervals thereafter.

*** At the time of publication (February 2008) SSRIs did not have UK marketing authorisation for the indication described. Informed consent should be obtained and documented.

8.5 Adverse effects of pharmacological interventions

BACKGROUND

A wide variety of pharmacological interventions are available for the treatment of irritable bowel syndrome (IBS). As the various classes of agents have different pharmacological mechanisms of action, people with IBS may potentially be troubled by a wide range of adverse effects, depending on which treatment they are taking. While people with IBS are unlikely to experience significant harm from short-term or intermittent therapy, potential problems may arise if the drugs were taken over a longer-term period.

In making informed treatment decisions, health care professionals and people with IBS need to carefully weigh up evidence on the anticipated benefits against that of any relevant concerns about the safety and tolerability of IBS drug therapy. There are a few fundamental questions that can potentially be usefully answered from a review of adverse effects data:

- For people with IBS and health care professionals choosing to use a particular drug therapy for IBS, the review can inform them of potential adverse effects that could be anticipated from that therapy
- Availability of comparative data among different drugs can help in reaching a treatment decision based on which safety profile (or nature and frequency of adverse effects) is more acceptable.

While the overall frequencies of any adverse effects have been evaluated in the parallel efficacy reviews of IBS, there was limited detail given on what the specific adverse effects were, and whether the classes of drugs differ in their safety and tolerability profile.

8.5.1 Adverse effects: antispasmodics, antimotility agents and laxatives

SELECTION CRITERIA

The selection criteria described in the general methodology section were used, but some were specific to the evaluation of adverse effects and are reported in the following sections.

Types of studies

We did not apply any specific inclusion criteria based on study design; however, we preferred to exclude:

- Single case reports, as there was substantial scope for reporting and publication bias (towards the esoteric, interesting cases), and such cases may not have been representative of the general patient population
- Crossover studies, as it was impossible to discriminate between events that arise as a medium-long term complication of the first (previous) treatment, or as events resulting from the present therapy. This was particularly so as the protocol was primarily interested in evaluation of long-term effects from chronic administration of drugs for IBS. Moreover,

adverse events are usually measured as dichotomous outcomes, (presence or absence of an adverse effect) and it was technically challenging to incorporate dichotomous measures from crossover studies into meta-analyses.

For the broad overall review, we accepted all studies evaluating the safety or tolerability of any drug therapy in populations of people with IBS.

We also looked at adverse effects for three specific classes of drugs for IBS; their selection criteria are listed below by each class of agent:

1. Antispasmodics

Interventions of interest:

- Dicyclomine bromide
- Hyoscamine (atropine)
- Hyoscine
- Alverine
- Mebeverine (including modified release)
- Peppermint oil.

Duration of intervention: minimum 4 weeks.

Outcomes

All outcomes reported within the categories of 'adverse effects, side effects, adverse events, complications, safety, or tolerability'.

2. Antimotility Agents

Interventions of interest:

1. Loperamide
2. Co-phenotrope/Lomotil/Diphenoxylate.

Duration of intervention: minimum 4 weeks.

Outcomes

All outcomes reported within the categories of 'adverse effects, side effects, adverse events, complications, safety, or tolerability'.

3. Laxatives

Types of participants

People with symptoms of IBS, including those with single symptom of IBS i.e. chronic constipation with no physical cause.

Excluded: studies of long-stay patients in hospital or nursing home setting, and palliative care patients (evidence too indirect as the groups are very different from people with IBS).

Interventions of interest:

1. Polyethylene glycol (PEG) laxatives
2. Lactulose.

Duration of intervention: minimum 4 weeks.

Outcomes

All outcomes reported within the categories of 'adverse effects, side effects, adverse events, complications, safety, or tolerability'.

Quality of Adverse Effects Data

The techniques used in this review were generally based on advice within the Cochrane Handbook of Systematic Reviews regarding the assessment of adverse effects. This states, in particular, that the value of the data relies heavily on two major factors:

- How thorough were the methods used in monitoring adverse effects?
- How complete or detailed was the reporting?

In view of this, we concentrated on recording the following parameters:

- What methods (if any) did the trials stipulate for the specific assessment of AEs?
- Did the investigators pre-specify any possible adverse events that they were particularly looking out for?
- What categories of adverse effects were reported?

Identification of studies

We used a mixed strategy of checking articles that had already been retrieved for the efficacy reviews, and a new search of MEDLINE, EMBASE, CINAHL and the Cochrane Controlled Trials Register (search string: *'drug-class'/ adverse-effects)* with a total of 7206 hits. The search strategies are listed in Appendix B.

A total of 71 full text articles were screened; adverse effects data were extracted from 17 papers.

Study Design

The following types of studies were included in the adverse effects analysis:

- One non-randomised study which carried out an adverse effects survey in people with IBS
- Six randomised trials of antispasmodic agents
- One randomised trial of antimotility agents

- Seven randomised trials of laxatives (including one with a crossover design that should be considered with caution) and one observational long-term follow-up study.

Population

The underlying diagnosis was stated to be IBS for people in the observational study, as well as in the antispasmodic and antimotility agent trials.

However, the included laxative trials were predominantly in people with chronic or simple constipation, with no obvious physical cause. It is assumed that some of these people would have IBS.

Intervention and Comparisons

There was a very diverse range of interventions and associated comparator agents across the trials.

Assessment and Reporting of Adverse Effects

The results for the included trials are shown in Table 4 to Table 9.

Although some trials stated that they specifically enquired about adverse effects, none of them actually stated whether this was an open question e.g. 'Are you having any problems with the treatment?' of if the enquiry was targeted at particular symptoms e.g. 'Have you had any diarrhoea?'

Moreover, some trials stated that people were asked to record problems in a diary, but the trial report gives no details about whether people had to record specific events (including when and how often) or if it was left to their discretion.

RESULTS

Overall Effects of Medication on people with IBS

Only one study looked at the overall impact of medication-related adverse effects on people with IBS (Lembo 2004). This was an online survey carried out in the United States, with people identified from a computer database. This survey collected data on medication use (questions on therapies used for symptoms of IBS) and self-reported assessment of adverse effects. Respondents were given a list of GI and non-GI adverse effects (including a free text entry box) and asked if they had experienced any side effects.

All respondents stated that they had been diagnosed with IBS by their physicians. Most of the participants were women (88%) with a median age of 45 years. The average number of medications they had tried was 3.3. Of the 668 respondents, 504 reported constipation as their primary symptom i.e. most people were of the IBS-C subtype.

The survey covered more than 10 drug classes, including laxatives, antispasmodics, antimotility agents, antidepressants etc., but the article reported mainly on laxatives and antispamodics. Overall 51% of people on antispasmodics complained of at least one adverse effect, in contrast to 59% of people on laxatives. Raw data from this survey was reported based on drug class, and the author did not specify what the individual agents and dosages were. The overall figures were:

Table 1.

Side Effect	Laxative		Antispasmodic	
	(n=171)	*%*	(n=189)	*%*
Any	100	*58*	96	*51*
Drowsiness			43	*23*
Dizziness	5	*3*	17	*9*
Insomnia	1	*1*	2	*1*
Nausea	32	*19*	4	*2*
Abdominal cramps	67	*39*	9	*5*
Abdominal pain	36	*21*	6	*3*
Abdominal discomfort	55	*32*	8	*4*
Bloating	36	*21*	6	*3*
Dry mouth	8	*5*	47	*25*
Headache	4	*2*	8	*4*
Decreased sexual interest	1	*1*	2	*1*
Constipation	7	*4*	9	*5*
Diarrhea	31	*18*	2	*1*
None	71	*42*	93	*49*
SEVERITY				
Mild	62	*36*	113	*60*
Moderate	94	*55*	55	*29*
Severe	14	*8*	21	*11*

The four most frequent adverse effects of antispasmodics are listed below. Figures for laxative users are given for purposes of comparison:

Table 2.

	Antispasmodic (N= 189)	Laxative (N= 171)	Relative risk (95% CI)
Dry mouth	47 (25%)	8 (5%)	5.32 (2.59 – 10.94)
Drowsiness	43 (23%)	0 (0%)	Not estimable (Odds Ratio 8.65)
Dizziness	17 (17%)	6 (3%)	2.56 (1.03- 6.34)
Constipation	9 (5%)	7 (4%)	1.16 (0.44-3.05)

The six most frequent adverse effects of laxatives are listed below. Figures for antispasmodic users are given for purposes of comparison.

Table 3.

	Laxative (N=171)	Antispasmodic (N=189)	Relative risk (95% CI)
Abdominal cramp	67 (39%)	9 (5%)	8.23 (4.24-16.0)
Abdominal discomfort	56 (32%)	8 (4%)	7.74 (3.80-15.8)
Bloating	36 (21%)	6 (3%)	6.63 (2.86-15.3)
Diarrhoea	31 (18%)	2 (1%)	17.13 (4.16-70.5)
Abdominal pain	36 (21%)	6 (3%)	6.63 (2.86-15.3)
Nausea	33 (19%)	4 (2%)	9.12 (3.3 – 25.2)

These findings indicated that laxatives wee significantly associated with GI adverse effects, while antispasmodics were associated with dry mouth, dizziness and drowsiness. The Relative Risk figures must be interpreted with caution as the treatment groups were not randomly allocated, and people with particular IBS symptoms may have been selectively channelled towards a specific class of treatment. However, it seems unlikely that channelling based on IBS subtype and existing gastrointestinal symptoms would have accounted for the marked difference seen with regards to side effects symptoms such as dry mouth, drowsiness and dizziness. Moreover, 504/668 (75%) of the respondents stated that constipation was their primary symptom. As the respondents had tried a mean of 3.9 IBS therapies, their adverse experiences with different classes of drugs could have been reflected within the survey responses.

Strengths of the study were that it surveyed people outside a trial setting, and they may potentially have been able to take the treatments over a longer time period. One important feature of the study was that it specifically enquired about certain adverse effects, covering both GI and non-GI problems.

The main weaknesses were that there was considerable potential for selection bias as the respondents may not have been typical of people with IBS. Recall bias was also a major problem if the treatments were taken a long time ago. We were also not certain of the diagnosis of IBS, as this was based on the respondents reporting that they had been diagnosed by a physician. As the survey was carried out in the US, larger or different dose regimens may have been used. Perhaps the most important limitation was that the individual agents were not listed, and lumping by drug class obscured any differences in the safety profiles of individual agents within a class.

RESULTS OF SPECIFIC CLASSES OF IBS THERAPIES

1. Antispasmodics

There were six included RCTs.

The interventions and comparators were extremely varied, as was the reporting of adverse effects outcomes. In view of this, no meta-analysis was performed and a descriptive summary is given in the appendix.

Mebeverine versus Dicyclomine

There was a trend towards a lower rate of adverse effects in the mebeverine group (RR 0.33, 95% CI 0.10, 1.04; p=0.06). GI symptoms were more frequently seen with dicyclomine.

Mebeverine standard preparation versus Mebeverine sustained release

No clear difference in safety or tolerability could be seen.

Mebeverine versus Trimebutine

Adverse effects were non-significantly more common in people taking mebeverine, with dry mouth being the most common complaint with mebeverine. Note: Trimebutine is not listed in the British National Formulary.

Alverine versus placebo

The authors reported 5 adverse events with alverine related to the nervous system but did not give any details.

2. Antimotility agents

We only identified two RCTs with adverse effects data. One was a crossover trial which should be treated with caution (Cann 1984).

No clear trend could be identified.

3. Laxatives

There were 7 included RCTs. Most of them did not specifically state that the participants had IBS, although it was very likely that some of the people with chronic constipation would fulfil the criteria for IBS.

The interventions and comparators were extremely varied, as was the reporting of adverse effects. A descriptive summary is given in the appendix.

Non-randomised study of TransiPEG.

One long-term (6 month) observational study on 231 people taking TransiPEG provided limited information as there was no comparator group (Paille 1999). In this study, 21 people (9%) reported adverse effects with 14 (6%) stopping therapy due to adverse events. The most frequently reported problems were abdominal pain (8 people), flatulence (5 people), and diarrhoea (4 people).

Lactulose versus Isphagula husk.

Two RCTs were evaluated, one of which was a crossover study (Quah 2006), and the findings must therefore be viewed cautiously. Abdominal pain occurred at a higher rate in the lactulose arms than the isphagula husk arms.

PEG versus lactulose (Ferguson and Attar 1999; Bouhnik 2004)

There were non-significant trends towards lactulose causing more abdominal pain and bloating, as compared to PEG. Flatus was also more common with lactulose (RR 1.72, 95% CI 0.99, 2.72).

PMF versus Placebo.

No clear trend could be identified from the two small studies (Corazziari 1996; Corazziari 2000).

Different formulations of PEG

PEG 3350 and PEG 4000 showed similar rates of adverse effects. Low dose PEG in either form was associated with fewer adverse effects compared to high dose (Chaussade 2003).

The RCT data on lactulose was consistent with the findings of the non-randomised data with regards to increased risk of abdominal symptoms.

Limitations of the results

There were four major limitations that arose in this adverse effects review. The first problem was that the studies were primarily aimed at assessing and reporting on the efficacy of the drug treatments. Evaluation of safety took a back seat, and reporting of adverse effects data was often cursory or non-existent, even in instances where the methods sections had explicitly

stated the intention of monitoring for adverse effects. Trial reports did not follow a structured format (e.g. by WHO system organ class) of reporting adverse effects, thus making it impossible to pool outcomes data.

The second major issue ws that none of the included studies appeared to anticipate, or pre-specify particular adverse effects of interest or concern. It was often possible to predict, based on pharmacological mode of action, the potential adverse effects of a drug therapy. Trial investigators could have designed specific aspects of the protocol to concentrate on detecting these adverse effects. While some of the trials did specify general measures for monitoring overall adverse effects, none of the reports stated whether they were checking for any specific problems. Given the wide-ranging nature of possible adverse effects, it may have been very difficult for trials to reliably pick up safety issues, unless there was some prior awareness of what the potential problems might have been.

The third major limitation was that many of the adverse outcomes of interest were very similar to the symptoms of the IBS itself. For instance, laxatives were associated with flatulence, cramps and abdominal pain – all of which are commonly seen in people with untreated IBS, and also form part of the efficacy assessment. This made it very difficult for the investigators to differentiate between the progress of the condition and the harmful effects of the drug. Moreover, some of these symptoms were listed within the efficacy section of the trial report, and it was not possible to determine whether a deterioration in these symptoms was due to lack of efficacy, the natural history of the condition, or the adverse effect of the drug.

The final limitation was the lack of specific non-randomised studies aimed at eliciting adverse effects of drug therapy in IBS. The only such study we looked at was not focused on particular drugs, and was only able to provide data on broad classes of IBS therapies, without naming specific drugs.

Table 4: Details of RCTs of Antispasmodic agents

Author	Year	Study design	Drug & Dose	Control	Age	Mean duration
Grillage	1990	Randomised, double-blind, parallel-group	Mebeverine 135 mg 3x daily	Dicyclomine 10 mg 3x daily	26	8 weeks
Gilbody	2000	Randomised, double-blind, double-dummy	Mebeverine 200 mg b.i.d.	Mebeverine 135 mg t.i.d.	33	8 weeks
Schaffstein	1990	Randomised, double-blind, parallel-group	135 mg mebeverine tablet	200 mg trimebutine tablet	Not stated	28 days
Mitchell	2002	Double-blind, randomised, placebo-controlled, parallel group	120 mg alverine citrate 3x daily	Placebo capsules 3x daily	40	12 weeks
Liu	1997	Randomised, double-blind, placebo-controlled	Colpermin 3-4x daily	Placebo capsules 3-4x daily	Not stated	1 month
Van Outryve	1995	Randomised, double-blind, crossover	Mebeverine plain 135 mg, 2 capsules t.i.d.	Mebeverine sustained release 200 mg, 2 capsules b.i.d.	49	6 weeks

Table 5: Details of RCTs of Antispasmodic agents

Study	Methods used for AEs	Reports	Drug	Comparator
Grillage 1990	Diary system		**Mebeverine**	**Dicyclomine**
		Total participants	23	28
		with any AE	3	11
		with severe AE	0	0
		stopped due to AE	1	2
		Specific details	Weight increase, headache, flatulence, tremor. Reason for drop-out: weight increase.	Gastrointestinal disturbance (nausea, dysphagia, flatulence, dyspepsia, diarrhoea) - 7 Back pain, headache, agitation. Reason for drop-out: nausea, agitation.
Gilbody 2000	Diary system, laboratory tests		**Mebeverine 200mg bd**	**Mebeverine 135mg tds**
		Total participants	106	107
		with any AE	63	66
		with severe AE	4	2
		stopped due to AE	0	0
		Specific details	Abdominal pain Diarrhoea (Total drop-outs appear unrelated to study medication: 4 for elective surgery, 1 pregnancy, 1 bloody diarrhoea - ulcerative colitis)	Abdominal pain Diarrhoea

Study	Methods used for AEs	Reports	Drug	Comparator
Schaffstein 1990	Specific enquiry at follow up, spontaneous reporting, urine biochemistry		**Mebeverine 135 mg**	**Trimebutine 200 mg**
		Total participants	100	99
		with any AE	8	2
		with severe AE	0	0
		stopped due to AE	1	1
		Specific details	Reason for drop-out: diarrhoea. Upper abdominal heaviness - 1 Dry mouth + nausea - 1 Erythrocyte count < normal on day 28 - 3	Reason for drop-out: headache, drowsiness, fever, pruritus. Dry mouth - 4 Hot flush - 3 Opthalmic pain, bitter taste, nausea - 1 Erythrocyte count < normal on day 28 - 9
Mitchell 2002	Spontaneous reports (unexpected events from people with IBS or investigators)		**Alverine**	**Placebo**
		Total participants	53	54
		with any AE	21 (40%)	26 (48%)
		with severe AE	0	0
		stopped due to AE	0	0
		Specific details	5 AEs related to nervous system	
Liu 1997	Liver function test		**Colpermin**	**Placebo**
		Total participants	52	49
		with any AE	0	0
		with severe AE	0	0
		stopped due to AE	0	0
		Specific details	Heatburn from chewing capsule - 1 Skin rash (mild, transient) - 1	
Van Outryve 1995	Clinical exam, spontaneous reporting, biological tests		**Mebeverine 270mg tds**	**Mebeverine 200 mg bd**
		Total. of participants	60	60

		No. with any AE	12	8
		No. with severe AE	0	0
		No. stopped due to AE	0	0
		Specific details	Limb cramps - 2 Diarrhoea - 1 Anorexia + nausea - 1 Flu/pharyngitis/rhinitis/sinusitis - 1 Headache - 2 Menorrhagia - 1 Palpitations - 1 Alopexia - 1 Cystitis - 2	Diarrhoea - 1 Abdominal pain, cramps - 1 Eructation - 1 Flu/pharyngitis/rhinitis/sinusitis - 1 Headache - 1 Headache + nasal obstruction - 1 Left paresthesia + asthenia - 1 Anaemia + leucopenia - 1

Table 6: Details of RCTs of Antimotility agents

Author	Year	Study design	Drug & Dose	Control	Age	Mean duration
Cann	1984	Randomised, double-blind, crossover	Loperamide 2mg 1-6X daily	Placebo	35	5 weeks
Lavo	1987	Randomised, double-blind, placebo controlled	Loperamide 2mg 1-4capsules at night	Placebo	43	13 weeks

Table 7: Details of RCTs of Antimotility agents

Study	Methods used for AEs	Reports	Drug	Comparator
Cann 1984	Not stated		**Loperamide**	**Placebo**
		Total participants	28	28
		with any AE	8	10
		with severe AE	NA	NA
		stopped due to AE	NA	NA
		Specific details	NA	NA
Lavo 1987	Specific enquiry at follow-up		**Loperamide**	**Placebo**
		Total participants	11	10
		with any AE	NA	NA
		with severe AE	NA	NA
		stopped due to AE	NA	NA
		Specific details	Constipation - 1 Swollen fingers - 1 Sleep disturbance - 1 Blisters in the mouth - 1	Blisters in the mouth - 1 Vertigo - 1 Numbness in the legs - 1 Headache - 1

Table 8: Details of RCTs on Laxatives

Author	Year	Study design	Diagnosis	Drug & Dose	Control	Mean duration	Age
Chaussade	2003	Double-blind, randomised, parallel-group	Chronic idiopathic constipation	PEG 3350 + electrolytes (Transipeg) standard dose (1 5.9g sachet / day) or Transipeg maximum dose (2 5.9g sachets / day)	PEG 4000 (Forlax) standard dose (1 10g sachet / day or Forlax maximum dose (2 10g sachets / day)	1 month	52
Bouhnik	2004	Randomised controlled parallel-group study	Chronic idiopathic constipation	PEG 4000 (Forlax) 10 g sachets. 2 sachets/day, option to take 1-3 sachets daily	Lactulose 10 g sachets. 2 sachets/day, option to take 1-3 sachets daily	4 weeks	57
Dettmar	1998	open study with random allocation	Simple constipation	Lactulose and other laxatives	Ispaghula husk 3.5 g sachet twice daily	4 weeks	Not stated
Quah	2006	Randomised crossover		Lactulose 10 ml twice daily, maximum 30 ml twice daily	Isphagula husk 3.5 g sachet once daily, maximum 2 sachets	4 weeks	50
Corazziari	2000	Double blind, placebo controlled, parallel group, randomised		PMF-100 17.5 g sachet twice daily, can be reduced to once daily	Placebo sachet twice daily, can be reduced to once daily	20 weeks	43
Corazziari	1996	Randomised, double blind, placebo controlled, parallel group	Chronic idiopathic constipation	PMF-100 17.5 g sachet twice daily, can be reduced to once daily	Placebo sachet	8 weeks	42
Ferguson, Attar	1999	Single blind, randomised, controlled	Chronic idiopathic constipation	PEGes 2 sachets (13 g PEG 3350 each). Adjusted to 1-3 sachets daily if required	Lactulose 2 sachets (10 g each). Adjusted to 1-3 sachets daily if required	4 weeks	Not stated

Table 9: Details of RCTs of Antimotility agents

Study	Methods used for monitoring adverse effects	Reports	Drug		Comparator	
Chaussade 2003	Diary system, spontaneous reporting, clinical examination, specific enquiry at follow-up, global impression (visual analogue scale		**PEG 3350 low dose**	**PEG 3350 high dose**	**PEG 4000 low dose**	**PEG 4000 high dose**
		Total participants	65	70	66	67
		with any AE	33	42	33	36
		with severe AE	NA	NA	NA	NA
		stopped due to AE	NA	NA	NA	NA
		Specific details	Diarrhoea / liquid stools – 9 (14%)	Diarrhoea / liquid stools – 25 (36%)	Diarrhoea / liquid stools – 11 (17%)	Diarrhoea / liquid stools – 24 (36%)
Bouhnik 2004	Diary system, faecal studies		**PEG 4000**		**Lactulose**	
		Total participants	32		33	
		with any AE	5		8	
		with severe AE	0		0	
		stopped due to AE	3		4	
		Specific details	Borborygmi - 9 Bloating - 10 Abdominal pain - 6 Flatus in excess - 15		Borborygmi - 12 Bloating - 11 Abdominal pain - 9 Flatus in excess - 16	

Study	Methods used for monitoring adverse effects	Reports	Drug	Comparator
Dettmar 1998	Diary system		**Isphagula husk**	**Lactulose**
		Total participants	224	91
		with any AE	NA	NA
		with severe AE	NA	NA
		stopped due to AE	NA	NA
		Specific details	Abdominal pain / griping – 34 Distension – 35 Diarrhoea – 5 Flatulence – 63 Indigestion – 25 Nausea – 18	Abdominal pain / griping – 20 Distension – 12 Diarrhoea – 6 Flatulence – 20 Indigestion – 8 Nausea – 7
Quah 2006	Diary system		**Isphagula husk**	**Lactulose**
		Total participants	39	39
		with any AE	NA	NA
		with severe AE	NA	NA
		stopped due to AE	NA	NA
		Specific details	Abdominal bloating – 11 Abdominal pain / cramps – 5 Nausea – 1 Wind / flatulence – 10 Headache – 2 Anorexia – 0 Urgency – 8	Abdominal bloating – 11 Abdominal pain / cramps – 10 Nausea – 3 Wind / flatulence – 16 Headache – 2 Anorexia – 1 Urgency – 14

Study	Methods used for monitoring adverse effects	Reports	Drug	Comparator
Corazziari 2000	Diary system, blood tests, specific enquiry, examination		**PMF-100**	**Placebo**
		Total participants	33	37
		with any AE	57 (events, not people)	41 (events, not people)
		with severe AE	0	0
		stopped due to AE	0	0
		Specific details	Number of adverse events (11 people reported 2 symptoms) Nausea - 22 Vomiting - 1 Anal pain - 5 Haematochezia - 7 Call to evacuate absent - 4 Anal itching - 2 Headache - 0 Epigastric pain / discomfort - 13 Faecal incontinence - 3 (Stopped due to nausea, incontinence, anal pain)	Nausea - 17 Vomiting - 1 Anal pain - 0 Haematochezia - 2 Call to evacuate absent - 0 Anal itching - 2 Headache - 3 Epigastric pain / discomfort - 16 Faecal incontinence - 0
Corazziari 1996	Uncertain		**PMF-100**	**Placebo**
		Total. participants	25	23
		with any AE	NA	NA
		with severe AE	NA	NA
		stopped due to AE	NA	NA
		Specific details	Abdominal pain - 8 Abdominal bloating - 16 Flatulence - 9 Borborygmi - 3 Anorexia - 3 Headache - 3 Asthenia - 1	Abdominal pain - 6 Abdominal bloating - 12 Flatulence - 5 Borborygmi - 8 Anorexia - 1 Headache - 1 Asthenia - 1
Study	**Methods used for monitoring adverse effects**	**Reports**	**Drug**	**Comparator**
Ferguson , Attar 1999	Diary system, blood tests (cell counts, electrolytes, glucose, urea nitrogen,		**PEG 3350**	**Lactulose**

	protein, creatinine, folate, B12)	Total participants	60	55
		with any AE	NA	NA
		With severe AE	NA	NA
		Stopped due to AE	2	1
		Specific details	(stop due to AE - reason: 1 acute diarrhoea with vomiting and fever 1 abdominal pain) Liquid stools - 7 Bloating - 11 Abdominal pain - 7 Flatus - 8 Rumbling - 2 Mild hypokalaemia - 1 (taking diuretics)	(stop due to AE - reason: depression) Liquid stools - 5 Bloating - 20 Abdominal pain - 11 Flatus - 15 Rumbling - 8 Mild hypokalaemia - 1 (taking diuretics)

8.5.2 Adverse effects: tricyclics and selective serotonin re-uptake inhibitors

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

Adverse effects data have been extracted from the randomised trials included in the clinical effectiveness review of antidepressants.

Search strategy for identification of studies

In discussion with colleagues at NICE, it was agreed that for adverse effects evidence, direct reference to Clinical Guideline 23 (Depression) was appropriate in order to supplement the RCT data. Contact with the National Collaborating Centre for Mental Health clinical effectiveness lead established the search strategy supporting their work, and evidence statements were lifted from the guideline in relation to the adverse effects for both TCAs and SSRIs.

PARAMETERS OF THE REVIEW

It is recognised that these drugs are typically used to treat large populations with psychiatric morbidities. The context for this review is to recognise the potential harmful effects of these drug types when prescribed at low dose for the treatment of IBS symptoms, namely pain and discomfort. In the last twenty years, tricyclics and SSRIs have been prescribed in the treatment of functional GI disorders such as IBS. The prevalence of anxiety and depressive disorders is high in people with severe and/or intractable IBS and may be present to some degree in all people with IBS. A recognised pharmokinetic effect from these drug types is an analgesic effect that is separate from inhibitor effects typically desired in the treatment of depression. There is growing evidence to suggest that visceral pain syndromes such as IBS may be effectively treated using these drugs, that appear to modulate the interactions between the central and enteric nervous systems.

The two drug classes (tricyclics, e.g. trimipramine, amitriptyline, doxepin, and SSRIs, e.g. paroxetine, fluoxetine) are among the medications that have been used as long-term maintenance therapy (i.e. for 3 months or more) for IBS.

Treatment (for example with amitriptyline, the lowest cost tricyclic) is generally initiated at 10mg with dose increases of 10mg no more frequently than every 2 weeks. Patients are encouraged to increase the dose until an effective dose is established or side-effects become problematic, up to a maximum dose of 30mg for tricyclics and 20mg for SSRIs. An exception to this is doxepin, where the smallest tablet size is 50mg. Patients who do not respond to maximum dose are switched to an alternative drug, with switches from first to second tricyclic considered and switches between tricyclics and SSRIs considered.

A. Tricyclics

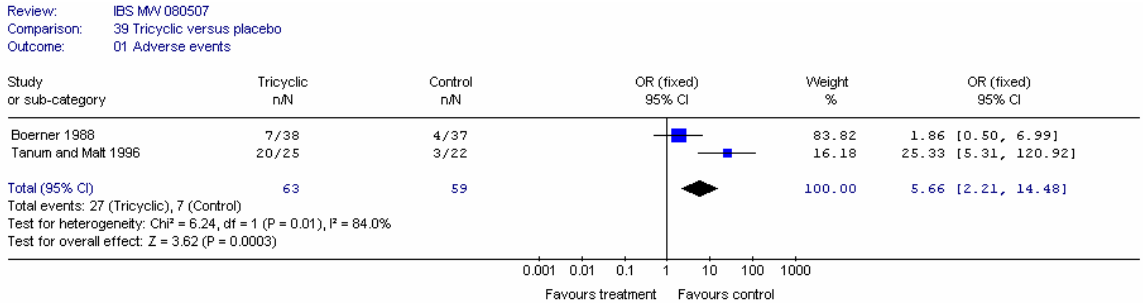
1. Adverse effects

All TCAs cause, to varying degrees, anticholinergic side effects (dry mouth, blurred vision, constipation, urinary retention, sweating), sedation and postural hypotension. These side effects necessitate starting with a low dose and increasing slowly. Mianserin is a sedating tricyclic.

Evidence is available for the adverse effects occurring for doxepin (Boerner 1988) and mianserin (Tanum and Malt 1996). Tanum and Malt (1996) included the adverse effect of mild sedation, and it is known that mianserin is a sedating tricyclic. All the trials compared tricyclics with placebo control.

In Boerner (1988), a dose of 50mg doxepin was compared with placebo. In Tanum and Malt (1996), the dose of mianserin was up to 120mg; we note that in this study only 60% of the participants had IBS. These doses are higher than those generally recommended for the use of these drugs in IBS.

Figure 1.



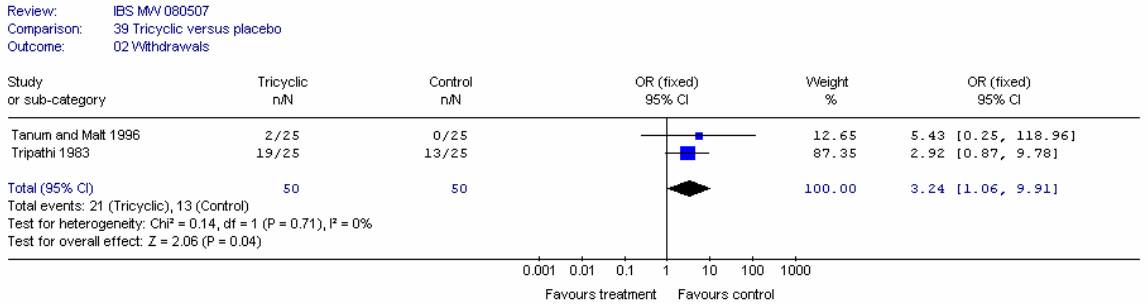
The Tanum and Malt (1996) study reported that significantly more patients were found to have adverse effects of mild sedation. In both studies the confidence intervals were wide.

One further study (Myren 1984) compared different doses of trimipramine (30 to 50mg). There were no significant differences between any of the trimipramine groups and placebo for palpitations, dizziness or dryness in the mouth. There was a significant increase in tiredness and morning drowsiness in the first 1 to 2 weeks for the antidepressant groups compared with placebo, but there were no significant differences at the end of treatment.

2. Number of patients withdrawing

Two studies recorded the numbers of withdrawals from the trials, for people receiving 120mg minaserin (Tanum and Malt 1996) and 10mg trimipramine (Tripathi 1983), compared with placebo. Meta-analyis showed a statistically significant effect in favour of placebo, but the confidence interval was wide.

Figure 2

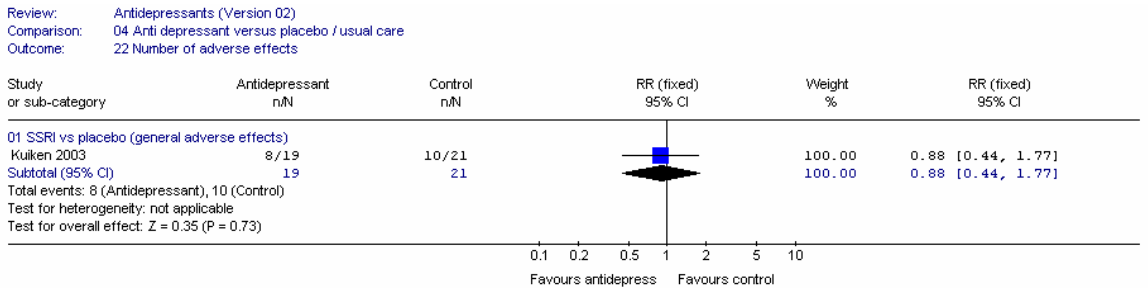


B. SSRIs

1. Adverse effects

Evidence is available for the adverse effects occurring for fluoxetine, in comparison with placebo (Kuiken 2003). It was used at a dose of 20mg in this study. The confidence interval was fairly wide, but there was no significant difference between interventions.

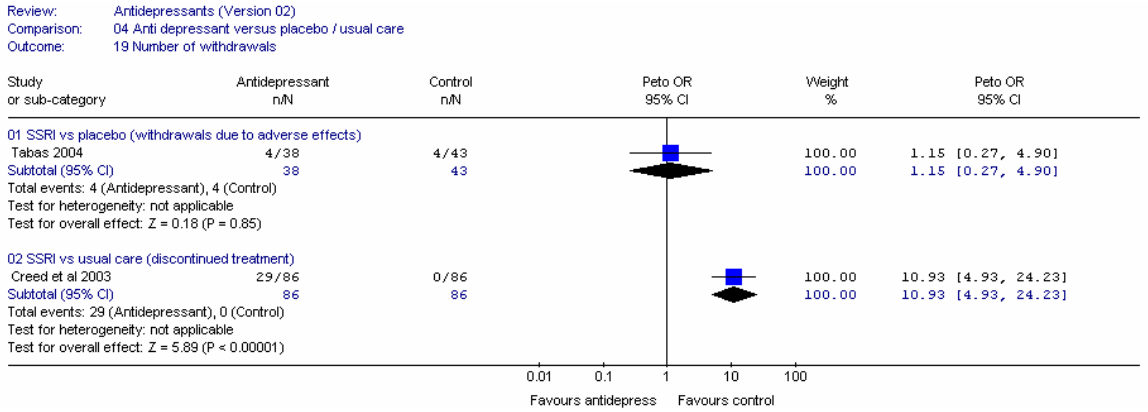
Figure 3



2. Number of people withdrawing because of side effects.

One study also investigated the number of participants withdrawing because of side effects for paroxetine compared with placebo (Tabas 2004); and Creed 2003 recorded the number who did not complete the treatment, for paroxetine compared with usual care. The confidence intervals were either wide or very wide, so conclusions could not be drawn about the non-significant results, but we noted there were significantly more people discontinuing treatment in the paroxetine group of the Creed (2003) study than in the usual care group. In Creed (2003), the dose of paroxetine was 20mg; and in Tabas (2004), the dose was up to 40mg.

Figure 4



C. Use of these drugs in the treatment of depression

Further evidence is available on the use of these medications (often at higher doses) for depression (NICE CG 23). For example, the effective dose of tricyclics for depression is usually taken to be 125mg. When used for depression, SSRIs are generally as effective as tricyclic antidepressants and are less likely to be discontinued because of side effects.

Tricyclics

Tricyclics are usually considered to have more side effects than other classes of drugs when used for depression, and people are less likely to stay in treatment on tricyclics than on other classes of drugs (RR= 0.71; 95% CI 0.65 to 0.78).

SSRIs

There is evidence suggesting that people are more likely to have side effects while on SSRIs than on placebo (RR=1.19; 95% CI 1.13 to 1.25), and are also more likely to withdraw from treatment due to side effects (RR=2.45; 95% CI 2.08 to 2.89). However, overall, a similar number of patients withdrew from treatment, so these withdrawals due to side effects of SSRIs may be offset by the number of people on placebo who withdrew for other reasons, for example due to lack of effectiveness of the treatment. Fewer people on SSRIs than on other antidepressants withdrew from treatment due to side effects (RR= 0.78; 95% CI, 0.71 to 0.85).

EVIDENCE STATEMENTS

Evidence statements for this review are mostly based on those in NICE Clinical Guideline 23 'Depression' (statements 2 to 4).

1. There is a moderate amount of good quality evidence to show there are significantly more patients discontinuing treatment with SSRIs compared with usual care.

2. Patients started on antidepressants who are not considered to be at increased risk of suicide should normally be seen after 2 weeks. Thereafter they should be seen on an appropriate and regular basis.

3. In people in primary care, there is insufficient evidence to determine whether there is a clinically significant difference between other antidepressants and amitriptyline (TCA) on reducing the likelihood of leaving treatment early either for any reason or due to side effects.

4. There is good evidence in trials of eight weeks and longer that there is no clinically significant difference between SSRIs and placebo on reducing the likelihood of leaving treatment early. This is not consistent when analysing the reasons for leaving treatment, which demonstrate a clinically significant difference favouring placebo over SSRIs in relation to leaving the treatment early due to side effects.

9 Psychological Interventions

Clinical Questions

1. Does CBT have a role in managing symptoms?
2. Do psychological interventions have a role in managing symptoms?
3. Does hypnotherapy have a role in managing IBS symptoms?
4. Does bio-feedback have a role in managing symptoms?
5. Does relaxation therapy have a role in managing symptoms?

BACKGROUND

Psychosocial factors are integral to the way in which people experience and interpret symptoms and they influence both illness behaviour and response to treatment. The effects on gastrointestinal function caused by emotional and psychological response include fluctuation in acid secretion; changes in motor activity and gut transit and have been well documented (Wolf 1981). Although it has been shown that there are no greater psychological disturbances in people with IBS than in the general population (Wilhelmsen 2000), anxiety and depression can be major contributing factors in the symptom profiles of IBS. Psychotherapy has been suggested as a possible treatment to reduce pain and symptoms and also to improve quality of life.

There are a range of psychological treatments which can be used in the management of IBS. Psychological therapies may be defined as the treatment of mental and emotional disorders through the use of psychological techniques designed to encourage communication of conflicts and insight into problems, with the goal being relief of symptoms, changes in behaviour leading to improved social and vocational functioning and personality growth.

Relaxation therapy is the simplest form of psychotherapy. The premise is that if response to stress contributes to IBS, reducing autonomic stress responses by relaxation will reduce symptoms, induce a feeling of well-being and increased confidence which will allow people with IBS to feel more able to control the condition. Relaxation can be taught using audio tapes and there are many readily available which people with IBS can access (Jones 2000).

More complex psychological interventions include biofeedback, cognitive behavioural therapy, dynamic psychotherapy and hypnotherapy are usually initiated for people with moderate or severe symptoms who have not responded to other management programmes. These therapies are effective, but time consuming to provide, require specialist input and currently availability varies widely across the UK.

Biofeedback

Biofeedback includes a number of techniques in which a physiological process is monitored and information regarding unconscious bodily functions are shown by audiovisual display to the patient. The patient is taught to bring about changes in the physiological process by using a number of strategies e.g. thoughts, sensations, feelings. The rationale is that the physiological process being monitored is causally related to a clinical condition, in this case IBS, and that alteration of the process can lead to a reduction or resolution of symptoms.

Cognitive Therapy

Cognitive therapy is a therapy that assumes that faulty thought patterns (called cognitive patterns) cause maladaptive behaviour and emotional responses. The treatment focuses on changing thoughts in order to solve psychological and personality problems. Behaviour therapy is also a goal-oriented, therapeutic approach, and it treats emotional and behavioural disorders as maladaptive learned responses that can be replaced by healthier ones with appropriate training. Cognitive-behavioural therapy (CBT) integrates features of behaviour modification into the traditional cognitive restructuring approach. Cognitive-behavioural therapy attempts to change clients' unhealthy behaviour through cognitive restructuring (examining assumptions behind the thought patterns) and through the use of behaviour therapy techniques. CBT can be used as a long-term treatment for irritable bowel syndrome. Different programmes comprise different elements in a variety of combinations, including: helping patients recognise the causes of disease; cognitive restructuring techniques to address unhelpful beliefs; changing underlying depressive or threatening ‘life scripts’; psychotherapy to cope with emotional problems and find new solutions; stress management or relaxation training, using progressive muscle relaxation techniques; breaking habits of learned illness behaviours; practising more adaptive behaviours; assertion and coping skills training. CBT can be administered to patients individually or as a group.

Hypnotherapy

Hypnosis describes a range of naturally occurring states of altered awareness which may vary from momentary distractions and 'absences' through much enhanced states of relaxation to very deep states of inward focus and awareness. The mental processes which can occur in any of these states, appropriately utilised are generally far more flexible and potentially far more powerful in effecting change than those we can achieve in most everyday states of active conscious awareness. These states may be induced quite formally or quite naturalistically, in an almost unnoticeable way, depending on the requirement of the problem, the capability of the practitioner and the needs of the client (UK Council for Psychotherapy (UKCP) 1992).

Gut-directed hypnotherapy is a specific form of hypnotherapy developed for the management of gastrointestinal disorders. It uses the therapeutic qualities of hypnotherapy, such as deep relaxation, and adds gut-specific treatments and suggestions. ‘Gut-directed hypnotherapy’ can

be used as a treatment for irritable bowel syndrome. IBS is ideal for treatment with hypnosis, as there is no structural damage to the body. During hypnotherapy people learn how to influence and gain control of their gut function and then seem to be able to change the way the brain modulates their gut activity (Whorwell 2005). Firstly, patients are given a brief outline of the anatomy and physiology of the gut and a schematic representation of their symptoms, using a diagram of the colon showing how smooth muscle spasm can give pain, bloating and a disordered bowel habit. Patients are told that the reduction of this spasm and normalisation of smooth muscle activity will reduce pain and bloating and encourage a more normal flow through the bowel. Hypnosis is induced by a standard technique, then over successive sessions, patients are asked to place a hand on their abdomen and feel warmth; then this warmth is related to reduction of spasm and the ability to alleviate pain and distension; patients are told that bowel habit will normalise as their control gradually improves; they visualise the gut as a meandering river and they can adjust the flow along it to a comfortable setting as one would open and close lock gates on a river. Patients may be given a self-hypnosis tape to use at home. Ego-strengthening and confidence-building comments can be made at the end of the sessions. Hypnotherapy can be administered to patients individually or as a group.

Dynamic Psychotherapy

In the NHS psychodynamic psychotherapy is practised by psychiatrists, psychologists, social workers and other professionals who have received additional specialised training in these techniques. Long-term dynamic psychotherapy aims to bring about extensive change in several aspects of a person’s functioning. It is a prolonged treatment typically comprising of hourly meetings every week for periods of time up to three years. Short-term or focal dynamic psychotherapy is a modification of the approach in which attention is focused on only one area of the person’s experience. This shortens the amount of time required and usually this form of treatment requires between 10 and 20 sessions (University of Newcastle 2005).

The selection of the appropriate psychological approach will depend on the individual person. They may express a preference for a particular intervention but in order to be able to make informed choices people with irritable bowel syndrome need to be made aware of the existence of these psychological treatments and the rationale for their use. It is important that they be made aware that using a psychological treatment does not mean that the syndrome is "all in the mind." Addressing psychosocial factors is increasingly recognised as an important part of the management of irritable bowel syndrome.

9.1 Relaxation

SELECTION CRITERIA

The selection criteria described in the general methodology section were used, except that crossover studies were excluded as inappropriate due to the carry-over effect of the relaxation interventions.

The following comparisons were included:

- Relaxation versus waiting list control, or symptom monitoring only
- Relaxation versus usual medical care
- Relaxation versus another intervention.

SEARCH STRATEGY FOR IDENTIFICATION OF STUDIES

Searches were performed on the following core databases: MEDLINE, EMBASE, CINAHL, and *The Cochrane Library (*1966 to current day with guidance from the GDG). Additionally, the PSYCINFO database was searched for this review. The search strategies are listed in Appendix B.

Study Design

Three parallel group design randomised trials were included (Blanchard 1993; Forbes 2000; Keefer 2001). Further details are given in the included studies table. Forbes (2000) was conducted in the UK, the other two studies were carried out in the USA. Trials lasted between 6 and 12 weeks. One study was conducted among patients recruited from their personal physician or media publicity (Blanchard 1993); one recruited from gastroenterologists and local media (Keefer 2001), and one recruited from secondary care (Forbes 2000). The total number of patients in the studies was 16 in Blanchard (1993) and Keefer (2001). Forbes (2000) included 25 and 27 patients in the two treatment arms respectively.

Population

All the studies included only people with IBS. Blanchard (1993) and Forbes (2000) did not report the number of participants with bloating; Keefer (2001) reported that seven (of 16) had bloating. None of the studies reported whether the symptoms were post-infective. The mean age of participants was 51.5 years in Keefer (2001), with participants aged between 34 and 76 years; the people with IBS were aged 22 to 64 years in Blanchard (1993), and the median age in Forbes (2000) was 37 years, with a range from 19 to 71 years. All the studies included more women than men. The patients in the Blanchard (1993) study had had IBS for more a mean of around 13 years, and in Keefer (2001) 15.8 years. The patients in Forbes (2000) had had IBS for more than six months.

In the Blanchard (1993) study, 56% of participants had an Axis I diagnosis; in Keefer (2001), 77% had an Axis I diagnosis, and participants were excluded if they had bipolar I or II,

schizophrenia or other psychoses, or if they were actively suicidal. Co-morbidities were not stated in Forbes (2000).

Interventions

Blanchard (1993) used progressive muscle relaxation, on an individual basis with two sessions per week for the first two weeks and then once a week for six additional weeks; regular home practice was emphasised with an audiotape to guide this. Keefer (2001) used relaxation response meditation, in six weekly 30-minute treatment sessions.

The following comparisons were included:

- Relaxation versus symptom monitoring only: two studies (Blanchard 1993; Keefer 2001).
- Relaxation versus another intervention
    - Relaxation versus hypnotherapy (Forbes 2000).

Outcomes

The outcomes reported were:

1. Global symptoms:
    a) Global improvement in symptoms (number of patients) (Blanchard 1993; Forbes 2000; Keefer 2001)
    b) Global symptom score:
        - Global improvement of IBS symptoms (mean Composite Primary Symptom Reduction [CPSR] score; CPSR represents proportional reduction in score from baseline; scale range -1 to +1; Blanchard 1993; Keefer 2001).

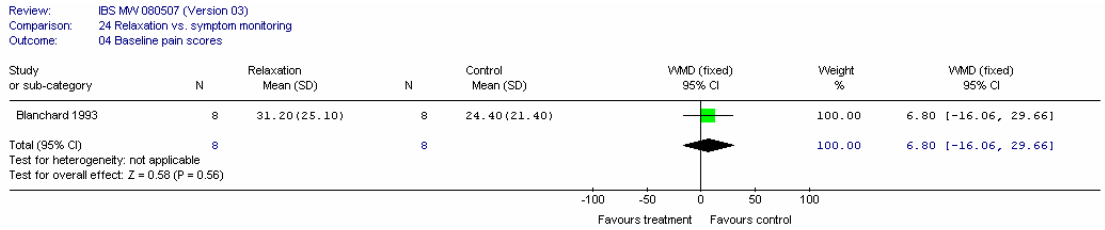
2. Individual symptoms:
    a) Pain
        - Pain score (0 to 4 recorded over 28 days where 0=absent to 4=debilitating; i.e. maximum 112) reported by Blanchard (1993).

METHODOLOGICAL QUALITY

The quality assessment for included trials is shown in Appendix D.

An adequate method of randomisation was reported in one study (computer-generated random numbers; Forbes 2000); the other studies did not state the method. Allocation concealment was also not reported. The patients were not blinded (because of the type of intervention). No study described an *a-priori* power calculation. The three studies included in the review demonstrated baseline comparability of the groups, although the baseline scores for Blanchard (1993) were higher for the relaxation group on abdominal pain (mean score 31.2 (SD 25.1) compared with 24.4 (21.4) for the symptom monitoring group). This was not a statistically significant difference (Figure 1).

Figure 1: Baseline pain scores



All the participants were followed up in Forbes (2000). There were 20% or fewer drop-outs overall in one study (Keefer 2001): 3/16 dropped out (19%) (2/8 (25%) from the intervention group and 1/8 from the control group). 7/23 dropped out (30.4%) in Blanchard (1993), 6/14 (43%) from the intervention group and 1/9 (11%) from the control group; this study was regarded with caution, as this large and unequal drop-out could have introduced a bias.

RESULTS

A. Relaxation versus symptom monitoring only

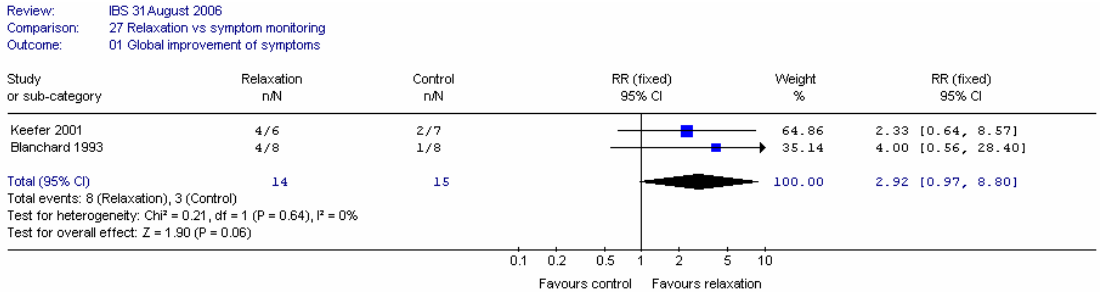
There were two studies that compared relaxation with symptom monitoring in people with IBS (Blanchard 1993; Keefer 2001).

1. Global symptoms

a) Number of patients with global improvement in symptoms

This outcome was reported by Blanchard (1993) and Keefer (2001).

Figure 2: Global improvement of symptoms



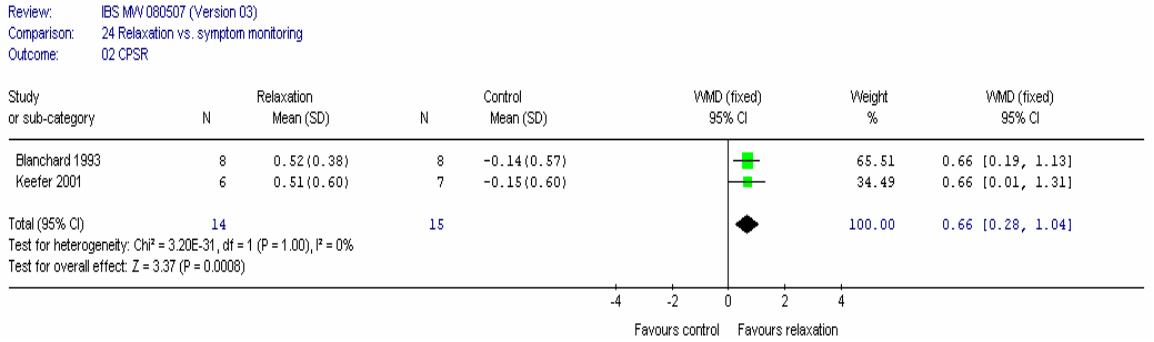
Meta-analysis of two studies in 29 patients showed a large effect, favouring relaxation, but the confidence interval was wide, such that the results are not significant. We noted that there was also attrition bias for the Blanchard (1993) study.

b) Global symptom score

The global improvement of IBS symptoms (mean Composite Primary Symptom Reduction [CPSR] score; CPSR represents proportional reduction in score from baseline; scale -1 to +1) was reported by Blanchard (1993) and Keefer (2001). There was a large statistically significant improvement in symptoms for the relaxation group, but the confidence interval was

also wide. We noted that there was also attrition bias for the Blanchard (1993) study, and the other study, Keefer (2001), was small (13 patients).

Figure 3: Global symptom score (CPSR)

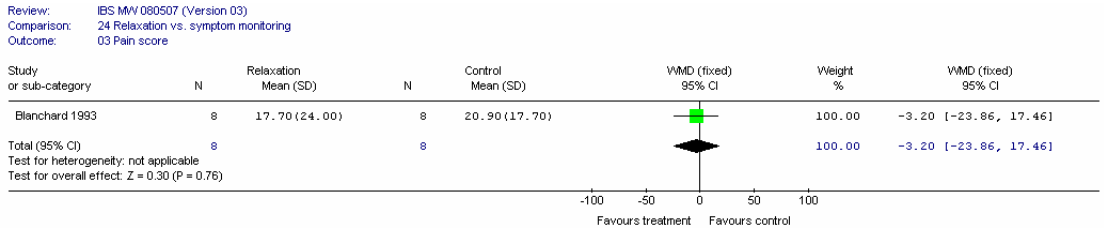


2. Individual symptoms

a) Pain

A pain score (0-4 recorded, over 28 days, where 0=absent and 4=debilitating, i.e. maximum 112) was reported by Blanchard (1993). There was no significant difference between interventions.

Figure 4: Pain score

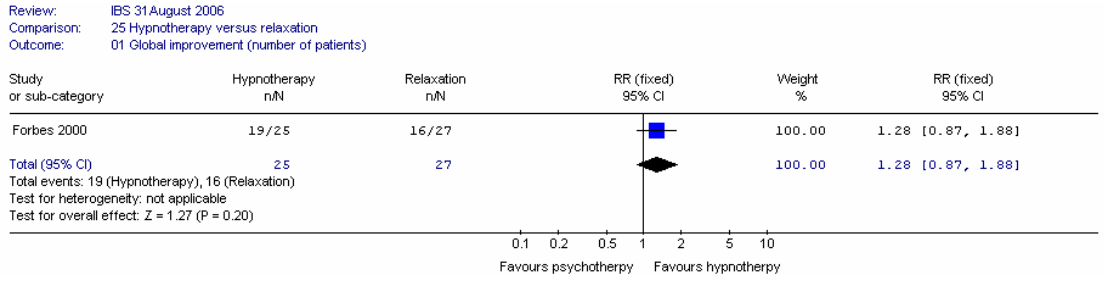


B. Hypnotherapy versus relaxation

1. Global symptoms

Global improvement in symptoms (number of patients) was reported by Forbes (2000) at 12 weeks. There was no significant difference between interventions.

Figure 5:



EVIDENCE STATEMENTS

1. There is insufficient evidence to show if there is a difference between relaxation and symptom monitoring, in the number of people with global improvement of symptoms, in people with long term IBS, at least half of whom had psychiatric co-morbidities.

2. There is a limited amount of weak evidence to show a large, significant improvement in global symptom score for people receiving relaxation, compared with symptom monitoring, in people with long term IBS, at least half of whom had psychiatric co-morbidities.

3. There is limited evidence to show no significant difference in pain score between relaxation and symptom monitoring, in people with long term IBS, at least half of whom had psychiatric co-morbidities.

4. There is a fair evidence to show no significant difference between relaxation and hypnotherapy in the number of people with global improvement of symptoms.

Evidence to recommendation

The GDG decided there is insufficient evidence to make a recommendation. This is discussed in the evidence to recommendation statement for relaxation and biofeedback (Section 9.3).

9.2 Biofeedback

SELECTION CRITERIA

The selection criteria described in the general methodology section were used, but some were specific to this review and are reported below.

Types of intervention

Both multiple and single component therapies were eligible for inclusion.

Search strategy for identification of studies

Searches were performed on the following core databases: MEDLINE, EMBASE, CINAHL and *The Cochrane Library* (1966 to current day with guidance from the GDG). Additional databases were not searched for this review. Biofeedback, aloe vera and reflexology were combined into one search. The search strategies are listed in Appendix B.

The search strategy identified 560 studies. The titles and abstracts of these studies were assessed. Fifty-four studies were identified as being potentially relevant to the reviews and the papers for these were retrieved in full. Four studies met the inclusion criteria for this review, two of which were reports of the same trial (Blanchard 1992; Meissner 1997). The reference lists of

these studies were inspected for further potential papers, but none were identified. The 17 excluded studies, with reasons for exclusion, are listed in the Appendix E.

DESCRIPTION OF STUDIES

Study Design

There were four randomised trials in this review, reported in three papers (Blanchard 1992; Leahy 1997; Neff 1987); two trials were from the same paper (Blanchard 1992), and one was reported only as an abstract (Leahy 1997). All the studies but one took place in the US. Leahy (1997) was carried out in the UK.

Population

All patients had a diagnosis of IBS and were treated in the secondary care setting in which the study took place. There was a higher proportion of women. The age range was 21 to 76 years.

Patients in the Leahy study were said to be resistant to conventional medical therapy. The other studies did not report whether the IBS was refractory.

Interventions

One study (Leahy 1997) evaluated a single intervention, using a computer-aided gut-directed biofeedback apparatus to teach relaxation for IBS patients when troubled by symptoms. Patients were randomised to biofeedback or counselling. Biofeedback patients received four half-hour sessions.

Three trials (Blanchard 1992 x 2; Neff 1987) evaluated multi-component therapy, which used a combination of educational information, progressive relaxation therapy, thermal biofeedback treatment and training in stress coping strategies. This was offered on an individual basis. The combination treatment consisted of twelve one-hour sessions spread over eight weeks.

In Blanchard (1992a), the same therapist delivered the treatments, but in Blanchard (1992b) eight different therapists took part.

In the two Blanchard 1992 trials, the patients were matched into triads, based on gender, age and predominant GI symptoms, and randomly assigned to multi-component biofeedback, attention placebo or symptom monitoring. Neff (1987) randomly assigned patients to multi-component biofeedback and symptom monitoring.

Comparisons

All the comparative studies used symptom monitoring or attention placebo controls. The latter was used in Blanchard (1992). A combination of two procedures was used: ‘pseudo meditation’

(in which patients were asked not to relax) and biofeedback using suppression of alpha-waves in the EEG (this is not associated with the relaxed state).

In the symptom monitoring control group, patients simply monitored their symptoms for the duration of the intervention. The symptom monitoring (control) group were offered treatment at a later stage.

The following comparisons were reported:

- Single component biofeedback versus counselling then both groups had biofeedback (Leahy 1997)
- Multi-component biofeedback versus symptom monitoring (Blanchard 1992 x2; Neff 1987)
- Multi-component biofeedback versus attention control (Blanchard 1992 x2).

METHODOLOGICAL QUALITY OF INCLUDED STUDIES

None of the RCTs reported details of the method of randomisation or allocation concealment. Patients were matched on age, gender and primary GI symptoms before randomisation in the Blanchard (1992) study. Patients in the Neff (1987) study were similar at baseline for age, duration of IBS, and years of education, but there were differences in the number of IBS-D patients: 5/10 in the biofeedback group and 2/9 in the control group.

In Blanchard (1992a) all patients completed the trial, 1/9 dropped out from the control group of the Neff study, and in Blanchard (1992b), 7/31 (22%), 8/30 (27%) and 10/31 (32%) dropped out of the study for multi-component, attention placebo and symptom monitoring respectively. Therefore the second Blanchard trial is at higher risk of bias and will be considered in sensitivity analyses as appropriate.

RESULTS

A. Single component biofeedback

In an abstract, Leahy (1997) reported that counselling had no effect on symptom score, but did not give separate results for the group randomised to biofeedback.

B. Multi-component biofeedback

Three randomised trials (Blanchard 1992a and b; and Neff 1987) in 30 and 115 patients, and 19 patients respectively gave a multi-component therapy as the biofeedback intervention.

1. Global symptoms

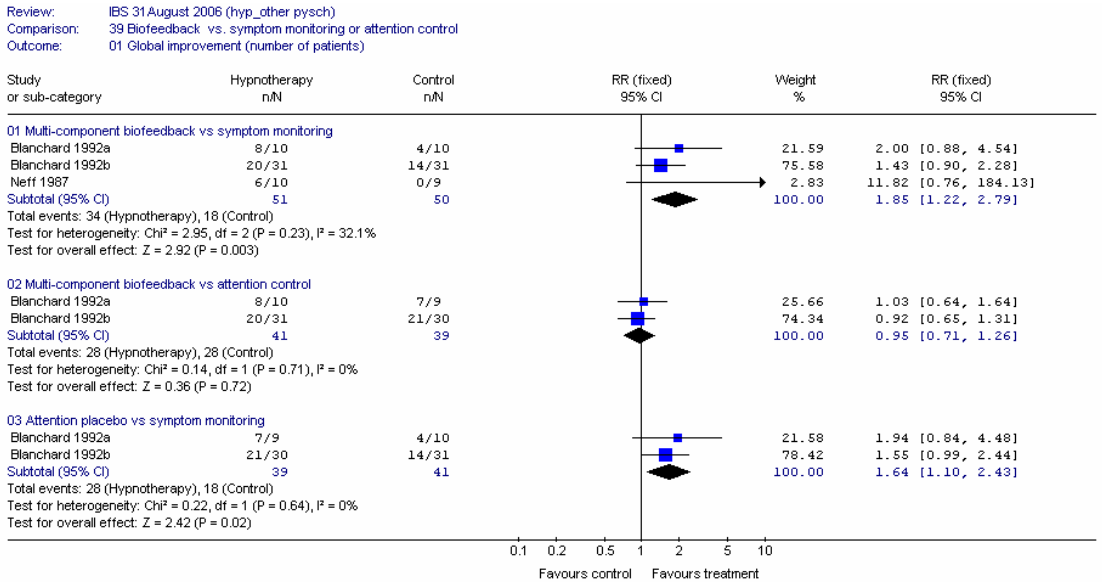
All studies reported a composite primary symptom reduction score (CPSR): firstly, each patient recorded in a daily diary a symptom score, comprising abdominal pain, tenderness, diarrhoea, constipation, flatulence, belching and nausea. This was used to calculate a reduction score using the formula:

(baseline symptom score – end of treatment score) / baseline symptom score *100.

a) Global improvement in symptoms (number of patients)

The RCTs reported the number of patients with an improvement in global symptoms; the Blanchard (1992) trials reported rater-assessments, but the patient assessment results were selected for the Neff (1987) study. Meta-analysis of three trials in 101 patients showed a statistically significant improvement in symptoms for biofeedback compared with symptom monitoring; RR 1.85 (95%CI 1.22, 2.79), with insignificant heterogeneity (I^2=32%, p=0.23). This corresponded to a number needed to treat of 4 (95%CI 3, 8), for a control group rate of 0 to 45%. However, there was no significant difference between biofeedback and attention placebo. The comparison of attention placebo versus symptom monitoring was also significant. We noted that the Blanchard (1992b) study had about 30% dropouts. A sensitivity analysis without this study for the comparison of biofeedback with symptom monitoring resulted in more heterogeneity and changed the relative risk to 3.14 (95%CI 1.35, 7.31).

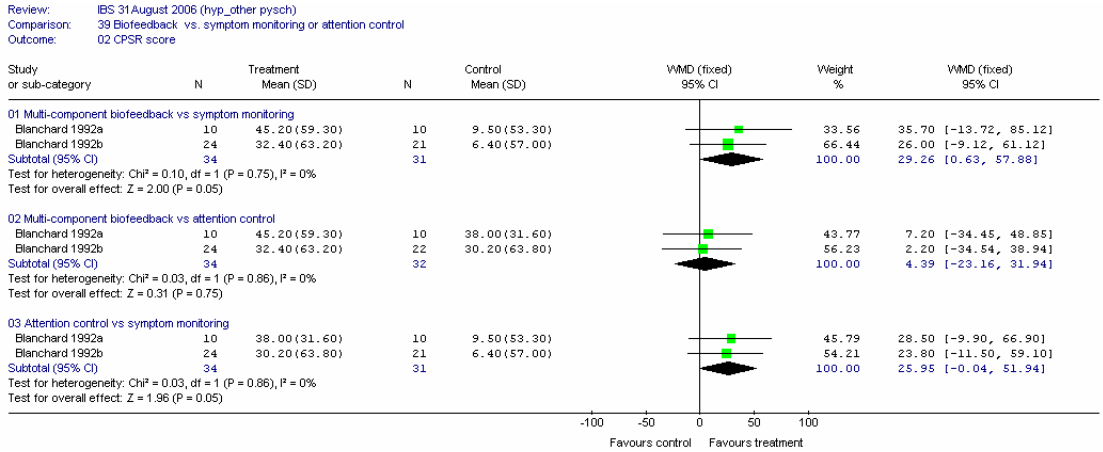
Figure 1



b) Global improvement of symptoms

The two trials within Blanchard (1992) reported the scores on the CPSR. There was a statistically significant difference, favouring multi-component feedback compared with symptom monitoring, but not in comparison with attention control, although the confidence intervals were fairly wide. We noted that around 30% of the patients in Blanchard (1992b) had missing data and we have assumed the numbers of patients in the analysis are the values for completers only.

Figure 2



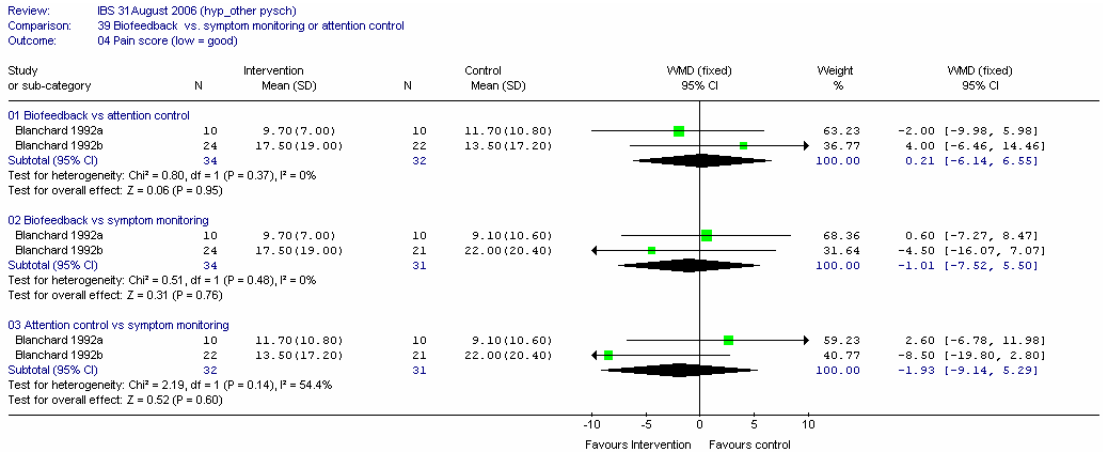
2. Individual symptoms

Neff (1987) reported means for these outcomes, but no standard deviations or p-values were given, so the rest of this review uses the results from Blanchard (1992).

a) Pain

The study reported daily abdominal pain and discomfort symptom scores on a scale of 0 to 4, recorded as weekly scores (i.e. maximum of 28). The confidence intervals were too wide to draw conclusions.

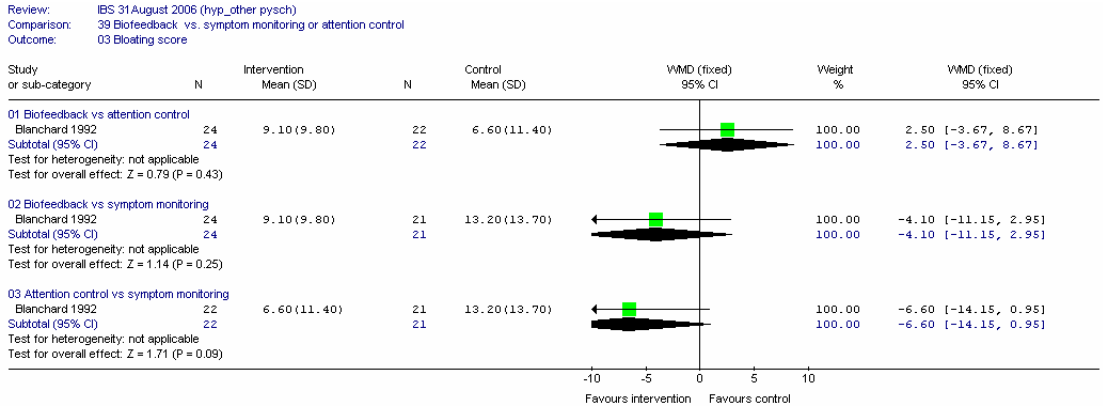
Figure 3



b) Bloating

The second study reported bloating scores. Generally the confidence intervals were wide, but the attention placebo gave significantly less bloating than the symptom monitoring.

Figure 4

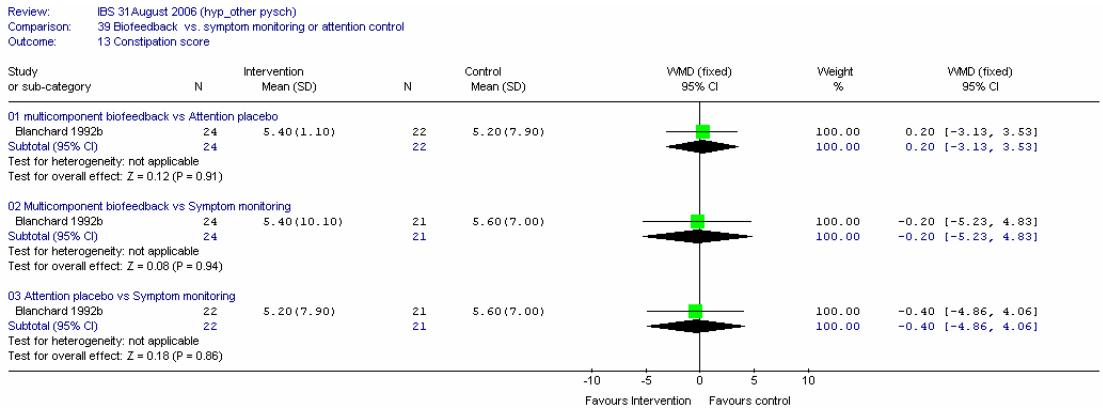


c) Bowel Habit

i. Constipation

The second study reported constipation scores. The scale used was 0 to 4 and the weekly average was used (i.e. maximum of 28). Generally the confidence intervals were too wide to draw conclusions.

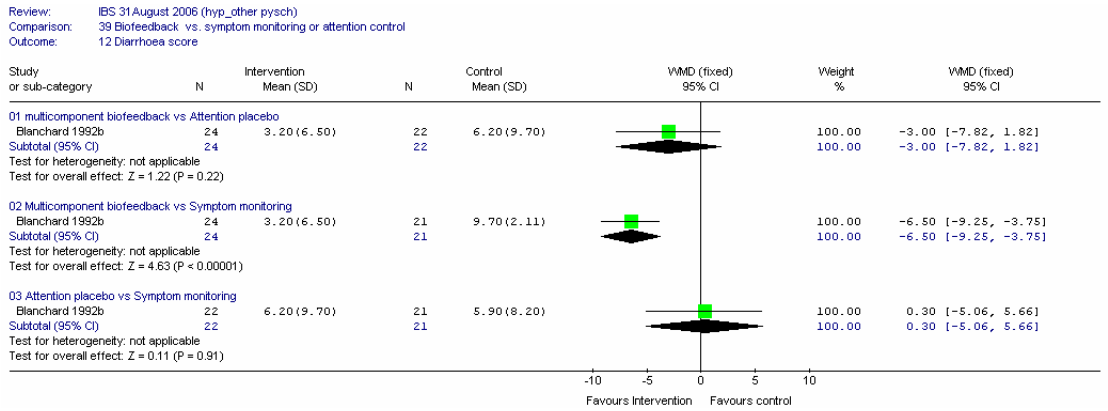
Figure 5



ii. Diarrhoea

The second study reported diarrhoea scores. The scale used was 0 to 4 and the weekly average was used (i.e. maximum of 28). Generally the confidence intervals were wide, but the multi-component biofeedback gave significantly lower diarrhoea score than the symptom monitoring.

Figure 6



GDG DISCUSSION

The GDG noted that multi-component biofeedback (consisting of education, progressive relaxation therapy, thermal biofeedback treatment and training in stress coping strategies) is effective for people with IBS in comparison with symptom monitoring. However, the attention placebo of pseudo meditation and alpha wave EEG biofeedback had similar efficacy for improving global symptoms. The GDG suggested that actively involving people in the management of their chronic condition may have a beneficial effect. They also noted that spending time with patients and taking them seriously is valuable, and that behavioural treatments are difficult to unravel.

EVIDENCE STATEMENTS

1. There is limited weak evidence to show a statistically significant improvement in global symptoms for biofeedback compared with symptom monitoring, although the confidence interval was fairly wide. There was no difference between biofeedback and attention placebo.

2. There was insufficient evidence to determine the effects of biofeedback on pain, bloating and constipation.

3. There is limited weak evidence to show a statistically significant improvement for reduction in diarrhoea for biofeedback compared with symptom monitoring, although the confidence interval was fairly wide. There was no significant difference between biofeedback and attention placebo and between symptom monitoring and attention placebo but there was much uncertainty due to wide confidence intervals.

EVIDENCE TO RECOMMENDATION

The GDG decided there is insufficient evidence to make a recommendation. This is discussed in the evidence to recommendation statement for relaxation and biofeedback (Section 9.3).

9.3 Evidence to recommendation: relaxation and biofeedback

The GDG took into consideration the limited clinical effectiveness evidence for relaxation and biofeedback. They noted that the relaxation review showed significant improvement in global symptoms for relaxation compared with symptom monitoring, but the trials were small and one of them had a large attrition bias. The biofeedback review compared biofeedback with symptom monitoring and with attention control: there was a significant effect on global symptoms in comparison with the former, but not with the latter and this led the GDG to conclude that attention may be an important factor for biofeedback.

The GDG considered the clinical evidence to be too limited, either to carry out cost effectiveness analyses or to make recommendations for practice. However, they considered these therapies to be worth following up, particularly in view of recent developments in computer-aided biofeedback techniques and positive patient experience within the GDG indicating a preference towards relaxation. Therefore, the GDG proposed a recommendation for research, involving a comparison of computer-aided biofeedback, relaxation and attention control. The research recommendation is given in chapter 12.

9.4 Psychotherapy

SELECTION CRITERIA

The selection criteria described in the general methodology section were used, except that crossover studies were excluded as inappropriate due to the carry-over effect of the interventions.

The following comparisons were to be included:

- Psychotherapy versus waiting list control/symptom monitoring
- Psychotherapy versus usual medical care
- Psychotherapy plus another intervention versus the other intervention alone
- Psychotherapy versus another intervention.

SEARCH STRATEGY FOR IDENTIFICATION OF STUDIES

Searches were performed on the following core databases: MEDLINE, EMBASE, CINAHL, and *The Cochrane Library* (1966 to current day with guidance from the GDG). Additionally, the PSYCINFO database was searched for this review.

The search strategies are the same as those for hypnotherapy, as these were searched together. Details of the search strategies are lisetd in Appendix B. The titles and abstracts of the studies identified by the searches were assessed. Fifteen were identified to be potentially relevant to the reviews and these papers were retrieved in full. The reference lists of the retrieved studies were inspected for further potential papers, but none were identified. Twelve studies were excluded and are listed in Appendix E, along with reasons for exclusion.

CHARACTERISTICS OF INCLUDED STUDIES

Study Design

Three randomised trials were included (Creed 2003; Guthrie 1991; Svedlund 1983), all in secondary care. Two of these were in the UK, the other in Sweden.

Population

The studies included patients between the ages of 17 and 75 years, although each had slightly different inclusion criteria and mean age of participants (Svedlund 1983: mean age was around 34 years, range 17 to 59 years; Guthrie 1991: mean around 48 years, range 20 to 75 years; Creed 2003: mean around 40 years, range 18 to 65 years). All the studies included more women than men.

IBS was stated, or implied, to be refractory in all of the studies. The patients in Guthrie (1991) had had IBS for more than 1 year (median around 4 years, range 1 to 20 years); their symptoms had not improved with medical treatment (bulking agents and/or antispasmodics) over six months. The patients in Creed (2003) had had IBS for more than six months; they had failed to respond to usual medical treatment. The patients in Svedlund (1983) had had IBS for at least a year, range 1 to 40 years, but their response to previous treatment was not stated.

Only one study gave details about IBS characteristics: Creed (2003) reported that the patients had severe abdominal pain (over 60 on a 100 mm visual analogue scale [VAS]); 29% of the patients had diarrhoea-predominant IBS; 23% were constipation-predominant; and 48% had 'general' IBS.

In two of the studies, around half the participants currently had a psychiatric diagnosis. Of the patients in Guthrie (1991), 30% had major depression and a further 18% had anxiety states; in Creed (2003), 47% had a psychiatric diagnosis (mainly anxiety or depression). In Svedlund (1983), 29% had previously had depression and a further 41% had had other mental disorders. It was unclear if this was their current diagnosis.

Svedlund (1983) stated that the patients were less representative of the general IBS population because they had to be prepared to participate in an extended socio-psychological investigation. Creed (2003) reported that the patients all had severe symptoms, but within this group were broadly representative, and Guthrie (1991) recruited patients from a tertiary referral centre, where there is likely to be a higher proportion with abuse and associated psychological problems.

None of the studies reported the number of participants with bloating or whether the symptoms were post-infective. Creed (2003) described IBS as severe. Guthrie (1991) reported that

gastroenterologists assessment of severity was median 5 (range 2 to 8) on scale 0 to 9. Svedlund (1983) did not report severity.

Interventions

All the studies examined the effect of psychotherapy on IBS symptoms. Two studies (Svedlund 1983; Guthrie 1991) compared psychotherapy plus medical therapy versus medical therapy alone; the third (Creed 2003) compared psychotherapy versus medical therapy and also had a second comparison with the SSRI antidepressant, paroxetine.

In Svedlund (1983), all patients received the same medical treatment but those in one group also received dynamically oriented individual psychotherapy in ten hour-long sessions spread over three months. In Guthrie (1991), patients received the same medical treatment but patients in one group also received dynamic psychotherapy in seven interviews over three months, plus a relaxation tape to use at home. At the end of the 3 month period, patients in the control group were given psychotherapy. Creed (2003) randomised patients into three groups: psychodynamic interpersonal therapy (8 sessions over 3 months); 20mg daily of the SSRI antidepressant paroxetine for 3 months; or 'usual care', in which 'patients continued to be seen either by their gastroenterologist and/or general practitioner, using whatever management was deemed appropriate' (Creed 2003). Other medical management was stopped during the trial period in the paroxetine and psychotherapy groups. In the follow-up period, patients were allowed other treatments, principally antidepressants.

Comparisons

The following comparisons were included:

- Psychotherapy plus medical care versus medical care only (Svedlund 1983; Guthrie 1991)
- Psychotherapy versus usual care (Creed 2003)
- Psychotherapy versus another intervention (antidepressant: SSRI – paroxetine) (Creed 2003).

METHODOLOGICAL QUALITY

The quality assessment for included trials is shown in the Appendix D.

The method of randomisation was adequate in Creed (2003) (computer generated random numbers) but not stated in either Svedlund (1983) or Guthrie (1991). Allocation concealment was adequate in Creed (2003) (randomisation list held by study administrator) but not stated in either Svedlund (1983) or Guthrie (1991). The patients were not blinded in any study (because of the type of intervention). The GDG did not consider blinding to be important for this review. Creed (2003) reported an *a priori* power calculation but the other two studies did not.

Svedlund (1983) and Creed (2003) demonstrated baseline comparability between the groups. The groups were mainly comparable in Guthrie (1991), except there was a higher proportion of males in the control group than the intervention group (17/49 vs. 8/53, $p<0.05$). Svedlund (1983) reported significant differences in the assessors rating of pain (however, this was not significantly different for the self-rating, which we used).

There were fewer than 20% drop-outs in all the studies. Svedlund (1983) reported 2 out of 101 participants dropped out. Guthrie (1991) reported that 7 of 53 participants dropped out of the treatment group plus 6 of 49 controls; data were available at 3 months for all but 2 participants (2% drop out), despite the withdrawal from treatment. In Creed (2003) there were missing data: 16% (14/86) in the paroxetine group; 14% (12/85) psychotherapy; 0% in the routine care group did not start the trial. A further 29/86 (34%) in the paroxetine group and 14/85 (16%) in the psychotherapy arm discontinued treatment, but these patients still appear to have been followed. Overall, loss to follow-up at three months was 12/86 (14%) for paroxetine, 11/85 (13%) psychotherapy and 7/86 (8%) usual care arm. At 15 months the authors contacted more of the patients. The authors reported that there were no significant differences at baseline between those who did and did not complete the treatments. For the 3 month pain score and SF36 outcome measures respectively, the patients included in the analysis were 74 and 59 (69%) paroxetine; 74 and 58 (68%) psychotherapy and 79 and 63 (73%) usual care, but some of these patients had discontinued treatment. We decided to include the results from this study, with some reservations, especially about the paroxetine arm and about the SF36 results. The study also recorded the number of patients with an improvement in global symptoms, based on the results from 74, 74 and 80 patients respectively. The GDG decided that this outcome was more representative because patients that dropped out due to side effects would not have rated their global symptoms as improved. The follow-up period allowed the patients to have paroxetine in all arms: 42% in paroxetine group; 19% in psychotherapy, and; 22% in the usual care group, i.e. the follow-up for the comparison of psychotherapy and paroxetine should be considered to be partly confounded. In addition, 10% of the usual care group were given psychological treatment. Therefore we did not report the results for the follow-up period for the comparison psychotherapy versus paroxetine, and the comparison psychotherapy versus usual care was also considered with caution.

Overall, we considered that none of the studies were at high risk of bias. Creed (2003) was treated with caution for the outcomes pain and SF36 because of missing data and non compliance. We also noted there was some confounding in the follow-up period.

RESULTS

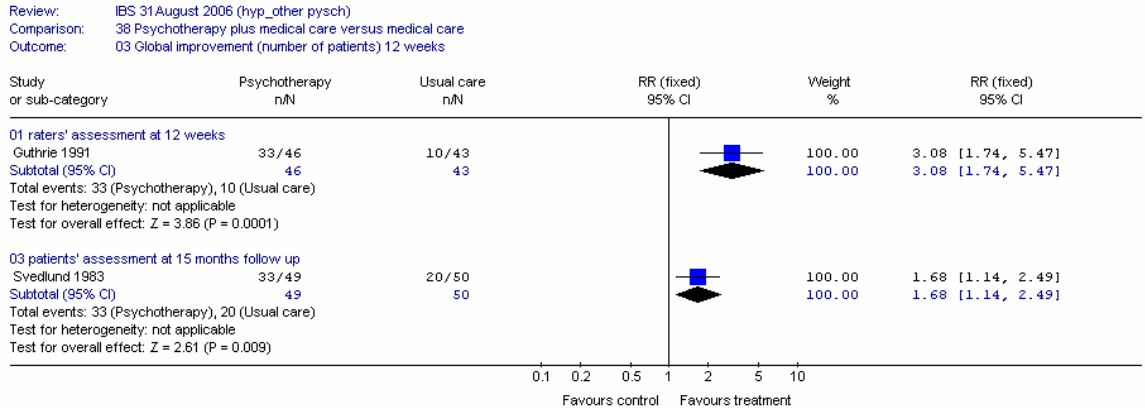
A. Psychotherapy plus medical therapy versus medical therapy only

1. Global symptoms

a) Global improvement in symptoms (number of patients)

Two studies reported the numbers of patients with an improvement in global symptoms: Guthrie (1991) gave the numbers as assessed by gastroenterologists at the end of treatment (12 weeks), and; Svedlund (1983) reported the patients' self-assessment at 15 months follow-up (treatment lasted three months). There are significantly more patients with global improvement at both times. The GDG preferred to use the patient assessment in all reviews. At 15 months follow-up, the number needed to treat was 4 (95% 3, 13), for a control group rate of 40%. [The rater assessed result at 12 weeks corresponded to an NNT of 3 (95%CI 2, 4) for a control group rate of 23%].

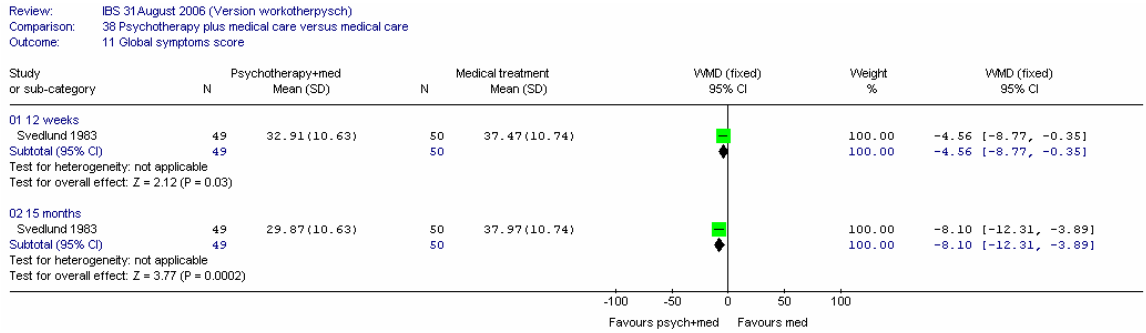
Figure 1:



b) Global symptom score

Svedlund (1983) reported a patient-rated global symptom score at 12 weeks and 15 months follow-up; this score rated somatic symptoms (19 items; each rated on a 7-point scale 0=absent to high=extremely; i.e. lower is better. It was unclear what the maximum of the scale was but it is assumed to be 6. This gave an overall maximum of 114). There was a small statistically significant difference at 12 weeks, favouring psychotherapy plus medical treatment, which increased to -8.10 (95%CI -12.31, -3.89) at 15 months follow-up. The control group score was 38.0.

Figure 2:

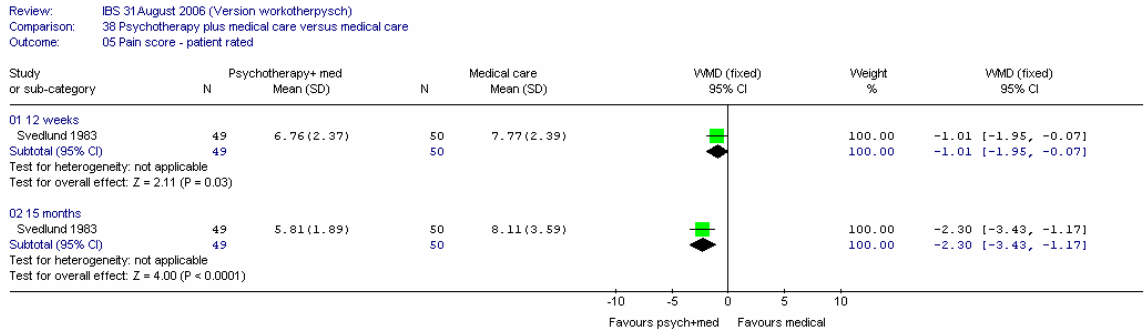


2. Individual symptoms

a) Abdominal pain

Svedlund (1983) reported a patient-rated pain score at 12 weeks and 15 months follow-up. It was unclear what the maximum of the scale was but the baseline was about 10 units. There was a small statistically significant difference at 12 weeks, favouring psychotherapy plus medical treatment, which increased to -2.30 (95%CI -3.43, -1.17) at 15 months follow-up. The control group score was 8.11.

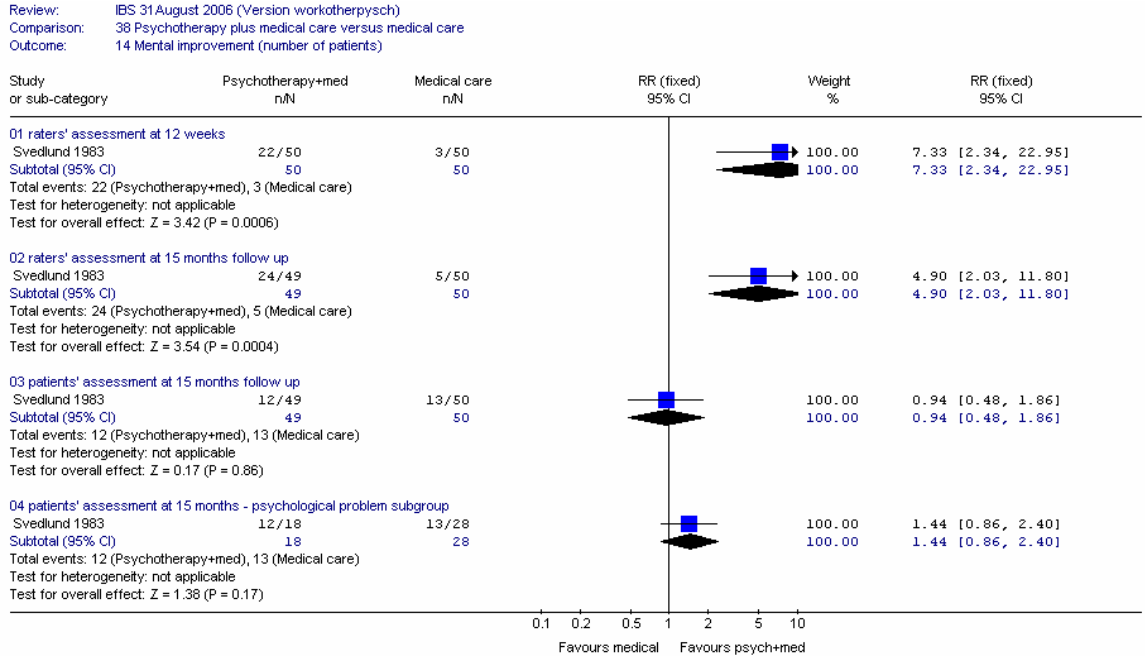
Figure 3:



3. Mental health outcomes (overall mental health; depression; anxiety)

Svedlund (1983) reported the number of patients with improved mental symptoms, as assessed by raters at 12 weeks and by raters and patients at 15-month follow-up. There were significantly more patients improving according to the raters, but the patients' rating showed no significant changes. The authors reported that several patients denied having mental complaints at baseline.

Figure 4:



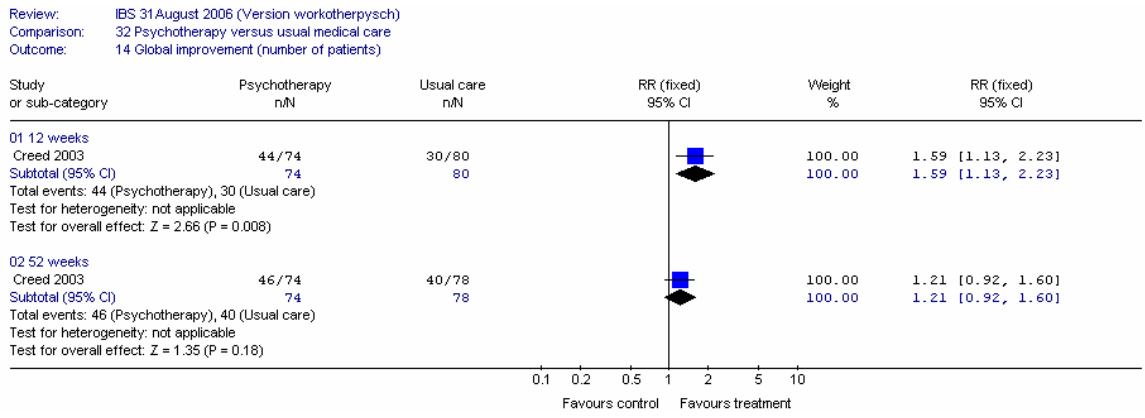
Guthrie (1991) reported a significant improvement, favouring the psychotherapy group, in the median scores on the Hamilton depression scale (p<0.001) and the Clinical anxiety scale (p<0.01), as assessed by the psychiatrist.

B. Psychotherapy versus usual medical therapy

1. Global symptoms

Global improvement in symptoms (number of patients) was reported by Creed (2003) at 12 and 52 weeks. There were significantly more patients with global improvement in the psychotherapy group compared to usual care, at 12 weeks: RR 1.59 (95%CI 1.13, 2.23). This corresponded to an NNT of 5 (95%CI 3, 15), for a control group rate of 38%. However, there was no significant difference at 12 months follow-up. We noted, however, that 10% of the usual therapy patients were given psychotherapy in the follow-up period, which may have reduced the relative effectiveness of the psychotherapy arm.

Figure 5:

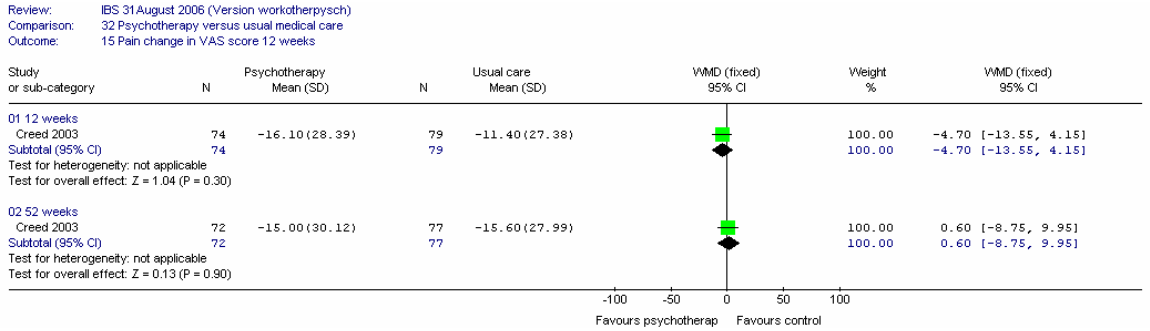


2. Individual symptoms

a) Pain

Pain (change in VAS score on a scale of 100 mm) was reported by Creed (2003) at 12 and 52 weeks. There was no significant difference between interventions at either time.

Figure 6:



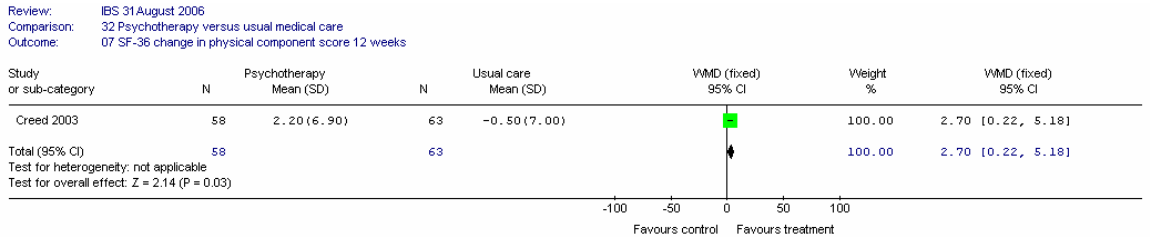
3. Quality of life

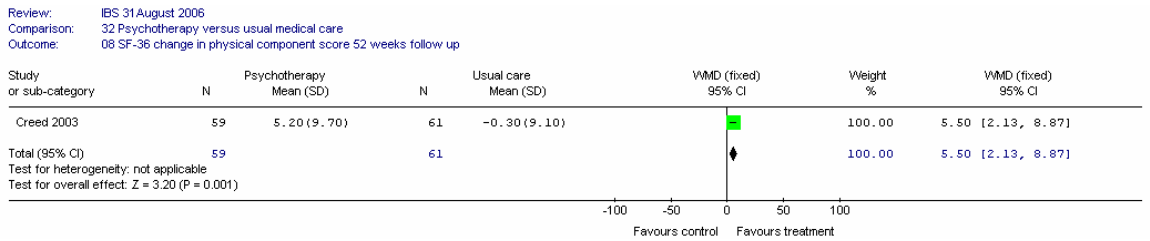
Creed (2003) measured the health-related quality of life using SF-36, recording both the physical and mental components. We noted that there was about 30% of missing data for these outcomes at three months follow-up.

a) Physical component

The physical component change score was reported at 12 weeks and at 52 weeks. On this 0 to 100 scale, an increase is a benefit and a negative change score is a worsening. There was a small statistically significant improvement favouring psychotherapy at 12 weeks, which increased slightly at 52 weeks to mean difference 5.50 (95%CI 2.13, 8.87) for a control group value of 38.1.

Figure 7:

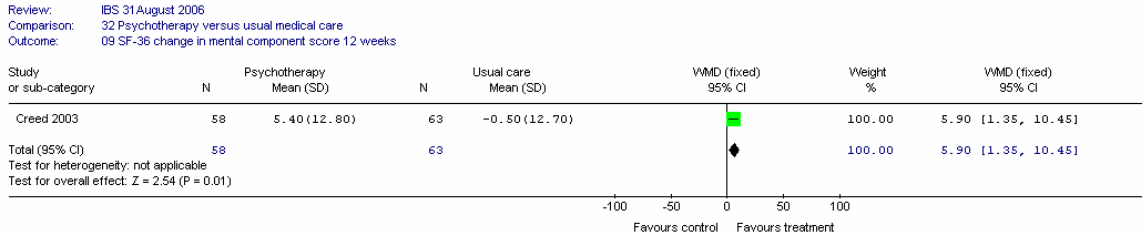


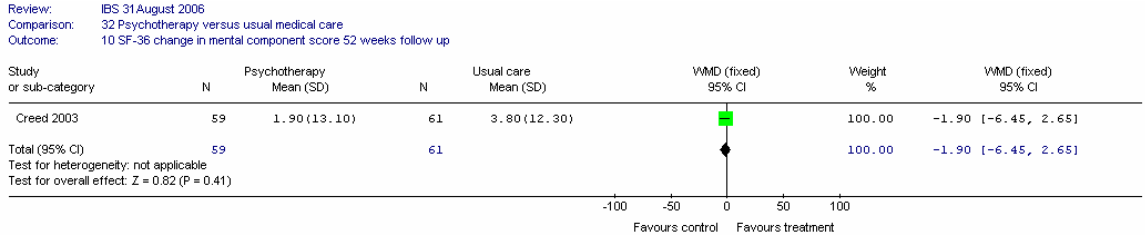


b) Mental component

The SF-36 mental component change score was reported by Creed (2003) at 12 weeks and at 52 weeks. There was a small statistically significant difference at 12 weeks, but no significant difference at one year.

Figure 8:

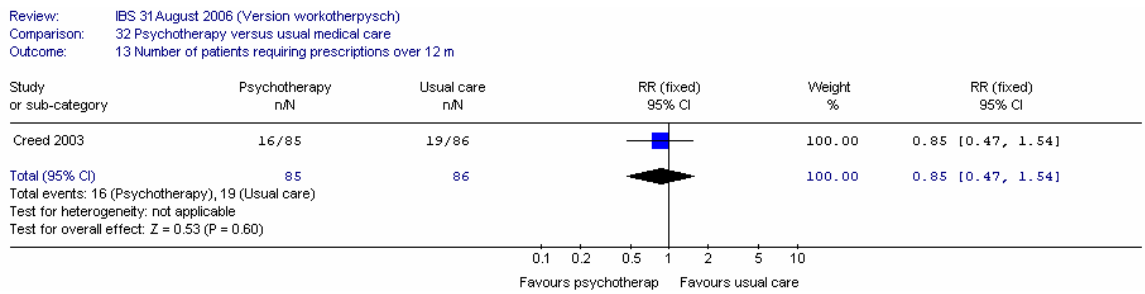




4. Number of patients receiving prescriptions for antidepressants in follow up year

Creed (2003) compared the number of patients receiving prescriptions for antidepressants in follow-up year. There was no significant difference between interventions.

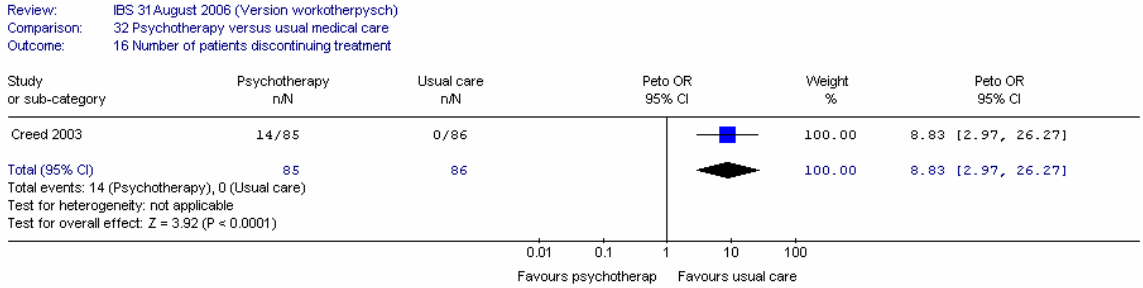
Figure 9:



5. Number of patients discontinuing treatment

Creed (2003) also reported the number of patients in each group who discontinued treatment. There was a large, statistically significant difference between interventions, favouring usual care.

Figure 10:



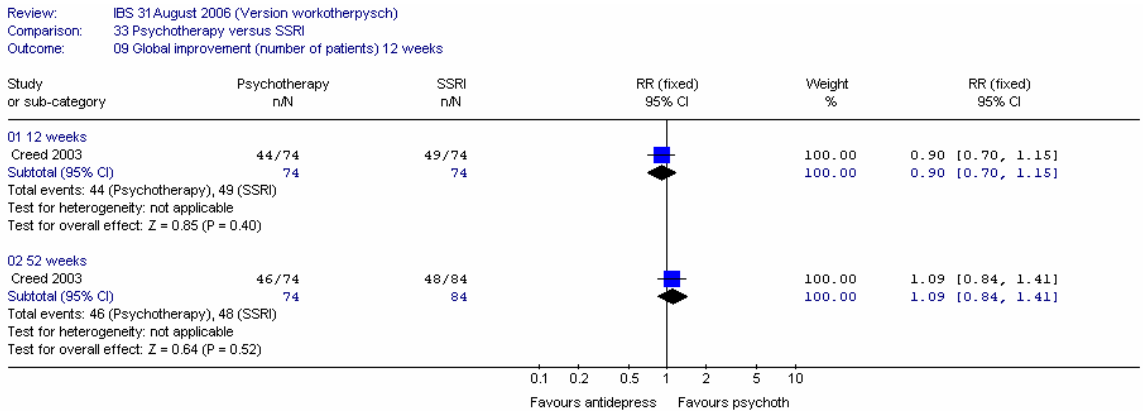
C. Psychotherapy versus antidepressant medication (SSRI - paroxetine)

1. Global symptoms

a) Global improvement in symptoms (number of patients)

The numbers of patients improved were reported by Creed (2003) at 12 weeks and at 52 weeks. There was no significant difference at either time, although we noted that the 52 week results are likely to be confounded by the use of antidepressants in both arms.

Figure 11:



2. Individual symptoms

a) Pain

Pain (change in VAS score) was reported by Creed (2003) at 12 weeks. There was no significant difference between interventions.

Figure 12:

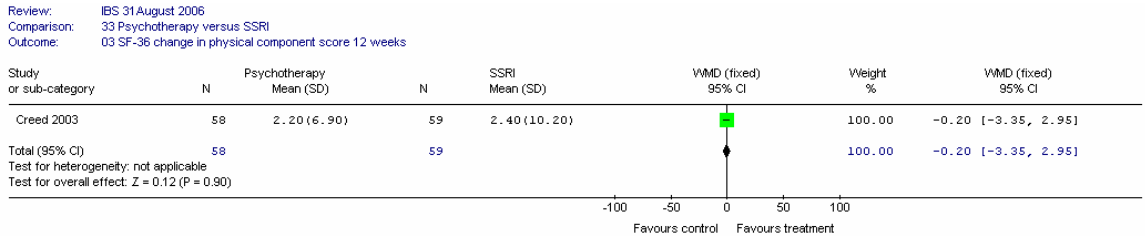
3. Quality of life

Creed (2003) measured the health-related quality of life using SF-36, recording both the physical and mental components. We noted that there was about 30% of missing data for these outcomes at three months follow-up.

a) Physical component

The physical component change score was reported at 12 weeks. There was no significant difference between interventions.

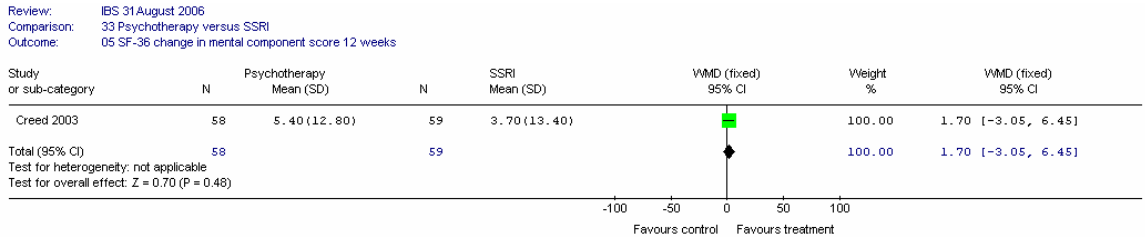
Figure 13:



b) Mental health outcomes

The SF-36 mental component change score was reported by Creed (2003) at 12 weeks. There was no significant difference between interventions.

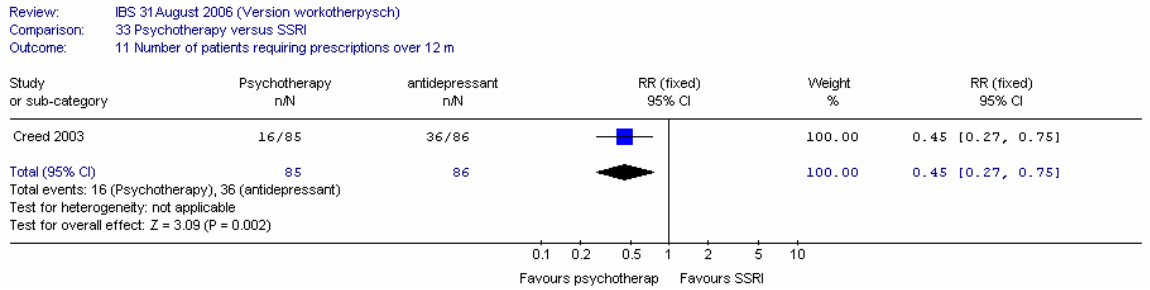
Figure 14:



4. Number of patients receiving prescriptions for antidepressants in follow up year

Creed (2003) compared the number of patients receiving prescriptions for antidepressants in follow-up year. There was a statistically significant difference between interventions, favouring psychotherapy: RR 0.45 (95%CI 0.27, 0.75). This corresponded to a number needed to harm of 5 (95%CI 3, 10), for an antidepressant group rate of 42%.

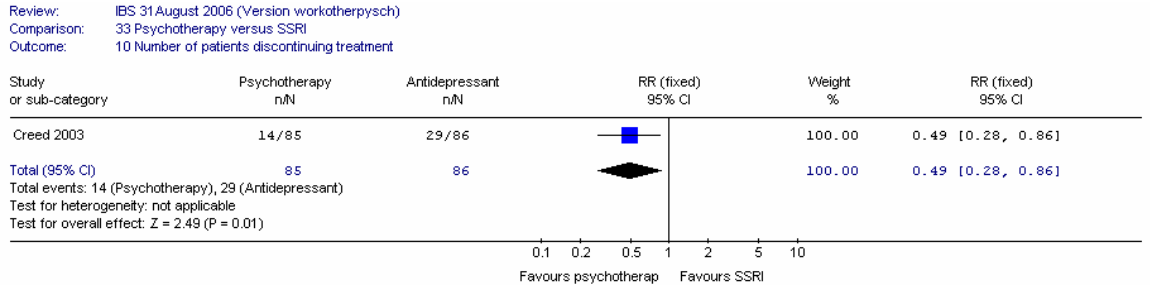
Figure 15:



5. Number of patients discontinuing treatment

Creed (2003) also reported the number of patients in each group who discontinued treatment. There was a statistically significant difference between interventions, favouring psychotherapy. This gave an NNH of 6 (95%CI 4, 20), for an antidepressant group rate of 34%.

Figure 16:



ECONOMIC LITERATURE FOR PSYCHOTHERAPY

One relevant health economic analysis was identified on the cost-effectiveness of psychotherapy in the treatment of IBS. Creed (2003) was a trial based economic evaluations conducted in the UK which recruited patients from secondary and tertiary care with severe IBS. This study aimed to assess whether psychotherapy would be superior to usual care in reducing abdominal pain and improving quality of life and whether these improvements could be achieved at no additional cost due to treatment costs being offset by reduced health care costs. It also included a comparison of SSRIs with usual care. The patient population considered were secondary and tertiary care patients with severe IBS who had not responded to usual treatment. The included patients had a mean duration of IBS of 8 years. This study was considered to be relevant to patients with refractory IBS only. The psychotherapy intervention consisted of 8 sessions over 3 months delivered by trained therapists. After three months, patients in the psychotherapy arm returned to their GP and received usual care for one year during which time they were followed-up. In the comparator arm patients received usual care from either their gastroenterologist or their GP for the three month treatment period and the following year of follow-up. The primary outcome was abdominal pain measured on a VAS of severity with secondary outcomes considering days with pain, overall change in symptoms and HRQofL measured by the SF-36. Direct health care costs per week were estimated for the intervention

and follow-up periods. This included hospital costs (inpatient days, outpatient, day-patient and A&E attendances), primary care costs (GP surgery and home visits, practice nurse and practice based counsellor visits), domiciliary care services (NHS and PSS) and day centres, use of alternative therapies and prescribed medications. These were adjusted to allow for any differences before baseline and bias corrected 95% confidence intervals were presented. The cost of providing psychotherapy was not presented separately from the other direct health care costs.

The number of patients with an improvement in global symptoms was significantly higher for psychotherapy at the end of treatment compared to usual care. The clinical outcomes from this trial have been summarised in detail in the clinical effectiveness review. Direct health care costs were significantly increased for psychotherapy compared to usual care during the intervention period and were significantly decreased during the following year. There was no significant increase in direct health care costs over the 15 month trial period.

This study was a partial economic evaluation as it did not assess the incremental cost of any benefit achieved in the form of a cost-effectiveness ratio. The evidence provided by this study was considered to be indirect as the patients were recruited from secondary and tertiary care and costs may differ for refractory patients managed in primary care. No potential areas of significant bias were identified. Direct health care costs were significantly increased by psychotherapy during the intervention period and they were significantly increased during the follow-up period. However, the study was powered to detect a specific change in clinical rather than cost outcomes. As this study did not provide an estimate of the cost per QALY for psychotherapy compared to usual care, it was not particularly useful in determining whether recommending psychotherapy for use in the NHS would result in the efficient use of NHS resources.

COST-EFFECTIVENESS ANALYSIS FOR PSYCHOTHERAPY

The section describes the health economic analysis undertaken to inform recommendations on the use of psychotherapy as one-off intervention in the management of IBS. The general methods used in the economic analysis for all management interventions are described in detail in Chapter 5 and the model inputs and assumptions relevant to this particular intervention are described below.

- The effectiveness of psychotherapy in addition to usual care compared to usual care alone in people with refractory IBS was based on the number of patients with an improvement in global symptoms (at the end of treatment) for psychotherapy vs usual care (RR = 3.08, 95%CI 1.74 – 5.47, based on Guthrie 1991).
- We assumed that the relative risk of response had fallen to 1.68 (95% CI 1.14 – 2.49) by 15 months based on follow-up data from Svedlund (1983).

- The evidence included in the clinical effectiveness review did not allow a subtype specific estimate of clinical effectiveness to be estimated. Therefore it was assumed that psychotherapy is equally effective in all IBS subtypes although it should be noted that the trials were carried out in patients with refractory IBS and a significant proportion of the trial population had a current or previous psychiatric diagnosis.
- It was assumed that psychotherapy is given over 12 weeks as this was the duration used in RCTs.
- The costs of psychotherapy were estimated from the number and duration of sessions and the unit cost for face-to-face time with a psychotherapist. The mean duration of psychotherapy from the three RCTs (Svedlund 1983; Guthrie 1991; Creed 2003) was 9.9 hours. The cost of face-to-face time with a psychotherapist was based on the reference cost for counselling services in primary care (£48 per hour) on advice from GDG members that psychotherapy is provided by counsellors and nurses in the NHS at present. This gave a total cost of £471 (range £348 - £672) over 12 weeks.

In the Creed (2003) economic analysis, there was a statistically significant lower cost per week for psychotherapy vs usual care (-£8.11 to -£0.04 95% CI) in the year following the intervention period (costs have been uplifted to reflect current prices). We took the mid-point of this interval which gave a cost per week of £-4.08 for psychotherapy compared to usual care in the year following treatment. This was applied in the basecase analysis for psychotherapy resulting in cost savings of £212 over the year following intervention.

The results of the Creed (2003) study also suggested that there was a reduction in service use during the intervention period, as whilst the weekly costs during this period were significantly higher for psychotherapy compared to usual care (£1.23 to £15.30), these were not comparable to the cost of providing psychotherapy which would be expected to have a mean cost of £40 per week based on the number and duration of sessions provided in this study and the unit costs presented above. This suggested that there was a significant reduction in other health care use during the intervention period. As it was not possible to separate the costs of psychotherapy from the costs offsets due to lower resource use during the intervention period of the Creed (2003) study, we have based the intervention cost on the estimate described above. However, as it seems reasonable that patients will access NHS services less whilst they are receiving an effective intervention, we have applied the reduction in resource use seen in the follow-up period as a cost off-set during the intervention period. The direct costs measured by Creed (2003) during the intervention period have been considered in a sensitivity analysis.

Modelled response rates

In the basecase scenario the response rate of 25% in the no treatment arm was taken from the mean placebo arm response rate from the behavioural therapy trials. This represents the group of patients whose symptoms improve under usual care. The RR for an improvement in global

symptoms for psychotherapy vs no treatment at the end of treatment is 3.08; therefore the response rate in the intervention arm is 78% after 12 weeks. The response rate has fallen to 43% by 15 months based on the 15 month follow-up data from Svedlund (1983). The time-frame of the analysis was limited to 15 months, with no further costs or benefits accrued beyond this time-point, as this was the longest follow-up available for psychotherapy in IBS.

Figure 17: Response rate in the basecase analysis

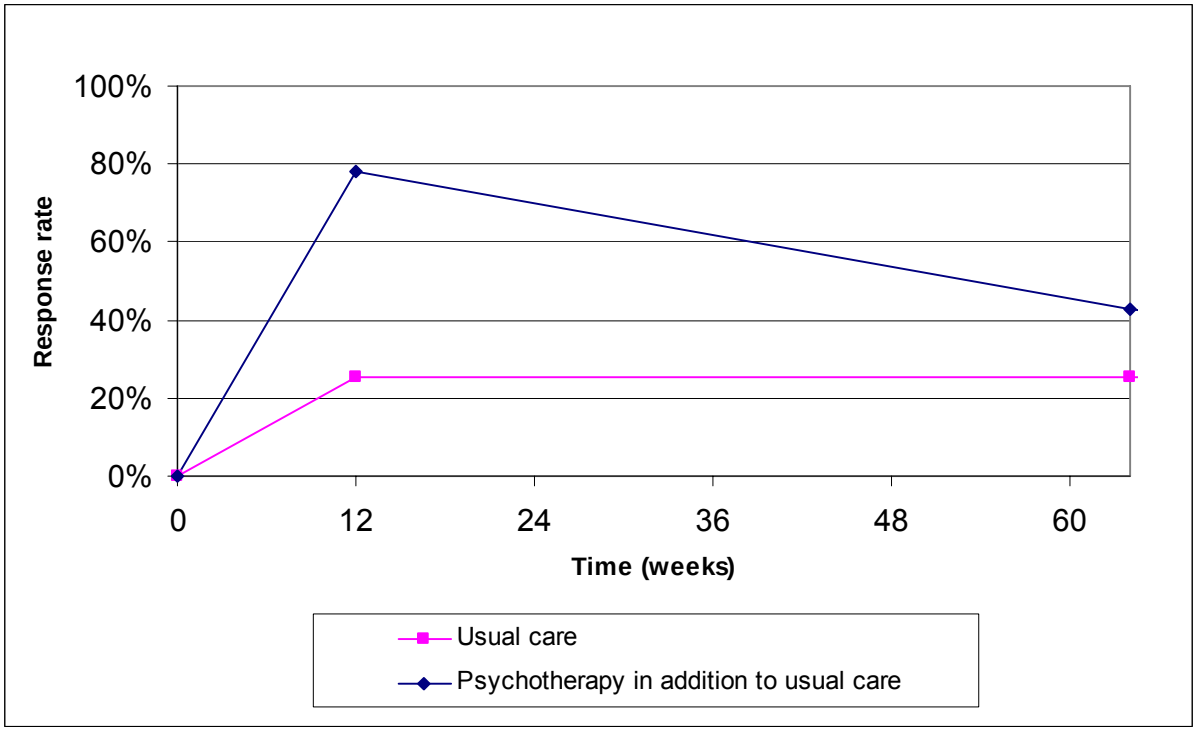


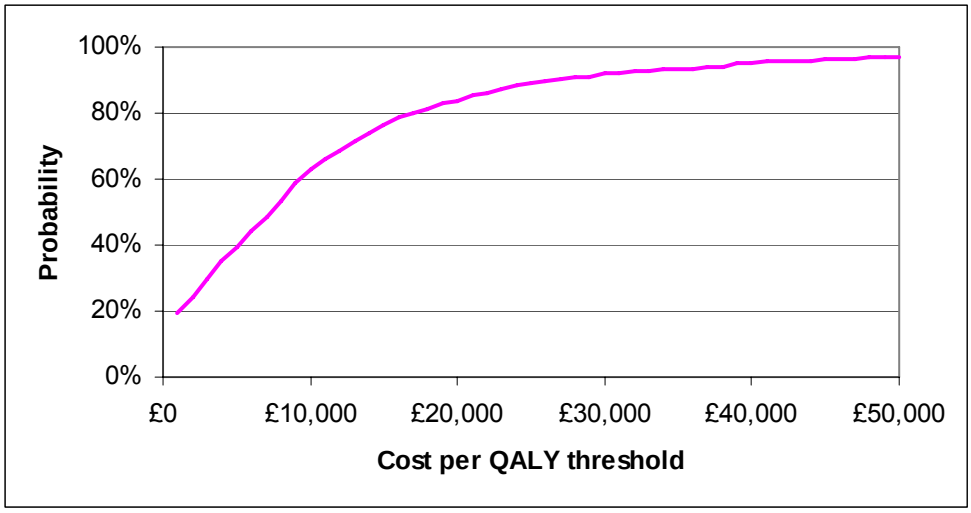
Table 1: Intervention specific parameters – Psychotherapy

Description	Value	Evidence
RR of response for intervention vs placebo (at end of treatment)	3.08 (1.74 – 5.47)	Guthrie (1991)
RR of response for intervention vs placebo (at 15 months)	1.68 (1.14 – 2.49)	Svedlund (1983)
Cost for psychotherapy	£471 (range £348 - £672) over 12 weeks	Weighted mean duration across studies and unit cost form Netten (2006)
Cost-offset due to reduced resource use during intervention and 1 year after	-$4.70 (95%CI -$9.34 to -$0.05) per week Equiv to -£4.08 (95% CI -£8.11 to -£0.04) at current UK prices*	Creed (2003)

* Uplifted to 05/06 prices using Hospital and Community Health Services Pay and Prices Index, Netten (2006)

Psychotherapy in addition to usual care for 100 patients with refractory IBS is estimated to gain an additional 2.94 QALYs for an additional cost of £21,035 compared to usual care alone under the basecase assumptions. The incremental cost per QALY is therefore £7,160. The probabilistic sensitivity analysis considers the uncertainty in this basecase estimate due to the uncertainty in the parameters used to estimate the cost-effectiveness. The CEAC in Figure 18 shows that given the parameter uncertainty, psychotherapy in additional to usual care has a 84% probability of having a cost per QALY under £20,000 and a 92% probability of having a cost per QALY under £30,000, compared to usual care alone.

Figure 18: CEAC for psychotherapy in addition to usual care compared to usual care alone in patients with refractory IBS



The incremental cost-effectiveness is dependent on the probability of an improvement for patients who receive usual care. When we applied a lower response rate of 9% in the usual care arm, the cost per QALY was increased to £14,629. As this sensitivity analysis significantly increased the cost per QALY estimate, the probabilistic sensitivity analysis was re-run using this lower response rate for the comparator arm. The mean cost per QALY from the 1000 samples was £17,577 and the cost per QALY had a 51% probability of being under £20,000 per QALY and a 62% probability of being under £30,000 per QALY.

The threshold analysis showed that a response to treatment would need to provide more than 0.026 QALYs per annum to give a cost per QALY of under £20,000 in the basecase analysis. When the utility gain associated with a response to treatment was increased to 0.135 (equivalent to the QALY gain expected for a complete remission of symptoms) the cost per QALY was significantly lower at £3,782.

When we assumed no fall-off in response up to 52 weeks post-intervention, the cost per QALY was £5,000. This would be further reduced by any continued response beyond 52 weeks. When

we assumed that there was no significant difference between psychotherapy and usual care at 12 months, the cost per QALY increased to £9,062.

When we estimated the incremental cost during the intervention and follow-up period directly from those measured in Creed (2003), psychotherapy was cost saving compared to usual care and resulted in greater QALY gain, dominating usual care. When we excluded the reduction in resource use observed in the Creed (2003) study from the analysis, the incremental cost of psychotherapy increased significantly to £47,154 and the cost per QALY increased to £16,051. As this is a significant increase in the cost per QALY, the probabilistic analysis was re-run under this assumption. In this conservative estimate the cost per QALY for psychotherapy in addition to usual care compared to usual care alone had a 57% probability that of being under £20K and a 77% probability of being under £30K.

Table 2: Sensitivity results for psychotherapy in addition to usual care compared to usual are alone for 100 patients with refractory IBS (all subtypes)

Scenario	Usual care		Behavioural intervention and usual care		Incremental
	Cost	QALY	Cost	QALY	Cost per QALY
Basecase	£0	2.02	£21,035	4.96	£7,160
Lower response rate in comparator arm (9%)	£0	1.30	£21,035	2.74	£14,629
No fall-off in effect for 1 year	£0	2.02	£21,035	6.23	£5,000
Effect falls off over 12 months	£0	2.02	£21,035	4.34	£9,062
No resource use reduction	£0	2.02	£47,154	4.96	£16,051
Costs as measured in Creed (2003)	£0	2.02	-£11,307	4.96	-£3,849 Psychotherapy dominates
High utility gain of 0.135	£0.00	3.83	£21,035	9.39	£3,782
Threshold analysis on lowest utility	A cost per QALY of £20,000 is reached when the QALY gain associated with responding to treatment lies between 0.025 and 0.026.				

Further analyses on the cost-effectiveness of psychotherapy compared to other behavioural interventions are given in section 9.7.

EVIDENCE STATEMENTS

For this review, the evidence was assessed using the GRADE process and tables are shown in Appendix F. The following evidence statements are derived from the GRADE tables.

1. There is fair evidence to show a significant global improvement in symptoms after 12 weeks and after 15 months, for dynamic psychotherapy in addition to medical therapy compared with medical therapy alone, given in secondary care to patients with long term or refractory IBS, approximately half of whom had psychological co-morbidities.

2. There is fair evidence to show a significant global improvement in symptoms after 12 weeks, for psychodynamic interpersonal therapy compared with medical treatment, given in secondary care to patients with refractory IBS, approximately half of whom had psychological co-morbidities.

3. There is weak evidence to show no significant global improvement in IBS symptoms after 12 months follow up, for psychodynamic interpersonal therapy compared with medical treatment, given in secondary care to patients with long term IBS, many of whom had had psychological co-morbidities. This fall-off in effect may have been caused by confounding in the control arm.

4. There is moderately good evidence to show a significant decrease in pain after 12 weeks and 15 months, for dynamic psychotherapy in addition to medical therapy compared with medical therapy alone, given in secondary care to patients with long term IBS, many of whom had had psychological co-morbidities.

5. There is fair evidence to show no significant reduction in pain after 12 weeks and 12 months follow up, for psychodynamic interpersonal therapy compared with medical treatment, given in secondary care to patients with refractory IBS, approximately half of whom had psychological co-morbidities.

6. There is weak evidence to show no significant difference in the patients' assessment of their mental health at 15 months, between patients given dynamic psychotherapy in addition to medical therapy compared with medical therapy alone, either for all patients or for a subgroup with a psychological co-morbidity history.

7. There is weak evidence to show a small, significant improvement in the physical component of the SF36 quality of life score after 12 weeks and 12 months follow up, and a small significant difference in the mental health score after 12 weeks, for psychodynamic interpersonal therapy compared with medical treatment, given in secondary care to patients with refractory IBS, approximately half of whom had psychological co-morbidities. There was no significant difference in the mental health score at 12 months follow up.

8. There is weak evidence to show no significant difference in the number of patients requiring a prescription for antidepressants over 12 months, for psychodynamic interpersonal therapy

compared with medical treatment, given in secondary care to patients with refractory IBS, approximately half of whom had psychological co-morbidities.

9. There is weak evidence to show significantly more patients discontinued treatment for psychodynamic interpersonal therapy compared with medical treatment, given in secondary care to patients with refractory IBS, approximately half of whom had psychological co-morbidities.

10. There is fair evidence to show no significant difference in global improvement in symptoms, pain and quality of life (physical and mental) after 12 weeks, between psychodynamic interpersonal therapy compared with an SSRI, given in secondary care to patients with refractory IBS, approximately half of whom had psychological co-morbidities.

11. There is weak evidence to show that significantly fewer patients required a prescription for antidepressants over 12 months, for psychodynamic interpersonal therapy compared with an SSRI, given in secondary care to patients with refractory IBS, approximately half of whom had psychological co-morbidities.

12. There is weak evidence to show significantly fewer patients discontinued treatment for psychodynamic interpersonal therapy compared with an SSRI, given in secondary care to patients with refractory IBS, approximately half of whom had psychological co-morbidities.

HEALTH ECONOMIC STATEMENT

Evidence from a trial based economic evaluation in secondary and tertiary care patients with a high level of NHS service use at baseline showed that direct health care costs are lower in the year following treatment for 3months of psychotherapy compared to 3 months of usual care. Health care costs were significantly higher during the intervention period for psychotherapy compared to usual care. This evidence is unlikely to be applicable to primary care patients except those with refractory IBS.

Evidence from a decision analytic model showed that the addition of psychotherapy to usual care is cost-effective in individuals with refractory IBS although the cost-effectiveness was sensitive to uncertainty around the proportion of patients experiencing an improvement in global symptom score with usual care alone. It was also sensitive to the whether or not there was any reduction in health care service use during and following treatment

GDG DISCUSSION

Despite the prevalence of psychiatric comorbidities in the trials for this review, the GDG considered that dynamic psychotherapy could be a useful option for all people with refractory IBS, and had potential to be a first line therapy. The GDG therefore decided to include

pyschotherapy in one of its top five research recommendations, with the potential for this intervention to be considered as a first line therapy option.

EVIDENCE TO RECOMMENDATION

The evidence to recommendation statement for psychotherapy, CBT and hypnotherapy is detailed in section 9.8.

The combined guideline recommendation for psychotherapy, CBT and hypnotherapy is also stated in section 9.8.

9.5 Cognitive behavioural therapy

SELECTION CRITERIA

The selection criteria described in the general methodology section were used, except that crossover studies were excluded as inappropriate due to the carry-over effect of the CBT interventions.

The following comparisons were to be included:

- CBT versus waiting list control or symptom monitoring only
- CBT type 1 versus type 2 (e.g. stress management versus contingency management)
- CBT individual versus CBT group
- CBT + another intervention (e.g. medical therapy) versus the other intervention alone
- CBT versus medical treatment.

SEARCH STRATEGY FOR IDENTIFICATION OF STUDIES

Searches were performed on the following core databases: MEDLINE, EMBASE, CINAHL, and *The Cochrane Library* (1966 to current day with guidance from the GDG). Additionally, the PSYCINFO database was searched for this review. The search strategies are listed in Appendix B.

Study Design

Seventeen parallel randomised trials were included (Bennett 1985; Bergeron 1983; Blanchard 1993; Bogalo 2006; Boyce 2003; Corney 1991; Drossman 2003; Fernandez 1998; Gong 2002; Greene 1994; Heymann-Monnikes 2000; Kennedy 2005; Lynch 1989; Payne 1995; Tkachuk 2003; Toner 1998; Vollmer 1998). Further details are given in the included studies table.

Six studies had more than one arm: Bergeron (1983) (stress management, relaxation, biofeedback); Boyce (2003) (CBT, relaxation, routine medical care); Drossman (2003) (half of the patients were randomised to CBT or attention control; the other half to desipramine or placebo tablet; the two halves were divided randomly initially); Fernandez (1998) (stress management, contingency management, conventional medical treatment or placebo); Payne

(1995) (CBT, self help group or waiting list control); Vollmer (1998) (CBT in a group, CBT individually or symptom monitoring waiting list control). Thus, there were 28 possible comparisons for this review. We did not include the comparison with desipramine because this drug is not licensed for use in the UK.

Two studies were reported only as abstracts (Bergeron 1983; Gong 2002). The former had no data reported. Three studies were RCTs with limited or incomplete data (Bennett 1985; Toner 1998; Bogalo 2006). The Bennett study gave little detail (e.g. it was unclear how many patients were assigned to each group; no primary data were given; only p values for ANOVAs). The Toner (1998) study was briefly reported as part of a larger article. This study enrolled 101 individuals with IBS, who were randomly allocated to group CBT, a psychoeducational group treatment (education about the condition and support) or usual medical treatment. No primary outcome data were reported. Bogalo (2006) appeared to use data from a randomised trial. However, this paper only reported outcomes for the intervention group not the controls. For the rest of this review, only the 14 studies with sufficient data are reported.

The studies were carried out in the UK (Corney 1991; Kennedy 2005), Europe, Canada, the USA and China. Trials lasted between 6 and 12 weeks (the duration of the Gong (2002) study was not stated). One study was conducted in primary care (Kennedy 2005); seven were in secondary care (Blanchard 1993; Corney 1991; Drossman 2003; Fernandez 1998; Gong 2002; Heymann-Monnikes 2000; Lynch 1989); one study (Boyce 2003) recruited equal numbers of patients through gastroenterology clinics and through newspaper advertisements, and the others did not report the setting. The total number of patients in the studies ranged from 20 to 431, with three studies including more than 100 patients (Boyce 2003; Drossman 2003; Kennedy 2005). All but four studies (Boyce 2003; Drossman 2003; Gong 2002; Kennedy 2005) had fewer than 25 patients in the treatment arm.

Population

All the studies included only patients with IBS, apart from Drossman (2003), for which 78% of the patients had IBS. None of the studies reported the number of patients with bloating or whether the symptoms were post-infective. The mean age of patients across studies was around 40 years, with those aged between 16 and 70 years included. All the studies included more women than men.

Four studies reported or implied that the patients had refractory IBS (Greene 1994; Heymann-Monnikes 2000; Lynch 1989; Tkachuk 2003): Tkachuk (2003) stated that the patients had refractory IBS; Lynch (1989) had patients referred from gastroenterology clinics and had duration of IBS of around 9 years; Heymann-Monnikes (2000) had tertiary referral patients. The patients in Greene (1994) had had IBS for 14.5 years. Boyce (2003) reported that about 50% of

patients had received medication for IBS. The other studies did not give any information about IBS duration.

Most studies reported whether the patients had an Axis I diagnosis (e.g. major depression; schizoaffective disorder; paranoid state) or other psychiatric or psychological co-morbidities:

- Heymann-Monnikes (2000) stated that patients were excluded if they had any mental disorder.
- Drossman (2003) reported that no patients had psychiatric disorders, but almost half had a history of physical or sexual abuse.
- Boyce (2003) excluded patients if they had major current psychotic illness, used psychological treatment, or antidepressants or antipsychotics.
- Two studies excluded patients with serious psychiatric disorders (Lynch 1989 (implied); Vollmer 1998).
- Five studies stated that the majority of patients had an Axis I diagnosis (Blanchard 1993, 50-73%; Greene 1994, 90%; Payne 1995, 80-92%; Tkachuk 2003, 68%; Vollmer 1998, 82-90%).
- Three studies mentioned that the patients had received psychiatric treatments: in Fernandez (1998) 49% had had psychiatric treatment; in Kennedy (2005) 43% had consulted a doctor because of a psychological problem; in Lynch (1989) 6/21 (29%) patients used psychotropic drugs.
- Corney (1991) had over 50% of the patients with one or more social problems.
- The remaining studies (Bergeron 1983; Gong 2002) did not mention Axis I diagnoses or psychiatric complaints/treatments.

Overall, therefore, eight studies can be considered to be representative or partly representative of the IBS population with concurrent psychiatric or psychological illnesses (Blanchard 1993; Fernandez 1998; Greene 1994; Kennedy 2005; Lynch 1989; Payne 1995; Tkachuk 2003; Vollmer 1998). Three studies can be considered to be in patients with IBS who do not have concurrent psychiatric or psychological illnesses (Heymann-Monnikes 2000; Drossman 2003; Boyce 2003). We noted that 15 to 20% of patients in primary care have a co-existing psychiatric condition and approximately half of those in secondary care.

Interventions

Twelve studies described some form of CBT: Boyce (2003); Corney (1991); Drossman (2003); Fernandez (1998) (one group had stress management sessions involving progressive muscle relaxation; another had contingency management sessions involving contingency contract for new behaviours; self-observation, shaping, stimulus control, neutralising inadequate habits and breaking learned illness behaviour, social skills training); Gong (2002); Greene (1994); Heymann-Monnikes (2000); Kennedy (2005); Lynch (1989); Payne (1995); Tkachuk (2003); Vollmer (1998). Two studies gave relaxation training (Bergeron 1983; Blanchard 1993).

The CBT interventions differed in the methods used (group or individual; administered by nurse practitioner or other professional); the number of sessions given (6 to 12), and; the duration of the study (6 to 12 weeks in the studies that stated this).

CBT was defined in different ways in different papers. Two studies had therapy delivered by nurses (Corney 1991; Kennedy 2005). Details are given in the included studies table (Appendix D).

It was decided to combine all CBT, behavioural therapy (BT) and cognitive therapy (CT) interventions under the general heading of CBT.

CBT was compared with relaxation training; symptom monitoring; self-help support groups; medical therapy or placebo. Two studies had placebo as a comparator (Drossman 2003; Fernandez 1998). Drossman (2003) randomised the patients into two groups and then randomised one group to CBT and attention control and the other group to desipramine and placebo desipramine. We decided to classify the CBT-attention control comparison as placebo and treat the desipramine placebo as no treatment. Fernandez (1998) had a placebo condition consisting of giving the patient exercises to visualise bowel function; and prompting their own capacity for self regulation through thought.

For the purposes of this review, we combined the comparators waiting list control, symptom monitoring, no treatment and placebo condition. The following comparisons were included:

1. CBT versus a waiting list control group, symptom monitoring only or placebo: nine studies, 12 comparisons (Blanchard 1993; Drossman 2003 x2; Fernandez 1998 x2; Gong 2002; Greene 1994; Lynch 1989; Payne 1995; Tkachuk 2003; Vollmer 1998 x2):
    - CBT versus waiting list control (Lynch 1989)
    - CBT versus symptom monitoring (Blanchard 1993; Greene 1994)
    - CBT versus waiting list control including symptom monitoring (Payne 1995; Tkachuk 2003; Vollmer 1998 x2)
    - CBT versus an attention control condition involving symptom monitoring plus education plus access to a therapist (Drossman 2003)
    - CBT versus placebo condition (Fernandez 1998 x2)
    - CBT versus no treatment (Drossman 2003; Gong 2002);
2. CBT + another intervention versus the other intervention alone:
    - CBT + mebeverine versus mebeverine (Kennedy 2005)
    - CBT (multicomponent behavioural therapy) + optimised medical treatment versus optimised medical treatment alone (Heymann-Monnikes 2000);
3. CBT 1 versus CBT 2 (three studies):

- Stress management versus relaxation (Bergeron 1983 – no data)
- CBT versus relaxation (Boyce 2003)
- Stress management versus contingency management (Fernandez 1998);

4. CBT individual therapy versus CBT group therapy:
   - Vollmer (1998);
5. CBT versus another intervention:
   - CBT versus biofeedback (Bergeron 1983 – no data)
   - CBT versus support group (Payne 1995)
   - CBT versus psychoeducational group (Toner 1998 – no data);
6. CBT versus routine medical treatment (five studies, six comparisons):
   - CBT versus fluphenazine (anti-anxiety), mebeverine and fybogel (Bennett 1985)
   - CBT vs 'routine medical care' (Boyce 2003 x2; Corney 1991; Fernandez 1998 x2).

Six studies stated that the patients were allowed to continue their IBS medical treatment: Fernandez (1998), although 50% did not take the medication properly; in Heymann-Monnikes (2000), 9/12 in the BT group and 11/12 in symptom monitoring had concurrent medication for IBS; Kennedy (2005); Lynch (1989), 10/21 had analgesics at recruitment and 6 used Metamucil or similar bulking agents; Tkachuk (2003); Vollmer (1998), no patients were excluded because of their ongoing IBS drug treatment. Gong (2002) reported that all patients received selective gastrointestinal calcium antagonists.

One study (Boyce 2003) stated that the 'vast majority' were not taking concurrent medication. The rest did not state the concurrent medications for IBS.

In view of the use of other IBS medication in both arms of the CBT versus placebo/symptom monitoring comparisons, we decided to combine interventions 1 and 2 as subgroups because they each could be considered to be variations of CBT versus no treatment/symptom monitoring. Furthermore, the GDG advised that CBT treatment would not interact with other medical treatments. We decided that if subgroup analysis were to be used, the attention control and placebo condition (Fernandez 1998; Drossman 2003) should be considered as a separate group to the other comparators.

Outcomes

The outcomes examined were:

1. Global symptoms:
   a) Global improvement in symptoms (number of patients)
   b) Global symptom score.
2. Individual symptoms:
   a) Pain
   b) Bloating

c) Bowel habits.

3. Adverse events
4. Quality of life
5. Number of patients withdrawing from the study
6. Mental health outcomes (overall mental health; depression; anxiety)

Five studies recorded longer term follow up: Vollmer (1998) at 12 weeks; Corney (1991) at 40 weeks; Boyce (2003) and Kennedy (2005) both at 26 and 52 weeks; Fernandez (1998) at 52 weeks.

The following outcome measures were recorded:

Table 1.

Outcome measure	Measured at treatment end (weeks)	Measured at follow up (weeks)
Global scores		
Global IBS symptom score (Bowel symptom severity scale 0-48 scale; high = severe)	Boyce 2003 (8)	Boyce 2003 (26) Boyce 2003 (52)
Global IBS symptom score (satisfaction, global wellbeing, diary pain scores, health related quality of life); high score = good; maximum unclear	Drossman 2003 (12)	
Global IBS symptom score (7 symptoms daily for 2 weeks each scored 0-4 from not a problem to debilitating symptom intensity; high score = bad)	Greene 1994 (8)	
Global IBS symptom score (20 items over 14 days); high score = bad	Heymann-Monnikes 2000 (10)	
Global IBS symptom score (<75=normal; 75-174 mild; 175-299 moderate; 300-500 severe symptoms)	Kennedy 2005 (6)	Kennedy 2005 (26) Kennedy 2005 (52)
Global IBS symptom score (pain, discomfort, diarrhoea, constipation each rated 0=no symptoms to 6=very severe symptoms)	Lynch 1989 (8)	
Global improvement of IBS symptoms (mean Composite Primary Symptom Reduction [CPSR] score; CPSR represents % reduction in score from baseline); i.e. high = bad	Blanchard 1993 (8) Greene 1994 (8) Payne 1995 (8) Vollmer 1998 (10)	Vollmer 1998 (12)
Global improvement of IBS symptoms (mean score) VAS (1=very much better to 7=very much worse; 4=no change)	Heymann-Monnikes 2000 (10)	
Global improvement of IBS	Blanchard 1993 (8)	Fernandez 1998 (52)

symptoms (no. patients)	Fernandez 1998 (10) Gong 2002 (duration of treatment not stated) Greene 1994 (8) Lynch 1989 (8) Payne 1995 (8) Tkachuk 2003 (9) Vollmer 1998 (10)	
Pain scores		
Pain score (0=not a problem; 4=debilitating symptoms) daily for 4 weeks	Blanchard 1993 (8)	
Pain score (VAS score); high = bad.	Corney 1991 (16)	Corney 1991 (40)
Pain score (McGill average daily pain); high score = bad	Drossman 2003 (12)	
Pain score (0=not a problem; 1=mild; 2=moderate; 3=severe; 4=debilitating; scores totalled for 1 week); high score = bad	Fernandez 1998 (10)	
Pain score (scored 0-4 daily for 2 weeks); high score = bad	Greene 1994 (8)	
Pain score (0=no pain; 6=very severe pain)	Lynch 1989 (8)	
Pain score (0=not a problem; 4=intense and incapacitating)	Tkachuk 2003 (9) Vollmer 1998 (10)	
Pain score (0=not a problem; 4=debilitating symptoms) daily for 4 weeks	Blanchard 1993 (8)	
Bloating		
Bloating score (0=no symptom; 6=very severe symptom)	Greene 1994 (8) Lynch 1989 (8)	
Bloating score (0=not a problem; 4=intense and incapacitating)	Tkachuk 2003 (9)	
Bloating score (0=not a problem; 4=debilitating symptoms)	Vollmer 1998 (10)	
Bowel habits		
Constipation (VAS score); high = bad	Corney 1991 (16)	Corney 1991 (40)
Constipation (0=not a problem; 4=debilitating symptoms)	Greene 1994 (8)	
Constipation (0=no symptom; 6=very severe symptom)	Lynch 1989 (8)	
Diarrhoea (VAS score); high=bad	Corney 1991 (16)	Corney 1991 (40)
Diarrhoea (0=not a problem; 4=debilitating symptoms)	Greene 1994 (8)	
Diarrhoea (0=no symptoms; 6=very severe symptoms)	Lynch 1989 (8)	
Mental health		
Dysfunctional cognitions (Cognitive Scale for Functional Bowel Disorders); scale 25-175; high=bad	Tkachuk 2003 (9)	
Mental health (max = 100)	Tkachuk 2003 (9)	
Psychological distress (Clinical		Corney 1991 (40)

Interview Schedule); 0-48; high=bad		
Overall anxiety and psychological distress (Anxiety, State-Trait Anxiety Inventory [STAI]); Scale range 20-80; high = bad	Greene 1994 (8) Heymann-Monnikes 2000 (10) Payne 1995 (8) Tkachuk 2003 (9)	
Psychological distress (HADS); range 0-56; high=bad	Boyce 2003 (8) Kennedy 2005 (8)	Boyce 2003 (26) Boyce 2003 (52) Kennedy 2005 (26) Kennedy 2005 (52)
Beck depression inventory (scale maximum 63; high=bad)	Greene 1994 (8) Heymann-Monnikes 2000 (10) Lynch 1989 (8) Payne 1995 (8) Tkachuk 2003 (9)	
Quality of life		
Disruption of daily life (0=no symptom; 6=very severe symptom)	Lynch 1989 (8)	
Physical health (SF-36 Physical Composite Scale); high = bad; scale max 100	Tkachuk 2003 (9)	
Quality of life (IBS-QOL) ; high score = good; max 84	Drossman 2003 (12)	
Quality of life (GLQI score); max score 144; high=good	Heymann-Monnikes 2000 (10)	
Work and social adjustment score (handicap in work, home, leisure and relationships; 0=not affected; 8 severely affected for each area; maximum total 40)	Kennedy 2005 (6)	Kennedy 2005 (26) Kennedy 2005 (52)
Other		
Satisfaction (responder = satisfaction 3 or more on a scale where each of 8 items were rated 1=strongly disagree to 5=strongly agree)	Drossman 2003 (12)	

Where necessary, linear scales that had a maximum value corresponding to a good outcome were inverted by subtracting the mean value from the maximum and using the same standard deviation. Studies could then be combined in a meta-analysis.

METHODOLOGICAL QUALITY

The results of the quality assessment for included trials are shown in Appendix D.

An adequate method of randomisation was reported in two studies (Drossman 2003 – computer generated; Kennedy 2005 – random number tables); the other studies did not state the method.

Allocation concealment was adequate in two studies (Drossman 2003 and Kennedy 2005 – independent third party); the other studies did not report allocation concealment.

Because of the type of intervention, the patients were not blinded. However, the GDG decided that blinding was not important for this review.

Two studies (Drossman 2003; Kennedy 2005) described an *a-priori* power calculation. All studies included in the review demonstrated baseline comparability of the groups apart from the two that were reported only as abstracts (Bergeron 1983; Gong 2002).

All the patients were followed up in four studies (Gong 2002; Greene 1994; Payne 1995; Tkachuk 2003). There were fewer than 20% missing data in five studies (Corney 1991: 2%; Drossman 2003: 7%; Heymann-Monnikes 2000: 7%; Kennedy 2005: 11%; Vollmer 1998: 6%).

There was more than 20% missing data at the end of treatment in five studies (Bennett 1985; Blanchard 1993; Boyce 2003; Fernandez 1998; Lynch 1989):

- Bennett (1985) reported 28% missing data
- Blanchard (1993) reported 6 drop-outs from relaxation group; 1 from controls; the 7 drop-outs out of the original 16 participants (44%) were replaced to give 16 participants (so not an ITT analysis); dropouts were unequal between the groups
- Boyce (2003) reported that 66 of the original 105 participants were left at the end of treatment (8 weeks; 63% left; 37% drop-out); within groups drop outs were 13/35 (37%) in the CBT group, 16/35 (46%) in the relaxation arm and 9/34 (26%) in the medical therapy group
- Fernandez (1998) reported that 33 patients dropped out at the end of treatment (16/23 (70%) from the placebo group; 6/21 (29%) for stress management; 7/23 (30%) for contingency management and 4/23 (17%) on medical treatment), i.e. 48% drop-out overall
- Lynch (1989) reported 6/27 missing data (22%; not stated from which group) and dropouts were replaced to achieve 21 patients in all.
- Drop-out was unclear in the remaining study (Bergeron 1983).

Of the five studies that reported longer term follow-up:

- Boyce (2003) reported that 52/105 patients were followed-up at one year (50% missing data)
- Fernandez (1998) had 53% missing data at 12 months
- Kennedy (2005) reported 28% and 36% loss to follow up in the CBT+ mebeverine and mebeverine groups respectively at 3 months; 26% and 24% at 6 months, and 27% and 25% at 12 months for the primary outcome (IBS symptom score)
- Corney (1991) appeared to lose one patient to follow-up at 9 months
- Vollmer (1998) had 45% loss to follow up at 3 months.

Overall, we regarded the comparisons with placebo in Fernandez (1998) as having high potential for bias and these were not included in the analysis. The other comparisons in Fernandez (1998), Blanchard (1993), Boyce (2003) and Lynch (1989) were treated with caution, especially the relaxation arm of the Boyce study. Sensitivity analyses were carried out as appropriate. We also noted that Drossman (2003) had a population in which only 78% of patients had IBS. This study was similarly treated with caution. At follow-up, Fernandez (1998), Boyce (2003) and Vollmer (1998) were treated as having high potential for bias, and Kennedy (2005) had some potential for bias.

RESULTS

A. CBT versus waiting list control group, placebo or symptom monitoring only; and CBT + IBS medication versus IBS medication alone

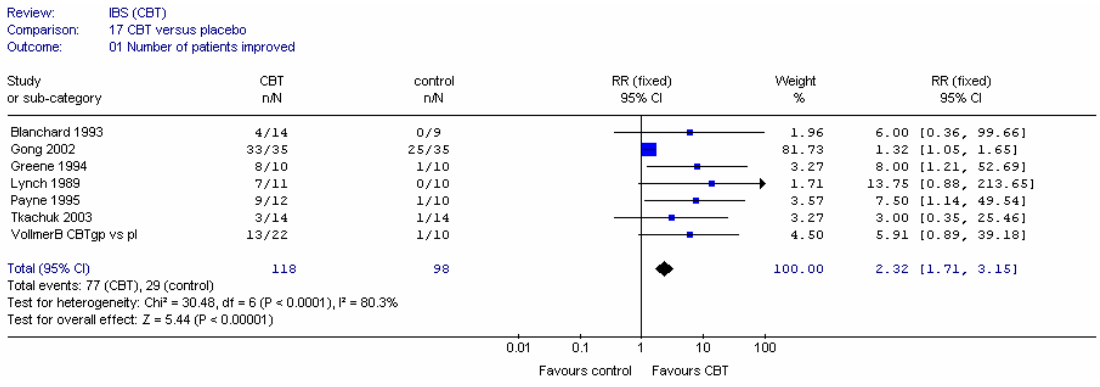
There were nine studies included in the analysis that compared CBT with a waiting list control group; symptom monitoring only, or; placebo condition in patients with IBS (Blanchard 1993; Drossman 2003; Fernandez 1998; Gong 2002; Greene 1994; Lynch 1989; Payne 1995; Tkachuk 2003; Vollmer 1998). Two studies compared the combination of IBS medication and CBT with IBS medication alone (Heymann-Monnikes 2000; Kennedy 2005). Heymann-Monnikes (2000) compared CBT plus optimised medical treatment versus optimised medical treatment alone. Kennedy (2005) investigated the addition of CBT to mebeverine in each arm.

1. Global symptoms

a) Number of patients with global improvement of symptoms

Eight studies with 217 patients compared CBT with symptom monitoring; no treatment, or; attention control (Blanchard 1993; Fernandez 1998; Gong 2002; Greene 1994; Lynch 1989; Payne 1995; Tkachuk 2003; Vollmer 1998 [individual and group CBT interventions]) for the outcome of global improvement in terms of the number of patients improved at the end of treatment. For this outcome measure the two CBT groups were combined in the Vollmer (1998) study.

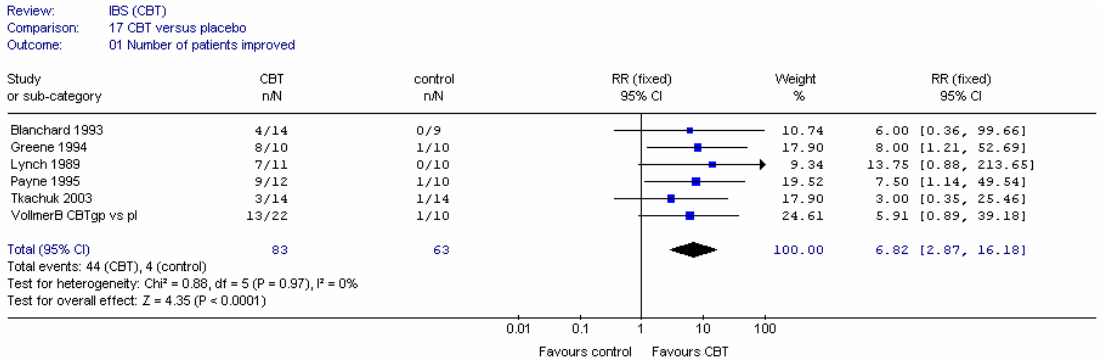
Figure 1



The relative risk analysis (Figure 1) showed significant heterogeneity (I^2=80%, p<0.0001), attributable to Gong (2002). This was a larger study in which nearly all the patients improved with CBT and many with no treatment. A sensitivity analysis of the relative risk without Gong (2002), gave no heterogeneity (I^2=0%, p=0.99) and the result was statistically and clinically significant (Figure 2). It was not clear why Gong (2002) should be so different, however, we noted that, whilst the majority of studies had patients with a psychiatric diagnosis or treatment, the exception was Gong (2002) (not stated). In addition, Gong (2002) was an abstract and all patients received selective GI calcium antagonists; the comparator was no treatment.

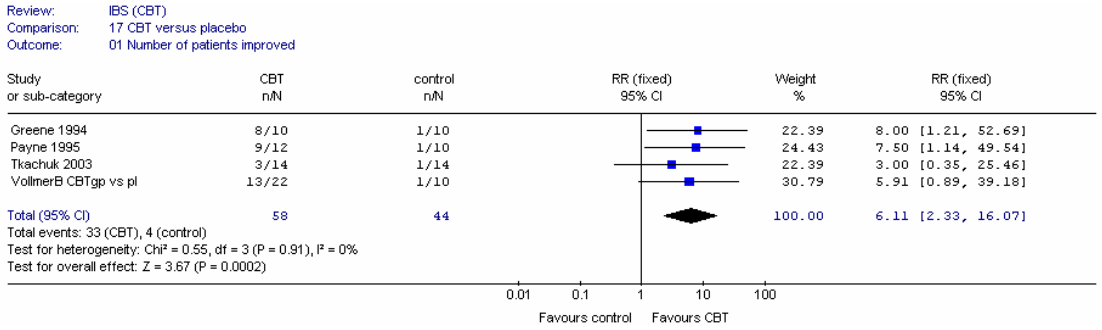
The RR was 6.82 (95%CI 2.87, 16.18), for the meta-analysis of 6 studies in 146 patients. This corresponded to a number needed to treat (NNT) of 3 (95%CI 2, 3), for a baseline risk of 0 to 10%.

Figure 2



Due to the high drop-out rates, a further sensitivity analysis was conducted excluding data from Blanchard (1993) and Lynch (1989). This made a slight difference (Figure 3) and therefore this figure was reported in the GRADE tables and used in the health economic modelling. This gave an NNT of 3 (95%CI 2, 4) for a control group risk of 7 to 10%.

Figure 3

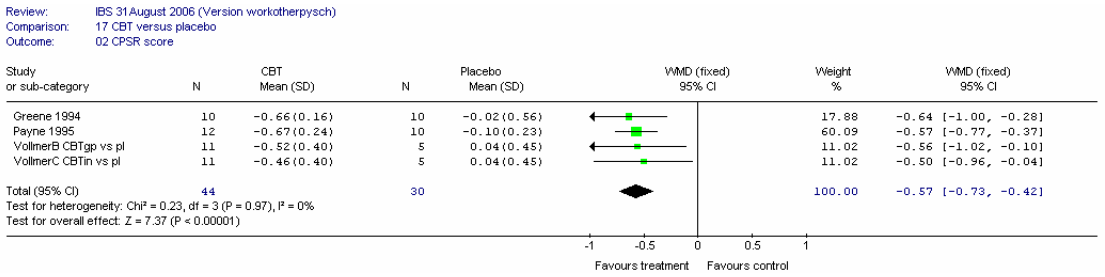


One study (Fernandez 1998) reported global improvement in terms of the number of patients improved at 1 year follow-up. This was likely to be flawed because of the high drop-out rate for the no treatment group and is not reported here.

b) Global symptom improvement score (CPSR)

Four studies (Blanchard 1993; Greene 1994; Payne 1995; Vollmer 1998) reported outcomes in terms of a global IBS change score, the 'Composite Primary Symptom Reduction (CPSR) score' (including measurements of pain, tenderness, diarrhoea, constipation). The scale ranged from -1 to +1, so for example -0.66 represented a 66% improvement from baseline; 0.04 represented a 4% worsening. There was a statistically significant difference in symptom score of: -0.57 (95%CI -0.73, -0.42), which is clinically significant.

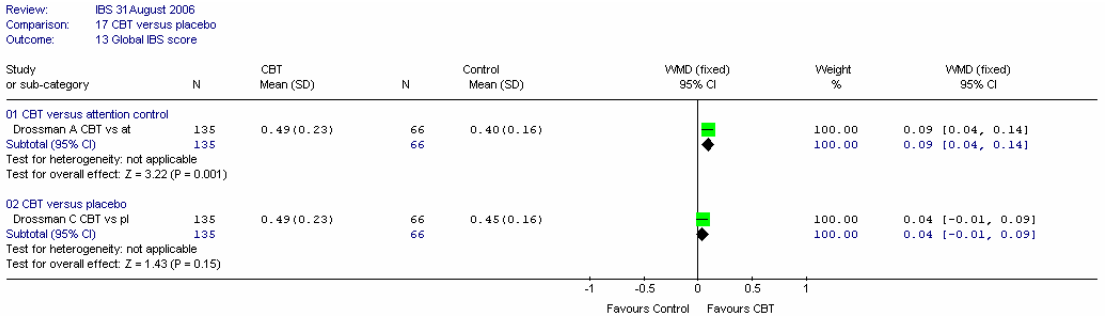
Figure 4



c) Global symptom score (scale: high is good)

One large study included a global IBS score based on 'satisfaction, global wellbeing, diary pain scores, and health related quality of life' (Drossman 2003). For this study, CBT was significantly better than attention control, MD 0.09 (95%CI 0.04, 0.14), but was not significantly different from the no treatment placebo for desipramine; MD 0.04 (95%CI -0.01, 0.09). However, the range for the composite scale was unclear, so the clinical significance could not be assessed.

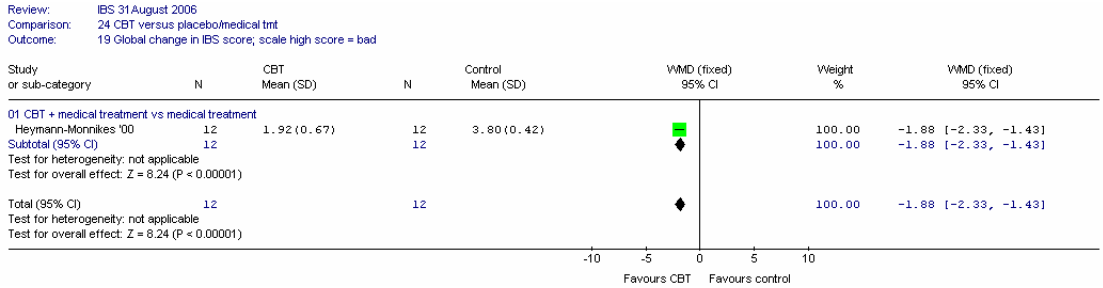
Figure 5



d) Global change in symptom score

Heymann-Monnikes (2000) also reported the change in overall wellbeing compared to pre-treatment on a visual analogue scale ranging from: 1=very much better, to; 7=very much worse, with; 4 indicating no change. This was a statistically significant improvement for the CBT + medical treatment compared with medical treatment alone.

Figure 6



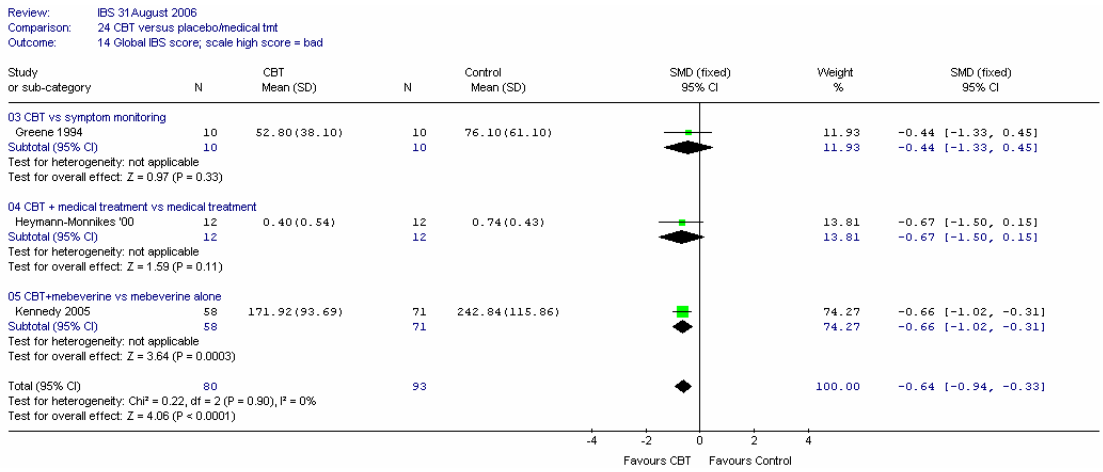
e) Global symptom score (scale: high = severe)

Another study (Lynch 1989) described an IBS score in terms of 'pain, discomfort, diarrhoea, and constipation, each rated 0 (no symptoms) to 6 (very severe symptoms)'. The treated patients had a reduction of 2.16 points compared with 0.36 points in the waiting list group (no SDs reported, p<0.05).

A further study (Greene 1994) of CBT versus symptom monitoring reported an IBS score based on 7 symptoms daily for 2 weeks each scored 0 to 4 (severe). The Heymann-Monnikes (2000) comparison of CBT+ medical treatment vs medical treatment alone reported a global symptom score derived from 20 items scored over 14 days. Kennedy (2005) reported the global IBS symptom score for patients receiving CBT plus mebeverine versus mebeverine alone. On the scale used, a score of <75 represented normal; 75-174 mild symptoms; 175-299 moderate symptoms and 300-500 severe symptoms.

Meta-analysis of these studies using the standardised mean difference showed a statistically significantly lower (better) global symptom scores for CBT compared with placebo.

Figure 7

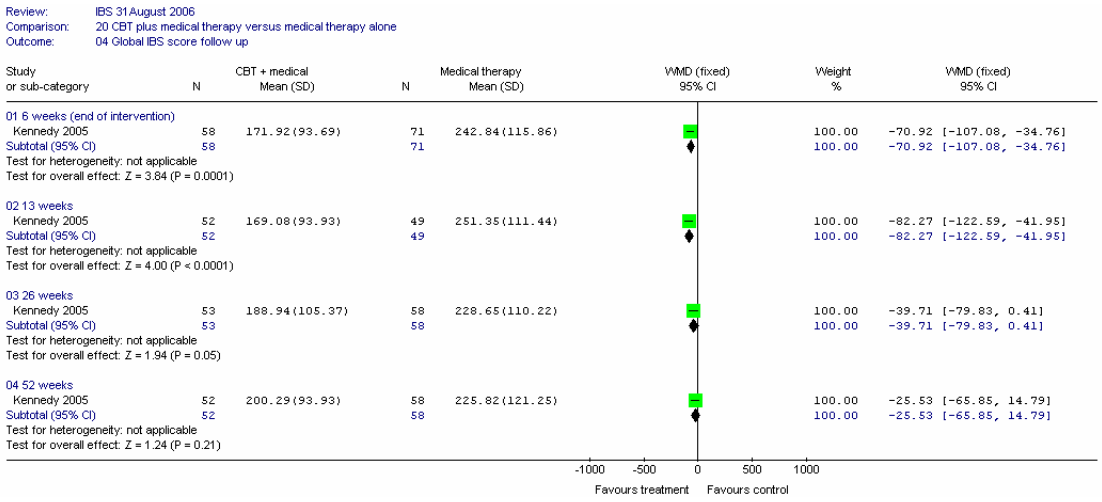


For the specific comparison of CBT plus mebeverine versus mebeverine alone, there was a statistically significant improvement; mean difference: -71 (95%CI -107, -35) on a scale of 0 to 500.

Follow-up in global symptom scores

Kennedy (2005) (CBT + mebeverine versus mebeverine alone) also reported this outcome at follow-up at 13; 26, and; 52 weeks. At 13 weeks there was a statistically significant difference in favour of CBT + mebeverine; MD: -82 (95%CI -123, -42); at 26 weeks there was a borderline significant difference between interventions; MD: -40 (95%CI -80, 0.4; p=0.05), and there was no significant effect at 52 weeks; MD: -26 (95%CI -66, 15). The data were extracted from a graph, but the latter two results do not agree with the 'estimated treatment effects' (-14 and 3 respectively) reported in table 10 of the paper. There was close agreement between the graph and the table for the effect size at the end of treatment and fairly close agreement at 13 weeks (table: -68 and -71 respectively). We have used the results from the graph because the table was said to be 'estimated'.

Figure 8



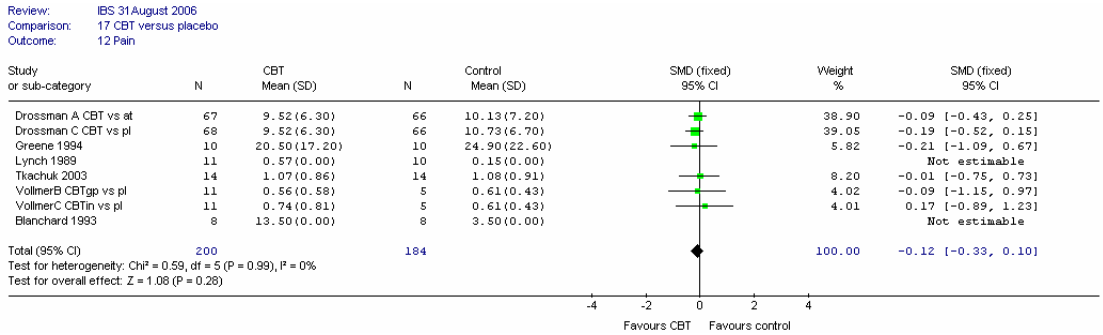
2. Individual symptoms

a) Pain

Seven studies (Blanchard 1993; Drossman 2003; Fernandez 1998; Greene 1994; Lynch 1989; Tkachuk 2003; Vollmer 1998) reported pain score outcomes. However, different pain scoring scales were used: Blanchard (1993): 0-4 scale daily added up over 4 weeks; Drossman (2003) used the McGill pain score (items scored 0-3, averaged, and added over 2 weeks); Fernandez (1998): 0 to 4 scale daily added up over 1 week; Greene (1994): 0 to 4 scale daily added up over 4 weeks; Lynch (1989) used a score ranging from 0 to 6; Tkachuk (2003) and Vollmer (1998) used a score ranging from 0 to 4 daily. In all cases, the maximum of the scale corresponded to severe pain.

The studies were combined in a meta-analysis (omitting Fernandez (1998) due to high drop-out rates) using standardised mean differences. There was no significant difference between CBT and control for pain score.

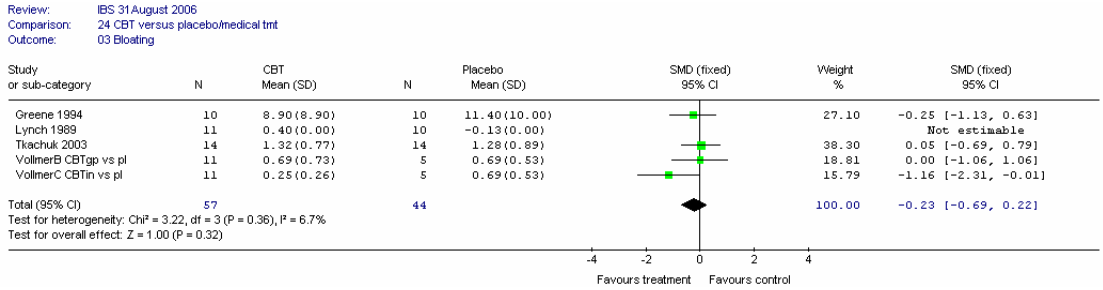
Figure 9



b) Bloating

Bloating was reported by Greene (1994) on a 0-4 daily scale added up over 4 weeks, i.e. maximum 112; Lynch (1989) on a 0-6 scale; Tkachuk (2003) on a 0-4 scale daily, and; Vollmer (1998) (group and individual CBT; on a 0-4 scale daily). In each case, the maximum of the scale corresponded to severe bloating. The studies were combined using standardised mean differences.

Figure 10



There was no significant difference between interventions in the bloating score.

c) Bowel habits

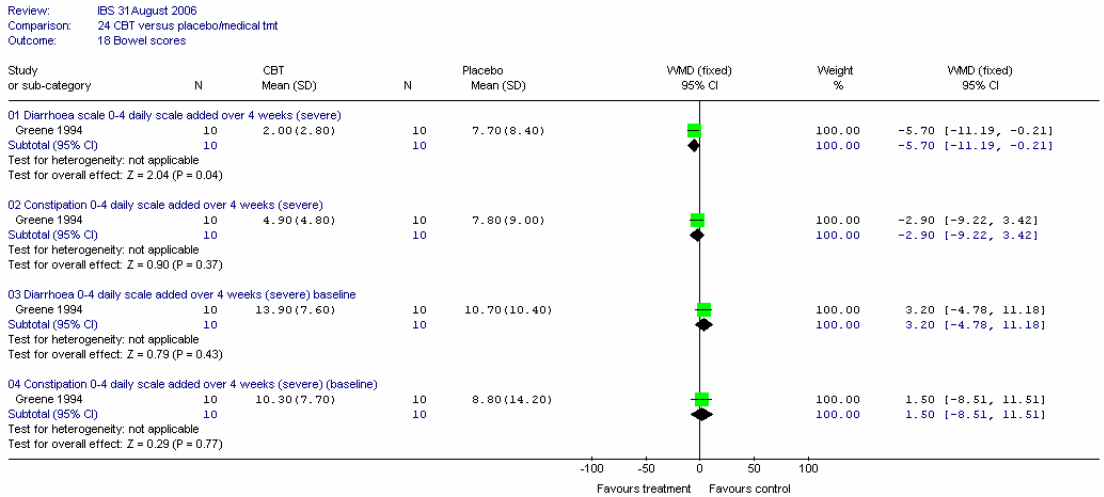
Ratings of constipation and diarrhoea were reported by Greene (1994) on a 0-4 scale daily added up over 4 weeks, i.e. maximum 112, and; Lynch (1989) on a 0-6 scale. In each case, the maximum of the scale corresponded to severe symptoms.

Both studies reported mean scores at baseline and after the intervention period. However, Lynch (1989) did not report standard deviations and was not analysed further.

In Greene (1994), baseline constipation scores were 10.3 (SD 7.7) in the CBT group compared with 8.8 (SD 14.2) in the placebo group. Baseline diarrhoea scores were 13.9 (SD 7.6) compared with 10.7 (SD 10.4). These are not significant differences.

Final scores at eight weeks showed a fairly small, statistically significant difference in the diarrhoea score (Figure 11). There was no significant difference in the constipation score.

Figure 11



3. Adverse events

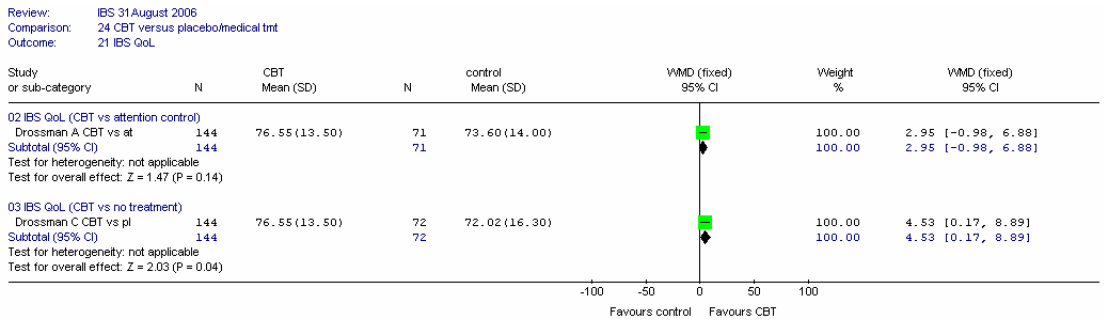
These were not reported in any of the studies.

4. Quality of life

The IBS-QOL scale (maximum 84; high is good) was used to report outcomes in Drossman (2003), whilst a scale of 'disruption of daily life' was used in Lynch (1989), although no standard deviations were reported.

In Drossman (2003), there was a small statistically significant difference between CBT and no treatment on the IBS QoL scale. There was no significant difference between CBT and attention control.

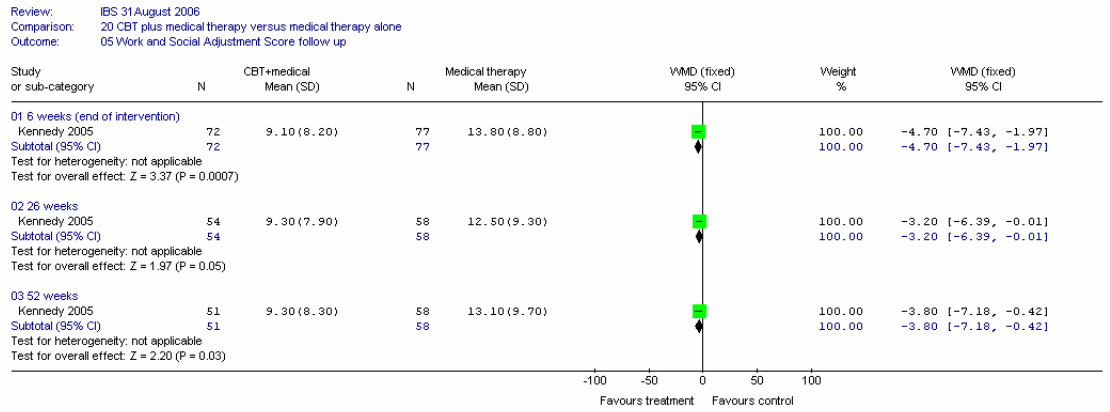
Figure 12



Kennedy (2005) (CBT+mebeverine versus mebeverine alone) also reported on a global 'Work and social adjustment score' (handicap in work, home, leisure and relationships; 0=not affected; 8=severely affected for each area; maximum total 40). This outcome was also

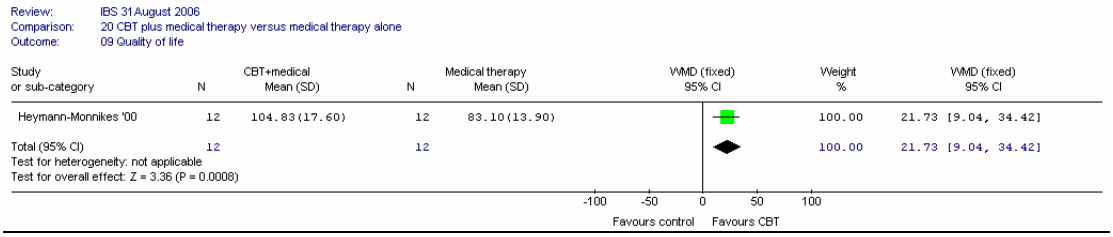
reported at 26 and 52 weeks follow-up. There was a statistically significant improvement in this score that was maintained over the 52 weeks of follow-up. The difference was fairly small though: MD at 6 weeks -4.70 (95%CI -7.43, -1.97) on a scale of 0 to 40.

Figure 13



Heymann-Monnikes (2000) (CBT + medical treatment versus medical treatment) reported scores on the GI quality of life instrument (scale maximum 144; high is good). There was a statistically and clinically significant improvement in quality of life for the CBT group.

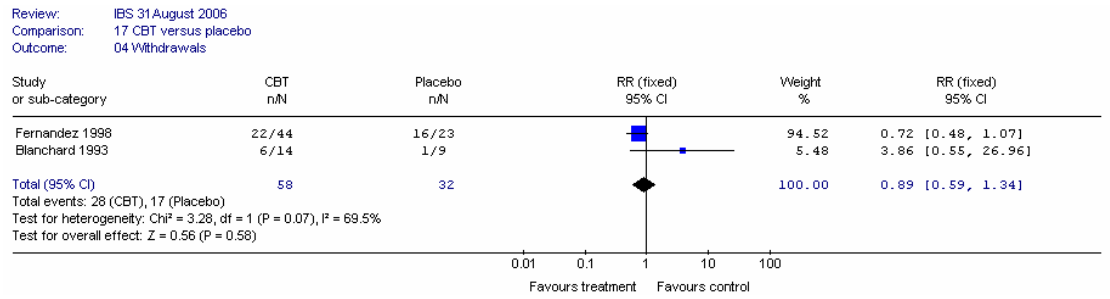
Figure 14



5. Number of patients withdrawing from study

Blanchard (1993) and Fernandez (1998) reported withdrawals from the study.

Figure 15



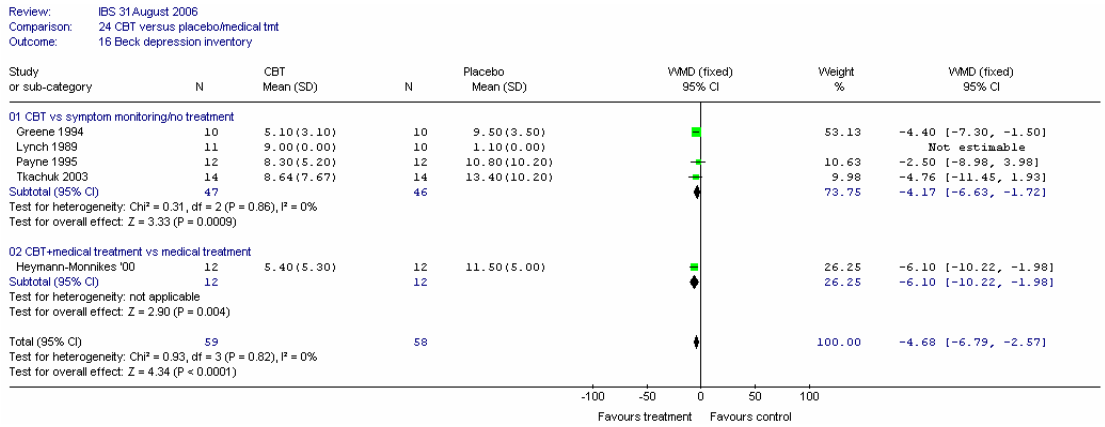
6. Mental health outcomes

Five studies (Greene 1994; Heymann-Monnikes 2000; Lynch 1989; Payne 1995; Tkachuk 2003) reported Beck depression inventory scores.

a) Beck depression inventory score

There was a statistically significant improvement in Beck Depression scores (scale maximum 63; high=bad), favouring CBT; WMD -4.68 (95%CI -6.79, -2.57), but the difference was fairly small. There was no heterogeneity between studies (I^2=0%, p=0.82).

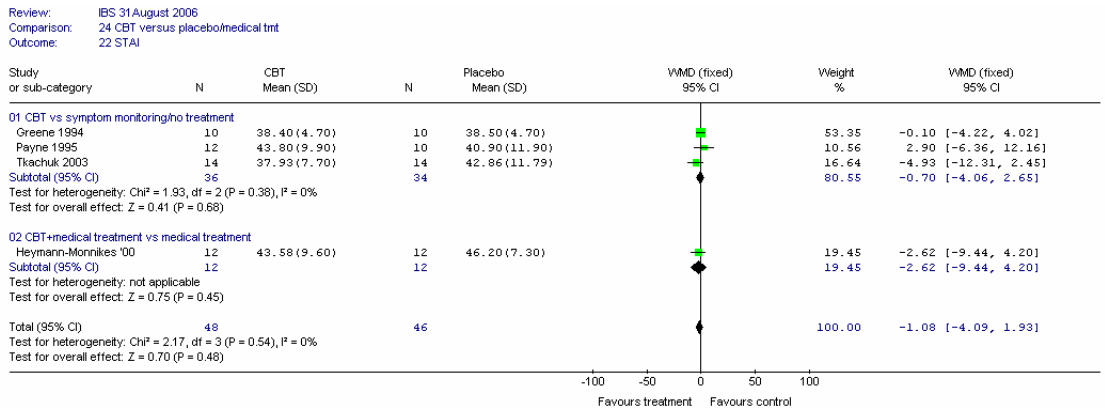
Figure 16



b) Overall anxiety and psychological distress: State-Trait Anxiety Inventory (STAI).

Four studies (Greene 1994; Heymann-Monnikes 2000; Payne 1995; Tkachuk 2003) reported anxiety using the State-Trait Anxiety Inventory (STAI) (scale range 20-80; high = bad). There was no significant difference between CBT and control.

Figure 17

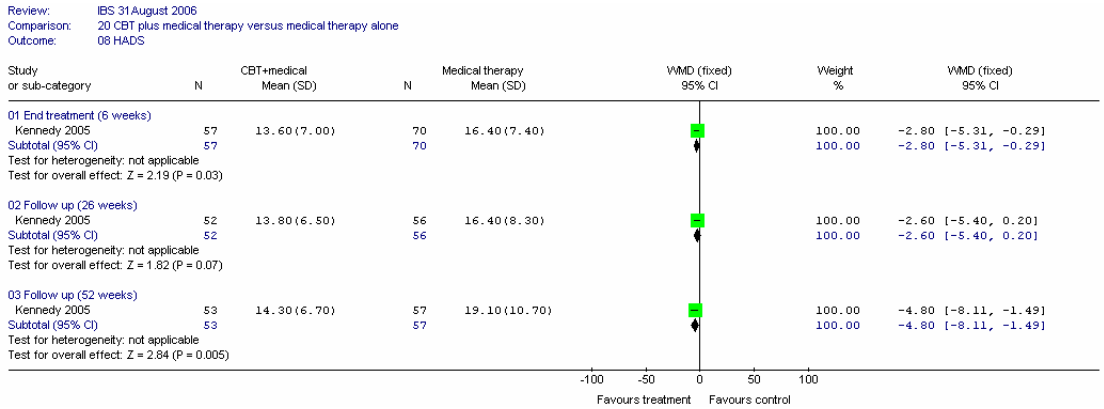


c) Psychological distress (HADS)

Kennedy (2005) (CBT plus mebeverine versus mebeverine) reported the HADS score (range 0 to 56; high=bad) at the end of treatment (6 weeks) and at follow-up at 26 and 52 weeks.

There was a small statistically significant difference favouring CBT which was maintained over 52 weeks; MD at 6 weeks: -2.80 (95%CI -5.31, -0.29).

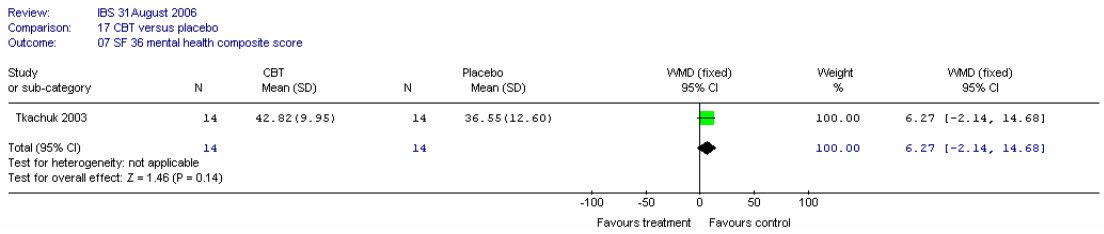
Figure 18



d) SF-36 mental health composite

One study (Tkachuk 2003) reported the SF-36 mental health composite score (maximum 100, high = bad). There was no significant difference between interventions.

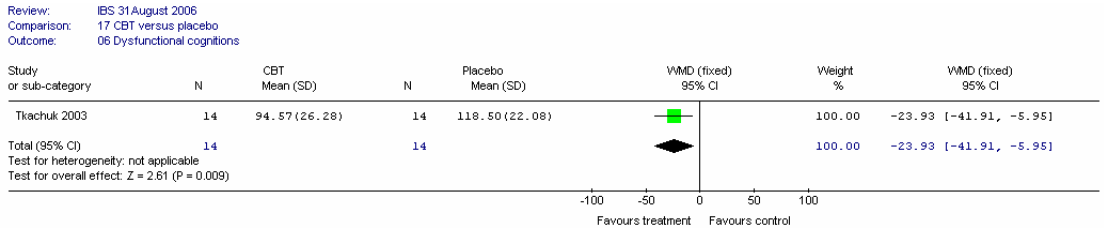
Figure 19



e) Dysfunctional cognitions score

One study (Tkachuk 2003) reported dysfunctional cognitions (scale 25-175; high=bad). This study showed a statistically significant improvement for the CBT patients compared with waiting list control with symptom monitoring. We noted that this study had the majority of patients with an Axis I diagnosis.

Figure 20



B. CBT type 1 versus type 2 (e.g. stress management versus contingency management)

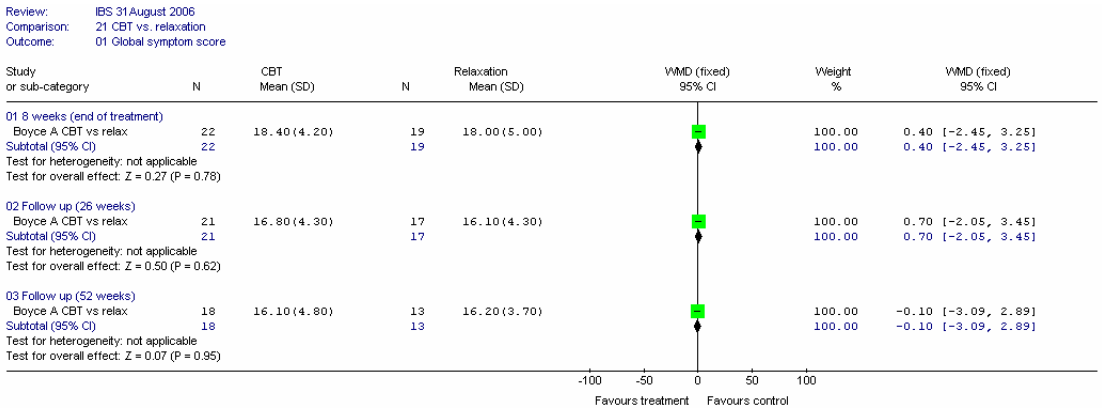
Boyce (2003) compared CBT with relaxation. Fernandez (1998) compared stress management with contingency management. Payne (1995) compared CBT with self-help groups.

B1. CBT versus relaxation

1. Global symptoms

Boyce (2003) reported Global IBS symptom score (symptom severity on a 0 to 48 scale) at the end of treatment (8 weeks) and at follow-up at 26 and 52 weeks. There was no significant difference between interventions at any time. We noted that there were large numbers of drop-outs, especially in the relaxation arm.

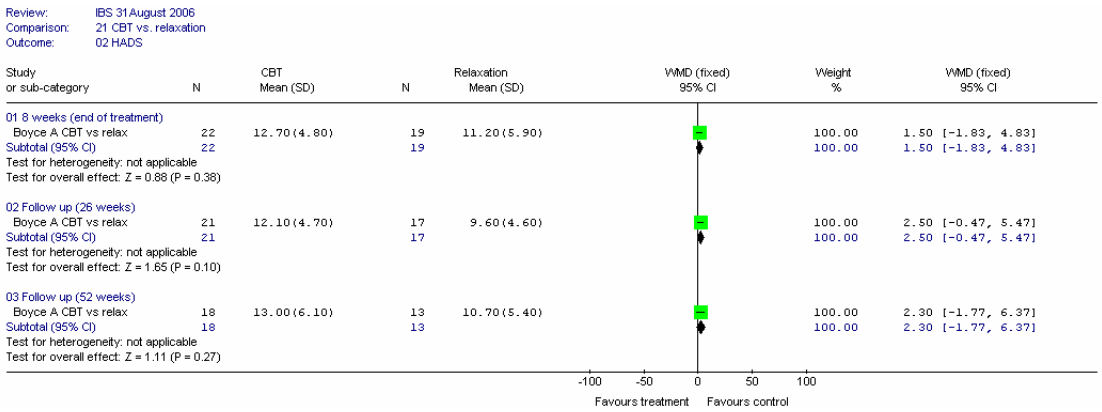
Figure 21



2. Mental health outcomes

Boyce (2003) reported the HADS score (0-56; high=bad) at the end of treatment (8 weeks) and at follow-up at 26 and 52 weeks. There was no significant difference between interventions.

Figure 22

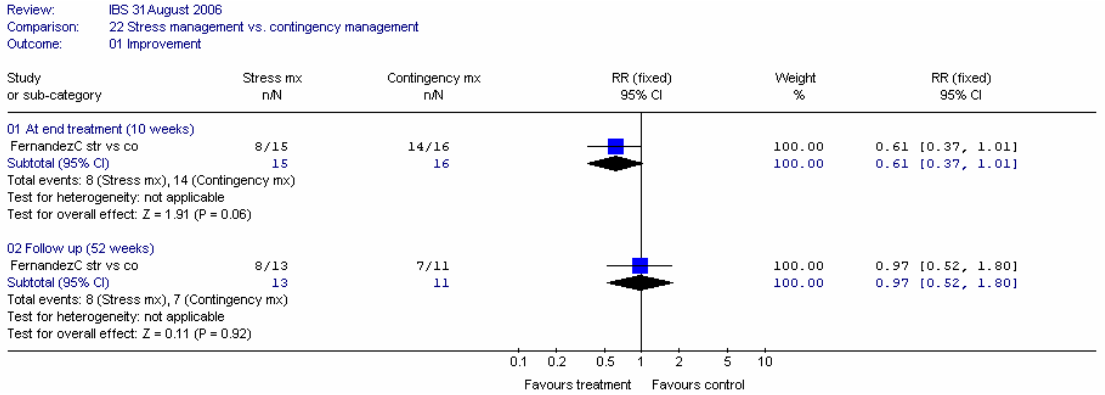


B2. Stress management versus contingency management

1. Global symptoms

Fernandez (1998) found that 8/15 of the stress management group and 14/16 of the contingency management group improved at the end of treatment (10 weeks). This study also reported global improvement in terms of the number of patients improved at 1 year follow-up: 8 of the 13 remaining patients in the stress management group versus 7 of 11 patients in the contingency management group. At both durations the confidence intervals were fairly wide and there was no statistically significant difference between interventions, however, at the end of treatment stress management was favoured.

Figure 23

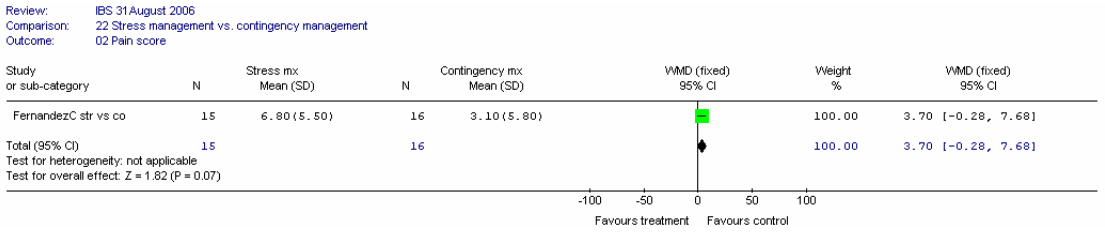


2. Individual symptoms

a) Pain

Fernandez (1998) reported mean pain scores on a scale of 0 to 4 (scores totalled for 1 week). There was no significant difference between interventions. No other individual symptoms were reported.

Figure 24



3. Number of patients withdrawing from study

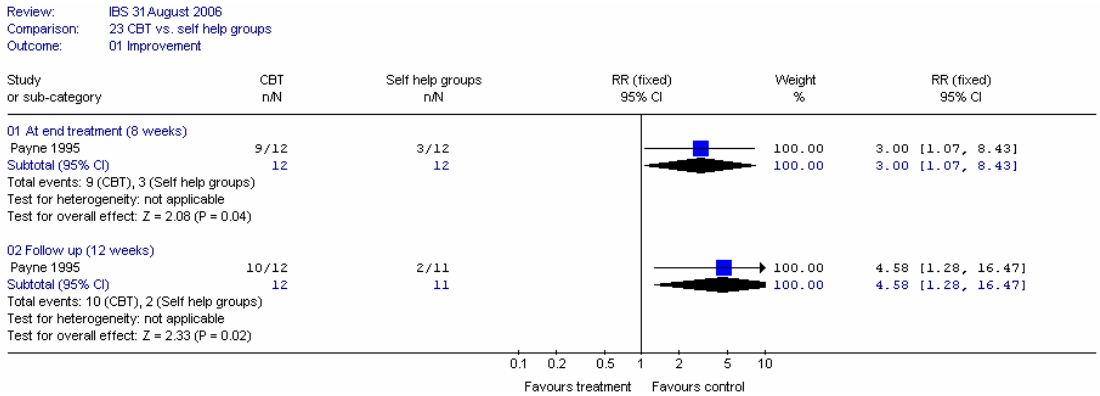
Fernandez (1998) reported 6/21 patients withdrawing from the stress management group compared with 7/23 for contingency management.

B3. CBT versus self help groups

1. Global symptoms

At the end of treatment (8 weeks), Payne (1995) reported that 9/12 CBT patients and 3/12 self-help group patients were improved after treatment. At follow-up (12 weeks) 10/12 CBT patients and 2/11 self-help group patients were improved. At both times there was a statistically significantly better result for the CBT group, but confidence intervals were wide.

Figure 25

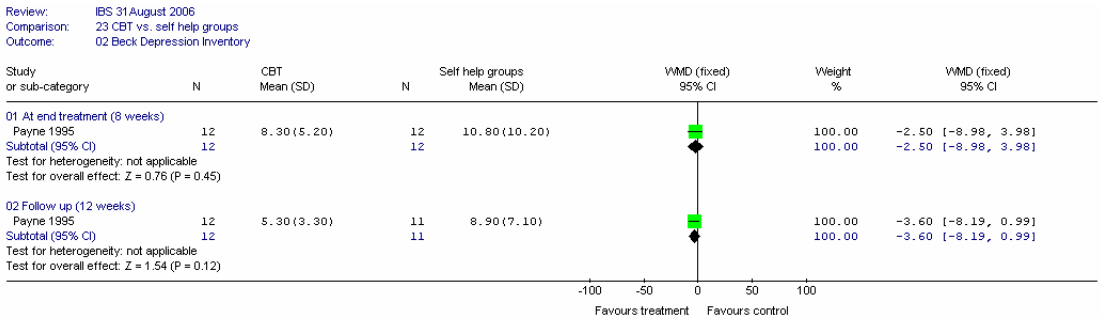


2. Mental health outcomes

a) Beck Depression Inventory

Payne (1995) reported Beck Depression Inventory scores (scale maximum 63; high=bad) at the end of treatment (8 weeks) and at follow-up at 12 weeks. There was no significant difference at either time.

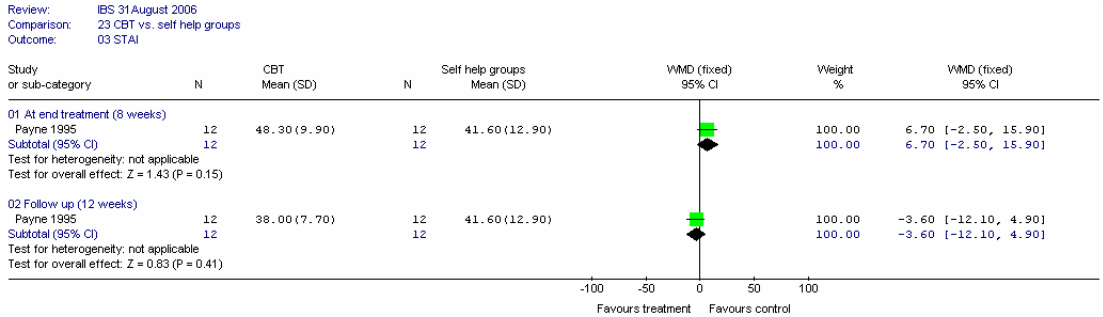
Figure 26



b) Overall anxiety and psychological distress: State-Trait Anxiety Inventory (STAI)

Payne (1995) reported STAI scores (20 to 80; high = bad) at the end of treatment (8 weeks) and at follow-up at 12 weeks. There was no significant difference between interventions.

Figure 27



C. CBT individual versus group

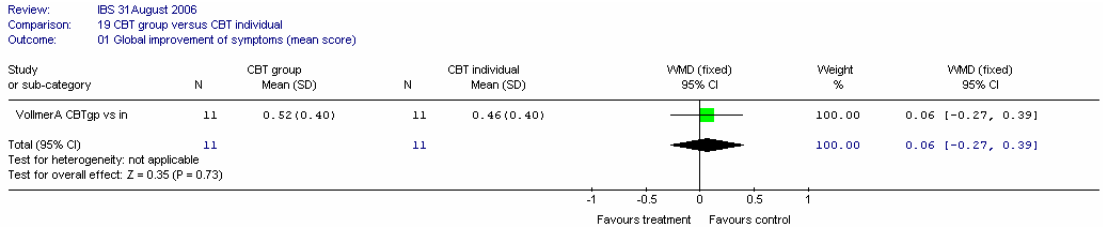
One study (Vollmer 1998) compared CBT on an individual basis with CBT on a group basis. Outcomes reported were global improvement in symptoms (mean score); global improvement in symptoms (number of patients); pain score, and; bloating score (0=not a problem; 4=debilitating symptoms).

1. Global outcomes

a) Global improvement in symptoms score

Vollmer (1998) reported the mean global improvement in symptoms score (CPSR; scale -1 to +1) for CBT group patients compared with individual CBT at the end of treatment. There was no significant difference between intervention, but the confidence interval was fairly wide, leading to uncertainty. No standard deviations were given for the follow-up scores.

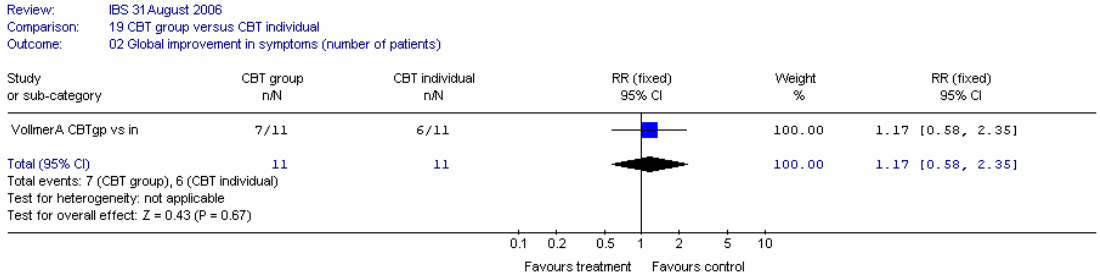
Figure 28



b) Global improvement in symptoms (number of patients)

Vollmer (1998) reported 7/11 patients improved with group CBT compared with 6/11 for individual CBT. There was no significant difference between intervention, but the confidence interval was fairly wide, leading to uncertainty.

Figure 29

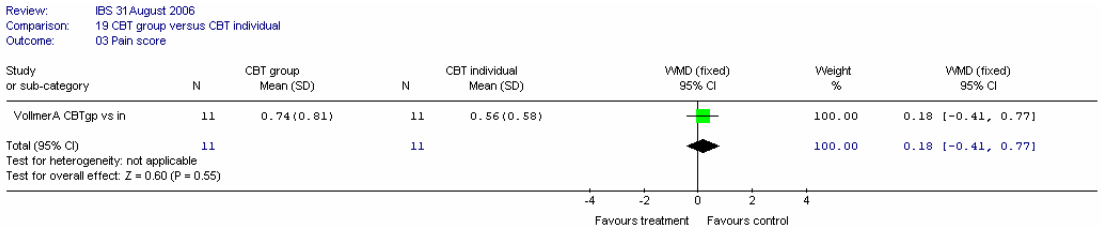


2. Individual symptoms

a) Pain

The mean pain score (scale 0 to 4) showed no significant difference between interventions.

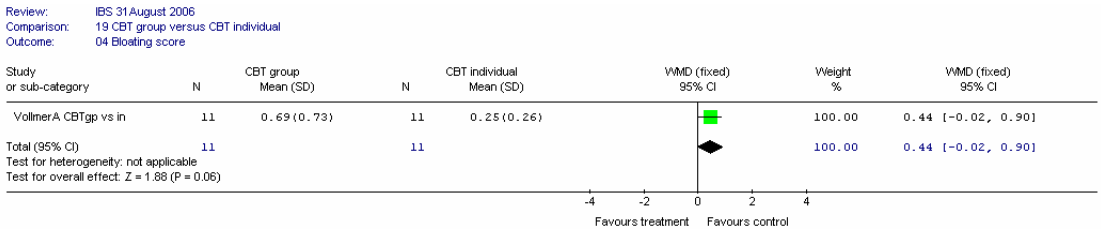
Figure 30



b) Bloating

The mean bloating score showed no significant difference between CBT group therapy and individual therapy, although individual therapy was favoured.

Figure 31



D. CBT versus medical therapy

Boyce (2003) compared CBT or relaxation with routine medical care. Corney (1991) compared behavioural psychotherapy (nurse behaviour therapist 6-15 one-hour sessions) with 'conventional medical treatment'. Fernandez (1998) compared stress management or contingency management with 'conventional medical treatment'.

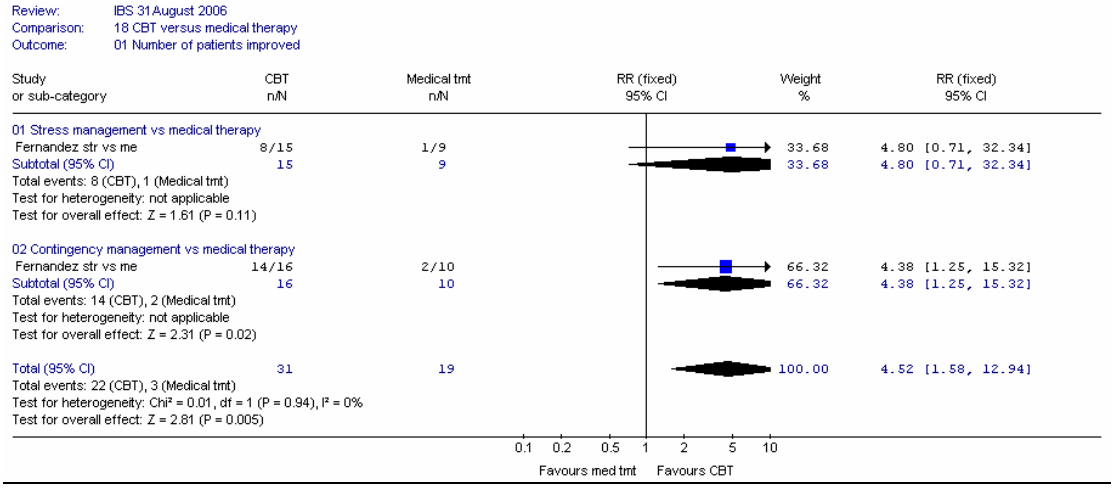
1. Global outcomes

a) Number of patients with improvement in global symptoms

One study (Fernandez 1998) reported the number of patients improved. Meta-analysis showed a statistically significant improvement for CBT compared with medical treatment, but

the confidence intervals were wide. At 52 week follow-up there were too many withdrawals for this to be reliable.

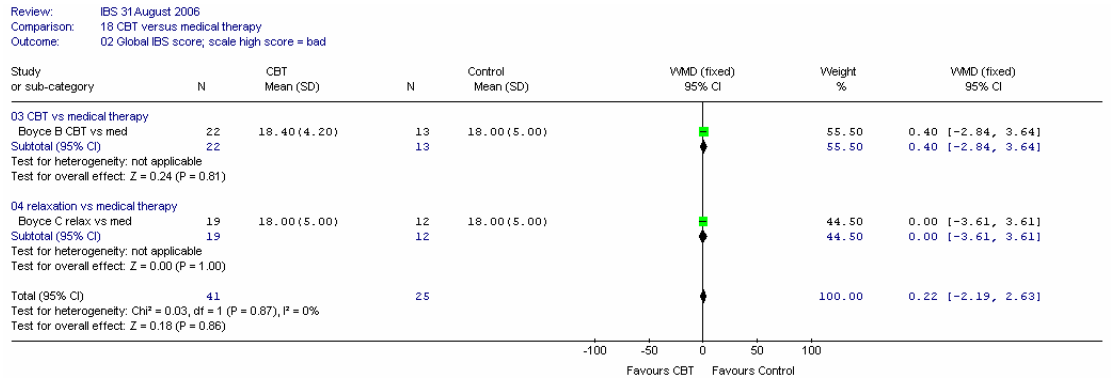
Figure 32



b) Global symptom score

Boyce (2003) (CBT or relaxation versus medical care) reported Global IBS symptom score (symptom severity on a 0 to 48 scale) in 66 patients at the end of treatment (8 weeks) and at follow-up at 26 and 52 weeks. At 8 weeks, there was no significant difference between interventions, although we noted that the drop-out rates were fairly high, especially for the relaxation arm of the study.

Figure 33

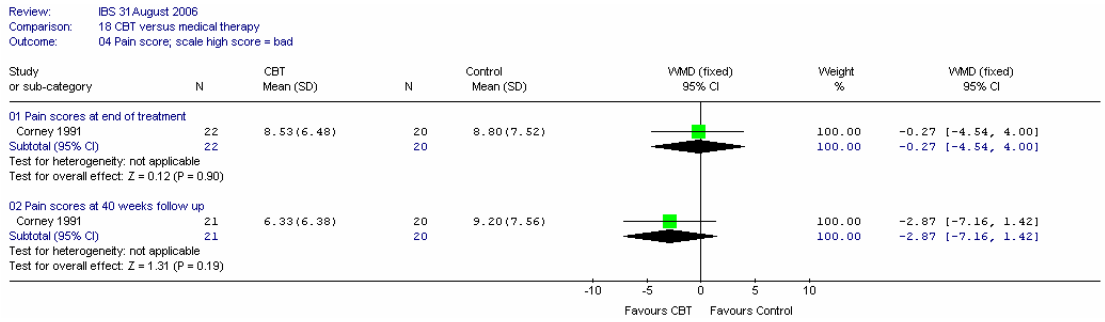


2. Individual symptoms

a) Pain

Corney (1991), in 42 patients, reported pain on a visual analogue scale (VAS) (the scale was unclear, but may be 0 to 8 scale in 3 dimensions) at the end of treatment (16 weeks) and at follow-up (40 weeks). There was no significant difference between interventions at either time, but the confidence intervals were fairly wide.

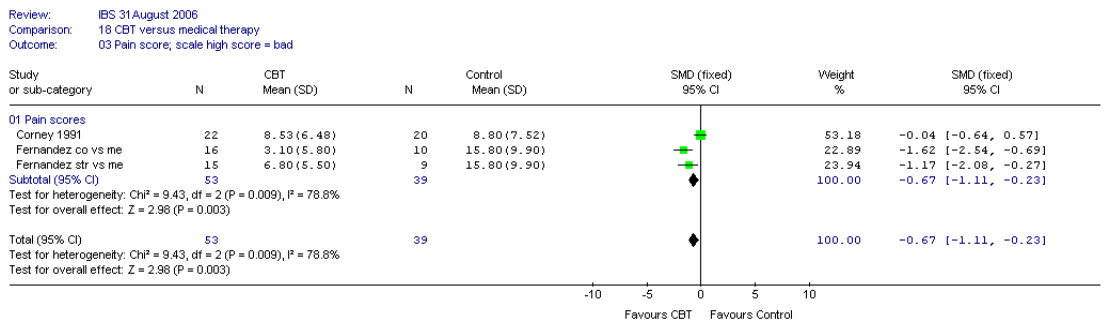
Figure 34



Fernandez (1998), in 50 patients, reported a pain score rated 0 (not a problem) to 4 (debilitating). There were significant differences between both active treatment groups and the medical treatment control group ($p<0.001$ for the contingency management group and $p<0.022$ for the stress management group). We noted that around 30% of each CBT group was missing data and 26% of the control group.

We combined these studies in a meta-analysis using standardised mean differences and found significant heterogeneity (I^2=79%, p=0.009). The source of heterogeneity was not clear, although one difference is that the CBT intervention in Corney (1991) was behavioural psychotherapy.

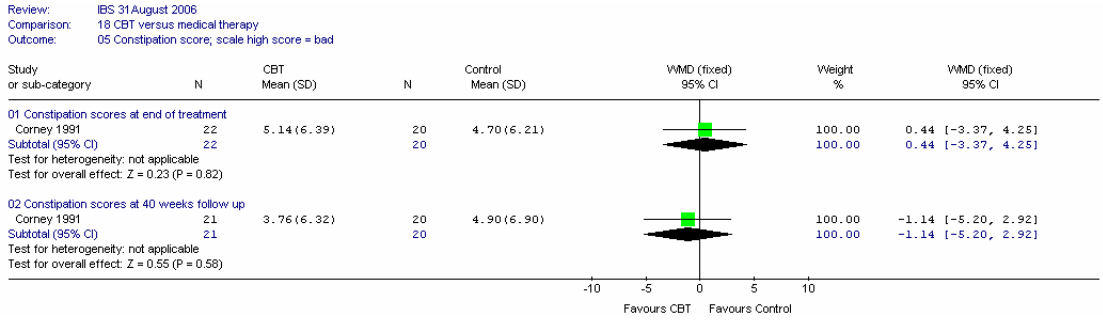
Figure 35



b) Bowel habits

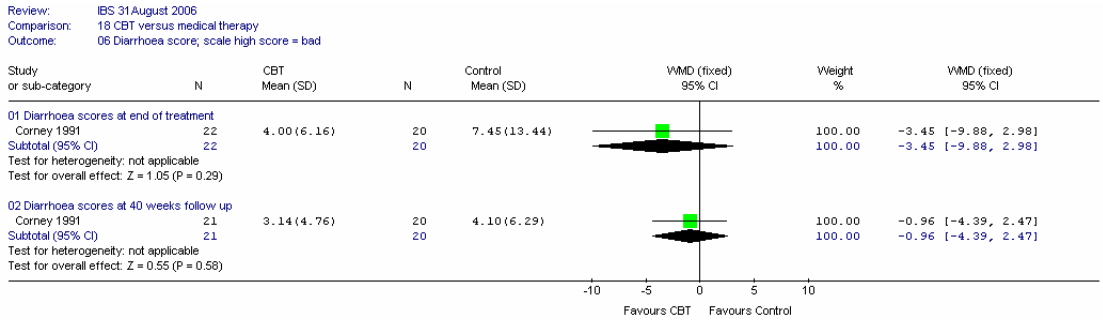
Corney (1991) reported constipation and diarrhoea on a visual analogue scale (VAS) at end of treatment (16 weeks) and at follow-up (40 weeks). The scale was unclear. There was no significant difference between interventions, although the confidence interval may have been wide.

Figure 36



For diarrhoea scores there was no significant difference, but the confidence interval was probably wide, depending on the scale.

Figure 37



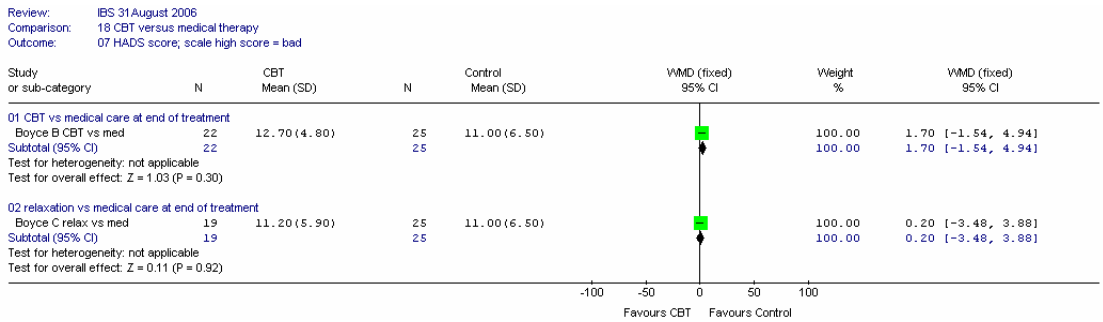
c) Number of patients withdrawing from study

Fernandez (1998) reported 6/21 withdrawals from the stress management group, 7/23 from the contingency management group and 4/23 from the medical treatment group.

d) Mental health outcomes

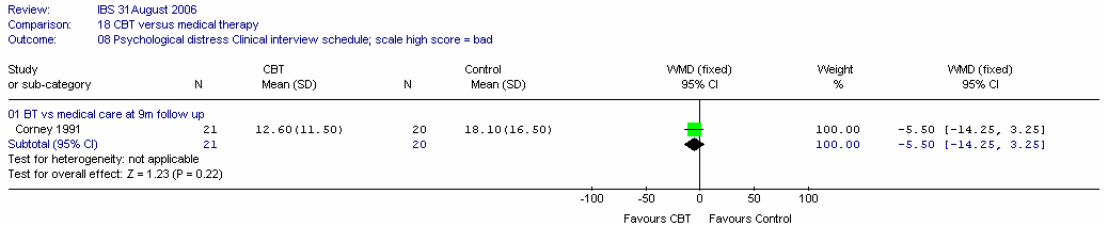
Boyce (2003) (CBT versus medical care) reported the psychological distress on the HADS scale (0-56, high is bad) at the end of treatment (8 weeks) and at follow-up at 26 and 52 weeks. At 8 weeks, there was no significant difference between interventions.

Figure 38



Corney (1991) reported psychological distress at 9 months follow up using the Clinical Interview Schedule (0-48, high=bad). There was no significant difference between interventions.

Figure 39



ECONOMIC LITERATURE FOR CBT

One relevant health economic analysis was identified on the cost-effectiveness of CBT in the management of IBS. Kennedy (2006) was a trial based economic evaluation conducted in the UK, which recruited patients from primary care with IBS symptoms of moderate or greater severity following 2 weeks of GP care and 4 weeks of mebeverine. Patients were randomised to receive either CBT plus mebeverine or mebeverine alone. CBT consisted of six 50-minute sessions delivered by face-to-face contact with a trained nurse. The primary effectiveness measure was global IBS symptom score. Direct and indirect costs were measured and cost-effectiveness acceptability curves were used to describe the probability that CBT plus mebeverine would be more cost-effective than mebeverine alone for various willingness to pay thresholds for a 10 unit change in global IBS symptom score.

The addition of CBT produced significantly better global IBS symptom scores at 3 months but the effect had diminished and was no longer significant after 6 and 12 months of follow-up. Similar results were observed in the secondary effectiveness measures and further details of the clinical outcomes have been given in the clinical effectiveness review. The mean intervention cost of CBT was £308 per patient. The addition of CBT did not reduce service costs at 3, 6 or 12 months. It is unclear whether service costs included intervention costs but given that the mean service costs at 3 months were less than £308 in both arms it is likely that they excluded the intervention cost. The CEACs presented show that CBT has a low probability (<25%) of being cost-effective when willingness to pay thresholds for a 10 unit change in global IBS symptom score are below £100. As this study did not provide an estimate of the cost per QALY for the addition of CBT to antispasmodic therapy, it was not particularly useful in determining whether recommending CBT for use in the NHS would result in the efficient use of NHS resources.

COST-EFFECTIVENESS ANALYSIS FOR CBT

This section describes the health economic analysis undertaken to inform recommendations on the use of CBT as a one-off intervention in the management of IBS. The general methods used in the economic analysis for all management interventions are described in detail in Chapter 5

and the model inputs and assumptions relevant to this particular intervention are described below.

- The effectiveness of CBT in addition to usual care compared to usual care alone in people with refractory IBS was based on the number of patients with an improvement in global symptoms (at the end of treatment) for CBT vs no treatment, symptom monitoring or attention control. (RR 6.11 (95%CI 2.33, 16.07) for baseline rate of 9%, from Figure 3 of CBT review).
- We assumed that the response rate for CBT fell by 55% over the first 6 months and that there was no significant difference between CBT and usual care by the end of 12 months. This assumption was based on follow-up data for global symptom score from the study by Kennedy (2005). The mean difference, after adjustment for baseline difference, was used to scale the response rate after the end of treatment.
- The evidence included in the clinical effectiveness review did not allow a subtype specific estimate of clinical effectiveness to be estimated. Therefore it was assumed that CBT is equally effective in all IBS subtypes.
- CBT was assumed to be given over 12 weeks with alternative durations of 6 and 8 weeks considered in a sensitivity analyses, in which the costs are assumed to remain constant, but the effect is achieved over a shorter intervention period (i.e. the same number of sessions given at the same cost over a shorter time-frame).
- A 15 month time-frame was used so that the cost-effectiveness could be compared to against other psychological interventions for which there was 15 month efficacy data.

Modelled response rates

In the basecase scenario the response rate of 25% in the no treatment arm was taken from the mean placebo arm response rate from the behavioural therapy trials. This represents the group of patients whose symptoms improve without any specific intervention. The RR for an improvement in global symptoms for CBT vs no treatment at the end of treatment is 6.11; therefore the modelled response rate in the intervention arm is 100% at the end of treatment (12 weeks). As shown in Figure 40, the response rate in the CBT arm decreases to 59% by 6 months and 25% by one year, based on the assumptions regarding fall-off in effectiveness described above.

We have also considered a maintained benefits scenario in which the response to CBT was assumed to be maintained for the one year after the end of treatment but we assumed no further benefit beyond that point.

The cost of CBT was calculated using the mean number and duration of sessions from the studies used to calculate the RR, giving a mean duration of 6.6 hours of CBT (excluding Payne (1995) which did not provide sufficient information). To this we applied the unit cost for face-to-

face time with a Cognitive Behavioural Therapist of £57 per hour (PSSRU 2006), which gave a total mean cost of £375 (95%CI £167 - £582).

The study by Kennedy (2005) found no significant difference in direct health care costs at 3, 6 or 12 months for CBT plus mebeverine compared to mebeverine alone in patients with severe symptoms after 3 months of mebeverine. It is likely that significant reductions in resource use would only be observed in patients who are high service users at baseline and who then experience a reduction in symptoms as a result of therapy. It is likely that the population included in the Kennedy (2005) study were not high service users since they were recruited from primary care after a failure to respond to only one intervention. This is in contrast with the Creed (2003) study which recruited patients from secondary and tertiary gastroenterology clinics who had a median of 6 visits to the doctor in the past 6 months, median symptom duration of 8 years and a median of 30 days with pain in the past 30 days. If an indirect comparison is made between CBT and psychotherapy, the odds ratios at the end of treatment suggest that CBT is at least as effective as the psychotherapy delivered in the Creed (2003) study (CBT compared to usual care OR=13.54, 95%CI 4.12-44.48, and psychotherapy vs usual care OR=2.44, 95%CI 1.28 – 4.67). It is therefore possible that similar reductions in resource use would be observed for CBT if the population were restricted to high service users. However, as there is no direct evidence for this we have excluded any reduced resource use for CBT in the basecase analysis. It was included in a sensitivity analysis by applying the reduction in resource use observed during the follow-up period of the Creed (2003) study for psychotherapy compared to usual care (£-4.08 per week, 95%CI-£8.11 to -£0.04) indirectly to CBT.

Figure 40: Response rate in the basecase analysis

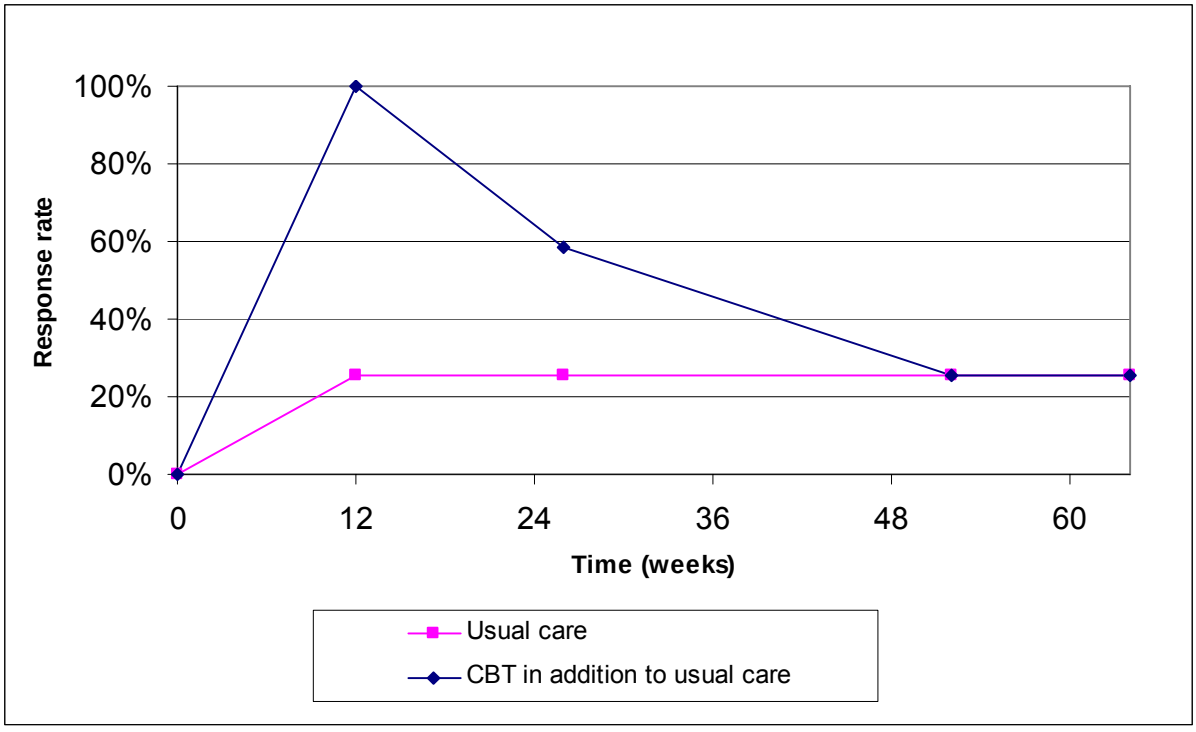
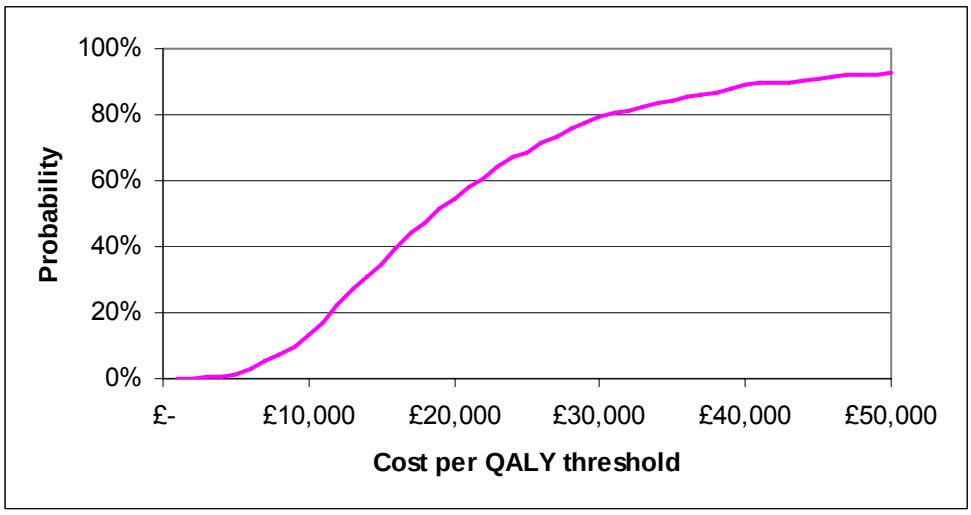


Table 2: Intervention specific parameters – CBT

Description	Value	Evidence
RR of response for intervention vs placebo (at end of treatment)	6.11 (2.33 – 16.07)	Meta-analysis of RCT evidence for improvement in global symptoms
Fall-off in effect at 6 months compared to end of treatment	56% (47% to 66%)	Kennedy (2005), global symptom score
Fall-off in effect at 12 months compared to end of treatment	100% (Fixed)	Kennedy (2005), global symptom score
CBT cost: equiv to 6.6 hours per patient	£375 (£167 - £582).	Weighted mean duration across studies and unit cost from Netten (2006)

CBT in addition to usual care for 100 patients with refractory IBS is estimated to gain an additional 2.24 QALYs for an additional cost of £37,460 compared to usual care alone under the basecase assumptions. The incremental cost per QALY is therefore £16,732. The probabilistic sensitivity analysis considers the uncertainty in this basecase estimate due to the uncertainty in the parameters used to estimate the cost-effectiveness. The CEAC in Figure 41 shows that given the parameter uncertainty, CBT in additional to usual care has a 55% probability of having a cost per QALY under £20,000 and a 79% probability of having a cost per QALY under £30,000, compared to usual care alone.

Figure 41: CEAC for CBT in addition to usual care compared to usual care alone in patients with refractory IBS



When we assumed that CBT is given over 6 or 8 weeks but at the same cost as in the basecase, the cost per QALY was £15, 771 or £16,079 respectively as the QALY gain was marginally increased (2.38 for 6 weeks and 2.33 for 12 weeks, compared to 2.24 in the

basecase). However, it should be noted that in this sensitivity analysis it was assumed that the response rate in the placebo arm was also achieved over a shorter duration, so that the RR was applied at the end of the intervention period to the same baseline response rate of 25%. These results suggest that assuming a 12 week intervention period in the basecase may have slightly underestimated the cost-effectiveness of CBT but it didn't significantly bias the cost per QALY estimate.

The RR for an improvement in global symptoms for CBT has been applied to a 25% response rate in the comparator arm giving a 100% response rate at 12 weeks for CBT. However, in the CBT trials, the mean response rate in the control arm was 9%. The sensitivity analysis using this lower response rate in the comparator arm gave a cost per QALY of £27,129. As this sensitivity analysis significantly increased the cost per QALY estimate, the probabilistic sensitivity analysis was re-run using this lower response rate for the comparator arm. The mean cost per QALY from the 1000 samples was £25,940 and the cost per QALY had a 31% probability of being under £20,000 per QALY and a 48% probability of being under £30,000 per QALY.

The threshold analysis on utility gain showed that the response to treatment would need to provide more than 0.059 QALYs per annum to give a cost per QALY of under £20,000 in the basecase analysis. When the utility gain associated with a response to treatment was increased to 0.135 (equivalent to the QALY gain expected for a complete remission of symptoms) the cost per QALY was significantly lower at £8,837.

When we assumed no fall-off in response up to 52 weeks post-intervention the cost per QALY was £6,317. This estimate would be further reduced by any continued response beyond 52 weeks. When we assumed that there was no significant difference between CBT and usual care from 6 months, the cost per QALY increased to £28,184. Whilst these two scenarios represent extreme possibilities for the estimated fall-off in response, they demonstrate that the cost-effectiveness is sensitive to the rate of fall-off in response after the end of intervention.

When we assumed that the reduction in resource use observed in the one year after psychotherapy from the Creed (2003) study could also be expected in patients receiving CBT, the incremental cost for CBT reduced to £11,342 and the cost per QALY reduced to £5,066.

Table 3: Sensitivity results for CBT in addition to usual care compared to usual care alone for 100 patients with refractory IBS (all subtypes)

Scenario	Usual care		Behavioural intervention and usual care		Incremental
	Cost	QALY	Cost	QALY	Cost per QALY
Basecase	£0	2.02	£37,460	4.26	£16,732
Intervention given over 6 weeks	£0	2.13	£37,460	4.50	£15,771
Intervention given over 8 weeks	£0	2.09	£37,460	4.42	£16,079
Lower response rate in comparator arm (9%)	£0	0.72	£37,460	2.10	£27,129
No fall-off in effect for 1 year	£0	2.02	£37,460	7.95	£6,317
Effect falls off over first 6 months	£0	2.02	£37,460	3.35	£28,184
Resource use reduction from Creed (2003) study	£0	2.02	£11,342	4.26	£5,066
High utility gain of 0.135	£0.00	3.83	£37,460	8.07	£8,837
Threshold analysis on lowest utility	A cost per QALY of £20,000 is reached when the QALY gain associated with responding to treatment lies between 0.059 and 0.060.				

Further analyses on the cost-effectiveness of CBT compared to other behavioural interventions are given in section 9.7.

EVIDENCE STATEMENTS

For this review, the evidence was assessed using the GRADE process and tables are shown in Appendix F. The following evidence statements are derived from the GRADE tables.

1. There is good evidence to show a significant global improvement in symptoms for CBT when compared with no treatment/symptom monitoring, mainly in patients with psychiatric co-morbidities and refractory IBS.

2. There is moderately good evidence to show a borderline global improvement in symptom score for CBT in addition to mebeverine compared with mebeverine alone, at 26 weeks follow up, but there is no significant difference at 52 weeks, in primary care patients with about 50% psychiatric co-morbidities and IBS that did not respond to three months treatment with mebeverine.

3. There is moderately good evidence to show no significant difference in pain and bloating for CBT when compared with no treatment/symptom monitoring in patients, most of whom had psychiatric co-morbidities

4. There is limited evidence to show no significant effect on constipation, but a small, significant improvement in diarrhoea for CBT when compared with no treatment/symptom monitoring in patients, most of whom had psychiatric co-morbidities

5. There is weak evidence to show no significant difference in quality of life (IBS QoL) for CBT when compared with no treatment/symptom monitoring in patients with psychiatric co-morbidities

6. There is moderately good evidence to show a significant global improvement in symptom score when CBT is added to mebeverine when compared with mebeverine alone.

HEALTH ECONOMIC STATEMENT

Evidence from a trial based economic evaluation showed that the addition of CBT to antispasmodic therapy does not result in lower service costs at 3, 6 or 12 months in individuals with symptoms of moderate or greater severity after 2 weeks of GP care and 4 weeks of mebeverine.

Evidence from a decision analytic model showed that the addition of CBT to usual care is cost-effective in individual with refractory IBS The ICER is sensitive to the proportion of patients experiencing an improvement in global symptom score with usual care alone and the efficacy in the 9 months after intervention, although none of the sensitivity analyses generated ICERs

above £30,000 per QALY. A threshold analysis showed that an improvement in global symptoms must result in a utility gain of at least 0.06 for the cost per QALY to remain below £20,000.

GDG DISCUSSION

The majority of people in the randomised trials had psychiatric co-morbidities and it is the view of the GDG that these could have skewed data when seeking to apply trial findings to the IBS population as a whole.

Generally, CBT has a positive benefit in improving global symptom scores for people with IBS in the trials. Meta-analysis demonstrates the benefit of CBT in producing an initial big treatment effect. The GDG view is that people with IBS are likely to feel that they are coping better with their symptoms, whilst recognising the potential for a treatment tail off. Even though there is some evidence that there is sustainable treatment effect, tail-off is usually addressed by a top up session.

CBT has not generally been used as a first line therapy for the management of IBS, but the GDG agreed that this needs to be investigated further. The GDG therefore decided to include CBT in one of its top five research recommendations.

EVIDENCE TO RECOMMENDATION

The evidence to recommendation statement for psychotherapy, CBT and hypnotherapy is detailed in section 9.8.

The combined guideline recommendation for psychotherapy, CBT and hypnotherapy is also stated in section 9.8.

9.6 Hypnotherapy

SELECTION CRITERIA

The selection criteria described in the general methodology section were used, except that crossover studies were excluded as inappropriate due to the carry-over effect of the hypnotherapy interventions.

The following comparisons were included:

- Hypnotherapy versus waiting list control, or symptom monitoring only
- Hypnotherapy versus usual medical care
- Hypnotherapy individual versus hypnotherapy group
- Hypnotherapy versus another intervention (e.g. psychotherapy or relaxation).

SEARCH STRATEGY FOR IDENTIFICATION OF STUDIES

Searches were performed on the following core databases: MEDLINE, EMBASE, CINAHL, and *The Cochrane Library* (1966 to current day with guidance from the GDG). Additionally, the PSYCINFO database was searched for this review. The search strategies are listed in Appendix B.

The titles and abstracts from the search strategy were assessed. Nineteen were identified to be potentially relevant to the review and these papers were retrieved in full. The reference lists of the retrieved studies were inspected for further potential papers, but none were identified. The 13 excluded studies are listed in Appendix E, along with reasons for exclusion.

Study Design

Six parallel group design randomised trials were included (Forbes 2000; Galovski 1998; Harvey 1989; Palsson 2002; Roberts 2006; Whorwell 1984). Further details are given in the included studies table.

Four of the studies were carried out in the UK (Forbes 2000; Harvey 1989; Roberts 2006; Whorwell 1984). The remaining studies were carried out in the USA (Galovski 1998; Palsson 2002). Trials lasted between 6 and 12 weeks. One study was conducted among patients recruited from primary care (Roberts 2006); the others were in secondary care.

The total number of patients in the studies ranged from 12 to 81. Only two studies included more than 25 patients in a treatment arm (Forbes 2000; Roberts 2006). Forbes included 25 and 27 patients in the two treatment arms respectively. In Roberts (2006) a power calculation was done, which suggested that 50 patients per group would be needed; however, the study only recruited 40 patients in one arm and 41 patients in the other, so it was underpowered. On the basis of this power calculation, it is likely that all the studies are underpowered.

Population

All the studies included only patients with IBS. None of the studies reported the number of patients with bloating or whether the symptoms were post-infective, and it was unclear if the patients had pain at baseline. The mean age of patients was around 40 years, with those aged between 18 and 65 years included. All the studies included more women than men.

IBS was stated, or implied, to be refractory all of the studies. The patients in Forbes (2000) had had IBS for more than six months and the inclusion criteria required that they had failed on conventional treatments, with the exception of antidepressants. Palsson (2002) stated that the patients all had symptoms refractory to standard medical management. Galovski (1998) had patients with a mean duration of IBS symptoms of six years (range 0.5 to 17years). Harvey (1989) did not report the duration of symptoms, but stated that the patients had refractory IBS.

Roberts (2006) included primary care patients with IBS for more than six weeks, who were said to have failed conventional management. Whorwell (1984) included patients with severe refractory IBS who had not responded to any therapy over at least one year (the mean number of therapies previously tried per patient was six).

The patients in Forbes (2000) and Roberts (2006) were allowed to continue pre-existing therapy for IBS, including antispasmodics and antidepressants; those in Palsson (2002) discontinued their IBS medication. Continued medication use was not stated in Galovski (1998), Harvey (1989), or Whorwell (1984).

In Galovski (1998), 67% of patients had an Axis I diagnosis; one patient with bipolar disorder with a current manic state was excluded. Forbes (2000) stated that 19/52 (37%) of patients were considered to be psychiatric cases according to the GHQ. Harvey (1989) reported that 8/22 (36%) had psychological problems (GHQ≥5). Patients requiring psychotropic medications were excluded from Palsson (2002). Psychiatric co-morbidities were not stated in the other two studies (Roberts 2006; Whorwell 1984).

Interventions

The hypnotherapy interventions were all 'gut-directed hypnotherapy' based on the methods described by Whorwell in 1984. All the trials assessed individual therapy; in one trial the comparator was group hypnotherapy (Harvey 1989). The studies varied in how hypnotherapy was delivered: Roberts (2006) had 5 weekly half-hour sessions and follow-up data were available at 3, 6 and 12 months (not end of therapy). Harvey (1989) had four 40-minute sessions over 7 weeks; Palsson (2002) had seven 45-minute sessions over 12 weeks; Forbes (2000) had six 30-minute sessions over 12 weeks, and; Whorwell (1984) had seven 30-minute sessions over 3 months.

Hypnotherapy was compared with relaxation training, psychotherapy, symptom monitoring, waiting list control, and usual care. In one trial (Harvey 1989), hypnotherapy in groups was compared with individual therapy. In the Whorwell (1984) trial, hypnotherapy was compared with 'psychotherapy', but author communication described this as 'supportive listening', more akin to attention control than psychotherapy. In Roberts (2006), IBS medication was continued in both groups, so that their comparison, hypnotherapy versus usual management, was, in reality, hypnotherapy versus no treatment. It was agreed to combine the comparators, waiting list control, attention control, symptom monitoring and no treatment / usual care.

The following comparisons were included:

- Hypnotherapy versus: a waiting list control group; attention control; symptom monitoring only, or; usual care (four studies: Galovski (1998); Palsson (2002); Roberts (2006); Whorwell (1984)):

    - Hypnotherapy versus waiting list control (Palsson 2002)
    - Hypnotherapy versus symptom monitoring (Galovski 1998)
    - Hypnotherapy versus usual management (conventional medication in primary care) (Roberts 2006)
    - Hypnotherapy versus attention control + placebo tablet (both therapies delivered by same therapist) (Whorwell 1984);
- Group hypnotherapy versus individual hypnotherapy:
    - Harvey (1989);
- Hypnotherapy versus another intervention:
    - Hypnotherapy versus audiotape on relaxation (tape produced by same therapist) (Forbes 2000).

METHODOLOGICAL QUALITY

The results of the quality assessment for included trials are shown in Appendix D.

One study (Forbes 2000) reported an adequate method of randomisation (computer-generated random numbers); the other studies did not state the method. Allocation concealment was partially adequate in one study (Roberts 2006, sealed envelopes); the other studies were unclear. The patients were not blinded (because of the type of intervention). However, the GDG did not consider this to be important for the behavioural interventions. One study (Roberts 2006) described an *a-priori* power calculation, but did not meet the required number of patients during recruitment.

The comparability of groups at baseline varied amongst the studies:

- Two studies demonstrated baseline comparability of the groups (Forbes 2000; Galovski 1998)
- Two were mainly comparable:
    - Roberts (2006) reported that there were more males in the intervention group (8/40 versus 4/41); and there were some differences in baseline quality of life scores (on three of eight subscales, p value not given)
    - Whorwell (1984) reported that bowel habit was more severely disordered in patients receiving hypnotherapy than in control patients (intervention group baseline score 17.2 versus controls 12.8; where abnormality of bowel habit was scored 0=none, 1=mild, 2=moderate or 3=severe, and scores totalled over 7 days, i.e. scale from 0 to 21, p=0.005 for baseline difference);
- Two did not state the comparability for the randomised population (Harvey 1989; Palsson 2002).
    - However, Palsson (2002) gave baseline pain and bloating scores and the proportion of hard/loose stools only for completers, and these were not comparable across

groups (more severe pain and bloating and lower proportion of hard/loose stools for the intervention group).

All the patients were followed up in two studies (Galovski 1998; Whorwell 1984). There were 20% or fewer drop-outs overall in two studies (Harvey 1989; Forbes 2000). In Harvey (1989), 3 out of 36 [8%] were missing and Forbes (2000) had 7/52 missing data for symptom diaries, but only 25/52 (48%) complied with the follow up for psychological outcomes. One study (Palsson 2002) had more than 20% missing data in the control group: the 6 drop-outs in the study were all from the control group (i.e. 40% drop-out in this group), however, the study stated that the drop outs were related to non-treatment related causes such as relocation, scheduling difficulties and unrelated medical problems. Nevertheless we regarded this study with caution because this unequal drop-out could still have introduced a bias. In the other study (Roberts 2006), data were missing for 18% of patients at 3 months; 17% at 6 months and 35% at 12 month follow-up. However, the study stated that analysis indicated that the missing data were 'missing completely at random', so that the results for the missing data would not be significantly different from those that completed the study.

Overall, there is a risk of bias in the Palsson (2002) study for the pain and bloating outcomes, and the uneven drop-out rates between the groups should be taken into consideration (40% drop-out among controls versus none from the intervention group) and the differences at baseline. Forbes (2000) was considered at high risk for the psychological outcomes. The Roberts (2006) 12 month follow-up data should be regarded with caution, also due to the fairly high drop-out rate (35%). The difference in baseline for bowel habit should be taken into consideration in the Whorwell (1984) study.

RESULTS

A. Hypnotherapy versus waiting list control group, attention control, symptom monitoring only or usual management

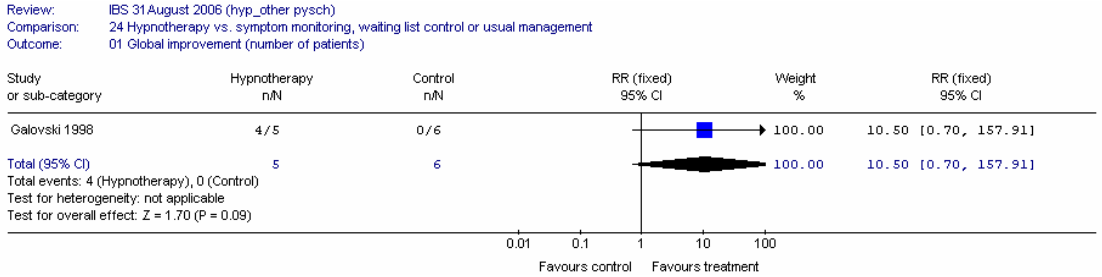
Four studies compared hypnotherapy with a waiting list control group; attention control; symptom monitoring only, or; usual management in patients with IBS (Galovski 1998; Palsson 2002; Roberts 2006; Whorwell 1984).

1. Global symptoms

a) Number of patients with global improvement in symptoms

This outcome was reported by Galovski 1998 at 6 weeks for hypnotherapy versus symptom monitoring in 11 patients.

Figure 1



The confidence interval was too wide to determine if there is an effect (but see next section for further evidence on global improvement of symptoms – number of patients).

b) Global improvement of symptoms score

The Whorwell (1984) study in 30 patients reported the overall improvement of symptoms and general wellbeing, scored weekly on a scale of 0 to 3 (where 0 is no improvement and 3 is maximum improvement). From a baseline score of 0 in both groups, patients in the hypnotherapy group increased to a mean weekly value of 2.95 and those in the psychotherapy group increased to 0.52, i.e. a difference of 2.43. This was reported to be statistically significant ($p<0.0001$), i.e. a large effect.

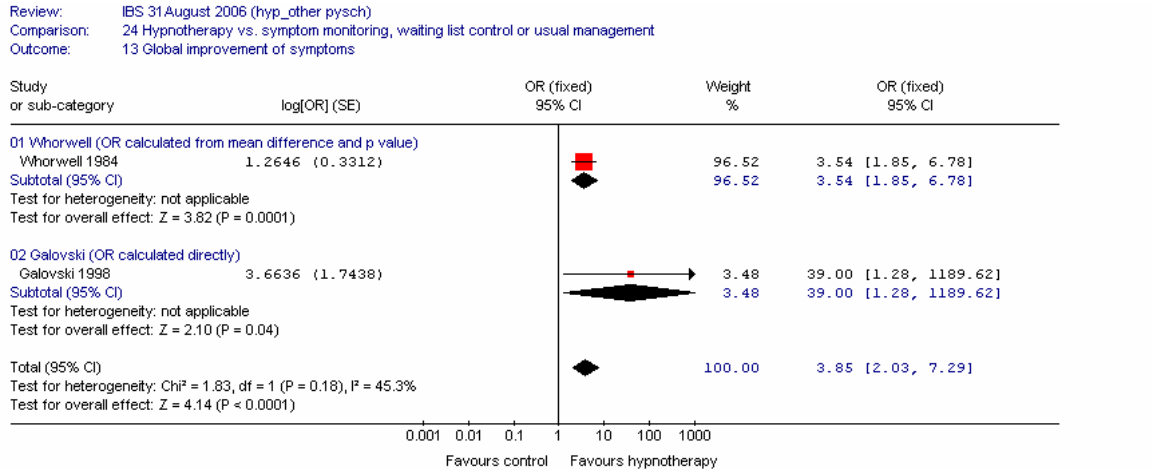
Chinn (2000) introduced a statistical approach that re-expresses standardised mean differences as odds ratios, according to the following simple formula:

$$\log OR = (\pi/\sqrt{3})\ SMD$$

The standard error of the standardised mean difference can be converted to the standard error of the log odds ratio by multiplying by $\pi/\sqrt{3} = 1.8140$. We carried out this procedure for Whorwell (1984) in order to combine the data with those of Galovski (1998). This involved calculation of the standard error from the p value, conversion of the mean difference to standardised mean difference by dividing both MD and standard error by the standard deviation and then converting to log OR.

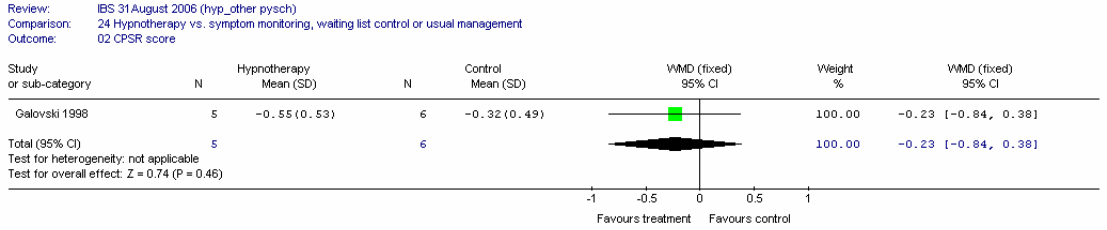
Meta-analysis of the two studies, in 41 patients, gave a pooled odds ratio of 3.85 (95%CI 2.03, 7.29), with non-significant heterogeneity (I^2=45%, p=0.16). This was statistically significant, in favour of hypnotherapy.

Figure 2: Meta-analysis for global improvement of symptoms (number of patients)



Galovski (1998) reported the global improvement of IBS symptoms at six weeks in 11 patients using the Composite Primary Symptom Reduction (CPSR) score; CPSR represents the proportional reduction in the score from baseline; scale -1 to +1. The confidence interval was too wide to determine if there was a difference between interventions.

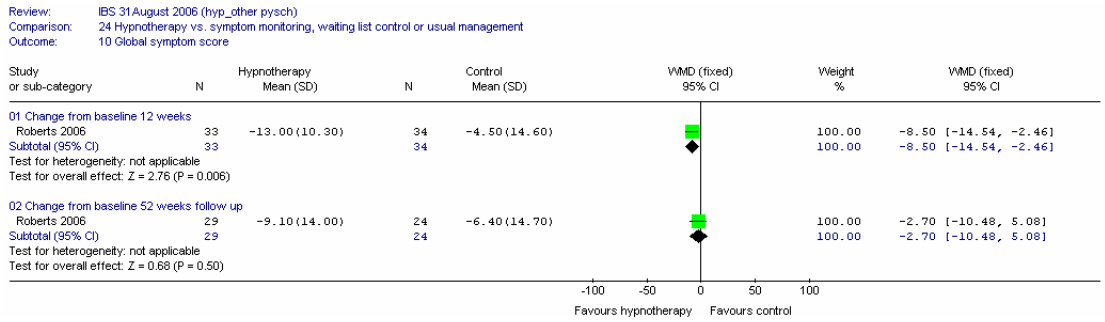
Figure 3



c) Global symptom score

The change over baseline in global symptom score was reported by Roberts (2006) at 12 weeks (about 7 weeks after the end of treatment) for hypnotherapy versus usual IBS care in 81primary care, refractory patients and at 26 and 52 weeks follow-up. 26 week standard deviations were not given, although the means were, and we noted that there was 35% missing data at 52 weeks (although the authors showed this to be missing-at-random, which made the results more acceptable). There was a statistically significant improvement in symptom score at 12 weeks, favouring hypnotherapy. The scale was not given, but reference was made to a questionnaire using 22 items each rated at 1-7 (7=high) (Wiklund 2003). This would have meant a maximum score of 154, but this was not entirely clear. The baseline scores were about 40, so a change of 8.5 units seems a reasonable effect size. At six months, the decreases in symptom score were 10 and 8 for the intervention and control groups respectively, i.e. a change of -2 units. At 12 months (follow-up) the change in symptom score was -2.70 (95%CI -10.48, 5.09), i.e., no longer significant.

Figure 4



2. Individual symptoms

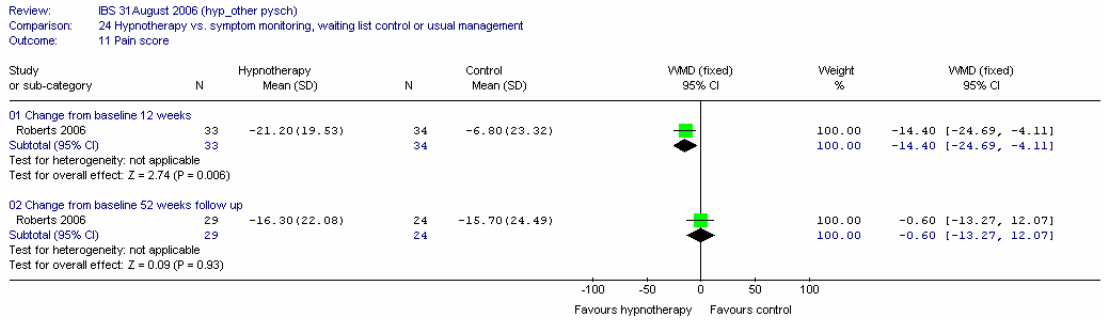
a) Pain

A pain score was reported by three studies (Palsson 2002; Roberts 2006; Whorwell 1984), all at 12 weeks. Palsson (2002) compared hypnotherapy versus waiting list control in 30 patients; neither had concurrent IBS medical treatments, and recorded pain score on a scale of 0 to 4 recorded over 14 days, where 0=none, 1=mild, 2=moderate, 3=severe and 4=incapacitating, i.e. maximum 56. We noted that this study had 40% missing data in the control group, in addition, there was a significant difference in the baseline pain score for completers in the intervention group was of 7.9 units, which was large compared to the difference in effect size (11.8 units). Therefore the results from this study were considered to be potentially biased and are therefore not reported here.

Roberts (2006) showed a significant difference in the pain score of -14.40 (95%CI -24.69, -4.11) at 3 months, but this was no longer significant at 12 months. The baseline scores were 53-55. Again there was 35% missing data, said to be missing-at-random.

Whorwell (1984) recorded a pain score (0-3 recorded over 7 days, where 0=none, 1=mild, 2=moderate, 3=severe, i.e. maximum 21). From a baseline score of 13 in both groups, patients receiving hypnotherapy reduced their mean score to 2.2 (i.e. a fall of 10.8), while those on psychotherapy had a mean score of 11.6 at 12 weeks (i.e. a fall of only 1.4); no standard deviations were given, but the difference between groups of -9.4 was reported to be statistically significant (p<0.0001).

Figure 5



b) Bloating

Two studies reported a bloating score at 12 weeks (Palsson 2002; Whorwell 1984). Palsson (2002) used a scale of 0 to 4 recorded over 14 days, where 0=none, 1=mild, 2=moderate, 3=severe and 4=incapacitating. However, the baseline values for bloating were much lower for the control group (data given for completers only, mean 13.6 at baseline) than the intervention group (mean 20.3 at baseline), and there was 40% missing data in the control group. The study was therefore considered to be confounded for this outcome and was not considered further.

Whorwell (1984) measured a bloating score (0-3 recorded over 7 days, where 0=none, 1=mild, 2=moderate, 3=severe). From a baseline score of around 16, patients receiving hypnotherapy reduced their mean score to 3.2 (i.e. a fall of 12.8), while those receiving supportive listening ('psychotherapy') had a mean score of 13.2 at 12 weeks (i.e. a fall of only 2.8); no standard deviations were given, but the difference between groups of -10.0 was reported to be statistically significant (p<0.0001).

c) Bowel habit

Roberts (2006) reported scores for constipation and diarrhoea. There was a non-significant difference (Figure 6), favouring hypnotherapy, in the diarrhoea score of –7.90 (95%CI -16.29, 0.49) at 3 months, but very little difference at 12 months. The baseline scores were about 33. Again there was 35% missing data, said to be missing-at-random. For constipation, there was no significant effect at any time (Figure 7). Baseline scores were around 38.

Figure 6

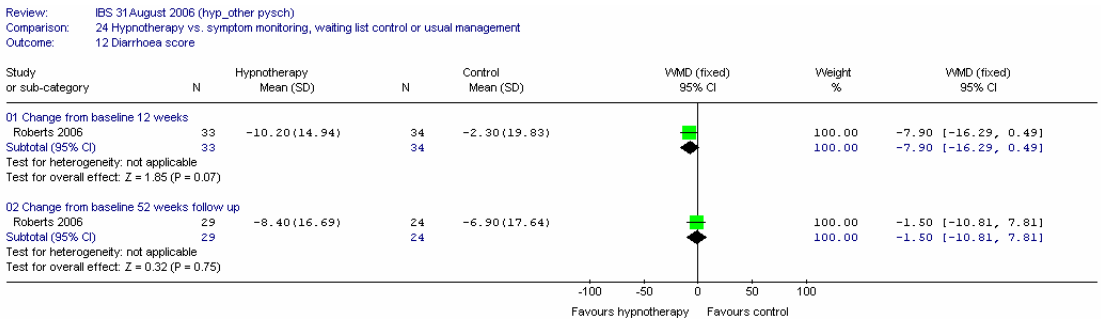
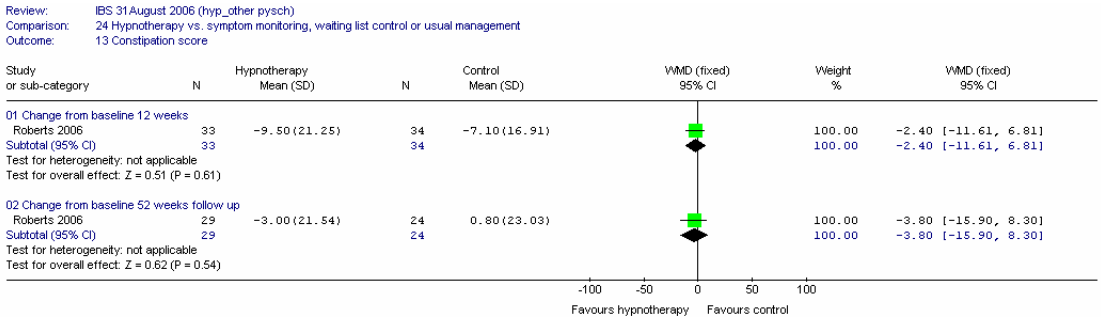


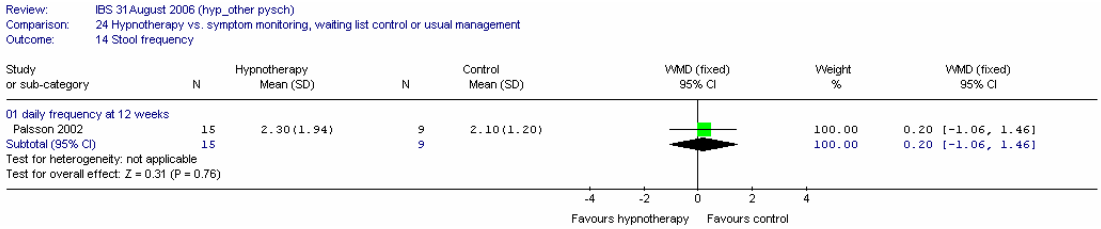
Figure 7



Abnormality of bowel habit was reported by Whorwell (1984). At baseline, this was more severely disordered in patients on hypnotherapy than in control patients (intervention group baseline score 17.2 versus psychotherapy 12.8 (i.e. baseline difference of 4.4); where abnormality of bowel habit was scored 0=none, 1=mild, 2=moderate or 3=severe, and scores totalled over 7 days, i.e. scale from 0-21, p=0.005 for baseline difference). The score fell from 17.2 to 1.6 (i.e. 15.6) in the hypnotherapy group compared with from 12.8 to 11.8 (i.e. 1.0) on psychotherapy (p<0.0001). The large baseline difference may have confounded this outcome measure.

Palsson (2002) reported stool frequency. There was no significant difference in the baseline values, or at 3 months.

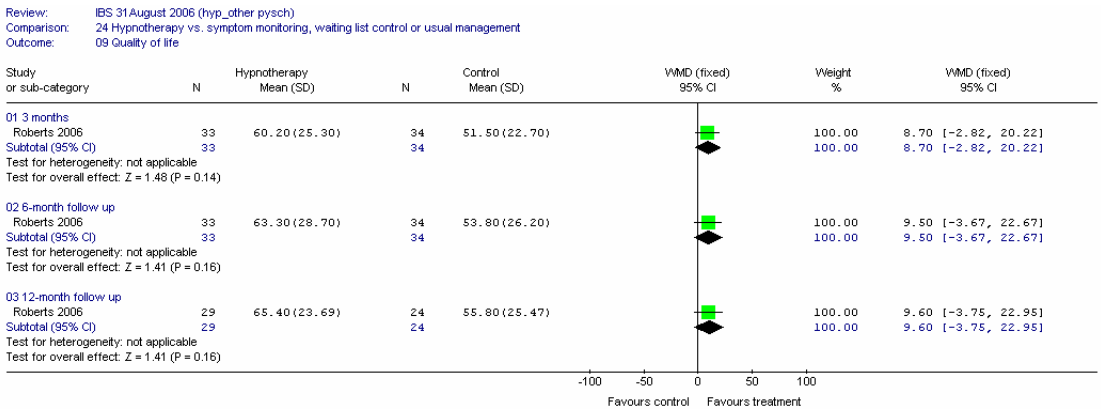
Figure 8



3. Quality of life

IBS-specific quality of life (high = good) was reported by Roberts (2006) at 3 months (about 7 weeks after end of treatment) in 81 patients and at 6 and 12 month follow-up. There was no significant difference at any time, although the difference in QoL score did not appear to change over time. Again the scale was not given, but reference to the Wiklund (2003) study suggested that the scale was 26 items with a 7 point Likert scale, giving a possible maximum of 182. Baseline scores were about 50.

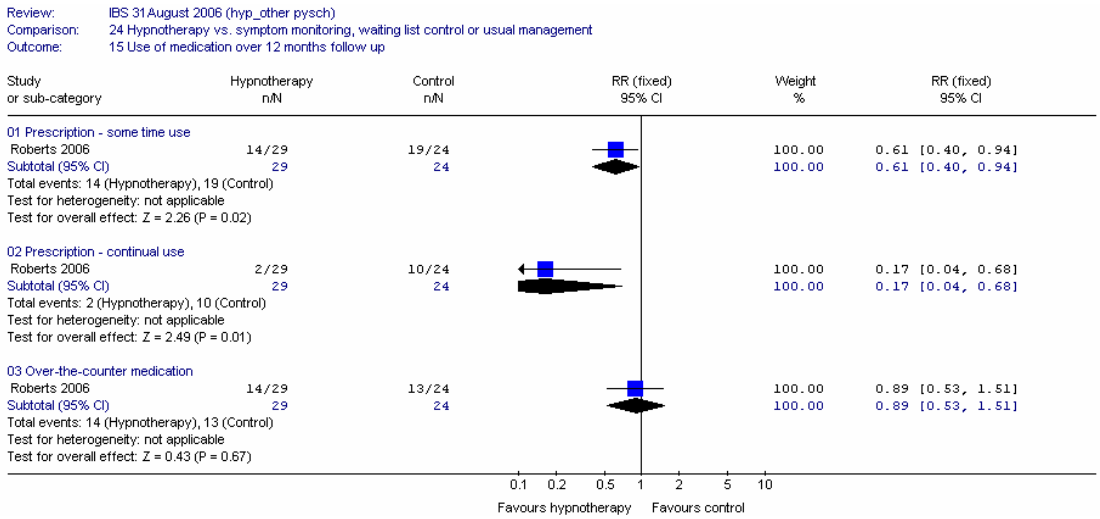
Figure 9



4. Use of IBS medication

One study (Roberts 2006) gave the self-reported use of prescription medication, either sometime, or continual, and over-the-counter medication (including antispasmodics, anti-motility agents, probiotics, herbal juices and teas, and incontinence pads) over the 12 months follow-up period. There were significantly more patients using prescription medication at some time during the 12 months; RR 0.61 (95%CI 0, 40, 0.94). This corresponded to an NNT of 4 (95%CI 2, 14), for a control group risk of 79%. There was no significant difference in the over-the-counter medication use.

Figure 10



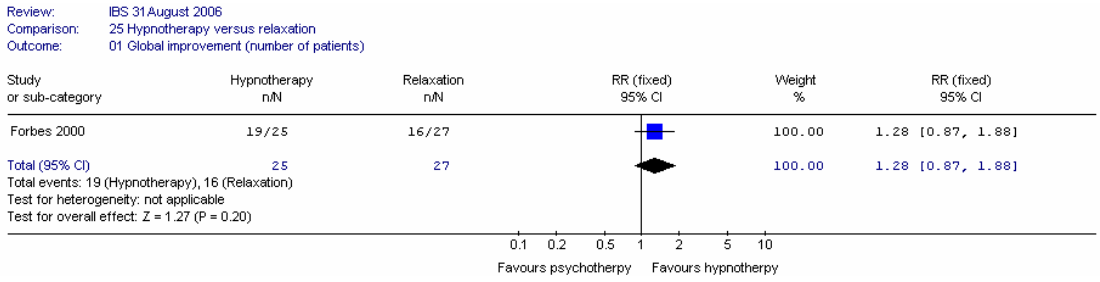
B. Hypnotherapy versus another intervention (relaxation)

Forbes (2000) compared hypnotherapy with relaxation in 52 patients. We noted that in both studies the two types of therapy were delivered by the same person, which could have introduced a therapist effect.

1. Global symptoms

Global improvement in symptoms (number of patients) was reported by Forbes (2000) at 12 weeks. There was no significant difference between interventions.

Figure 11



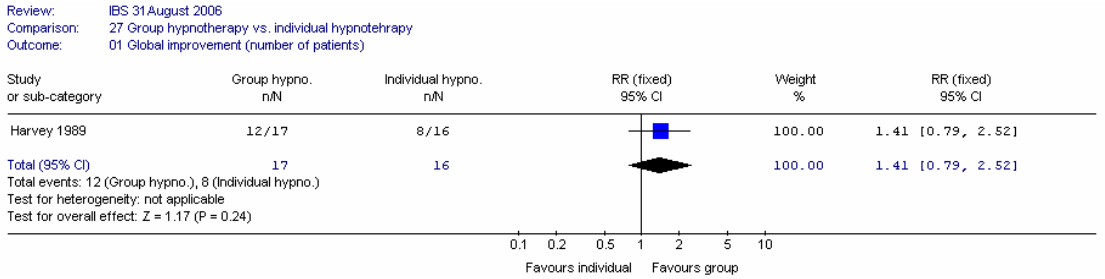
C. Group hypnotherapy versus individual hypnotherapy

One study in 33 patients (Harvey 1989) compared hypnotherapy on an individual basis versus hypnotherapy on a group basis (6 to 8 patients); the outcome reported was the global improvement in symptoms (number of patients). There was no significant difference between interventions.

1. Global outcomes

Global improvement in symptoms (number of patients)

Figure 12



ECONOMIC LITERATURE FOR HYPNOTHERAPY

No relevant health economic analyses were identified on the cost-effectiveness of hypnotherapy in the management of IBS.

COST-EFFECTIVENESS ANALYSIS FOR HYPNOTHERAPY

This section describes the health economic analysis undertaken to inform recommendations on the use of hypnotherapy as a one-off intervention in the management of IBS. The general methods used in the economic analysis for all management interventions are described in detail in Chapter 5 and the model inputs and assumptions relevant to this particular intervention are described below.

- The effectiveness of hypnotherapy in addition to usual care compared to usual care alone in people with refractory IBS was based on the number of patients with an improvement in global symptoms (at the end of treatment) for hypnotherapy vs waiting list control, symptom monitoring, attention control or usual care. (OR 3.85, 95%CI 2.03- 7.29, from meta-analysis of Whorwell (1984) and Galvoski (1998), giving a RR of 2.23, 95% CI 1.16 – 2.80, for a 25% response rate in the control arm).
- We assumed that there is no further benefit after 12 months based on a non significant difference in mean global symptom score at 12 months (Roberts 2006). A linear fall-off was assumed between the end of treatment and 12 months. A sensitivity analysis assuming no further benefit after 6 months was carried out as the mean difference in global symptom score is similar at 6 months and 12 months but it is not possible to calculate statistical significance from the data presented for 6 months (Roberts 2006).

- The evidence included in the clinical effectiveness review did not allow a subtype specific estimate of clinical effectiveness to be estimated. Therefore it was assumed that hypnotherapy is equally effective in all IBS subtypes.
- Hypnotherapy was assumed to be given over 12 weeks as this was the duration of intervention in the Whorwell (1984) and Galovski (1998) studies.
- A 15 month time-frame was used so that the cost-effectiveness could be compared to against other psychological interventions for which there was 15 month efficacy data.

Modelled response rates

In the basecase scenario the response rate of 25% in the no treatment arm is taken from the mean placebo arm response rate from the behavioural therapy trials. This represents the group of patients whose symptoms improve without any specific intervention. The RR for an improvement in global symptoms for hypnotherapy vs no treatment at the end of treatment is 2.23, therefore the response rate in the intervention arm is 57% at the end of treatment (12 weeks). As shown in Figure 13, the response rate in the hypnotherapy arm has decreased to 46% by 6 months and 25% by one year, based on the assumptions regarding fall-off in effectiveness described above.

We have also considered a maintained benefits scenario in which the response to hypnotherapy is maintained for the one year after the end of treatment but there is no further benefit beyond this point.

There was no NHS reference cost available for hypnotherapy, even though it is funded in some regions of the NHS. A typical salary for a hypnotherapist falls within the Agenda for Change band 6 (based on personal communication from Peter Whorwell). This is the same salary used in estimating the reference cost for counsellors, on which the cost estimate for psychotherapy has been based. We have assumed that hypnotherapists have a similar working pattern to counsellors undertaking psychotherapy in terms of the proportion of their time that is spent on direct client contact and the proportion that is spent on research, administration, education and other activities. Therefore the cost per hour for hypnotherapy has been taken to be equivalent to the cost per hour for psychotherapy. The costs of hypnotherapy were based on the mean number and duration of sessions used in the Whorwell (1984) and Galoviski (1998) studies, weighted by their contribution to the meta-analysis. This gave a mean duration of 3.6 hours of hypnotherapy. As there were only two studies used to estimate the RR, the cost range was based on the range from the various studies included in the clinical effectiveness review (2.2 – 4.9 hours). This gave a total cost for hypnotherapy of £171, (range £105 - £237).

For hypnotherapy there was evidence from Roberts (2006) that hypnotherapy resulted in a significant reduction in the use of prescriptions in the 1 year following intervention: RR of 0.61 (0.40 – 0.91) for any prescription use and RR of 0.17 (0.04 to 0.68) for continual prescription use

for hypnotherapy compared to control. We have assumed no reduced resource use in the basecase analysis as reduced prescription rates are unlikely to have a significant cost impact. It was included in a sensitivity analysis by applying the reduction in resource use observed during the follow-up period of the Creed (2003) study for psychotherapy compared to usual care (£-4.08 per week, 95%CI-£8.11 to -£0.04) indirectly to hypnotherapy. This is plausible given that the odds ratio for an improvement in global symptom score at the end of treatment is larger for hypnotherapy compared to usual care (3.85, 95% CI 2.03 – 7.29) than the odds ratio observed for psychotherapy vs usual care in the Creed (2003) study (OR=2.44, 95%CI 1.28 – 4.67).

Figure 13: Response rate in the basecase analysis

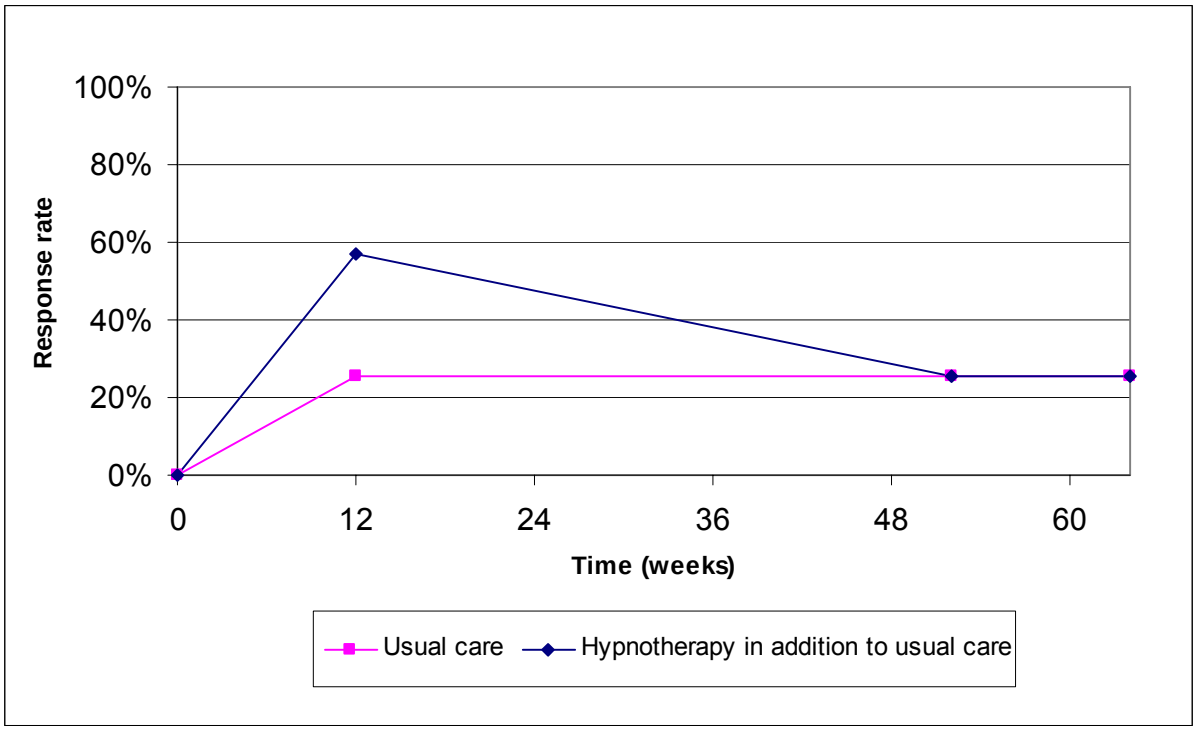
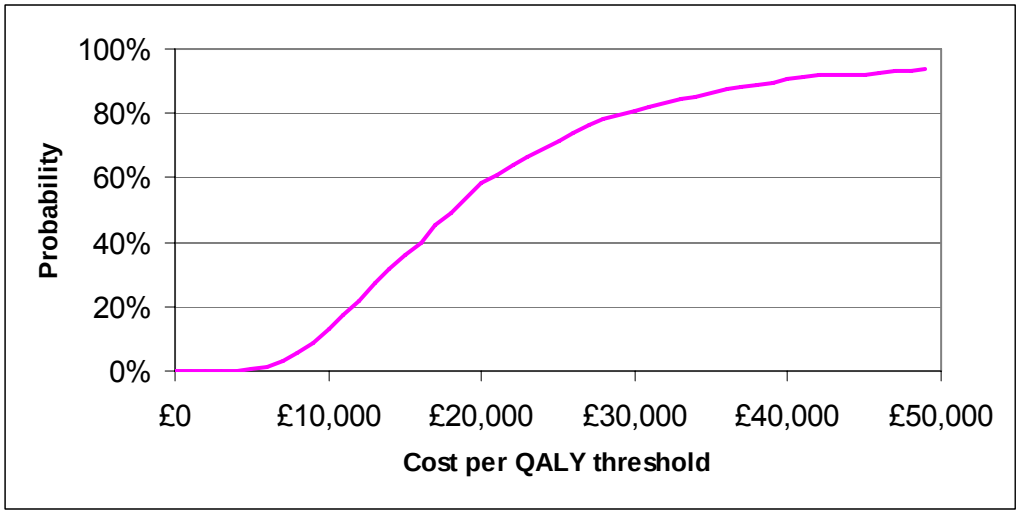


Table 1: Intervention specific parameters – Hypnotherapy

Description	Value	Evidence
RR of response for intervention vs placebo (at end of treatment)	2.23 (1.61 – 2.80)	Meta-analysis of RCT evidence for improvement in global symptoms
Fall-off in effect at 12 months compared to end of treatment	100%	Roberts (2006) global symptom score
Hypnotherapy cost: equiv to 3.6 hours per patient	£171, (range £105 - £237)	Weighted mean duration across studies and unit cost from Netten (2006)

Hypnotherapy in addition to usual care for 100 patients with refractory IBS is estimated to gain an additional 1.12 QALYs for an additional cost of £17,092 compared to usual care alone under the basecase assumptions. The incremental cost per QALY for is therefore £15,300. The probabilistic sensitivity analysis considers the uncertainty in this basecase estimate due to the uncertainty in the parameters used to estimate the cost-effectiveness. The CEAC in Figure 14, shows that given the parameter uncertainty, hypnotherapy in additional to usual care has a 59% probability of having a cost per QALY under £20,000 and a 81% probability of having a cost per QALY under £30,000, compared to usual care alone.

Figure 14: CEAC for hypnotherapy in addition to usual care compared to usual care alone in patients with refractory IBS



The incremental cost-effectiveness is dependent on the probability of an improvement for patients who receive usual care. When we applied a lower response rate of 9% in the usual care arm, the cost per QALY was increased to £25,809. It should be noted that the odds ratio rather than the RR was kept constant for this analysis as this was the efficacy estimate available from the clinical effectiveness review. As this sensitivity analysis significantly increased the cost per QALY estimate, the probabilistic sensitivity analysis was re-run using this lower response rate for the comparator arm. The mean cost per QALY from the 1000 samples was £25,770 and the cost per QALY had a 28% probability of being under £20,000 per QALY and a 51% probability of being under £30,000 per QALY.

The threshold analysis showed that a response to treatment would need to provide more than 0.054 QALYs per annum to give a cost per QALY of under £20,000 in the basecase analysis. When the utility gain associated with a response to treatment was increased to 0.135 (equivalent to the QALY gain expected for a complete remission of symptoms) the cost per QALY was significantly lower at £8,081

When we assumed there was no fall-off in response up to 52 weeks post-intervention, the cost per QALY was decreased to £6,859. This would be further reduced by any continued response beyond 52 weeks. When we assumed that there was no significant difference between hypnotherapy and usual care from 6 months, then the cost per QALY is increased to £30,601. Whilst these two scenarios represent extreme possibilities for the estimated fall-off in response, they demonstrate that the cost-effectiveness is sensitive to the rate of fall-off in response after the end of intervention.

When we assumed that the reduction in resource use observed in the one year after psychotherapy from the Creed (2003) study could also be expected in patients receiving hypnotherapy, the cost of providing hypnotherapy in additional to usual care was lower than the cost of providing hypnotherapy alone. Under these assumptions hypnotherapy in addition to usual care dominated usual care alone by providing significant health gains, whilst lowering cost.

Table 2: Sensitivity results for hypnotherapy in addition to usual care compared to usual care alone for 100 patients with refractory IBS (all subtypes)

Scenario	**Usual care**		**Behavioural intervention and usual care**		**Incremental**
	Cost	QALY	Cost	QALY	Cost per QALY
Basecase	£0	2.02	£17,092	3.14	£15,300
Lower response rate in comparator arm (9%)	£0	0.72	£17,092	1.38	£25,809
No fall-off in effect for 1 year	£0	2.02	£17,092	4.51	£6,859
Effect falls off over first 6 months	£0	2.02	£17,092	2.58	£30,601
Resource use reduction from Creed (2003) study	£0	2.02	-£9,026	3.14	-£8,080 Hypnotherapy dominates
High utility gain of 0.135	£0	3.83	£17,092	5.94	£8,081
Threshold analysis on lowest utility	A cost per QALY of £20,000 is reached when the QALY gain associated with responding to treatment lies between 0.054 and 0.055.				

Further analyses on the cost-effectiveness of hypnotherapy compared to other behavioural interventions are given in section 9.7.

EVIDENCE STATEMENTS

For this review, the evidence was assessed using the GRADE process and tables are shown in Appendix F. The following evidence statements are derived from the GRADE tables.

1. There is moderately good evidence to show a significant global improvement in symptoms after 12 weeks, for hypnotherapy compared with attention control or symptom monitoring or usual management, mainly in patients with refractory IBS, both in primary and secondary care.

2. There is moderately good evidence to show no significant improvement either in global symptoms or in pain after 52 weeks, for hypnotherapy compared with usual management, in patients with refractory IBS in primary care.

3. There is moderately good evidence to show a significant reduction in pain for hypnotherapy compared with attention control or usual management, in patients with refractory IBS, both in primary and secondary care.

4. There is limited evidence to show a significant reduction in bloating for hypnotherapy compared with attention control, in patients with refractory IBS, in secondary care.

5. There is moderately good evidence to show no significant improvement in diarrhoea or constipation or quality of life, after 12 weeks, for hypnotherapy compared with usual management, in patients with refractory IBS in primary care.

6. There is limited evidence to show a significant reduction over 12 months, in the number of prescriptions for other IBS medications, for hypnotherapy compared with usual management, in patients with refractory IBS in primary care.

7. There is limited evidence to show no significant difference between group and individual hypnotherapy, in patients with refractory IBS and psychological problems in secondary care.

HEALTH ECONOMIC STATEMENT

Evidence from a decision analytic model showed that the addition of hypnotherapy to usual care is cost-effective in individual with refractory IBS although the cost-effectiveness was sensitive to uncertainty around the proportion of patients experiencing an improvement in global symptom score with usual care alone. The ICER is sensitive to the proportion of patients experiencing an improvement in global symptom score with usual care alone and the efficacy in the 9 months after intervention. A threshold analysis showed that an improvement in global symptoms must result in a utility gain of at least 0.05 for the cost per QALY to remain below £20,000.

GDG DISCUSSION

The GDG's view was that hypnotherapy may be considered a developing intervention for IBS and the amount of evidence is limited. Despite this, the judgement and experience of GDG clinicians together with the limited RCT evidence from the review suggest that gut directed hypnotherapy strategies provide people with IBS with benefits in a cost-effective manner. Currently hypnotherapy is used as a second line therapy option, usually for people with unresolved IBS symptoms, who have failed to respond to a combination of management strategies. It features on the patient care pathway as one of the psychological interventions that primary care clinicians should consider if symptoms persist.

Although there is currently a lack of research in hypnotherapy, the GDG agreed there is potential for long-term benefits to the NHS from this behavioural therapy that need to be investigated further, including its use as a first line therapy. The GDG therefore decided to include hypnotherapy in one of its top five research recommendations, with the potential for this intervention to be considered as a first line therapy option.

EVIDENCE TO RECOMMENDATION

The evidence to recommendation statement for psychotherapy, CBT and hypnotherapy is detailed in section 9.8.

The combined guideline recommendation for psychotherapy, CBT and hypnotherapy is also stated in section 9.8.

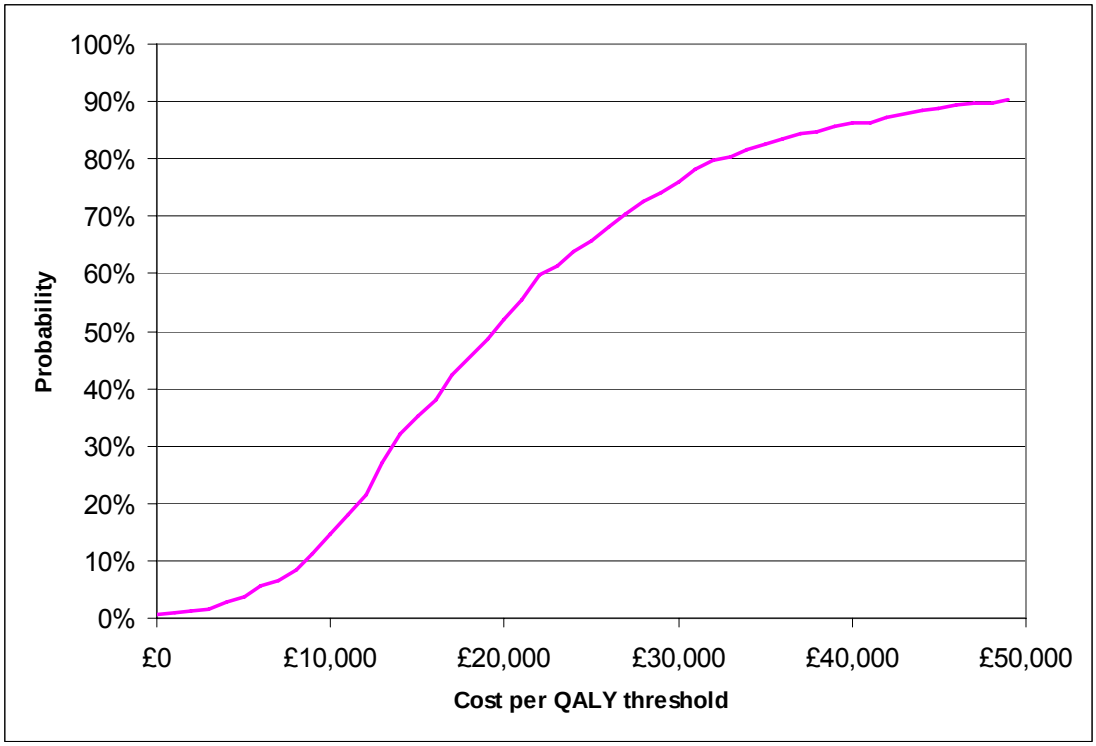
9.7 Indirect comparison of psychological interventions

We have undertaken an indirect comparison to assess the relative cost-effectiveness of the psychological interventions (CBT, psychotherapy and hypnotherapy). It is indirect because it is based on the cost-effectiveness of each intervention compared to usual care as no trials were identified which compared behavioural interventions head-to-head. The results are presented for two scenarios. In the first scenario the basecase assumptions are maintained from the analysis of each intervention compared to usual care. In the second scenario the basecase assumptions are maintained except that the resource use reduction from the Creed (2003) study has been excluded from the cost-effectiveness estimate for psychotherapy. This has been done because the GDG felt that there was a lack of similar evidence for CBT and hypnotherapy but that this was due to a lack of trials reporting economic outcomes for these interventions rather than a true difference in the cost-effectiveness compared to psychotherapy.

Hypnotherapy provided the smallest QALY gain compared to usual care but is likely to be cost-effective compared to usual care as discussed in section 9.6. As CBT provided more QALY gain than hypnotherapy at additional cost, we have considered the incremental cost-effectiveness of CBT compared to hypnotherapy. The CEAC in Figure 1 shows that CBT has a 52% probability

of being cost-effective compared to hypnotherapy at a cost per QALY threshold of £20,000 and a 76% probability of at a threshold of £30,000. The mean cost per QALY for CBT compared to hypnotherapy under the basecase assumptions was £18,158 for the deterministic model. There was concern that this comparison had been biased by the use of different unit costs for therapy sessions for CBT and hypnotherapy so we carried out a sensitivity analysis using the unit costs for CBT for both psychological interventions. This gave a cost per QALY of £15,301.

Figure 1: CEAC for CBT vs hypnotherapy



Under the basecase assumptions, psychotherapy provided additional QALY gain compared to CBT but the mean cost for psychotherapy was less than for CBT. The CEAC in Figure 2 shows the incremental cost-effectiveness of psychotherapy compared to CBT. Psychotherapy has a 68% probability of providing additional QALY gain at no additional cost compared to CBT and a 73% probability of providing additional QALY gain for less than £20,000 per QALY. There was concern that this comparison had been biased by the use of different unit costs for therapy sessions for CBT and psychotherapy so we carried out a sensitivity analysis using the unit costs for CBT for both psychological interventions. This raised the intervention cost for psychotherapy, but it still had a lower overall cost than CBT.

The lower cost of psychotherapy is driven by the assumption on lower resource use for psychotherapy compared to usual care. When this factor was excluded from the analysis psychotherapy had a mean cost per QALY of £11,314 compared to hypnotherapy with a 61% probability of a being under £20,000 and a 70% probability of being under £30,000 per QALY.

These results suggest that each of the interventions would result in the cost-effective use of NHS resources but it does not address which is the most cost-effective.

Figure 2: CEAC for psychotherapy compared to CBT

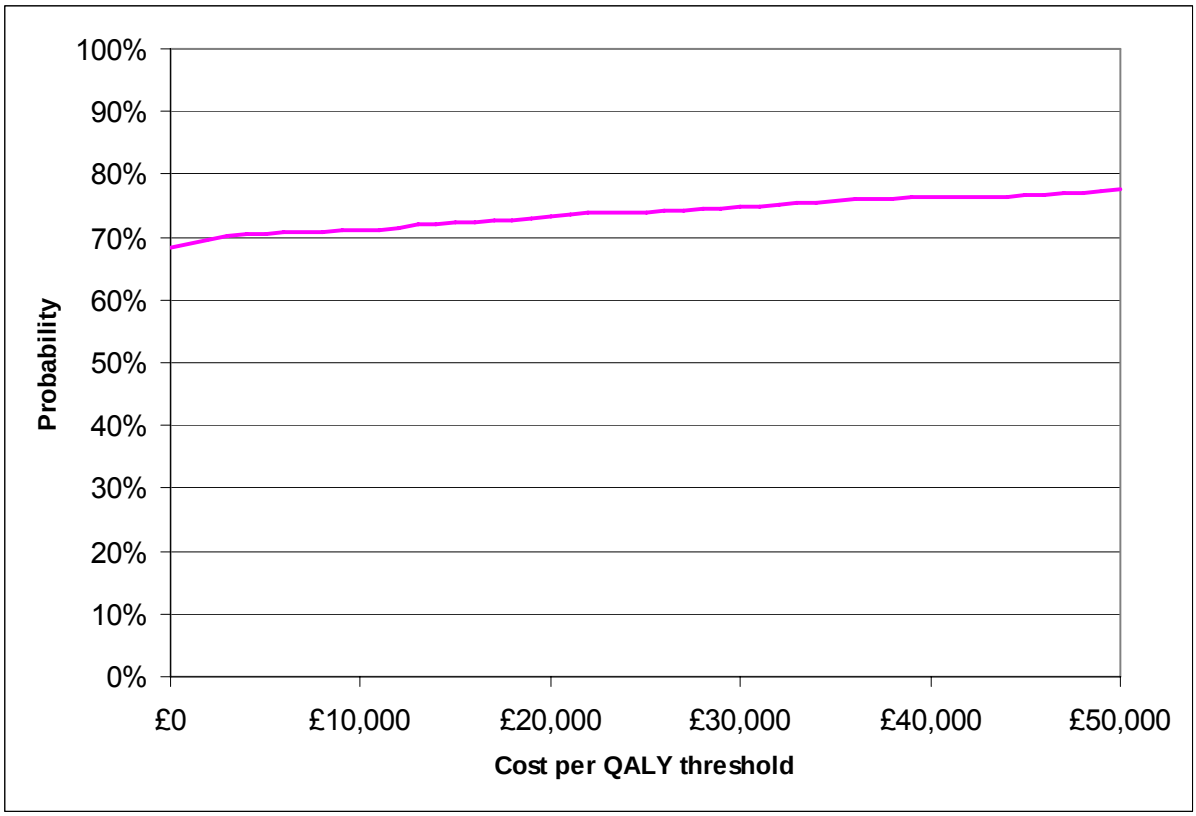


Figure 3 is a multi-way cost-effectiveness acceptability curve which shows the probability that each of the three psychological interventions is optimal compared to the other two at various cost per QALY thresholds. The optimal intervention is the one that provides the most QALY gain at a cost per QALY under the threshold. This is most easily described by considering the incremental net benefit of each intervention, which is the (monetary) value of a strategy compared with an alternative strategy for a given cost-effectiveness threshold. For example, if society is willing to pay £20,000 for an additional QALY then the incremental NB is:

Net benefit = (Additional QALY gain x £20,000) – additional cost

The strategy with the greatest incremental net benefit compared to usual care, at a given cost per QALY threshold, is the optimal strategy at that threshold. We used the results of the probabilistic sensitivity analysis to estimate the probability that each behavioural therapy is optimal at various cost per QALY thresholds. Figure 3 shows that under the basecase assumptions, psychotherapy has the highest probability of being the optimal strategy at willingness to pay thresholds of £10,000 to £50,000.

Figure 4 shows that when a similar exercise is carried out for the second scenario, in which we assumed that none of the three interventions result in reduced resource use, psychotherapy had a lower probability of being the optimal strategy, but it is still the most likely to be optimal for willingness to pay thresholds of £20,000 to £50,000 per QALY. Hypnotherapy has the highest probability of being the optimal strategy for cost per QALY thresholds under £20,000.

These results suggest that providing psychotherapy for people with refractory IBS is likely to result in more efficient use of NHS resources than providing CBT or hypnotherapy. However, the analysis did not take into account factors that may be important in deciding the optimal treatment for an individual. For example, if the effectiveness of these behavioural interventions is higher in patients who are committed to a particular intervention then choosing to provide the intervention preferred by the patient may result in treatment being more cost-effective. The results of the cost-effectiveness modelling suggest that all three behavioural interventions would result in the cost-effective use of NHS resources at willingness to pay thresholds of £20,000 to £30,000, given the evidence currently available.

HEALTH ECONOMIC STATEMENT

A decision analytic model was used to carry out an incremental analysis for the three psychological interventions. This was an indirect comparison based on the effectiveness of each behavioural therapy compared to usual care and therefore may be biased. Psychotherapy was the most cost-effective intervention when considering a cost per QALY threshold in the £20,000 to £30,000 range. This conclusion was not dependent on whether the reduction in resource use for psychotherapy compared to usual care, as observed in Creed (2003), was included in the analysis.

Figure 3: Multi-way CEAC for psychological interventions under the basecase assumptions

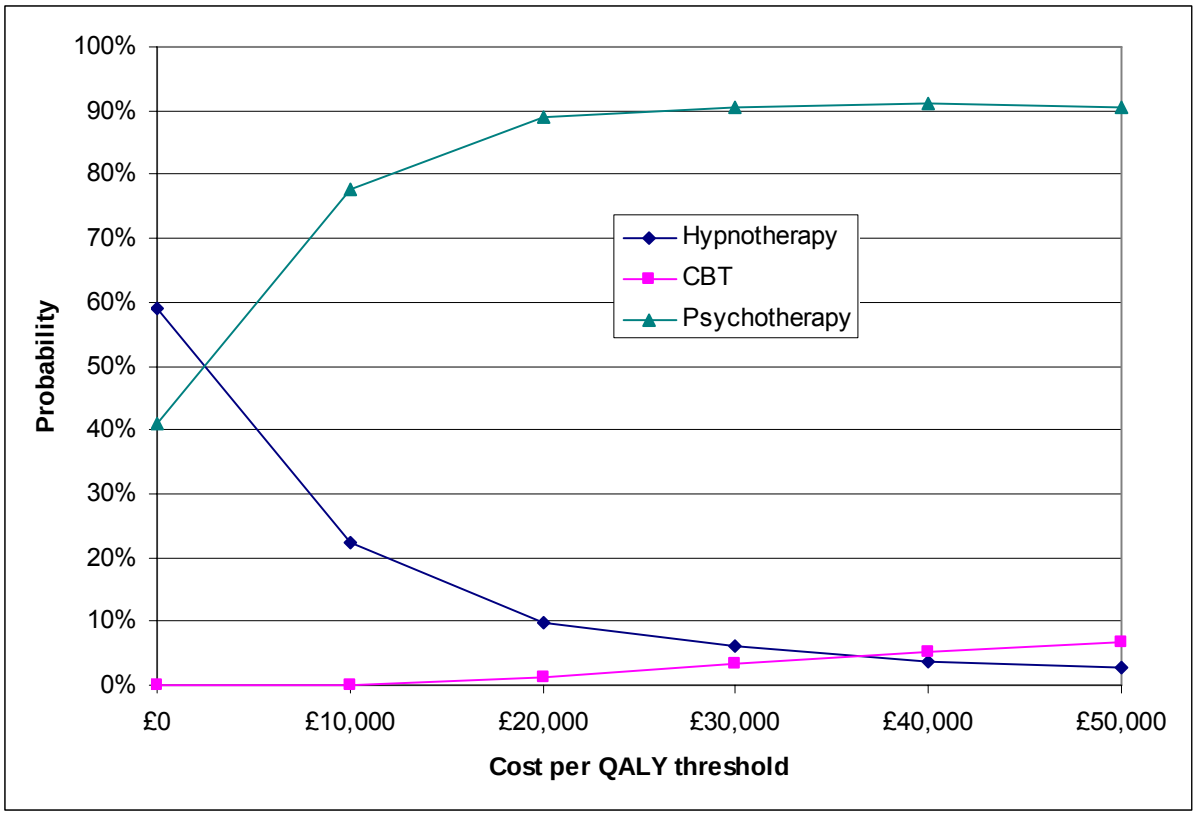
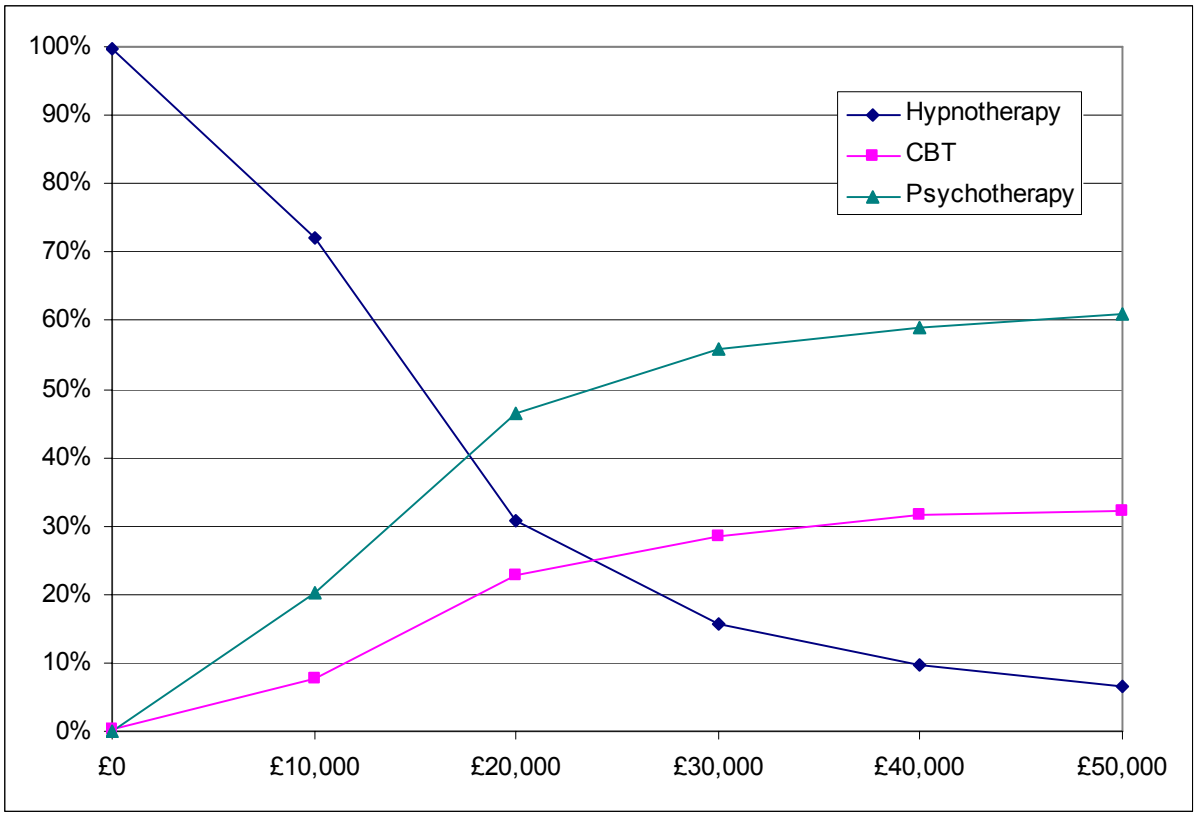


Figure 4: Multi-way CEAC for psychological interventions when we assumed that there is no resource use reduction associated with any of the therapies



9.8 Evidence to recommendation: psychotherapy, CBT and hypnotherapy

The GDG considered CBT, hypnotherapy and psychotherapy, as a group of similar, but distinct therapies when making recommendations, and took into account several factors:

Firstly, they considered the clinical effectiveness reviews and cost effectiveness modelling that have been carried out mainly for the treatment of people with refractory IBS. The GDG interpreted the cost effectiveness analyses, including the indirect comparisons between the three therapies. The GDG noted that the trials were mainly in people with refractory IBS, and, for this group, the therapies were all cost effective.

Secondly, the GDG highlighted the current national variation relating to where these therapies are accessed, and noted that this is dependent on the commissioning patterns of individual strategic health authorities. Typically, they are more available in secondary care.

Thirdly, the GDG took into consideration the need to give people with IBS and their primary care clinician a choice in which behavioural therapy was most appropriate for them, and what might be available locally.

On balance, the GDG decided not to distinguish between the three therapies, and recommended that any one of them should be considered for people who have had IBS for at least 12 months, and who have not responded to first line therapies and whose symptoms continued. This patient profile has been defined for the purpose of this guideline as refractory IBS.

The GDG discussed whether there was an optimum time for treatment with any of these psychological therapies: leaving patients too long may have meant the person was no longer able to respond. In addition, the GDG was keen to determine whether these therapies could be used as first line treatments, as they had potential to enable people with IBS to cope with their symptoms by giving initial treatments which would have long term sustainability. This view was supported by evidence in children with IBS, which showed that hypnotherapy is clinically effective as a first line therapy. The GDG therefore proposed a recommendation for research to compare, head-to-head, the three therapies as first line therapies, with follow-up at various time points up to a year.

During GDG discussion relating to psychological therapies, it was recognised that it would be very useful for clinicians to be able to predict which people would have refractory IBS and which factors put them at risk. Therefore a second research recommendation was proposed to investigate what factors are important. These research recommendations are given in chapter 12.

RECOMMENDATION

Referral for psychological interventions (cognitive behavioural therapy [CBT], hypnotherapy and/or psychological therapy) should be considered for people with IBS who do not respond to pharmacological treatments after 12 months and who develop a continuing symptom profile (described as refractory IBS).

10 COMPLEMENTARY AND ALTERNATIVE THERAPIES

Clinical Questions

1. Is acupuncture an effective intervention in managing IBS symptoms?
2. Is reflexology an effective intervention in managing IBS symptoms?
3. Is herbal medicine an effective intervention in managing IBS symptoms?

BACKGROUND

Complementary and alternative medicine (CAM) may be defined 'as wide ranging therapies which may be used exclusively i.e. complete healing systems, or in combination with orthodox medical treatment' (House of Lords Select Committee on Science and Technology 2000 p.2). The terms 'Alternative' and 'Complementary' are used to define the use and setting of a therapy in relation to orthodox medicine. 'Alternative' usually refers to treatment modalities that are generally a substitute for orthodox treatment whereas 'complementary' refers to treatments that are used alongside orthodox medical treatments. CAM is usually considered to include the practice of therapies that are not considered integral to the dominant health care model of a country, society or culture.

The House of Lords Select Committee on Science and Technology Sixth Report addressed the future of CAM in relation to research, service delivery, education and training and regulation. The report stated that there is very little evidence about the efficacy of many complementary and alternative treatments but the use of CAM is widespread and is increasing across the developed world. There is a clear need for more effective guidance for the public and health professionals who advise patients as to what does and does not work and what is and is not safe.

In order to begin to establish the effectiveness of CAM it is important to identify specific therapies and particular conditions where the use of CAM may be appropriate. It is not uncommon for those suffering from chronic conditions, for whom conventional medicine has been less than successful in alleviating symptoms, to seek complementary and alternative medicine (CAM). Irritable Bowel Syndrome is an example of such a condition.

The guideline considered commonly used therapies, Acupuncture, Chinese Herbal Medicine, Homeopathy and Reflexology. Hypnotherapy was considered with the psychological interventions.

Homeopathy

Homeopathy is defined as a system of therapy based on the concept that disease can be treated with drugs (in minute doses) thought capable of producing the same symptoms in

healthy people as the disease itself. Homeopathy was invented by the German physician Samuel Hahnemann (1755-1843) in the late 18th and early 19th centuries. It was both refined and popularized by the American physician James Tyler Kent. Homeopathy is based on the theory that each naturally occurring element, plant, and mineral compound will, when ingested or applied, result in certain symptoms. Hahnemann believed that, by diluting these substances in a standardized manner, one could reach the true essence of that substance. Hahnemann described this process of dilution as "potentizing" (German: "potenziert") the substance. These dilute amounts could then be used to treat the very symptoms they were known to produce.

An initial search idenitified two trials using homeopathy for IBS, both conducted about 30 years ago and reported in German.No trials have been done since. Only randomised trials were to be considered for this review and the absence of further studies suggested no need to carry out a full review.

Acupuncture

Acupuncture is defined as a therapeutic and/or preventive medical procedure used in or adapted from Traditional Chinese Medicine (TCM) performed by the insertion of 1 or more specially manufactured solid metallic needle(s) into specific location(s) on the body. The intent is to stimulate acupuncture points, with or without subsequent manual manipulation. The acupuncture points are situated on fourteen major ‘meridians’. The TCM theory is that acupuncture stimulates ‘qi’ (translated as life force) that circulates through the meridians. In optimum health the flow of ‘qi’ is unobstructed. Interruption or stagnation of the flow of ‘qi’ results in diverse symptoms. The theory is that insertion and manipulation of needles at particular points stimulates the energy flow, restoring the balance and thus normalising the function of the organ. An alternative theory is that acupuncture is a specialised sensory stimulation that is analysed through sensory neural pathways.

Reflexology

Reflexology is an ancient form of complementary medicine thought to originate in China, however research has shown that reflexology was also used by some early African tribes, Native American Indians and early Egyptians. Reflexology is a complementary therapy based on the theory that by the application of pressure to specific reflex points on the feet and hands, which correspond to the organs of the body, it is possible to ‘normalise’ function. In conventional medical terms reflexology could be said to facilitate homeostasis. Reflexology is a widely used therapy; it has been estimated that between 6 and 12% of the population use it and anecdotal evidence suggests that many people find it extremely effective for a range of chronic conditions including functional bowel conditions, although there is little rigorous research to support this view.

People with IBS may be drawn to acupuncture and reflexology’s ancient roots and the desire for non-pharmacological treatment. Alterations in pain modulation, motility, and autonomic nervous

system function are likely mechanisms of IBS symptoms, which may have physiological responses to acupuncture and reflexology.

Herbal Medicine

Emerging evidence for herbal medicine (Chinese and non Chinese) suggesting a possible benefit informed one of the guideline's research recommendations.

People with IBS are interested in CAM and will continue to use these modalities as long as medical therapy fails to relieve their symptoms. To optimise the care of people with IBS there is a need for further evidence of the potential benefits and safety of these treatments. Integration of CAM into Western medical practice will require more than selection of a few isolated acupoints, or yoga positions. A wider understanding of the paradigm specific use of these techniques, mechanisms of action, and potential pitfalls is required.

10.1 Reflexology

SELECTION CRITERIA

The selection criteria described in the general methodology section were used. Interventions were any form of reflexology.

SEARCH STRATEGY FOR IDENTIFICATION OF STUDIES

Searches were performed on the following core databases: MEDLINE, EMBASE, CINAHL, and *The Cochrane Library* (1966 to current day with guidance from the GDG). Additionally, the AMED database was searched for this review. Search strategies are given in Appendix B.

The search strategy identified 560 studies. The titles and abstratcs of these studies were assessed. One was identified to be potentially relevant to this review and this paper was retrieved. The reference lists of these studies were inspected for further potential papers, but none were identified.

DESCRIPTION OF STUDIES

Types of Studies

Only one study was identified: a quasi randomised trial in a UK primary care setting (Tovey 2002).

Types of Participant

Thirty four patients were allocated treatments. The groups were comparable at baseline as regards age; gender; duration, and; severity of condition.

Inclusion criteria were that patients had to have a diagnosis of IBS in line with Rome II criteria, and they should be currently under the care of a primary care physician following referral to a

gastroenterologist to exclude organic GI disease. Patients were excluded if they had organic GI disease or had previously used reflexology.

Intervention

Six 30-minute sessions of reflexology delivered in a way that was as close as possible to normal practice conditions, over an eight week period. The control group received six 30-minute sessions of foot massage that excluded pressure on key points of the foot.

METHODOLOGICAL QUALITY

Sequence generation was by alternation, and the allocation concealment was inadequate. A power calculation was carried out and the sample size required was 18 patients per group for the outcome of abdominal pain. 4/19 (21%) in the reflexology group were lost to follow-up and 2/15 in the control group.

The study reported no significant differences in baseline characteristics (pain; diarrhoea; constipation; bloating).

RESULTS

Individual symptoms of IBS were recorded daily using a 5 point scale, but global symptoms were not reported.

a) Pain

Pain was the primary outcome measure. There was no significant difference between the reflexology and control groups for this outcome, either at assessment 2 weeks after completion of the intervention (p=0.32) or at 3 month follow-up.

Table 1.

Reflexology Baseline **Pain score (0-4 scale)**	Change from baseline: reflexology post treatment	Control Baseline	Change from baseline: control post treatment
Median:1.4 IQR: 0.6 to 2.1	End of treatment: Median: -0.10 (IQR: -0.80 to 0.10) 3 months follow up: Median 0.00	Median:0.7 IQR:0.5 to 1.3	Median:-0.40 (IQR: -0.90 to 0.00) 3 months follow up: Median -0.25

b) Bowel function

There was no significant difference, 2 weeks after completion of the intervention, in bowel function (change in constipation or diarrhoea) (p=0.47) between intervention and control groups.

Table 2.

Reflexology Baseline **Bowel Function (scale 0-4)**	Change from baseline: reflexology post treatment	Control Baseline	Change from baseline: control post treatment
Median: 1.9 IQR: 1.2 to 2.1	Median: 0.05 IQR: -0.53 to 0.43	Median: 1.2 IQR: 0.3 to 1.7	Median:-0.30 IQR: -0.80 to 0.20

c) Bloating

There was also no significant difference, 2 weeks after completion of the intervention, in bloating (p=0.0.17) between intervention and control groups.

Table 3.

Reflexology Baseline **Bloating (scale 0-4)**	Change from baseline: reflexology post treatment	Control Baseline	Change from baseline: control post treatment
Median: 2.5 IQR: 1.3 to 3.1	Median: -0.10 IQR: -0.60 to 0.20	Median:2.0 IQR: 1.0 to 2.2	Median: -0.40 IQR: -1.05 to -0.15

HEALTH ECONOMIC EVIDENCE

The cost effectiveness of reflexology was not taken into consideration for this review because reflexology is not prescribed with treatment being purchased independently by people with IBS.

EVIDENCE STATEMENT

There is limited evidence from a single study in people with IBS in Primary Care showing no significant effect on pain, bowel function and bloating compared with the foot massage placebo group.

GDG CONSENSUS

The GDG was concerned that the foot massage group may not have been reliable as a placebo group. The limited evidence from this small, quasi-randomised trial does not lend support to the use of reflexology in the management of IBS in adults. However, there may be a need for further research.

EVIDENCE TO RECOMMENDATION

The review reported limited evidence that showed reflexology is not effective in the management of IBS symptoms. The GDG's clinical view was that the current lack of effectiveness precludes a positive recommendation.

RECOMMENDATION

The use of reflexology should not be encouraged for the treatment of IBS.

10.2 Acupuncture

SELECTION CRITERIA

The selection criteria described in the general methodology section were used, but some were specific to the acupuncture review and are reported below.

Types of studies

Crossover trials could be included, but those with a washout period of less than 2 weeks were to be excluded. All study designs were included for adverse effects. Specific searches for adverse effects were not carried out.

Types of intervention

Studies to be considered for inclusion included the following interventions:

- Single acupuncture needling point
- Combination acupuncture needling points.

Methods of acupuncture that do not involve needle insertion for example laser or acupressure were to be excluded. For the purposes of this review the minimum acceptable dose was to be two treatments of acupuncture. Studies that included a single acupuncture treatment were to be excluded.

Types of comparisons

The following comparisons were to be included:

- Single acupuncture versus sham acupuncture (placebo)
- Combination acupuncture versus sham acupuncture (placebo)
- Single acupuncture versus another type of treatment
- Combination acupuncture versus another type of treatment
- Acupuncture + treatment 2 versus treatment 2

Subgroup analyses

Subgroup analyses were to be carried out if there is heterogeneity as follows:

- Symptom severity
- Dose
- Type of acupuncture.

SEARCH STRATEGY FOR IDENTIFICATION OF STUDIES

Searches were performed on the following core databases: MEDLINE, EMBASE, CINAHL and *The Cochrane Library* (1966 to current day with guidance from the GDG). Additionally, the AMED database was searched for this review. The search strategies are listed in Appendix B. The search strategy identified 764 studies. The titles and abstracts of these studies were assessed. Of these studies, 20 were identified on the basis of the title and abstract as being

potentially relevant to the review and these papers were retrieved in full. All reference lists of these studies were inspected for potential papers for inclusion in the review, but no further potential studies were found in addition to the titles already identified. Nineteen studies and one Cochrane review were identified (Manheimer 2006). Of these, eight were excluded and these are listed in Appendix E, along with reasons for exclusion.

DESCRIPTION OF STUDIES INCLUDED IN THE REVIEW

Twelve studies met the inclusion criteria for the review (Chung 2003; Burford-Mason 2003; White 2001; Ernst and White 1997; Ernst and White 2001; MacPherson 2001; Yamashita 2001; Schneider 2006; Lowe 2000; Forbes 2005; Conboy 2006; Fireman 2001). Five studies (Schneider 2006; Lowe 2000; Forbes 2005; Conboy 2006; Fireman 2001) investigated the effectiveness of acupuncture for the treatment of IBS. One was conducted in the UK (Forbes 2005) and one each in Germany, Canada and Israel. Seven studies investigated adverse effects (Chung 2003; Burford-Mason 2003; White 2001; Ernst and White 1997; Ernst and White 2001; MacPherson 2001; Yamashita 2001).

Study Design

All the studies in the review were parallel studies, with the exception of Fireman (2001) which was a crossover study. The latter had a three week washout period, but first period results were also reported, which were used in preference because of the uncertainty about carry-over effects. One study (Lowe 2000) was only reported as a conference abstract.

All the studies took place in secondary care. The studies investigating adverse effects included medical doctors in primary and secondary care and non-medical acupuncturists.

The Cochrane Review ‘Acupuncture for treatment of irritable bowel syndrome’ (Manheimer 2006) included six trials. Two were excluded from the guideline review: one used electrical ear acupuncture (Liu 1995) and the other was a study in Chinese (Liao 2000). The Cochrane review authors stated that there was a possibility that Liao (2000) was not an RCT.

Population

All studies included people with a diagnosis of IBS, although the definition varied. Three used the Rome I criteria (Fireman 2001; Forbes 2005; Lowe 2000) and two used the Rome II criteria (Schneider 2006; Conboy 2006). All studies included a combination of IBS types and none of the studies stated that any participants had IBS as result of gastrointestinal infection. All studies included some participants with bloating. One study (Schneider 2006) identified all patients as having bloating, and in another (Fireman 2001) 80% had bloating.

All of the studies described symptom severity as mixed. The age range of participants was 17 to 79 years with the average mean age being approximately 46 years. No study particularly identified elderly participants. All studies had more women than men.

The Forbes (2005) study only included people who were refractory to other treatments; Fireman (2001) had participants who had had clinical symptoms for at least a year.

The numbers of participants ranged from 25 to over 100 (Conboy 2006; Liu 1997).

Interventions

The included studies all used different acupuncture protocols, but all used Chinese style acupuncture. One study used a single acupuncture point (Fireman 2001) and the remainder used a combination of points (Lowe 2000; Forbes 2005; Conboy 2006; Schneider 2006). The number of sessions of acupuncture varied from two (Fireman 2001) to ten (Forbes 2005; Schneider 2006).

Comparisons

The majority of studies compared true acupuncture with sham acupuncture. One study compared acupuncture plus psychotherapy with acupuncture alone and psychotherapy alone (Liu 1997).

The sham acupuncture varied between studies:

- Multiple needling versus sham needling at non acupuncture points (Schneider 2006)
- Single needling versus sham needling at an inappropriate acupuncture point (Fireman 2001)
- Multiple needling versus sham needling at inappropriate acupuncture points (Forbes 2005)
- Multiple needling versus non-needling at the same acupuncture points (Lowe 2000; Conboy 2005).

Two studies used a validated sham needling device (Conboy 2005; Schneider 2006).

Outcomes

The studies measured a range of outcomes using different scales.

1. Global score

a) Number of people with global improvement of symptoms

The Forbes (2005) study reported the number of people who recorded a reduction in symptom score of four points, which constituted an improvement. The Lowe (2001) study recorded a patient-determined success rate, which was based on individual patient expectations stated at baseline.

b) Global improvement of symptoms score

Fireman (2001) used a visual analogue scale (1 to 5), on which 5 equated to significant improvement in global symptoms. Liu (1997) used a three point scale, 1 = cured, 2 = improved, 3 = no effect.

c) Global symptom score

Forbes (2005) used a global symptom score with a scale of 0 to 30 based on symptom diaries plus the Bristol Stool Form Scale. A reduction of 4 points was considered clinically significant.

2. Individual symptoms

a) Pain

Three studies reported a pain score (Fireman 2001, Lowe 2000, Scheider 2006). In all cases the highest rating meant worst symptoms, although the scales used were not the same. The Lowe (2000) study only gave p-values for the pre-post comparison for each group and the Scheider (2006) study recorded scores on the pain subscale of SF36.

b) Bloating

One study reported bloating as an individual symptom (Fireman 2001).

c) Bowel habits

No studies reported bowel habit as an individual symptom in all patients, although Fireman (2001) reported diarrhoea scores for 11 patients with diarrhoea and defaecation difficulty scores in 13 people with constipation. We decided that these small subgroups broke the randomisation and were likely to give unreliable results.

3. Mental health

One study (Forbes 2005) assessed participants using the Hospital Anxiety and Depression (HAD) scale and recorded the change score.

4. Quality of Life

One study (Forbes 2005) assessed participants using using the EuroQol quality of life questionnaire.

Schneider (2006) used the FDDQL (scale 0 to 100), which assesses the disease related impact of bowel symptoms on quality of life; and the SF36 health-related quality of life measure. The primary outcome of the study was improvement in the global score of the FDDQL i.e. a reduction in score after 10 sessions. Lowe (2001) used the validated quality of life tool, IBS-36, but only reported p-values for changes from baseline.

METHODOLOGICAL QUALITY

The quality assessment for included trials is shown in Appendix D.

The method of randomisation was reported in three studies, all of which were classified as adequate (computer generated: Forbes 2005; Schneider 2006; Conboy 2006). The other studies did not state the method of randomisation (Fireman 2001; Lowe 2000).

Allocation concealment was reported in two studies (Forbes 2005; Schneider 2006). The Schneider (2006) study had adequate concealment (sequence retained by a central telephone centre) and the Forbes (2005) had partial concealment (sealed envelopes).

Three studies reported that the outcome assessors and the patients were blinded to the interventions (Fireman 2001; Forbes 2005; Schneider 2006). It was unclear whether the patients were blinded in Lowe (2000).

Most studies described the details of the placebo and active intervention giving the location of acupuncture points used. Lowe (2000) was the exception.
Four studies (Lowe 2000; Forbes 2005; Schneider 2006; Conboy 2006) described an *a-priori* power calculation. Two studies used an intention to treat analysis (Schneider 2006; Forbes 2005). Most studies included in the review demonstrated some level of baseline comparability of the groups, but one provided no data regarding baseline characteristics (Lowe 2000). The number of people who withdrew from the studies or were lost to follow-up was minimal. None of the studies were considered to be at high risk of bias.

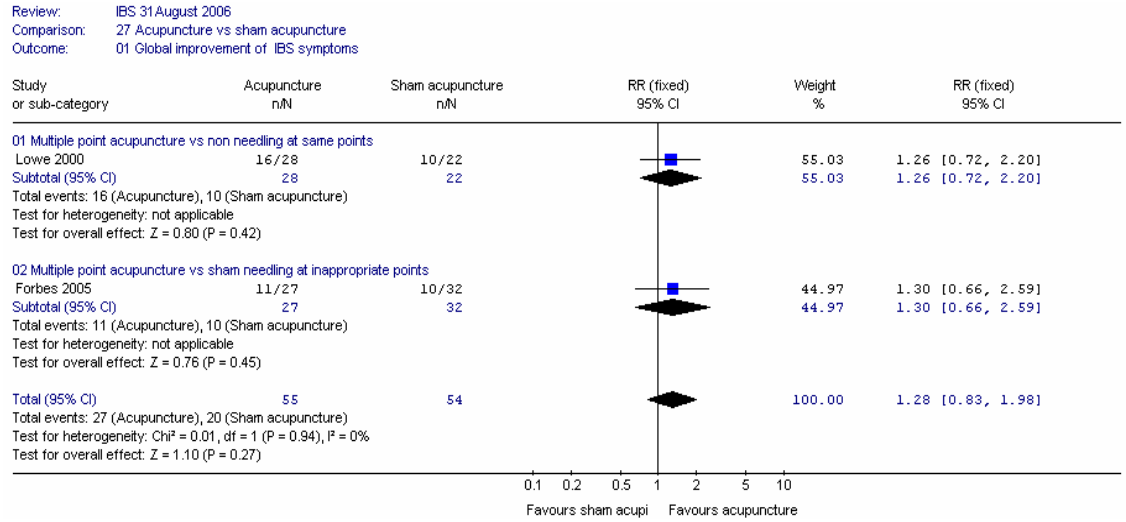
RESULTS

1. Global symptoms

a) Number of people with global improvement of symptoms

Two studies recorded the number of people with an improvement in global symptoms (Lowe 2000, Forbes 2005). These two studies were combined in a meta-analysis of 109 participants, even though the studies used different types of sham acupuncture. There was no statistically significant difference between acupuncture and sham acupuncture.

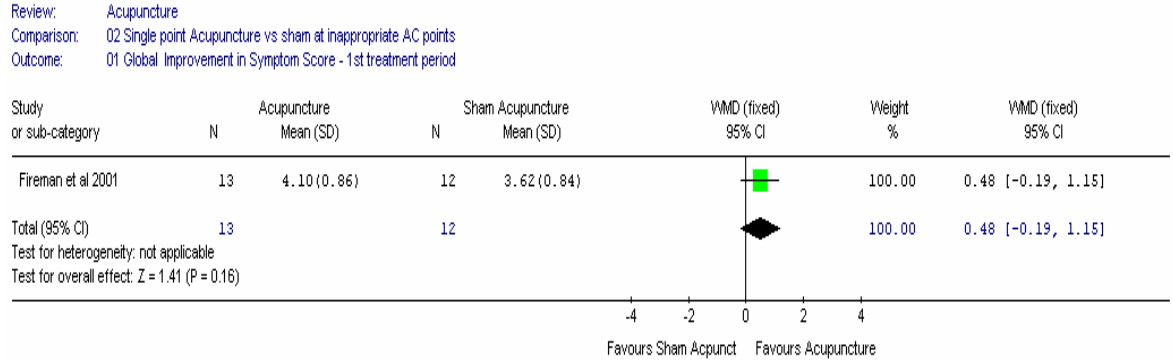
Figure 1: Number of people with global improvement of symptoms



b) Global improvement of symptoms score

Fireman (2001) recorded the global improvement in symptoms score (based on symptoms of pain; defaecation difficulties; diarrhoea; alternating diarrhoea and constipation; bloating; abdominal discomfort relieved by defaecation, and; mucus in stools), in 25 patients, using a visual analogue scale (1 to 5), on which 5 equated to significant improvement in global symptoms. As this study was a crossover design, data were used from the first period only. There was no significant difference between interventions.

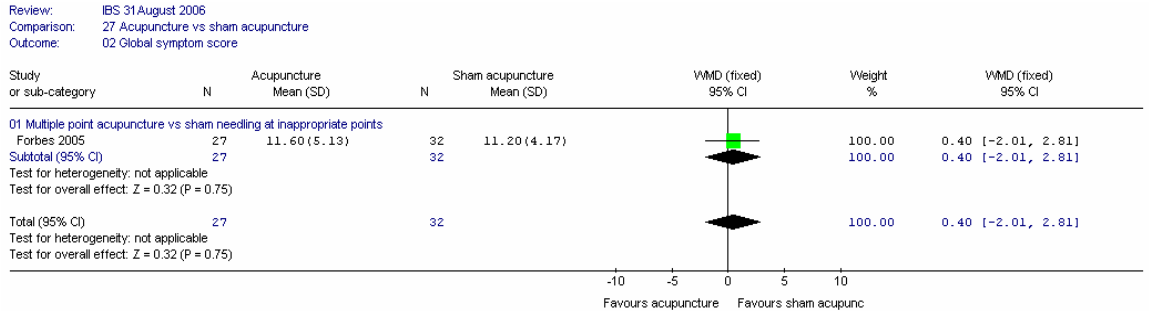
Figure 2: Global improvement of symptoms score



c) Global symptom score

One study (Forbes 2005) recorded the global symptom score on a scale of 0 to 30. There was no significant difference between acupuncture and sham acupuncture.

Figure 3: Global symptom score



2. Individual symptoms

a) Pain

Two studies recorded pain scores, Fireman (2001) and Scheider (2006). The latter used the discomfort subscale of SF36. The studies differed in the type of acupuncture used (single versus multiple point, respectively), and therefore were not combined in a meta-analysis. There was no significant difference between interventions in either study, although the sham acupuncture is favoured in the Fireman (2001) study.

Figure 4: Pain score

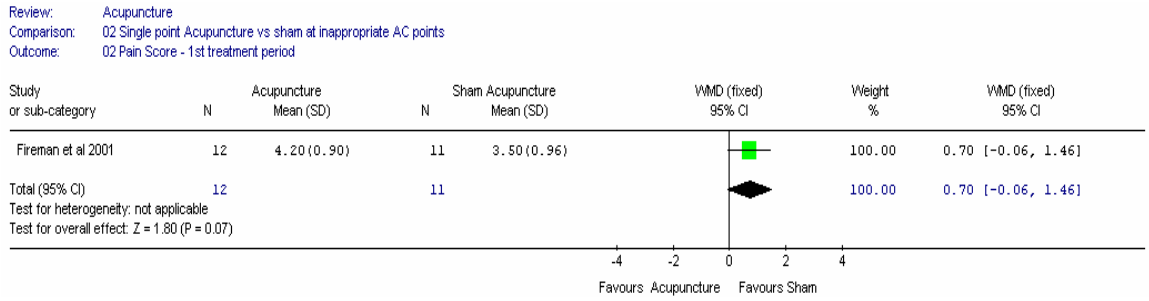
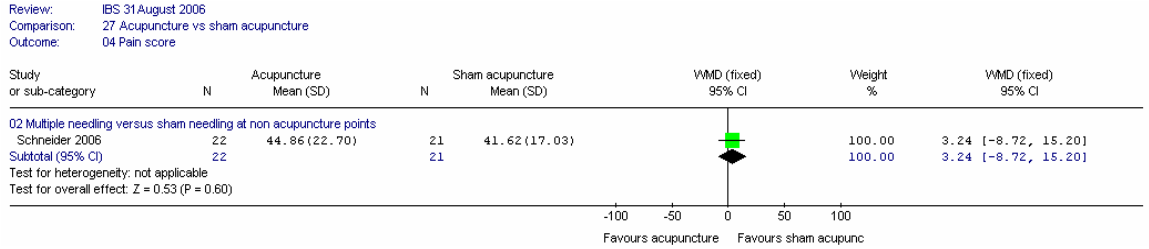


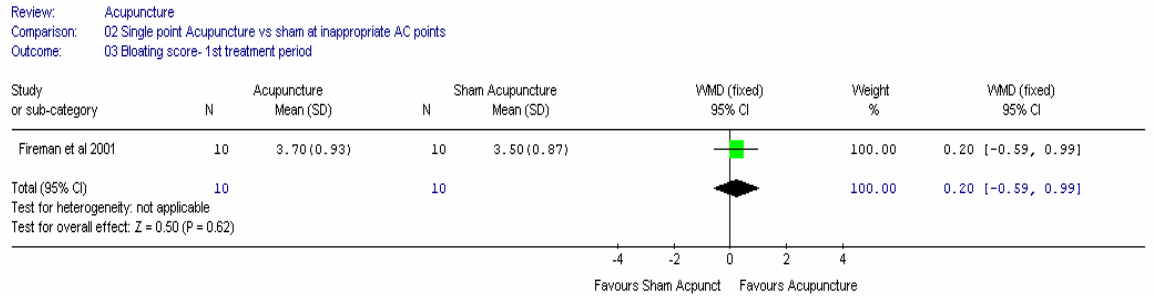
Figure 5: Oain component of SF 36



3. Bloating

Fireman (2001) reported a bloating score on a VAS of 1 to 5 in 20 participants. There was no significant difference between acupuncture and sham acupuncture.

Figure 6: Bloating score



4. Quality of life

Three studies reported quality of life measurements (Forbes 2005, Lowe 2000 and Schneider 2006). Forbes 2005 reported a small improvement in the EuroQol scores over baseline in both the acupuncture (59.4 to 64.6%) and sham acupuncture (64.6 to 65.6%) groups, neither difference was significant. Lowe (2000) reported a marked improvement in the IBS-36 quality of life score in both true and sham groups. There was no significant difference between the two groups. Schneider reported a mean difference of 1.98 (95%CI -3.59, 7.39) in 43 people, at the end of treatment, on a scale of 0 to 100, i.e. no significant difference. After three months follow-up, there was still no significant difference (MD 3.41 (95%CI -3.02, 9.83)

5. Adverse effects

The benefit of acupuncture cannot be evaluated without considering the risks associated with treatment. The incidence of adverse effects is largely unknown. However, for the purposes of this review, we included seven studies investigating adverse effects (Chung 2003; Burford-Mason 2003; White 2001; Ernst and White 1997; Ernst and White 2001; MacPherson 2001; Yamashita 2001). Three of these were systematic reviews (Ernst and White 1997; Ernst and White 2001; Yamashita 2001), two were surveys of acupuncture practice and one a commentary. The systematic reviews identified ten reports which included surveys from Europe and eighty-nine reports from the Far East. The most common adverse events identified in Europe were:

- Pain at the site of needling
- Pain due to aggravation of the presenting condition
- Bleeding – petechia, ecchymosis, haematoma
- Nausea and/or vomiting
- Fainting
- Tiredness.

Potentially serious adverse effects are rare: two cases of pneumothorax and two cases of needle fracture requiring surgical removal of the fragment, and one case of burn injury following moxibustion. There were no reports of infection complications or transmission of disease through needling.

The review from the Far East (Yamashita 2001) synthesised 89 papers that reported 124 cases of adverse events. These were classified into five categories:

- Injuries or foreign bodies (42 cases)
- Infections (32 cases, including 11 cases of Hepatitis B)
- Neurological problems (29 cases, including 18 cases of spinal cord injury, 10 of which were caused by needle breakage)
- Dermatological problems (17 cases)
- Other (4 cases).

The reviewers had previously demonstrated that severe adverse effects seem to be uncommon in standard practice for adequately trained acupuncturists.

The two Ernst and White, European reviews also found that there was no standard definition of adverse effects and estimated that there may be under-reporting of adverse events. It is also possible that there is over reporting of adverse effects so that the true incidence of serious complications may be very low. They emphasise the need to ensure appropriate training standards and appropriate regulatory and surveillance systems to enable more accurate assessment.

HEALTH ECONOMIC EVIDENCE

The cost effectiveness of acupuncture was not taken into consideration for this review because acupuncture is not prescribed, with the majority of acupuncture treatment being purchased independently by people with IBS.

EVIDENCE STATEMENTS

1. There is fair evidence to show no significant effect of acupuncture on IBS global symptoms, pain, and quality of life compared with placebo.

2. There is limited evidence of potentially serious adverse effects associated with acupuncture treatments.

GDG DISCUSSION

The GDG was concerned about the reported adverse effects (some of which were severe), non-registration and the safety of acupuncture. They noted an additional adverse effect that occurs with moxibustion, which can lead to burns. Members of the GDG were not surprised that acupuncture has been shown to have no significant effect in IBS: this might be expected because acupuncture is thought to work by producing endorphins which give pain relief, but they have no effect on visceral pain.It was noted that the patient community widely supports Traditional Chinese Medicine acupuncture.

The GDG's clinical view was that, although people with IBS widely support the use of acupuncture, the current lack of effectiveness and potential harm precludes a positive recommendation.

EVIDENCE TO RECOMMENDATION

The GDG took into consideration the lack of effectiveness of acupuncture, the limited evidence showing harm, and registration and regulation difficulties, and decided they would not recommend the use of acupuncture for IBS.

RECOMMENDATION

The use of acupuncture should not be encouraged for the treatment of IBS.

10.3 Herbal Medicine

SELECTION CRITERIA

The selection criteria described in the general methodology section were used, but some specific to the herbal medicine review are reported below.

Types of studies

The GDG decided that crossover studies should not be included in this review because it was unclear whether herbal medicines effected longer term changes or how long they were retained in the gut.

Types of intervention

Studies were to include the following classes of interventions:

- Single Chinese herbal medicines
- Combination Chinese herbal medicines
- Single non-Chinese herbal medicines
- Combination non-Chinese herbal medicines.

The following comparisons were to be included:

- Single Chinese herbal medicines versus placebo
- Combination Chinese herbal medicines versus placebo
- Single non-Chinese herbal medicines versus placebo
- Combination non-Chinese herbal medicines versus placebo
- Single Chinese herbal medicines versus Combination Chinese herbal medicines
- Single non-Chinese herbal medicines versus Combination non-Chinese herbal medicines
- Herbal medicine type 1 versus type 2.

The review was concerned only with longer-term maintenance treatment.

Subgroup analyses

We planned to carry out subgroup analyses as follows:

- Sub-types of IBS (diarrhoea-predominant, constipation-predominant and alternating)
- Dose of herbal medicine.

SEARCH STRATEGY FOR IDENTIFICATION OF STUDIES

Searches were performed on the following core databases: MEDLINE, EMBASE, CINAHL and *The Cochrane Library* (1966 to current day with guidance from the GDG). The MEDLINE search strategy is given in Appendix B.

Six studies met the inclusion criteria for the review. The reference lists of these were inspected for further potential papers, but none were identified.

DESCRIPTION OF STUDIES INCLUDED IN THE REVIEW

Six studies met the inclusion criteria for the review (Bensoussan 1998; Brinkhaus 2005; Leung 2006; Madisch 2004; Wang 2006; Yadav 1989). Two studies were conducted in China (Leung 2006; Wang 2006), two in Germany (Brinkhaus 2005; Madisch 2004) and one each in Australia (Bensoussan 1998) and India (Yadav 1989).

The total sample sizes ranged from 60 to 208, with all but one study (Wang 2006) having more than 100 participants.

Study Design

Setting: The setting was not stated in majority of studies; one was in primary care (Madisch 2004) and one took place in secondary care (Wang 2006).

All the studies included in the review had a parallel design.

Three studies had two arms (Leung 2006; Wang 2006; Yadav 1989). Two studies (Bensoussan 1998; Brinkhaus 2005) had three arms: one study (Bensoussan 1998) compared standard Chinese herbal medicine, individualised Chinese herbal medicine and placebo and the other study (Brinkhaus 2005) compared the single non-Chinese herb curcuma with another single non-Chinese herb fumitory and with placebo. This gave a total of 12 comparisons in the review.

Population

The definition of IBS varied between studies: one used the Rome I criteria (Bensoussan 1998); two used the Rome II criteria (Leung 2006; Wang 2006); two used authors' definitions (Brinkhaus 2005; Madisch 2004) and one used the Sandler (1984) criteria (Yadav 1989).

All studies but two included people who had a range of IBS types; the other two studies specified diarrhoea predominant IBS symptoms (Leung 2006; Wang 2006). No studies stated that the participants had IBS as result of gastrointestinal infection.

The majority of studies did not state the number of participants with bloating; only two stated that some people had bloating (Madisch 2004; Yadav 1989).

One study described symptom severity as severe (Brinkhaus 2005); the rest did not state symptom severity.

The age range of participants across studies was 13 to 65 years, with the mean age (where given) ranging from 28.4 to 48 years. No study particularly identified elderly participants. There were approximately equal numbers of men and women in total.

Interventions

The studies varied in the type of herbal medicines used:

- Single Chinese herbal medicines: none
- Combination Chinese herbal medicines
    - One used individualised combination herbal preparations from a formulary of 81 Chinese herbs; 15 capsules (dose not stated) (Bensoussan 1998)
    - One used a standard formula Chinese powdered herb capsule containing a combination of 20 different herbs; 15 capsules (Bensoussan 1998)
    - One used a standard formula Chinese herbal preparation containing 11 herbs; water-extracted herbs as granules, which were dissolved in water (Leung 2006)
    - One used the combination Chinese herbal formula Tong-xie-ning granule (TXNG), aqueous extract containing 4 herbs; three times per day, 15 g/day (Wang 2006)
- Single non-Chinese herbal medicines
    - One study used curcuma tablets; three times per day, 60 mg/day of aqueous spray dried extract (Brinkhaus 2005)
    - One study used fumitory tablets; three times per day, 1500 mg/day of aqueous spray dried extract (Brinkhaus 2005)
    - One used bitter candytuft; three times per day, 20 drops (Madisch 2004)
- Combination non-Chinese herbal medicines
    - One used the commercially available preparation STW 5 containing 9 herbs; three times per day, 20 drops (Madisch 2004)
    - One used STW 5-II, a research preparation containing 6 herbs; three times per day, 20 drops (Madisch 2004)
    - One used an Ayurvedic combination containing two herbs plus excipient (polyvinylpyrrolidone, glucose, citric acid); granules taken three times per day, 15 g/day (Yadav 1989).

The doses used, where given, varied across studies, ranging from 60mg to 15g/day, with some studies being unclear on the dose used (Bensoussan 1998; Leung 2006; Madisch 2004).

The duration of the intervention ranged from 3 to 18 weeks. One study (Wang 2006) was only 3 weeks duration and the GDG decided not to consider this further. One study had a duration of 4 weeks (Madisch 2004) one had 6 weeks (Yadav 1989), one 8 weeks (Leung 2006), one 16 weeks (Bensoussan 1998) and one 18 weeks (Brinkhaus 2005).

Comparisons

The included studies covered the following comparisons:

- Single Chinese herbal medicines versus placebo: none
- Combination Chinese herbal medicines versus placebo:

    - Individualised Chinese combination herbal preparation versus placebo (Bensoussan 1998)
    - Standard formula Chinese powdered herb capsule containing a combination of 20 different herbs versus placebo (Bensoussan 1998)
    - Standard formula Chinese herbal preparation containing 11 herbs versus placebo (Leung 2006)
    - Tong-xie-ning granule (TXNG) containing 4 herbs versus placebo (Wang 2006)
- Single non-Chinese herbal medicines versus placebo:
    - Curcuma versus placebo (Brinkhaus 2005)
    - Fumitory versus placebo (Brinkhaus 2005)
    - Bitter candytuft versus placebo (Madisch 2004)
- Combination non-Chinese herbal medicines versus placebo:
    - STW 5 containing 9 herbs versus placebo (Madisch 2004)
    - STW 5-II, a research preparation containing 6 herbs versus placebo (Madisch 2004)
    - Ayurvedic combination containing 2 herbs versus placebo (Yadav 1989).
- Combination Chinese herbal medicines versus single Chinese herbal medicines: none
- Combination non-Chinese herbal medicines versus single non-Chinese herbal medicines
    - STW 5 containing 9 herbs versus bitter candytuft (Madisch 2004)
    - STW 5-II, a research preparation containing 6 herbs versus bitter candytuft (Madisch 2004)
- Single Chinese herbal medicines type 1 versus type 2: none
- Combination Chinese herbal medicines type 1 versus type 2:
    - Individualised Chinese combination versus standard formula Chinese powdered herb capsule (Bensoussan 1998)
- Single non-Chinese herbal medicines type 1 versus type 2:
    - Curcuma versus fumitory (Brinkhaus 2005)
- Combination non-Chinese herbal medicines type 1 versus type 2:
    - Commercially available STW 5 containing 9 herbs versus STW 5-II, a research preparation containing 6 herbs (Madisch 2004).

OUTCOMES

The studies measured a range of outcomes.

1. Global symptoms

a) Number of people with an improvement in global symptoms

Four studies recorded the participants' assessment of improvement at the end of the study (ranged from 6 to 18 weeks) (Bensoussan 1998; Brinkhaus 2005; Leung 2006; Yadav 1989).

b) Global symptom score (mean)

The global symptom score was recorded by two studies: Madisch 2004 at 4 weeks on a scale of 0 to 12 (severe) and Bensoussan 1998 at 16 weeks on a 4 x 100mm VAS.

c) Global assessment of IBS discomfort

This outcome was recorded by one study at 4 weeks (Madisch 2004) on a VAS of 0 to 100mm (most intense discomfort).

d) Global assessment of treatment on symptoms

This outcome was recorded by one study (Madisch 2004). Madisch (2004) recorded the physician's assessment of the efficacy of the drug at 4 weeks.

2. Individual symptoms

a) Pain

Pain was reported in several ways, either giving the number of people with pain at the end of the study, the number of people whose pain improved or worsened compared with the baseline, and pain scores. The latter recorded a range of features, including severity, frequency and duration, or a combination of these. In addition, studies recorded the final scores, mean daily scores or the change from baseline. The studies reporting these outcomes are as follows:

- Number of people with an improvement in pain symptoms: one study (Yadav 1989).
- Pain score: two studies (Leung 2006 [scale 0 to 4 (high = bad)]; Madisch 2004 (scale 0 to 21 [high = bad]).
- Change in pain score: one study (Brinkhaus 2005); scale 0 to 50mm VAS (high = worse).

b) Bloating

- Number of people with no bloating: one study (Madisch 2004)
- Change in bloating score: one study (Brinkhaus 2005); scale 0 to 50mm VAS (high = worse).

c) Bowel habits

- Stool score: one study using Bristol stool score (Leung 2006).
- Stool frequency: one study (Leung 2006).
- Number of people with improvement in bowel habit (alternating diarrhoea and constipation): one study (Yadav 1989)
- Number of people with absence of bowel habit problems (diarrhoea or constipation or both): one study (Madisch 2004)
- Number of people with an improvement in bowel symptoms (Yadav 1989).

3. Quality of Life

- One study reported quality of life as an outcome (Leung 2006).

- Two studies reported the number of patients with improvement in psychological distress (Brinkhaus 2005 [psychosocial stress], Yadav 1989 [Hamilton scale]).

4. Adverse effects

- Two studies reported adverse effects (Brinkhaus 2005; Madisch 2004).

METHODOLOGICAL QUALITY

The quality assessment for included trials is shown in the Appendix. The method of randomisation was adequate (computer generated) in two studies (Leung 2006; Wang 2006), partially adequate in two (Bensoussan 1998; Madisch 2004) and unclear in two (Brinkhaus 2005; Yadav 1989).

Allocation concealment was adequate in two studies (Brinkhaus 2005; Leung 2006), and partially adequate in one (Wang 2006).

All the studies reported that the participants were blinded to the interventions; outcome assessors were blinded in four studies (Bensoussan 1998; Leung 2006; Madisch 2004; Wang 2006) but this was unclear in two studies (Brinkhaus 2005; Yadav 1989). All described in detail the appearance and taste of the placebo and active intervention.

Four studies (Bensoussan 1998; Leung 2006; Madisch 2004; Wang 2006) described an *a-priori* power calculation. Three studies used an intention to treat analysis (Brinkhaus 2005; Madisch 2004; Wang 2006). All studies included in the review demonstrated some level of baseline comparability of the groups.

Two studies had no loss to follow-up (Brinkhaus 2005; Madisch 2004). One study (Yadav 1989) reported that more than 20% of participants in at least one arm (or overall) were not analysed or were lost to follow-up (21% overall; 11/68 on herbal therapy [16%] and 18/70 on placebo [26%]), while in the other three studies, fewer than 20% of participants were lost to follow-up.

One study had a duration of intervention of only three weeks (Wang 2006) and was not considered further.

The risk of bias was assessed for each included study and only Yadav (1989) was considered to be at higher risk of bias due to the attrition rate of 26% in the placebo arm. This was considered, where possible, in sensitivity analyses.

RESULTS

A. Herbal medicines versus placebo

A1. Combination Chinese herbal medicines versus placebo

All comparisons were of combinations of herbs versus placebo, rather than single herbs:

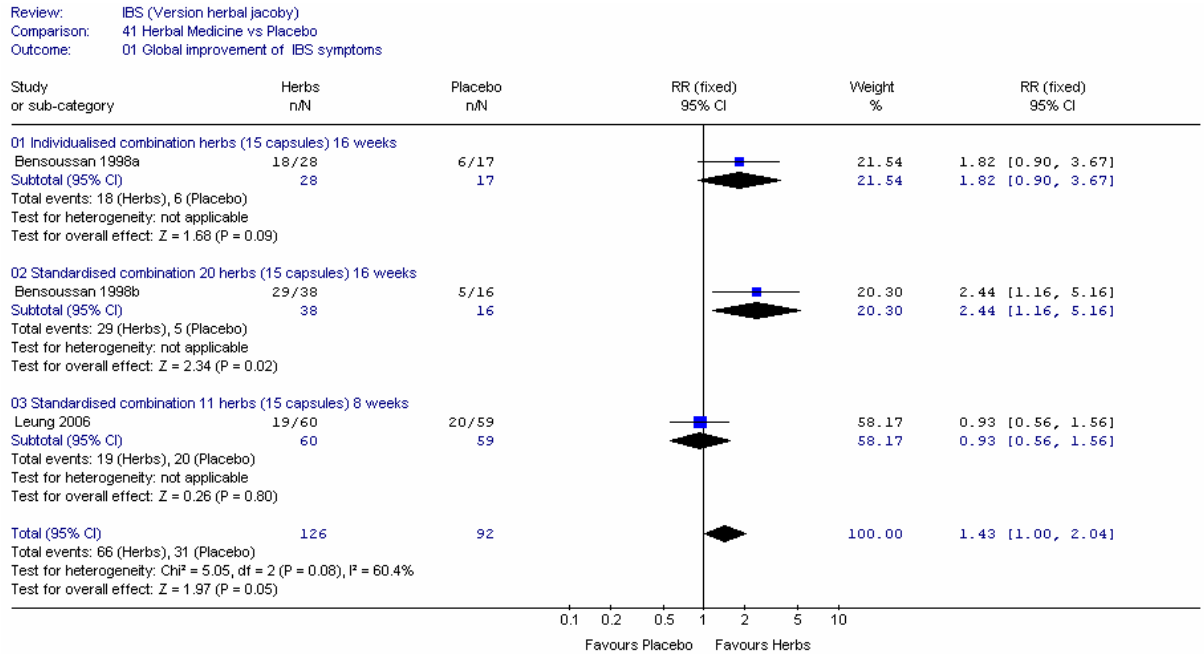
- Individualised Chinese combination herbal preparation versus placebo (Bensoussan 1998)
- Standard formula Chinese powdered herb capsule containing a combination of 20 different herbs versus placebo (Bensoussan 1998)
- Standard formula Chinese herbal preparation containing 11 herbs versus placebo (Leung 2006)
- Combination Chinese herbal formula Tong-xie-ning granule (TXNG) containing 4 herbs versus placebo (Wang 2006).

I. Global symptoms

a) Number of people with an improvement in global symptoms

Two studies (three comparisons) in 218 people recorded the participants' assessment of improvement at the end of treatment (Bensoussan 1998; Leung 2006).

Figure 1: Global improvement of symptoms (number of people)



There was significant heterogeneity across studies (I^2=60, p=0.08). It is unclear if the cause of the heterogeneity is:

- Different types of herbs
- Different durations of intervention (Bensoussan 1998 had 16 weeks; Leung 2006 had 8 weeks)
- Differences in dose (although the doses were not stated)

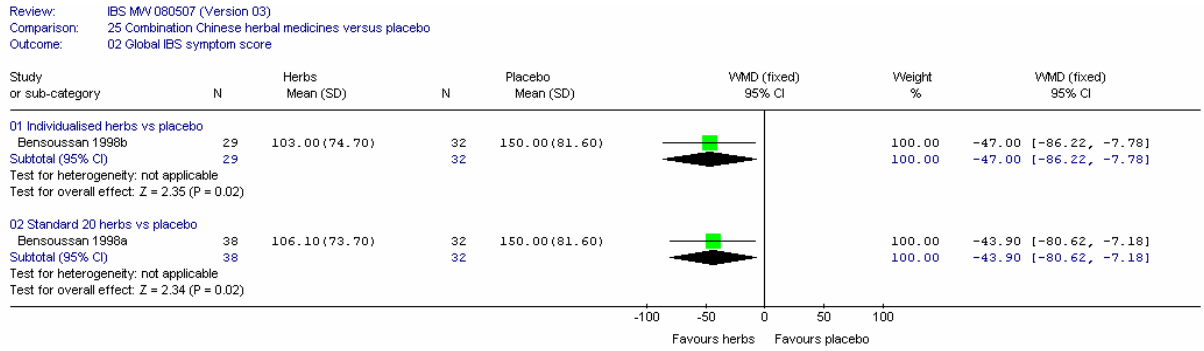
- Differences in the solubility of the herbs (the Leung 2006 intervention was aqueous granules; Bensoussan 1998 had encapsulated herbs)
- Differences in the type of IBS (Leung 2006 patients had diarrhoea predominant; Bensoussan 1998 had mixed types of IBS).

Bensoussan (1998) also measured this outcome at a follow up 14 weeks after the end of the trial, however only 51% of the participants originally randomised to placebo were available at this point, and we decided not to report the results here.

b) Global symptom score (mean)

The global symptom score was recorded by one study (Bensoussan 1998) in 61 people at 16 weeks on a scale of maximum 400.

Figure 2: Global symptom score



There was a significantly lower score for the herbs groups compared with placebo.

II. Individual symptoms

a) Pain

i. Pain score

One study in 119 people recorded a pain score (Leung 2006). This was rated from 0 (none) to 4 (very severe). The median score for people taking herbs was 1 (range 0 to 4) and for those on placebo was 1.5 (range 0 to 4); this was not significantly different.

b) Bowel habits

i. Stool score

Stool score was assessed in one study (Leung 2006) using the Bristol Stool Scale. The participants in the herb group scored a median of 5 (range 3 to 6) and those on placebo scored 5 (1 to 6); this was not significantly different.

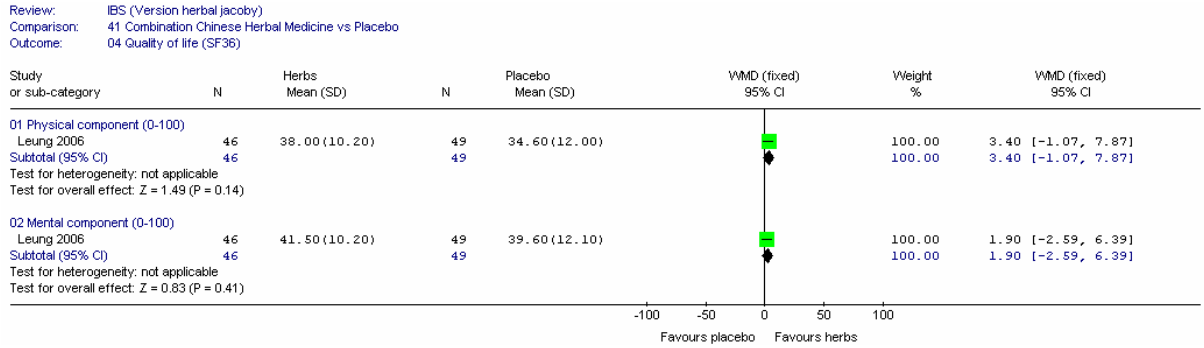
ii. Stool frequency

Stool frequency (daily) was assessed in one study (Leung 2006). The people in the herb group scored a median of 2 (range 1 to 7) and those on placebo scored 2 (1 to 6); this was not significantly different.

III. Quality of Life

One study in 119 people reported quality of life as an outcome using the SF-36 physical and mental scales, each of which has a maximum score of 100 (Leung 2006). There was no significant difference between herbs and placebo.

Figure 3: Quality of life



A2. Single non-Chinese herbal medicines versus placebo:

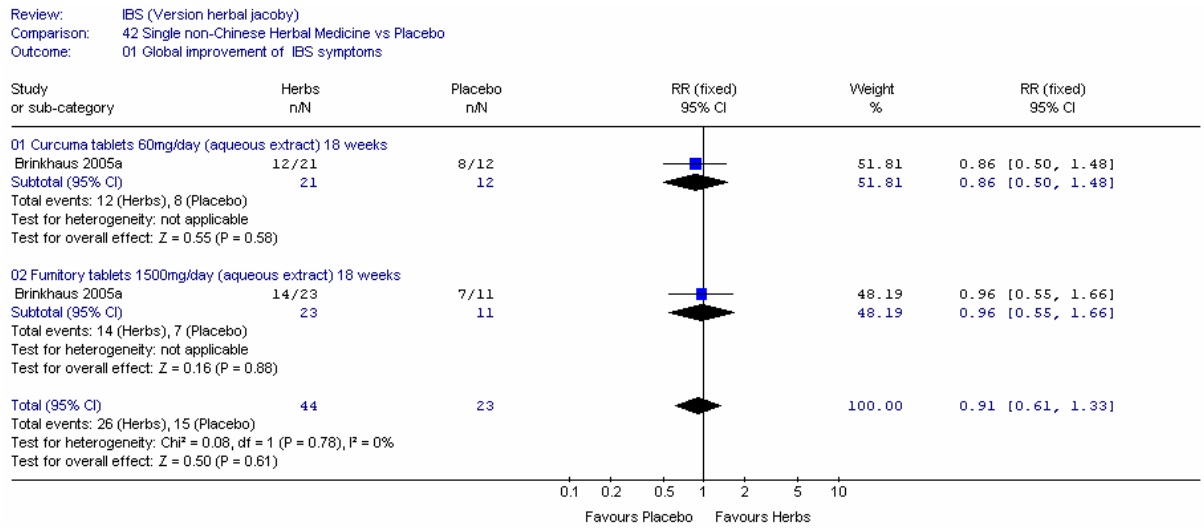
- Single non-Chinese herb curcuma versus placebo (Brinkhaus 2005)
- Single non-Chinese herb fumitory versus placebo (Brinkhaus 2005)
- Single non-Chinese herbal preparation bitter candytuft versus placebo (Madisch 2004).

I. Global symptoms

a) Global improvement in symptoms (number of patients)

One study recorded the participants' assessment of improvement in 67 people (Brinkhaus 2005). There was no significant difference between interventions.

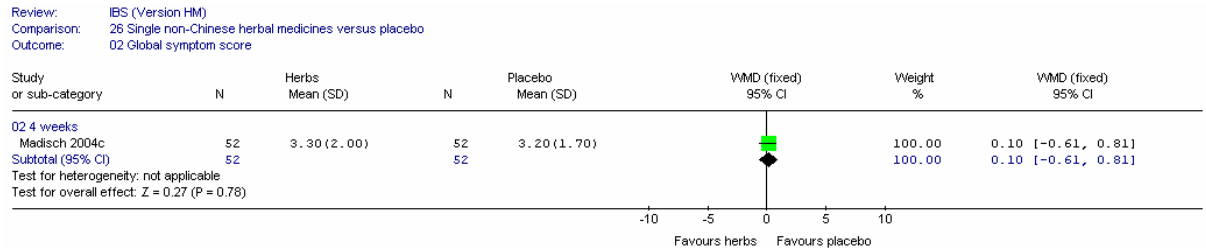
Figure 4: Global improvement of symptoms



b) Global symptom score (mean)

The global symptom score (scale 0 to 12) was recorded in one study (Madisch 2004) in 104 people at 4 weeks. There was no significant difference between interventions.

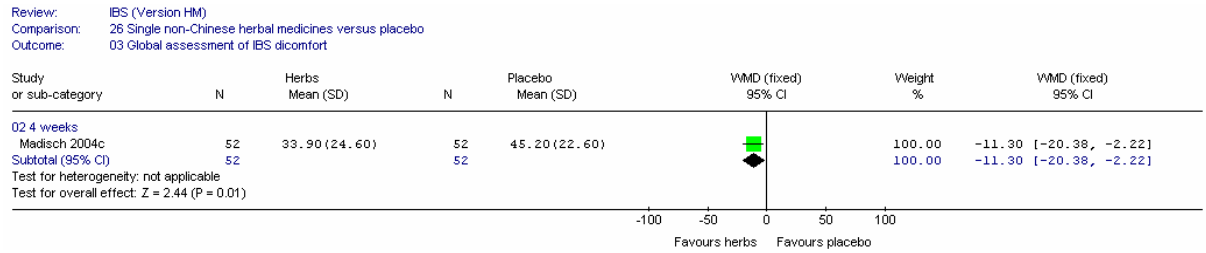
Figure 5: Global symptom score



c) Global assessment of IBS discomfort

This outcome was recorded by one study at 4 weeks (Madisch 2004) on a 100mm VAS. There was significantly more global discomfort for the group given placebo.

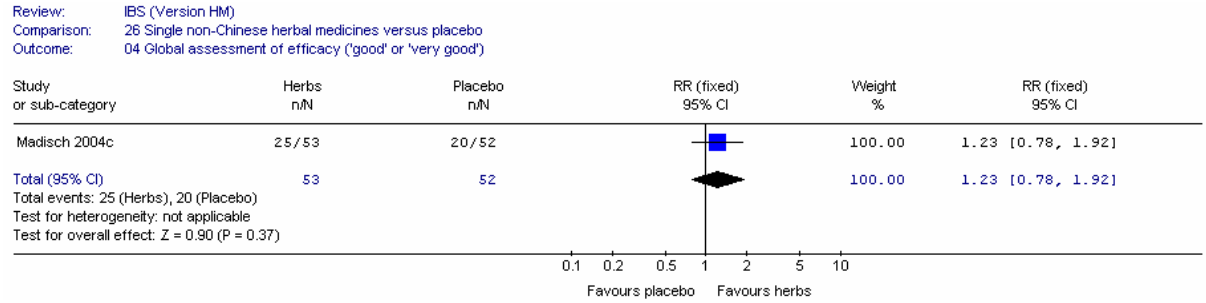
Figure 6: Global assessment of IBS discomfort



d) Global assessment of treatment on symptoms

This outcome was recorded by one study (Madisch 2004), which recorded the physician's assessment of the efficacy of the intervention at 4 weeks (number of people recorded as 'good' or 'very good'). There was no significant difference between interventions.

Figure 7: Global assessment of efficacy (by clinician)



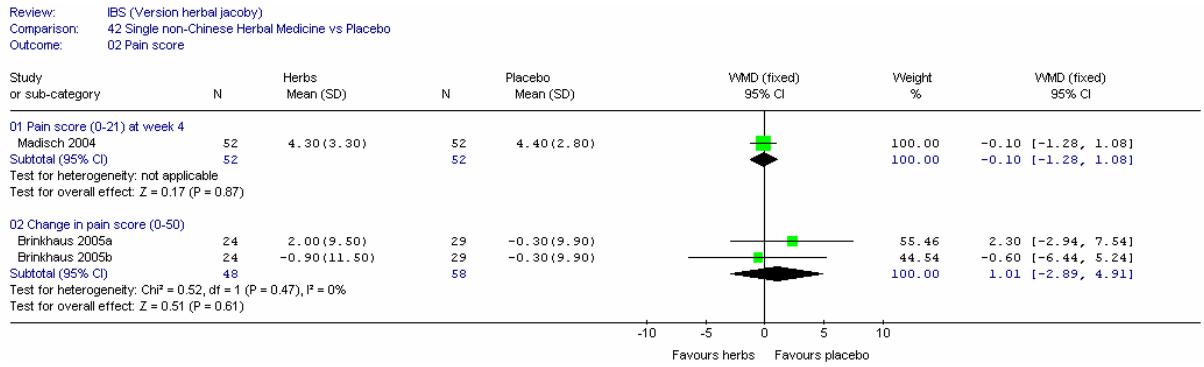
II. Individual symptoms

a) Pain

i. Pain score

Two studies recorded a pain score. Brinkhaus (2005) (in 106 participants) recorded the change in pain on a VAS 0 to 50mm, with high being good; Madisch (2004) (in 104 participants) reported a pain score on a scale of 0 to 21, where a high score was more severe pain. These studies were analysed separately, but neither showed a significant effect of herbs on pain.

Figure 8: Pain score and change in pain score

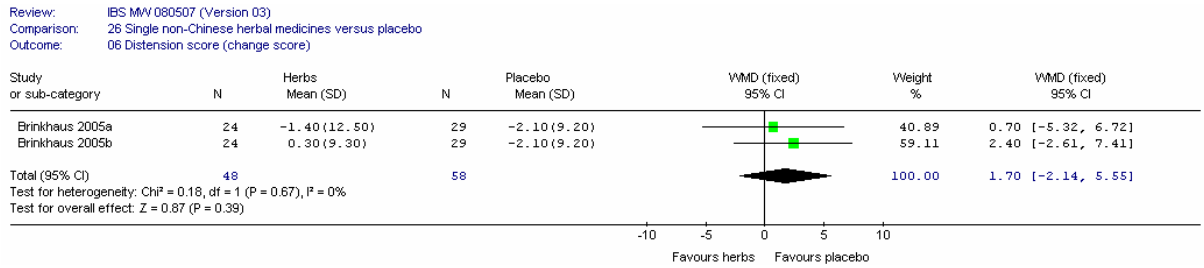


b) Bloating

i. Bloating score

One study recorded the change in bloating score on a scale of 0 to 50mm (Brinkhaus 2005). There was no significant difference between interventions.

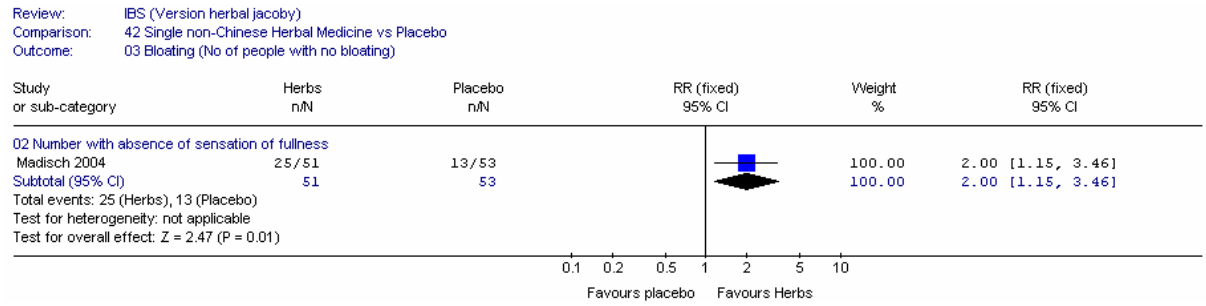
Figure 9: Change in bloating score



ii. Number of people with bloating

One study (Madisch 2004), in 104 participants, recorded the number of people with no bloating. There were significantly more people with an absence of bloating for the herbs group compared with placebo; RR 2.00 (95%CI 1.15, 3.46).

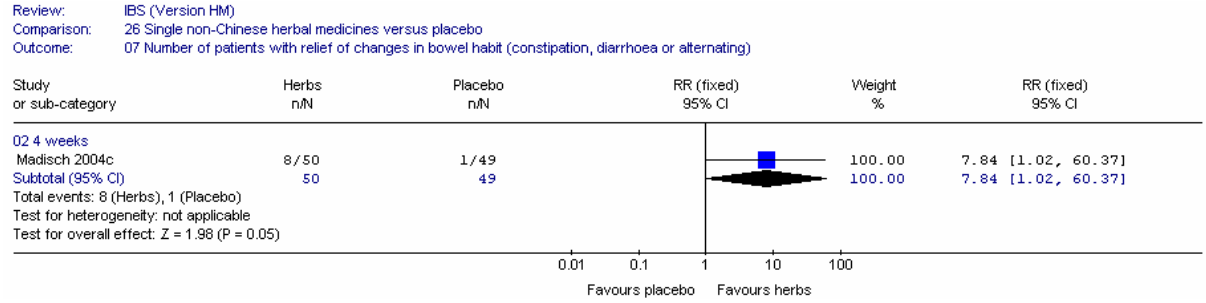
Figure 10: Number of people with no bloating



c) Bowel habits

One study (Madisch 2004) recorded the number of people with complete relief or absence of changed bowel habit (constipation, diarrhoea or alternating bowel habit). There was a significant effect in favour of the herbal medicine, but the confidence interval is very wide, so this conclusion is uncertain.

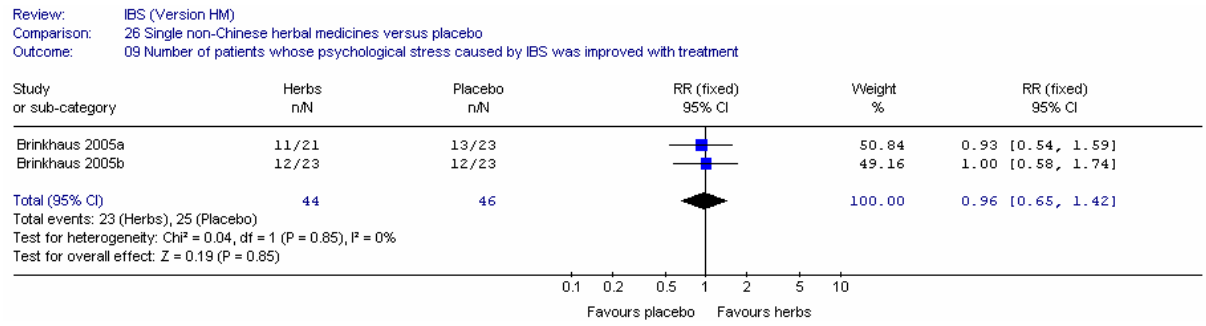
Figure 11: Number of people with absence of changed bowel habit



III. Psychological distress

One study in 90 participants reported the number of people whose psychological distress caused by IBS was improved with treatment (Brinkhaus 2005). There was no significant difference between interventions.

Figure 12: Number of people with reduction in psychological stress

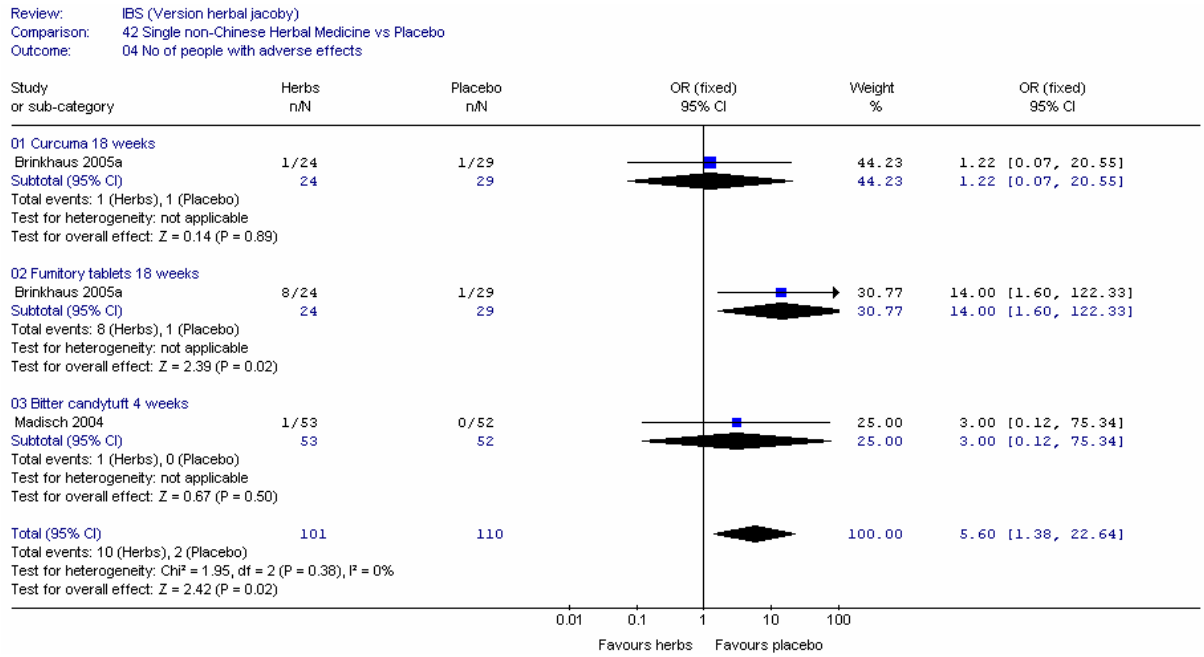


IV. Adverse effects

a) Adverse effects related to treatment

Two studies reported adverse effects related to the study treatment (Brinkhaus 2005; Madisch 2004). There were significantly more adverse effects in the herbal medicine group, but the confidence interval was wide, and the type of herbal medicine seemed to be important.

Figure 13: Number of people with adverse effects

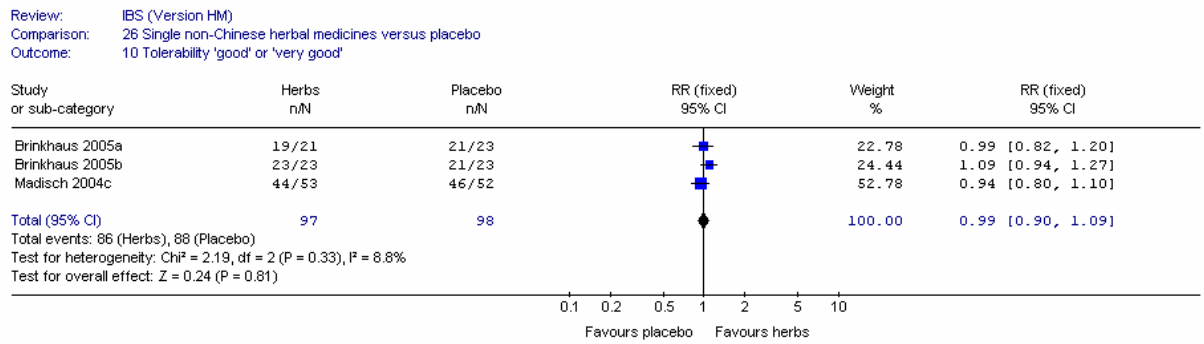


NB: Scale 0.01 to 100

b) Number of people reporting tolerability

Two studies gave the number of people reporting tolerability to treatment. There was no significant difference between interventions and no heterogeneity across studies (I^2=9%, p=0.33)

Figure 14: Number of people reporting tolerability



A3. Combination non-Chinese herbal medicines versus placebo:

- Non-Chinese herbal preparation STW 5 containing 9 herbs versus placebo (Madisch 2004)

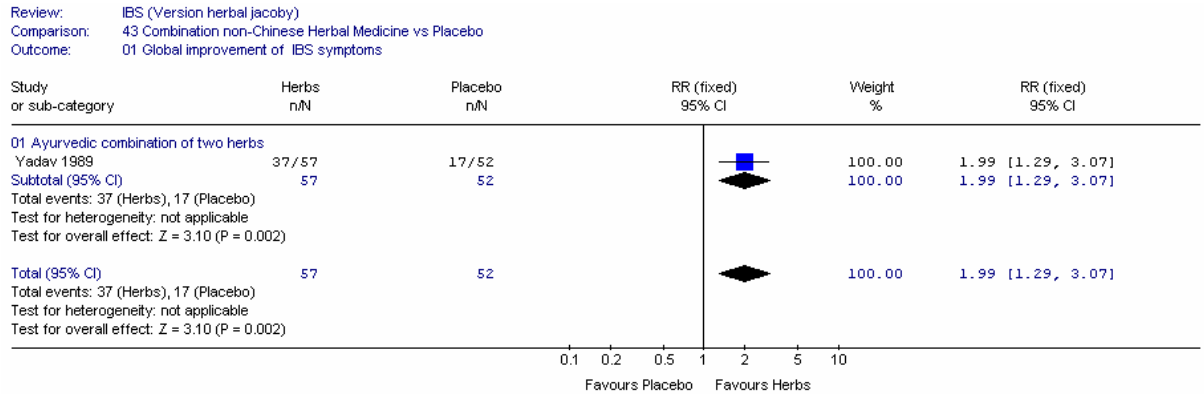
- Non-Chinese herbal preparation STW 5-II, a research preparation containing 6 herbs versus placebo (Madisch 2004)
- Non-Chinese Ayurvedic combination containing two herbs (Yadav 1989).

I. Global symptoms

a) Number of people with an improvement in global symptoms

One study (Yadav 1989) in 109 participants recorded their assessment of improvement ('good' or 'satisfactory' response) after 6 weeks. There were significantly more people with improvement in symptoms in the herbal medicine group; RR 1.99 (95%CI 1.29, 3.07). However, this study was considered to be at higher risk of bias due to the attrition rate of 26% in the placebo arm.

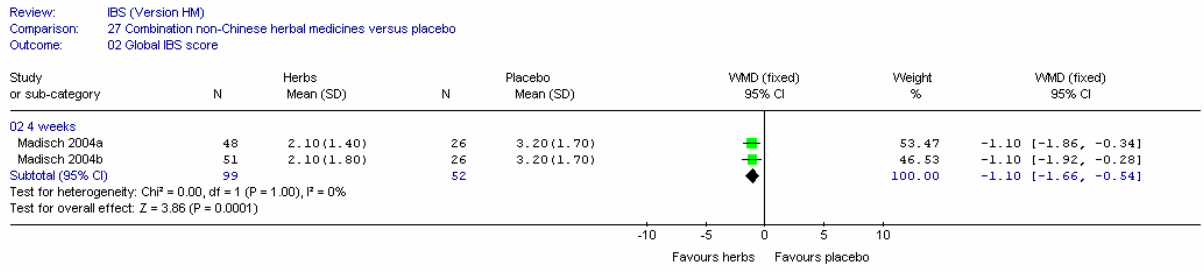
Figure 15: Global improvement of symptoms



b) Global symptom score (mean)

The global symptom score was recorded by one study (Madisch 2004) in 151 people at 4 weeks. The scale was 0 to 12. There was a significant difference between interventions, favouring the combination herbal medicine group.

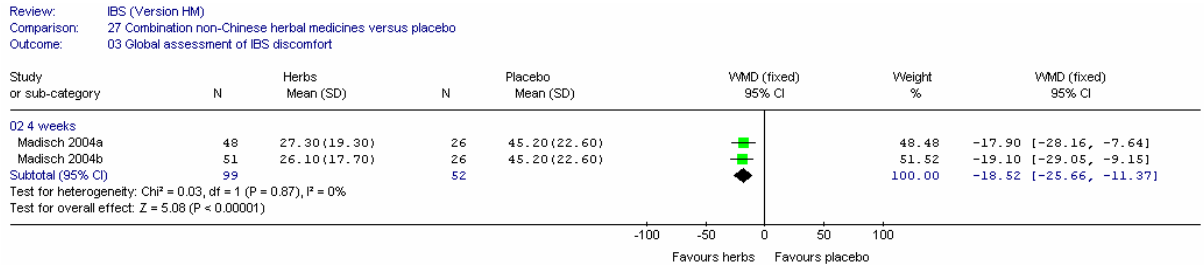
Figure 16: Global symptom score



c) Global assessment of IBS discomfort

This outcome was recorded by one study at 4 weeks on a 100mm VAS (Madisch 2004). There was significantly more global discomfort for the group given placebo.

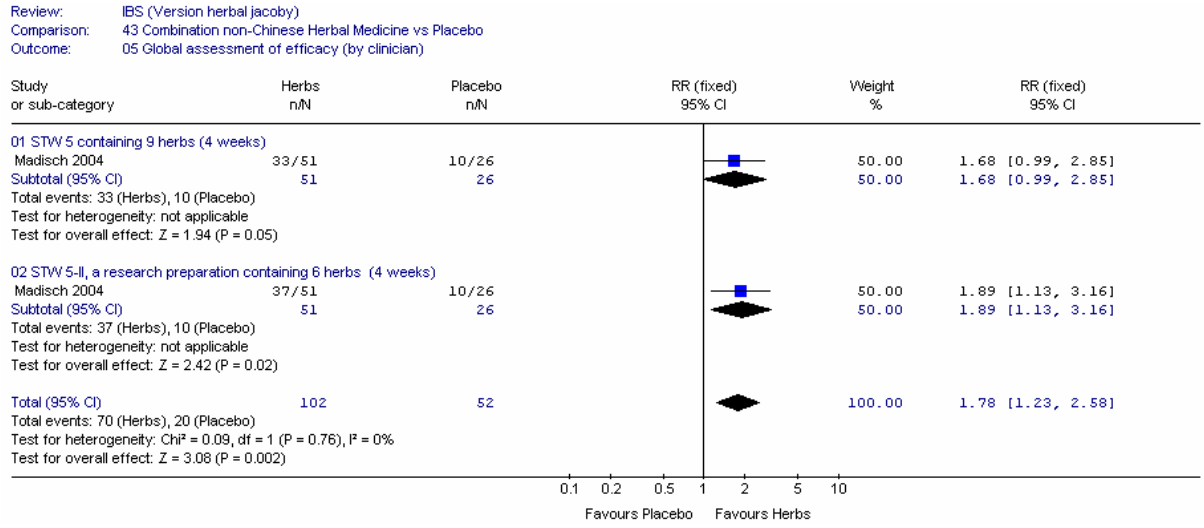
Figure 17: Global assessment of IBS discomfort



d) Global assessment of treatment on symptoms

This outcome was recorded by one study (Madisch 2004) in 154 participants, which recorded the physician's assessment of the efficacy of the intervention at 4 weeks. The herbal medicines were judged to be significantly more efficacious than placebo; RR 1.78 (95%CI 1.23, 2.58).

Figure 18: Global assessment of treatment on symptoms



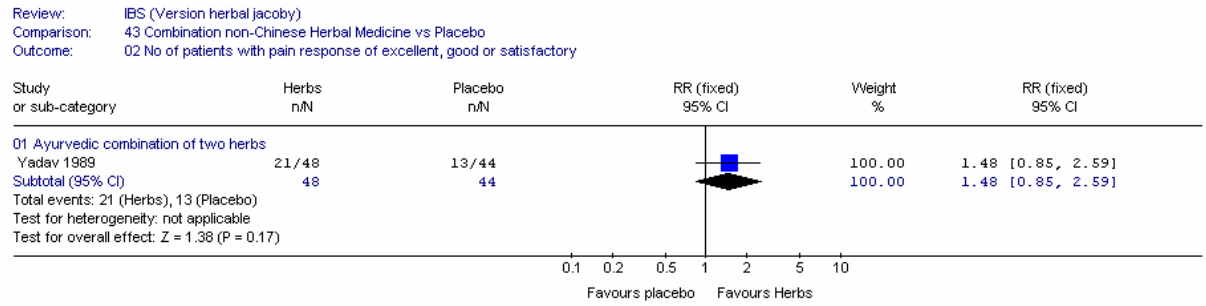
II. Individual symptoms

a) Pain

i. Number of people with improved pain response

One study (Yadav 1989) reported the number of people with an improvement in pain symptoms (excellent', 'good' or 'satisfactory' improvement). There was no significant difference between interventions. However, this study was considered to be at higher risk of bias due to the attrition rate of 37% in the placebo group and 29% in the herbal medicines group for this outcome.

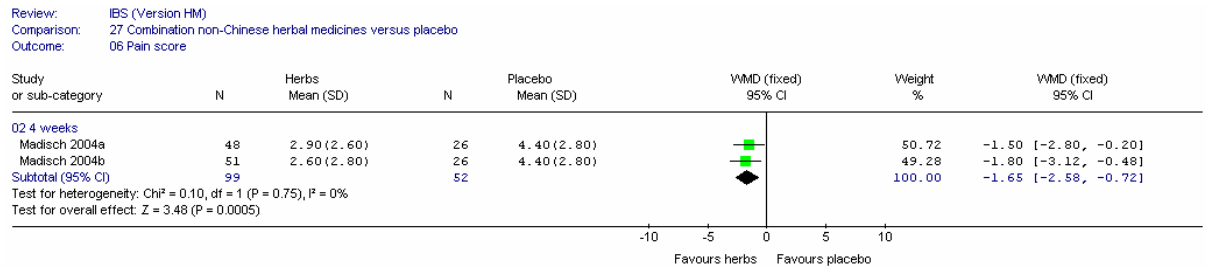
Figure 19: Improvement in pain symptoms



ii. Pain score

One study recorded a pain score in 151 participants on a scale of 0 to 21 at 4 weeks (Madisch 2004). There was a statistically significant reduction in pain for the herbal medicines group: WMD -1.65 (95%CI -2.58, -0.72).

Figure 20: Pain score



b) Bowel habits

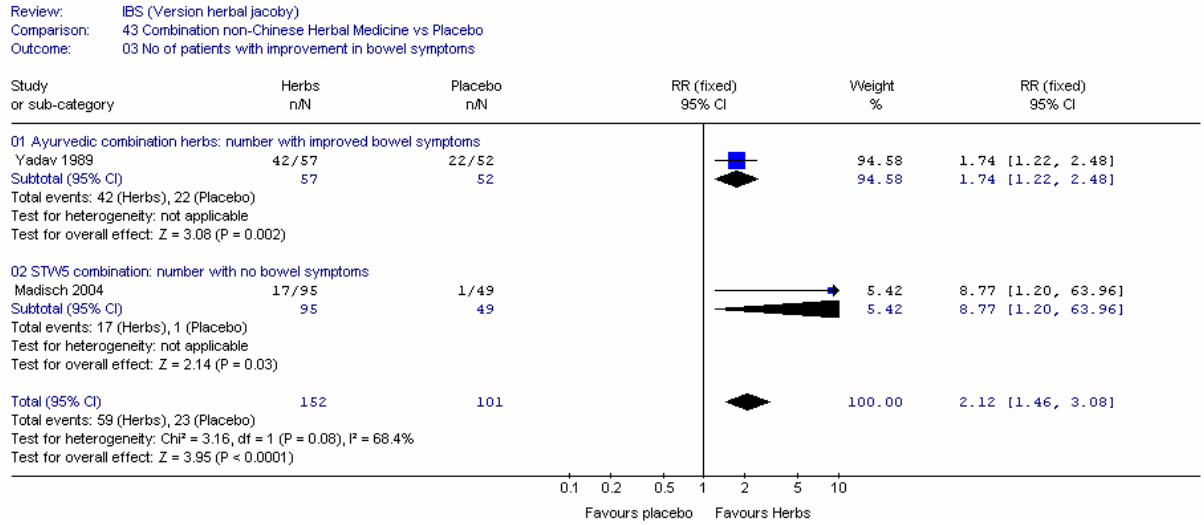
i. Improvement in symptoms of bowel habit (constipation, diarrhoea or alternating)

One study (Yadav 1989) reported the number of people with an improvement in bowel symptoms. Overall there was a significant improvement for the people given herbal medicines. However, this study was considered to be at higher risk of bias due to the attrition rate of 26% in the placebo group.

The study also reported sub-group analyses by type of IBS, but the participants were not stratified before randomisation and so we have not included the results in this review.

One other study (Madisch 2004) reported the number of participants with an absence of bowel problems and found significantly more people had no bowel problems in the herbal medicine groups (shown combined in Figure 21). The confidence interval was very wide, however.

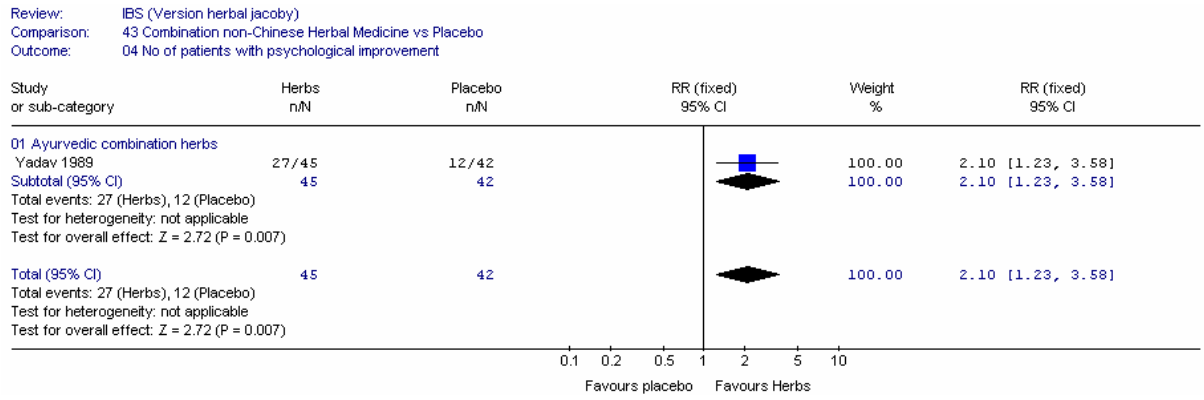
Figure 21: Improvement of bowel symptoms



III. Psychological improvement

One study reported the number of patients with a psychological improvement (Yadav 1989). There was a significantly greater improvement for the herbal medicine group; RR 2.10 (95% CI 1.23, 3.50). However, this study was considered to be at higher risk of bias due to the attrition rate of over 20%.

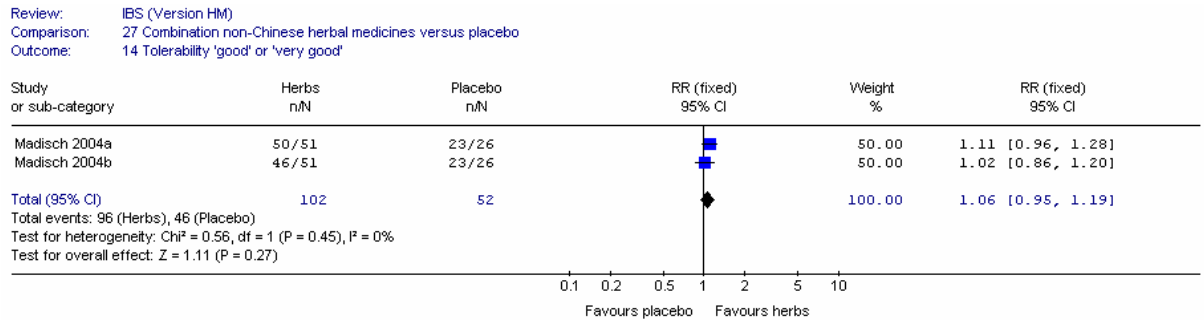
Figure 22: Psychological improvement



IV. Adverse effects

The Madisch (2004) study reported that only one person in the STW 5 herbal medicine group had an adverse event and none in the placebo group. The Yadav (1989) study reported that two participants had an adverse effect (drowsiness) and there was none in the placebo group. One study (Madisch 2004) reported tolerability (Figure 23). There was no significant difference between interventions.

Figure 23: Tolerability



B. Herbal medicine type 1 versus herbal medicine type 2

B1. Combination non-Chinese herbal medicines versus single non-Chinese herbal medicines

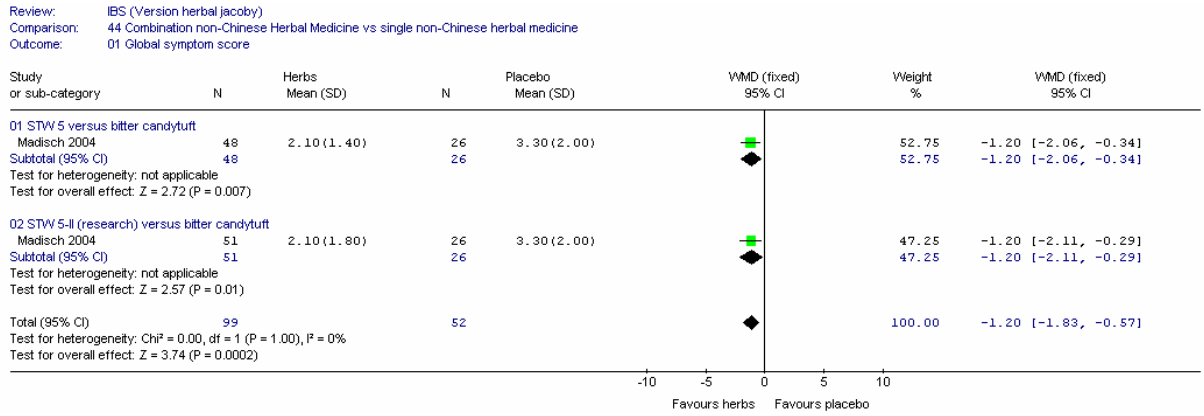
- Commercially available non-Chinese herbal preparation STW 5 containing 9 herbs versus single non-Chinese herbal preparation bitter candytuft (Madisch 2004)
- Non-Chinese herbal preparation STW 5-II, a research preparation containing 6 herbs versus single non-Chinese herbal preparation bitter candytuft (Madisch 2004)

I. Global symptoms

a) Global symptom score (mean)

A global symptom score was recorded by one study (Madisch 2004) in 102 participants at 4 weeks. The scale was 0 to 12. There were significantly lower symptom scores for the herbal medicine group: WMD -1.20 (95%CI -1.83, -0.57).

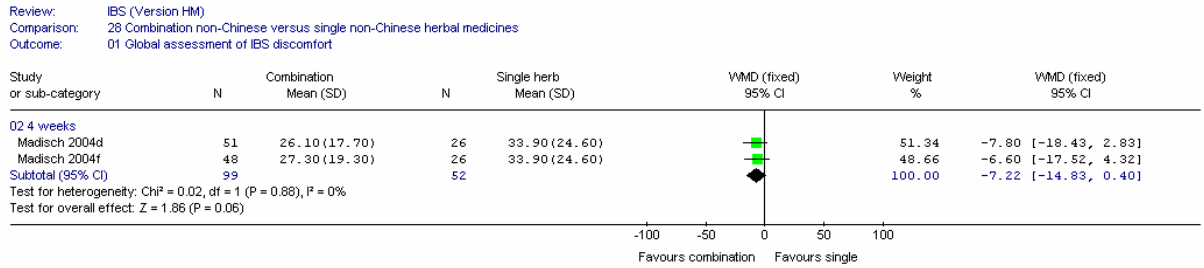
Figure 24: Global symptom score



b) Global assessment of IBS discomfort

This outcome was recorded by one study at 4 weeks (Madisch 2004) on a 100mm VAS. There was no significant difference between interventions.

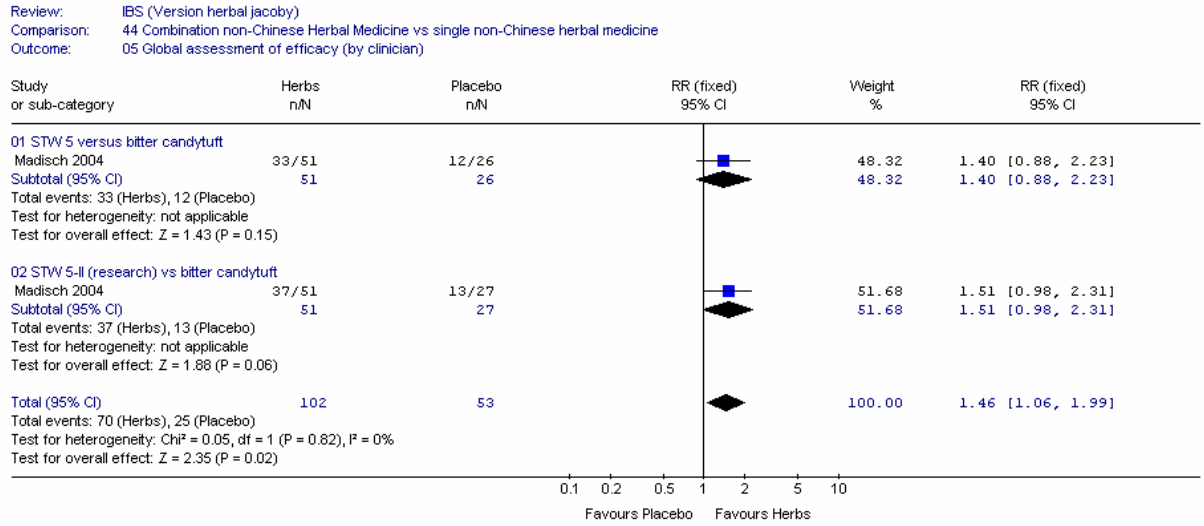
Figure 25: Global assessment of IBS discomfort



c) Global assessment of treatment on symptoms

This outcome was recorded by one study (Madisch 2004), which recorded the clinician's assessment of the efficacy of the intervention at 4 weeks (number of people recorded as 'good' or 'very good'). There were significantly more people assessed to be efficaciously treated in the combined group compared to the single herbal medicine: RR 1.46 (95% CI 1.06, 1.99). This corresponds to an NNT of 5 (95% CI 3, 20).

Figure 26: Global assessment of efficacy (by clinician)

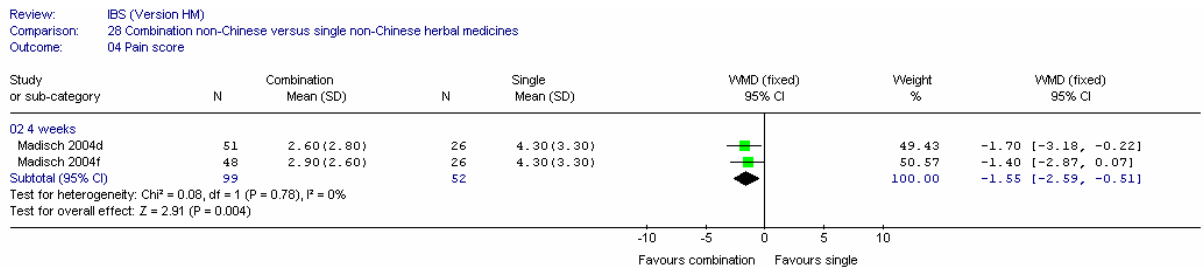


II. Individual symptoms

a) Pain

One study (Madisch 2004) reported a pain score on a scale of 0 to 21. There was significantly less pain for the group treated with combination herbal medicines.

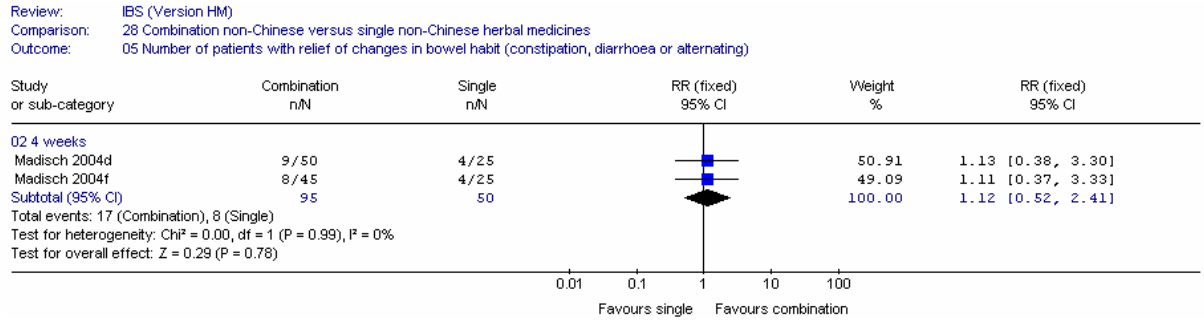
Figure 27: Pain score



b) Bowel habits

One study (Madisch 2004) recorded the number of people with complete relief or absence of changes in bowel habit (constipation, diarrhoea or alternating bowel habit). There was no significant difference between interventions.

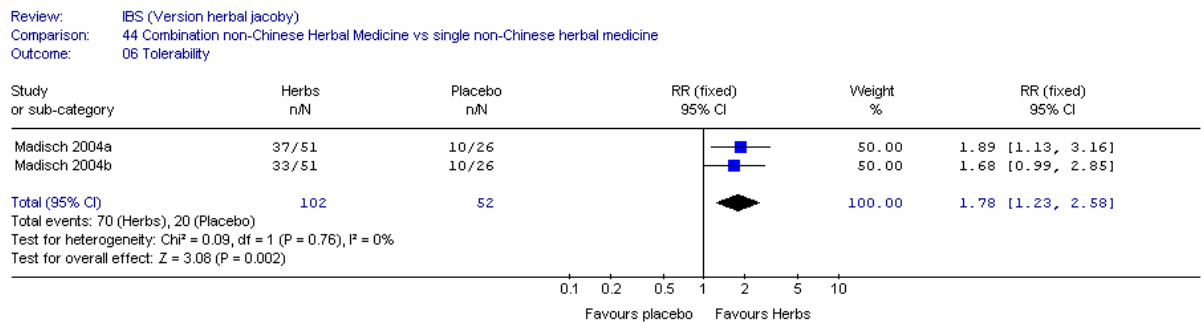
Figure 28: Number of people with no change in bowel habit



III. Adverse effects

One study reported tolerability (Madisch 2004). The combination herbal medicines were significantly better tolerated than the single bitter candytuft herb.

Figure 29: Tolerability



B2. Combination Chinese herbal medicines type 1 versus type 2

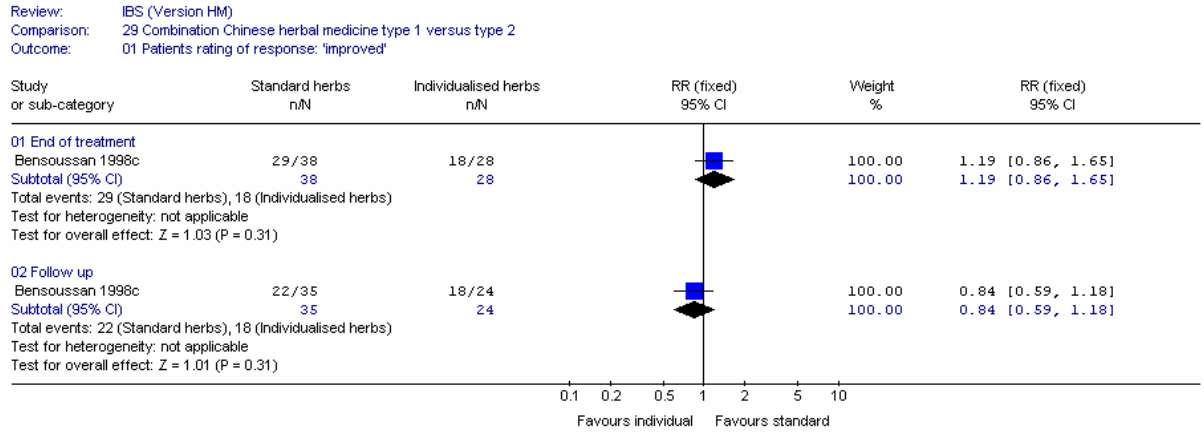
- Individualised Chinese combination versus standard formula Chinese powdered herb capsule (Bensoussan 1998c).

I. Global symptoms

a) Number of people with an improvement in global symptoms

One study recorded the participants' assessment of improvement in 66 people at the end of the 16-week treatment period and at follow up 14 weeks later (Bensoussan 1998). There was no significant difference between interventions.

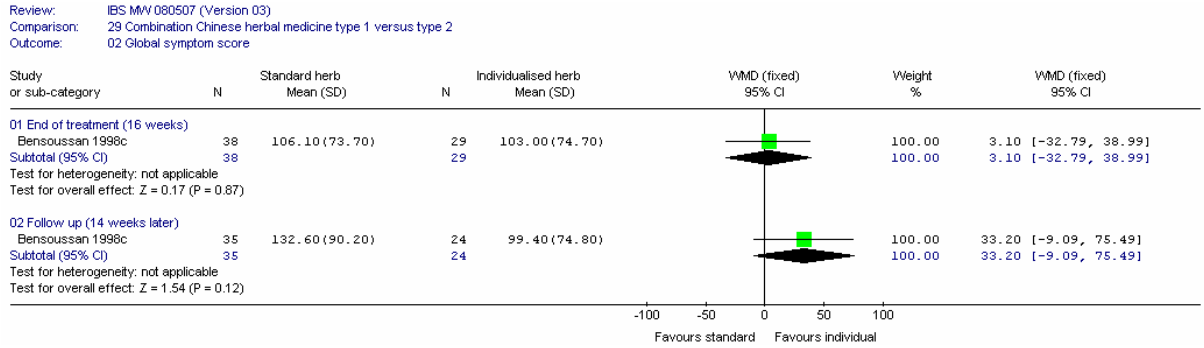
Figure 30: Global improvement of symptoms



b) Global symptom score (mean)

The global symptom score was recorded by one study: Bensoussan (1998) at 16 weeks (end of treatment) and at follow up 14 weeks later, on a scale of 4 x 100mm. There was no significant difference between interventions.

Figure 31: Global symptom score



B3. Single non-Chinese herbal medicines type 1 versus type 2:

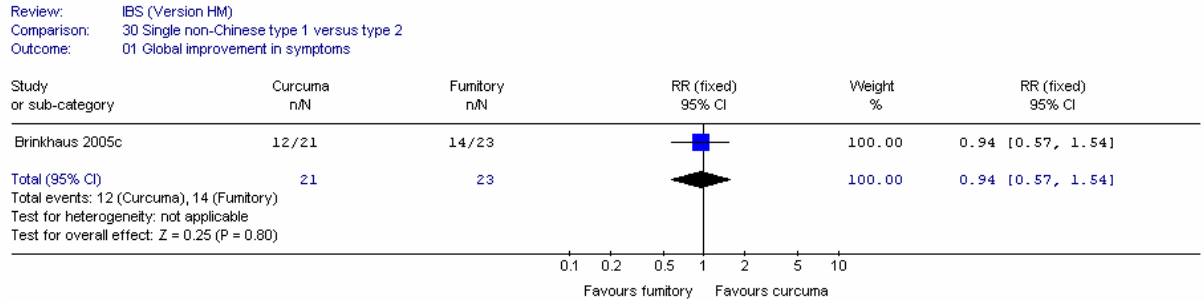
- Single non-Chinese herb curcuma versus single non-Chinese herb fumitory (Brinkhaus 2005).

I. Global symptoms

a) Number of people with an improvement in global symptoms

One study recorded the participants' assessment of improvement in 44 people (Brinkhaus 2005). There was no significant difference between interventions.

Figure 32: Global improvement of symptoms

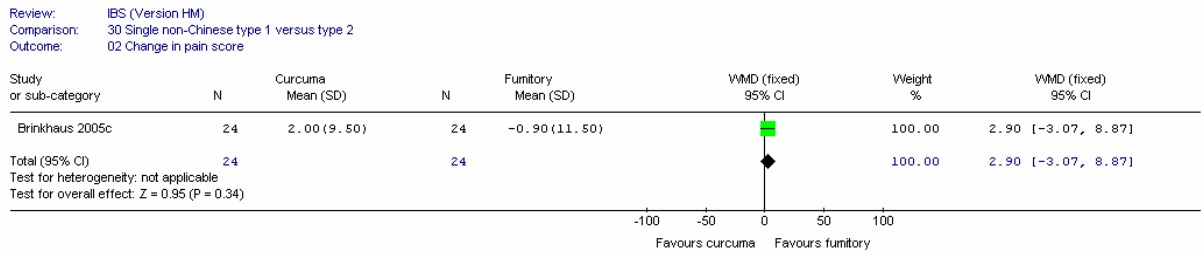


II. Individual symptoms

a) Pain

One study recorded a pain score on a VAS of 0 to 50mm (Brinkhaus 2005). There was no significant difference between interventions.

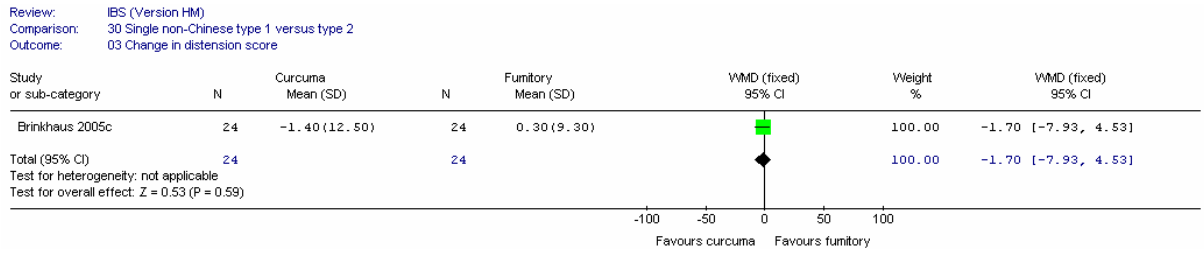
Figure 33: Pain score



c) Bloating

One study (Brinkhaus 2005) recorded a bloating score on a VAS of 0 to 50mm. There was no significant difference between interventions

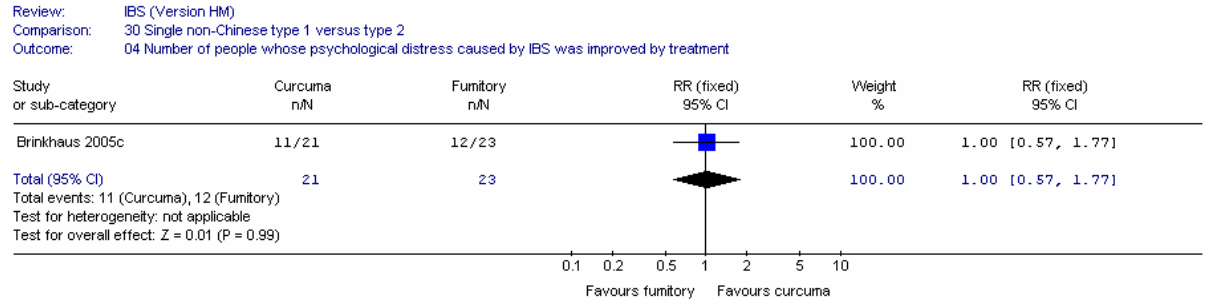
Figure 34: Bloating score



III. Psychological distress

One study reported the number of people whose psychological distress caused by IBS was improved with treatment (Brinkhaus 2005). There was no significant difference between interventions.

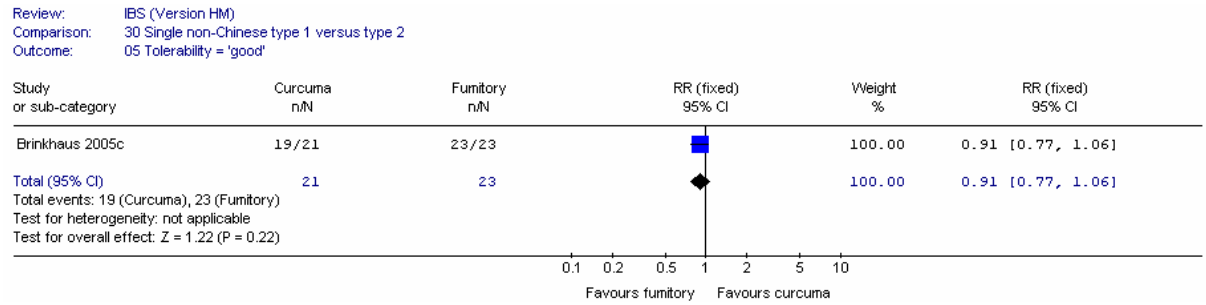
Figure 35: Global improvement of symptoms



IV. Adverse effects

One study reported tolerability (Brinkhaus 2005). There was no significant difference between interventions.

Figure 36: Tolerability



B4. Combination non-Chinese herbal medicines type 1 versus type 2:

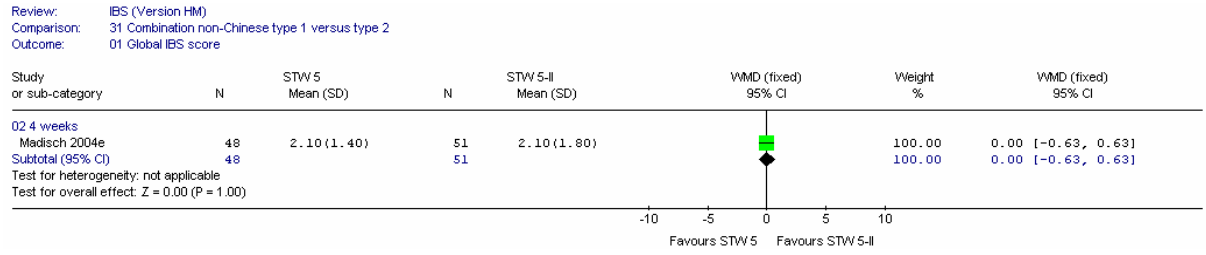
- Commercially available non-Chinese herbal preparation STW 5 containing 9 herbs versus non-Chinese herbal preparation STW 5-II, a research preparation containing 6 herbs (Madisch 2004).

I. Global symptoms

a) Global symptom score (mean)

The global symptom score was recorded by one study in 99 people (Madisch 2004) at 4 weeks on a scale of 0 to 12. There was no significant difference between interventions.

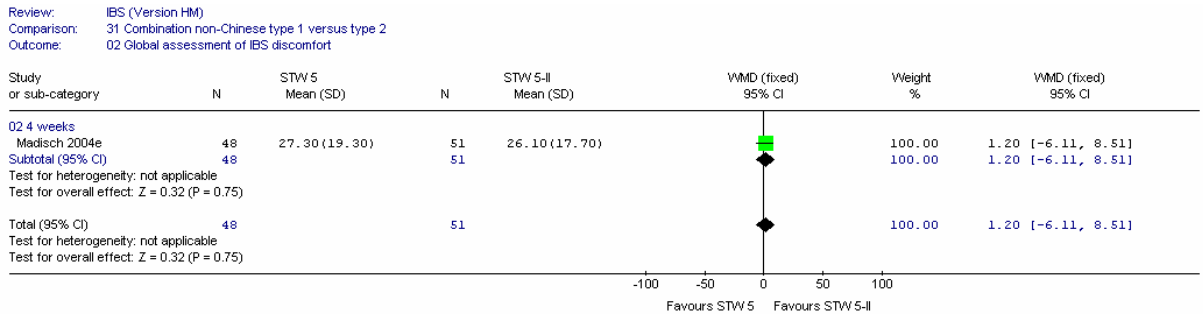
Figure 37: Global symptom score



b) Global assessment of IBS discomfort

This outcome was recorded by one study at 4 weeks (Madisch 2004) on a scale of 0 to 100mm. There was no significant difference between interventions.

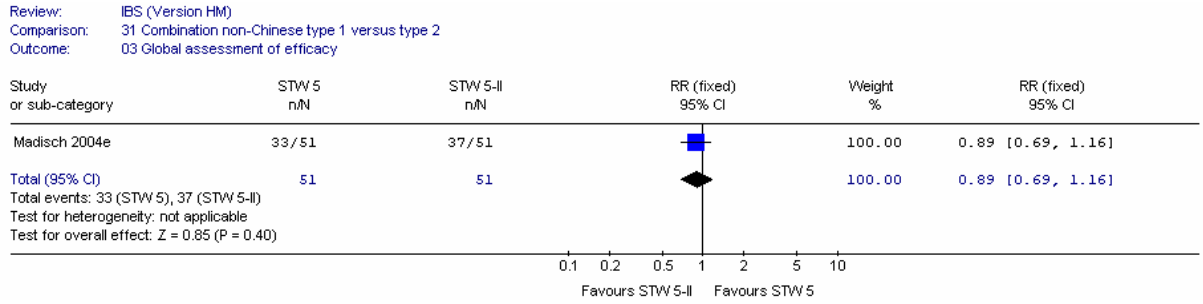
Figure 38: Global assessment of IBS discomfort



c) Global assessment of treatment on symptoms

This outcome was recorded by one study (Madisch 2004) in 102 people, which recorded the clinician's assessment of the efficacy of the drug at 4 weeks (number of people recorded as 'good' or 'very good'). There was no significant difference between interventions.

Figure 39: Global assessment of treatment on symptoms

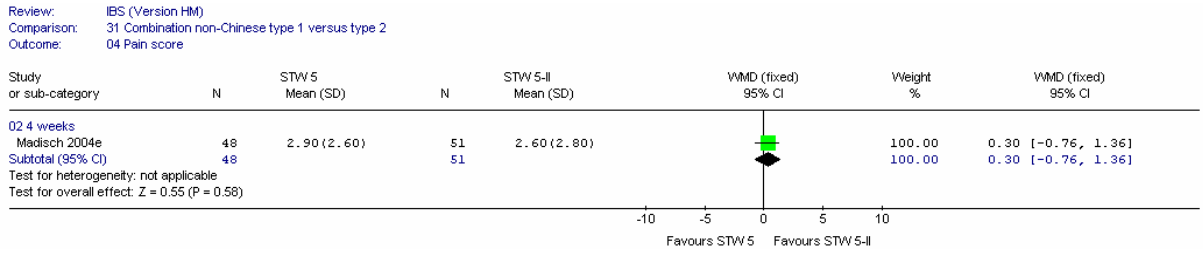


II. Individual symptoms

a) Pain

One study (Madisch 2004) reported a pain score on a scale of 0 to 21. There was no significant difference between interventions.

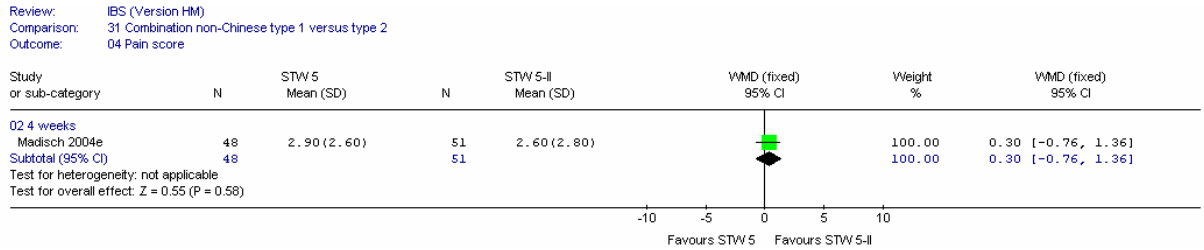
Figure 40: Pain score



b) Bowel habits

One study (Madisch 2004) recorded the number of people with complete relief or absence of changes in bowel habit (constipation, diarrhoea or alternating bowel habit). There was no significant difference between interventions.

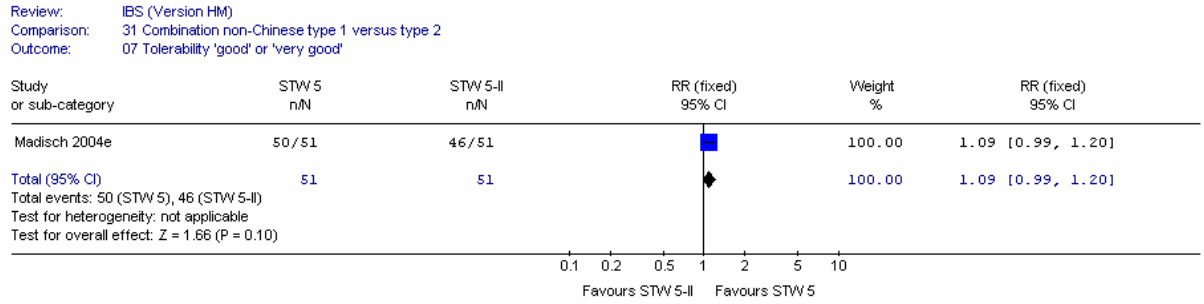
Figure 41: Number of people with no changes in bowel habit



III. Adverse effects

One study reported tolerability (Madisch 2004). There was no significant difference between interventions.

Figure 42: Tolerability



EVIDENCE STATEMENTS

1. There is inconsistent evidence to show if Chinese combination herbs give an improvement in global symptoms compared with placebo.

2. There is moderate evidence to show there is no significant effect of combination Chinese herbal medicines on pain, bowel habits or quality of life.

3. There is moderate evidence to show no significant difference between single non-Chinese herbal medicines and placebo in global symptoms or in pain score, but inconsistency or uncertainty in the bloating and bowel habit outcomes respectively.

4. There is moderate evidence to suggest that combination non-Chinese herbal medicines give a significantly greater improvement in global symptoms, compared with placebo, however, there was inconsistency or uncertainty in the pain and bowel habit outcomes respectively.

5. There is moderate evidence to suggest that combination non-Chinese herbal medicines give a significantly greater improvement in global symptoms, pain and tolerability, but no significant difference in bowel habits, compared with single non-Chinese medicines.

6. There is moderate fair evidence to suggest that there is no significant difference between individualised combination Chinese medicines and standard formula Chinese medicines, in global symptoms.

7. There is limited evidence to show that there is no significant difference between two single non-Chinese herbs, curcuma and fumitory, in global symptoms, pain, bloating, tolerability or psychological distress.

8. There is moderate evidence to show that there is no significant difference between two combination non-Chinese herbs, STW5 and STW-II, in global symptoms, pain, bowel habits, tolerability or psychological distress.

EVIDENCE TO RECOMMENDATION

The review evidence suggests that some herbal preparations may be clinically effective in people with IBS and are well tolerated. However, the GDG believed there were too many uncertainties regarding type and dose of herbal medicines to make a recommendation for practice, and proposed that these interventions should be investigated further in a research recommendation.

11 Psychosocial interventions: patient information and support groups

Clinical Questions

1. Do psychosocial interventions have a role in managing IBS symptoms?
2. Do self help/support groups have a role in managing IBS symptoms?
3. Information determines patient experience by facilitating informed choices.
4. What role does patient information play in IBS?

BACKGROUND

Psychosocial factors contribute to the predisposition to IBS; some authors believe it the most important factor in terms of who manifests IBS, how severe it becomes and how people with IBS cope with managing the condition. The multifaceted nature of IBS requires an appreciation and understanding of psychosocial principles that relate to the disorder and the way these may be addressed in treatment strategies. It is important to explore the possible indicators of psychological distress which may affect the ways in which a person with IBS presents their condition and the associated coping behaviours. A history of physical and sexual abuse is twice more common in people first presenting with IBS than in people with organic gastrointestinal disease prior to a definitive diagnosis. Anxiety and other major life stress and/or trauma have been shown to correlate with the development of IBS and the severity of its symptoms (Gunn 2003; Camilleri 2001; Jones 2000). The presence of psychosocial factors is also an indicator for the likelihood that people will seek medical attention for IBS as well as other medical conditions.

Addressing psychosocial factors with an ongoing collaborative multi-disciplinary approach leads to improvement in the clinical outcomes and while psychosocial factors do not cause IBS symptoms, they do influence the patients' response both to the condition and treatment (Gaynes 1999).

Support groups and patient information

People with IBS often experience a sense of frustration, isolation, and a need to identify a niche in the health/sick role continuum. Frustration may arise from their perceived inability to control symptoms, prevent episodes, identify episode triggers, and obtain medical validation of the condition. Many people with IBS consider their condition to be severe and greatly affecting their lives. They feel that some health care professionals do not give credence to IBS as a chronic debilitating condition and that information which may help them understand more about how to live with the condition is often not forthcoming. The constant anticipation of the next IBS episode, the nature of the bowel symptoms, the

requirement for quick and easy access to toilet facilities, often results in embarrassment and withdrawal from social activities with resultant isolation (Bertram 2001). Providing people with IBS appropriate information about their disorder may promote a strong physician-patient interaction and may reduce healthcare use. Most people with IBS feel insufficiently informed, particularly in relation to risk of serious disease and the role of diet (Dancey 1993; O'Sullivan 2000).

The isolation people with IBS experience in many aspects of their lives may also be addressed by the use of support groups. Support groups have been suggested as a way for people to help one another by having the opportunity to discuss coping strategies with others who are experiencing similar issues. However provision and access to IBS support groups may vary throughout the UK.

"*There is no self help group near to me at the moment, but maybe that will happen in due course. I am sure that to talk with fellow sufferers must be a great help. So many people are striving to get the better of this awful affliction without much luck, but, ever the optimist, I shall continue to look for an answer*."

This anonymous quote is not atypical of the IBS patient experience, and to address these concerns through effective diagnosis and management interventions is an essential aspect of this clinical guideline. Support group discussion may provide people with an opportunity to share others' difficulties with IBS, which may affirm their own IBS experiences. They may be relieved to finally be able to discuss their problems and symptoms with others who understand the challenges.

People appear to cope better with this chronic illness if they have sufficient information about IBS and appropriate support networks. Within the context of the whole IBS patient journey, evidence suggests that an important feature of effective coping and improved quality of life is for people to take responsibility through shared management with their primary care clinician (Kennedy 2003; Lacy 2007; Rogers 2007). Therefore, due consideration of the information needs of people with IBS is fundamental to the provision of effective management strategies.

Review of the literature for psychosocial interventions, support groups and patient information led to two reviews, one on support groups and self help, and the other on patient information. There was no evidence for other psychosocial interventions. The support groups and patient information reviews are closely linked: a common theme is the investigation of the effectiveness of a guidebook giving patient information. The two reviews are presented in sections 11.1 and 11.2; section 11.3 describes the process of evidence to recommendation for both reviews, leading to a single recommendation.

11.1 Support Groups and Self Help

SELECTION CRITERIA

The selection criteria described in the general methodology section were used, except that crossover studies were excluded as inappropriate due to the carry-over effect of the interventions.

The following comparisons were to be included:

- Support group versus waiting list control
- Support group plus other intervention versus other intervention only
- Support group versus other intervention.

SEARCH STRATEGY FOR IDENTIFICATION OF STUDIES

Searches were performed on the following core databases: MEDLINE, EMBASE, CINAHL, and *The Cochrane Library* (1966 to current day with guidance from the GDG). Additionally, the PSYCINFO database was searched for this review. The search strategies are given in Appendix B.

The titles and abstracts of these studies were assessed. Three studies were identified as being potentially relevant to the review and these papers were retrieved in full. The reference lists for each of the retrieved studies were inspected for further potential papers, but none were identified. The one excluded study is listed in Appendix E, along with reasons for exclusion.

CHARACTERISTICS OF INCLUDED STUDIES

Study Design

Two randomised trials were found (Payne 1995; Robinson 2006). One was carried out in the USA (the setting was not stated) (Payne 1995); the other was carried out in primary care in the UK (Robinson 2006).

Population

The 34 patients (5 men and 29 women) in the Payne (1995) study had IBS satisfying the Rome I criteria; their mean age was around 40 years (range 22 to 70 years); 29/34 had an Axis I disorder.

The 420 patients (50 men and 370 women) in the Robinson (2006) study had IBS, of whom 38% satisfied Rome II criteria (the rest diagnosed by GP or specialist if they had previously been referred); patients were excluded if they were unable to read or understand English; their mean age was 40 years (SD 14.4 years); psychiatric co-morbidities were not stated. They had had bowel symptoms for a mean of 6 years (SD 7.2 years).

Neither of the studies reported the number of participants with bloating or whether the symptoms were post-infective.

Interventions and comparisons

Payne (1995) compared three groups: 1) support group; 2) cognitive behavioural therapy; 3) waiting list control for 8 weeks. The self-help group intervention involved guided discussion on aspects of IBS, for example, stress and diet, for 1 hour 15 minutes per week for 8 weeks.

Robinson (2006) compared three groups: 1) self-help support group plus educational guidebook; 2) guidebook only; 3) usual care. The self-help guidebook included information on: lifestyle; diet; drugs, and; alternative therapies. The self-help meeting was a one-off 2-hour meeting of 8 to 12 people at a time; only 59 of 139 attended. The study carried out some additional qualitative research and noted that some people were unwilling to discuss bowel related symptoms with strangers, which may have been the cause of the poor attendance rate. The control group had usual care at the discretion of the primary care physician. Data were collected at one year.

People in Payne (1995) continued to take their medication unchanged. Participants in Robinson (2006) were informed that they were free to continue to visit their primary care physician without restriction.

Comparisons were:

- Support group versus waiting list control for 8 weeks
- Self-help support group plus educational guidebook versus guidebook only, followed at one year
- Guidebook only versus usual care, followed at one year
- Support group versus cognitive behavioural therapy (this is reported in the CBT review), at 8 weeks.

Outcomes

The outcomes examined were:

1. Global symptoms:
    a) Global improvement in symptoms (number of patients) (Payne 1995)
    b) Global symptom score on a 7-point scale from unbearable to no symptoms (i.e. higher score is better) (Robinson 2006)
    c) Global improvement of IBS symptoms (mean Composite Primary Symptom Reduction [CPSR] score; CPSR represents the proportional reduction in score from baseline); i.e. high = bad (Payne 1995)
    d) Global assessment of treatment on symptoms (Robinson 2006).

2. Mental health outcomes (overall mental health; depression; anxiety)

Overall anxiety and psychological distress (Anxiety, State-Trait Anxiety Inventory [STAI]); Scale range 20 to 80; high = bad (Payne 1995)

Beck depression inventory (scale maximum 63; high=bad) (Payne 1995).

METHODOLOGICAL QUALITY

The quality assessment for included trials is shown in Appendix D.

The method of randomisation was adequate in Robinson (2006), which stated that it used a randomisation system based on minimisation. Allocation concealment was adequate in one study using a central telephone randomisation system (Robinson 2006) and not stated in the other (Payne 1995). The patients were not blinded (because of the type of intervention). Neither study reported an *a priori* power calculation. Payne (1995) demonstrated baseline comparability between the groups; this was not stated in Robinson (2006). All the participants were followed up in Payne (1995), while in Robinson (2006) data were missing for 56 patients overall (13%). Overall, neither study was considered to be at risk of bias.

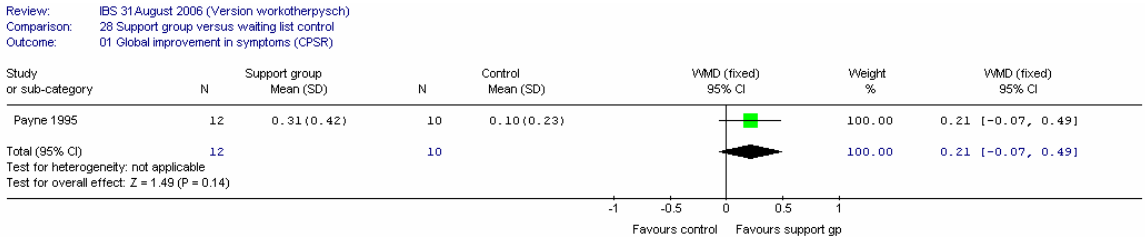
RESULTS

A. Support group versus waiting list control

1) Global symptoms

Global improvement of IBS symptoms was reported by Payne (1995) at 8 weeks, in 22 people, using the mean Composite Primary Symptom Reduction [CPSR] score; CPSR represents the proportional reduction in score from baseline. The study gave individual patient data, allowing calculation of standard deviations. There was no significant difference between interventions, but the confidence interval was fairly wide.

Figure 1:

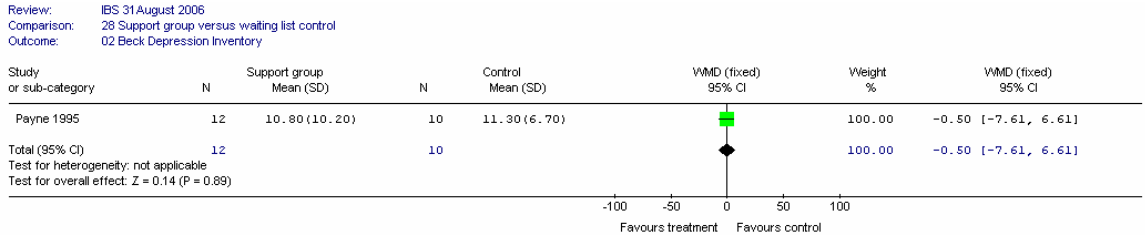


2) Mental health outcomes

a) Beck Depression Inventory

Payne (1995) reported Beck Depression Inventory scores (scale maximum 63; high=bad) at the end of treatment (8 weeks). There was no significant difference between interventions.

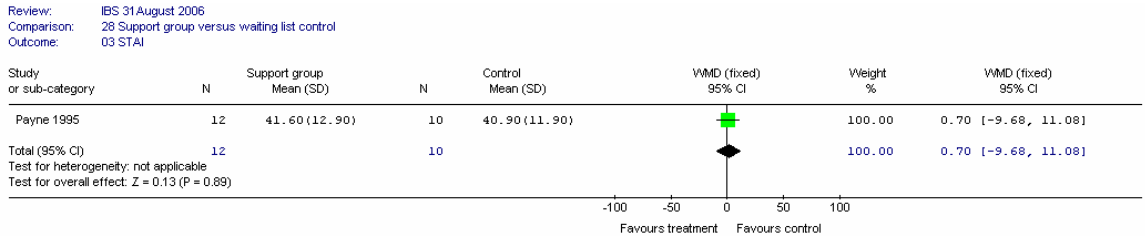
Figure 2:



b) Overall anxiety and psychological distress: State-Trait Anxiety Inventory (STAI)

Payne (1995) reported STAI scores (20 to 80; high=bad) at the end of treatment (8 weeks). Again there was no significant difference between interventions.

Figure 3:



B. Self-help support group plus educational guidebook versus guidebook only

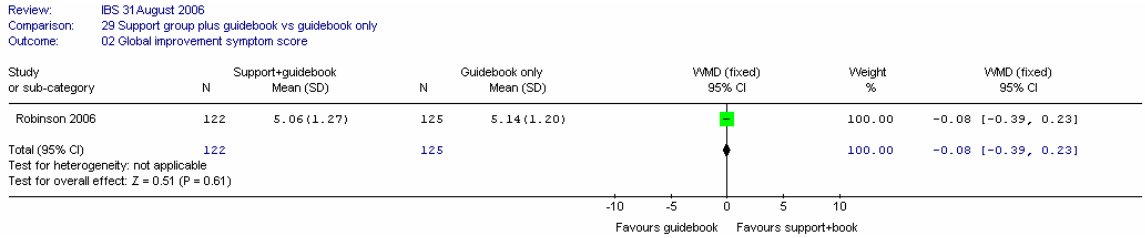
1. Global symptoms

Robinson (2006) reported a global IBS symptom score on a 7-point scale from unbearable to no symptoms (i.e. higher score is better) at the 52-week follow-up in 247 patients. There was no significant difference between interventions. We note, however, that only 59 of the 139 participants attended the support group meeting (although the global symptoms scores were still reported).

Figure 4:

People also reported their assessment of treatment on symptoms (global improvement of symptoms score) on a 7-point scale from very much worse to very much improved (i.e. higher score is better). There was no significant difference between interventions.

Figure 5:

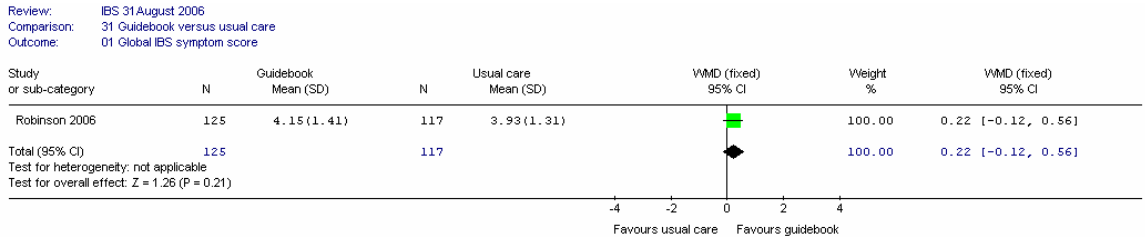


C. Guidebook only versus usual care

1) Global symptoms

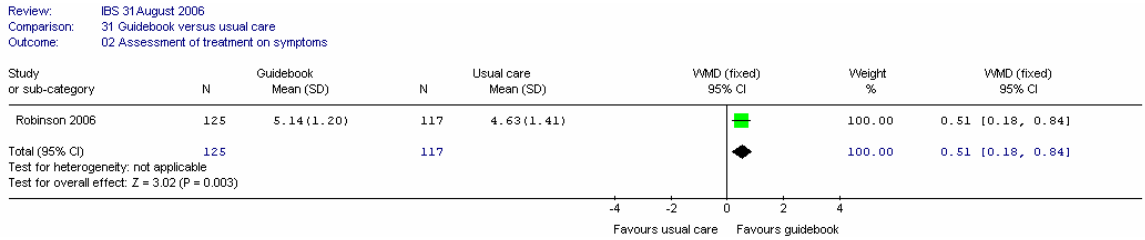
Robinson (2006) reported a global IBS symptom score on a 7-point scale from unbearable to no symptoms (i.e. higher score is better) at the 52-week follow up in 242 patients. There was no significant difference between interventions.

Figure 6:



Patients also reported their assessment of treatment on symptoms (global improvement of symptoms) on a 7-point scale from very much worse to very much improved (i.e. higher score is better). There was a statistically significant difference, in favour of the guidebook.

Figure 7:



The results from Robinson (2006) suggest that the guidebook may have helped patients, with little additional benefit from the support group (a single 2-hour meeting, which only 59 of the 139 patients in this randomisation arm actually attended).

ECONOMIC LITERATURE FOR PSYCHOSOCIAL INTERVENTIONS / SUPPORT GROUPS

One relevant health economic analysis was identified on the cost-effectiveness of psychosocial interventions or support groups in the management of IBS. Robinson (2006) was a trial based economic analysis looking at the impact of two self help interventions (a guidebook and a self-

help group session) on clinical and economic outcomes in primary care patients with IBS. Only the economic outcomes are described here as the clinical effectiveness results have been described in the clinical effectiveness review. The economic outcomes reported were GP visits, hospital consultation rates, prescription costs and overall costs.

This study provided evidence that the provision of a self-help guidebook reduced GP visits (-1.56 visits per annum, P<0.001), hospital visits (-0.22 visits per annum, p=0.038) and prescription costs (£24, p=0.031) but the addition of a self-help group session did not further reduce resource use. Overall costs for GP visits, hospital visits and prescribed drugs were reduced for those who received the guidebook (-£73, 95%CI -£43 to -£103, p<0.001) but there was no significant effect on overall costs from the addition of the self-help session. The guidebook was also associated with a significant increase in the use of self-care activities such as dietary interventions and relaxation therapy.

This study was a partial economic evaluation as it did not assess the incremental cost of any benefit achieved by the provision of a guidebook or self-help group session in the form of a cost-effectiveness ratio. A particular limitation of this study was the failure to include intervention costs for the guidebook or self-help group. This limitation would only affect the conclusions drawn from this study if the cost of providing the guidebook exceeded the cost-savings resulting from reduced resource use in patients provided with a guidebook. The evidence provided by this study was considered relevant to the guideline as it considered both costs and effects for the intervention in an appropriate population and setting. No potential areas of significant bias were identified except for the exclusion of intervention costs. Whilst this study did not provide a full economic analysis of the provision of guidebooks, with or without a self-help group session, this evidence was considered alongside the clinical effectiveness evidence to inform recommendations on the use of self-help groups and self-help information in the management of IBS.

EVIDENCE STATEMENTS

1. There was limited evidence to show no significant difference in global improvement of symptoms or in depression on the Beck inventory for a self help group intervention, involving guided discussion on aspects of IBS, for example, stress and diet, for 1hour 15 minutes per week for eight weeks, compared with waiting list control.

2. There was good evidence to show no significant additional effect on global symptoms of a single two-hour self help meeting of 8 to 12 people at a time, in people already receiving a guidebook. It is noted that less than half the people attended the self help meeting.

3. There was good evidence to show no significant additional effect on the number of primary care consultations and hospital visits of a single two-hour self help meeting of 8 to 12 people

at a time, in people already receiving a guidebook. It is noted that less than half the people attended the self help meeting.

4. There was good evidence to show no significant additional effect of a single two-hour self help meeting of 8 to 12 patients at a time, in patients already receiving a guidebook, on the overall cost of GP visits, hospital visits and prescription drugs. It is noted that less than half the people attended the self help meeting.

5. There was good evidence to show a significant improvement in global symptoms for people receiving a self-help guidebook, which included information on lifestyle, diet, drugs and alternative therapies, in comparison with usual care.

6. There was good evidence to show a significant decrease in the number of primary care consultations and hospital visits for people receiving a self-help guidebook, which included information on lifestyle, diet, drugs and alternative therapies, in comparison with usual care.

7. There was good evidence to show a significant reduction in the overall cost of GP visits, hospital visits and prescription drugs for people receiving a self-help guidebook, which included information on lifestyle, diet, drugs and alternative therapies, in comparison with usual care.

GDG DISCUSSION

The GDG commented that people may not attend support groups because of travel difficulties (due to lack of control of symptoms) and a general reluctance to discuss bowel problems with others. The superior effect of the guidebook compared to usual care was not surprising, and the GDG noted that a simple guide to IBS has proved popular in the past. It was also noted that many people with IBS do make a great effort to attend support groups and those that attend find these beneficial.

11.2 Patient Information

OBJECTIVE

To review the evidence on the information needs of people who have been diagnosed with IBS, assessing the impact that information has in their self management of the syndrome and their ability to maximise quality of life when living with the syndrome.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

Quantitative (RCTs, prospective studies, survey) and qualitative (eg. focus group) study designs were considered for this review.

SEARCH STRATEGY FOR IDENTIFICATION OF STUDIES

Searches were performed on the following core databases: MEDLINE, EMBASE, CINAHL, and *The Cochrane Library.* Searches were performed from the beginning of each database and updated to June 2007. The search strategies are given in Appendix B:
Following sifting, five studies were included in the review.

CHARACTERISTICS OF CLINICAL STUDIES INCLUDED IN THE REVIEW

Five studies were included in this review: three were prospective studies (Kennedy 2003, Lacy 2007, Bogalo 2006) and two were separate papers from a randomised trial (Robinson 2006, Rogers 2007). One study was excluded and is given in Appendix E.

Prospective non-randomised studies

The Lacy (2007) study used a questionnaire that addressed two main domains:

- Participant knowledge of IBS (epidemiology and natural history; aetiology; symptoms; diagnosis and treatment)
- Participant attitudes towards IBS (relationships of IBS to functional status; concerns and fears about IBS; ability of the medical system to address patients' needs).

People with IBS were identified from a search of the medical records in Lebanon, New Hampshire, USA and the records were examined to ensure that the participants met the Rome II criteria. 261 of 664 contacted (39%) returned the questionnaires.

Bogalo (2006) was a prospective study of 31 people assigned to the treatment group in an RCT. These participants received a self-help treatment manual over six weeks, with one chapter per week. Each chapter was task oriented. Topics covered in each of the six weeks were: IBS explained; assessing symptoms and self monitoring; managing IBS symptoms; cognitive restructuring, personal expectations and activity patterns; relaxation and stress management; and maintenance. The study investigated the hypothesis that treatment group participants who had a higher level of engagement in the homeworking tasks would experience greater relief from their IBS symptoms.

The Kennedy (2003) study used focus groups of 12 people to explore participants' knowledge and experience of IBS. Participants were recruited from an article in a regional paper asking for volunteers. Focus group meetings were held over a two week period and lasted 1¼ to 1½ hours. Each session was taped and transcribed. Transcripts were read and analysed using a framework developed for the study. Four main areas were outlined (perceptions and expectations; experience of IBS; information needs and sources; managing IBS) and these were divided into 16 subheadings. Each comment in the focus group was allocated to one of the sub-headings. The patients' views and experiences were used in the development of a self-help guidebook.

Randomised studies

The Robinson (2006) study measured the clinical and cost effectiveness of three interventions: the Kennedy self-help guidebook; the guidebook together with a two-hour one-off support group meeting; and usual care. It is noted that less than half of the people in the support group arm attended the support group meeting. This study has been reported and discussed in the Support groups review (section 11.1)

Rogers (2007) is a report of a qualitative study of a purposefully selected group of 12 of the Robinson (2006) trial patients: four of these participants had received the guidebook only; four had received the guidebook and had attended the support group meeting; one who had received the guidebook but did not attend the meeting; and three control group participants. Interviews were carried out with the participants, lasting between 40 and 90 minutes. These were transcribed and transcripts were analysed thematically, against one another by constant comparison. Key themes included: the lived experience of IBS (impact on everyday life; experience of symptoms; and reaction of others); ways of managing; lay epidemiology; experience of medical management and diagnosis; alternative help-seeking views about medication; the guidebook as projected identification with others; use of the guidebook, together with perceived changes; and continuity from being part of the trial.

Quantitative and qualitative narrative review was carried out to assimilate the evidence on the reported benefits of information in enabling people with IBS to better understand their condition and make lifestyle adjustments. A thematic analysis was carried out across included studies.

RESULTS

From the qualitative study data, several distinct themes emerge. These are:

- There is a lack of clear information to support people with IBS, which creates misunderstanding and misconception
- People with IBS are often misinformed at the point of diagnosis, not fully understanding the diagnosis and its potential impact on quality of life
- Medical management is often one-dimensional, with no attention given to lifestyle and other therapeutic interventions
- Developing coping mechanisms are augmented by structured information. Patient experience was improved through exposure to a guidebook which focused on self-management in partnership with the primary care clinician
- Structured information provides an instant source of help, sensitive to the episodic nature of IBS, facilitating the sharing of experience and ongoing IBS management
- Patient information is essential for shared decision-making and partnership between clinicians and people with IBS
- Information should be patient-centered with involvement of the person with IBS

- Primary care clinicians should take responsibility to ensure that their knowledge of IBS enables expressed concerns to be answered, offering support through clear explanation
- People with IBS need information relating to cause, cure and long-term prognosis for IBS
- Appropriate sources of information for people with IBS include magazine articles, leaflets in shops, books, support groups, internet, medical journals and books.

Information needs

The importance of good information is highlighted in this review of published papers relating to the information needs, experiences, and quality of life issues for people with IBS. Given the chronic nature of IBS, information quality will contribute to the development of an effective shared decision making model between primary care clinician and the person with IBS. The primary care clinician is a key resource for the person who presents with IBS, and following positive diagnosis the importance of information sharing and shared decision making relating to their symptom profile and treatment response is a key aspect.

Respondents in the Kennedy study (2003) highlighted that primary care clinicians had little knowledge about IBS, and subsequently were unable to provide much in the way of clear information that encouraged self-help strategies for people with IBS. Magazine articles, leaflets, books, support groups, internet sources and published journal articles were highlighted as useful. The inclusion of patients in producing patient information emerged as a contemporary theme within this study, this is consistent with NICE's approach to developing patient information, and is produced as part of this clinical guideline suite of information. Lacy (2007) supports points raised for discussion from the Kennedy study, highlighting that specific guidance on diagnosis, treatment, misconceptions about natural history of the disease and subsequent confusion should all feature in prepared information.

Information clearly has an educative role, in correcting inappropriate concerns relating to cancer, and in developing the shared care model that provides clarity in symptom based presentation and subsequent treatment interventions that are appropriate for that particular person with IBS.

The Robinson (2006) study found that use of the self-help guidebook compared with usual care resulted in fewer primary care consultations, and a greater improvement in global symptoms. Well prepared information appears to be at least cost neutral, with a cost per patient reduction reported as £73. This aspect is discussed further in the support groups review (section 11.1)

Understanding the importance of patients as agents of change is a key aspect to effective implementation of evidence, where patients become the drivers for change in healthcare behaviours. The success of the patient self-help booklet reported in the Kennedy study (2003) is a clear example of the importance of patient information, in meeting the needs of people learning to live with IBS or adapting lifestyle for those people who have lived with IBS for a significant period of time.

Quality of life

Chronic illness remains a significant challenge to the individual in terms of effective coping, and to the NHS in identifying the appropriate level of support to that individual. In this review, quality of life issues are raised consistently in studies that ask people with IBS questions relating to the level of impact that IBS has on their daily living activities. People often express the desire for cure and information relating to long term prognosis, reflecting the over-medicalised language relating to effective coping. Living with IBS is the challenge, and symptom based management relating to the quality of life experience is key in the shared care model. In the Lacy (2007) study, nearly all participants (n=261) reported that IBS affected their lives in some way. Clearly this relates to severity and quality of life when considered as a continuum, and one can see the person moving from coping to not coping, reflecting the episodic nature of the syndrome.

The role of information and its added value in addressing misconceptions, diagnosis, providing reliable answers to questions, treatment interventions and indicating when access to a primary care clinician should be considered due to continued worsening of symptoms are all aspects highlighted within this clinical guideline. If addressed, collectively they should provide a foundation for the patient to develop effective coping strategies.

GDG DISCUSSION

Information should be clear, concise and relate to the symptom-based management of the syndrome. It should deal with areas of misconception, embarrassment and quality of life issues. This should be provided at the earliest opportunity by the primary care clinician following positive diagnosis of IBS.

The role of well prepared information provides the basis for the development of the shared care model between the primary care clinician and the person with IBS. Evidence supports the use of information booklets that encourage self help activity.

EVIDENCE STATEMENTS

1. There is fair evidence indicating that if people with IBS receive directed information and encouragement to be actively involved in the management of their condition that this contributes to:
    - A positive impact on treatment outcomes
    - An improvement in quality of life perception and reduction in symptom severity
    - Reduction in primary care consultations.

2. There is weak evidence indicating that people with IBS lack appropriate information relating to their condition. This can lead to misunderstanding and reduced quality of life experiences.

11.3 Evidence to Recommendation

The GDG took into consideration the evidence in both reviews. This included the clinical and cost effectiveness results from the quantitative studies, and the qualitative analysis in the patient information review, which was supported by the experiences of all members of the GDG. The evidence from the support groups review showed improved clinical outcomes and reduced health care costs for people provided with a self-help guidebook, and indicated that providing self-help information in the management of IBS is likely to be clinically and cost-effective. There did not appear to be an additional effect from a support group meeting, but this may have been confounded by the poor attendance. Some members of the GDG had extensive experience of self-help groups and reported that they are a current voluntary sector patient provision, providing social support, and that people with IBS comment positively on their involvement in self help organisations. The GDG decided not to make a recommendation on the usefulness of support groups.

Based on the qualitative data in the patient information review and their own experience, the GDG recognised the need for clear unambiguous information, and indicated its role and importance in helping people with IBS develop coping strategies in partnership with their primary care clinician. The GDG noted that patient information should be provided early in the patient pathway following a positive diagnosis of IBS, and that self-help information should be wide ranging, covering areas such as general lifestyle, physical activity, diet and symptom-targeted medication.

RECOMMENDATION

People with IBS should be given information that explains the importance of self-help in effectively managing their IBS. This should include information on general lifestyle, physical activity, diet and symptom-targeted medication.

12 RECOMMENDATIONS FOR RESEARCH

1. Tricyclic antidepressants, SSRIs and SNRIs

Are low-dose tricyclic antidepressants (TCAs), SSRIs and SNRIs effective in the treatment of IBS as a first line therapy, and which is the more effective and the safer option?

Why is this important?

Reviews have shown that TCAs and SSRIs have each been compared with placebo, but not at low dose. In practice, TCAs are used at higher doses and concordance with treatment is poor because of side effects. GDG clinicians believe that at low doses (e.g. 5 to 10 mg equivalent of amytriptyline), TCAs could be the treatment of choice, but there is a lack of evidence. Newer antidepressants, SNRIs, maybe useful in the treatment of IBS pain. A large randomised trial is proposed, comparing an SSRI, a TCA, an SNRI and placebo. Participants should be adults with a positive diagnosis of IBS, stratified by type of IBS and randomised to treatments. The primary outcome should be global improvement in IBS symptoms. Health related quality of life should also be measured. Adverse effects should be recorded. Study outcomes should be assessed at 12, 26 and 52 weeks after the start of therapy.

2. Psychological interventions

Are psychological interventions (psychological therapy, hypnotherapy and CBT) equally effective in the management of IBS symptoms, either as first line therapies in primary care, or in the treatment of people with IBS that is refractory to other treatments?

Why is this important?

Reviews show some evidence of effect when comparing psychological interventions with control, mainly in people with refractory IBS. Many trials are small in size. The psychological interventions of psychological therapy, hypnotherapy and CBT are thought to be useful in helping people with IBS cope with their symptoms, but it is unclear at what stage these should be given, including their use as first line therapies in primary care. A large randomised trial is proposed, comparing CBT, hypnotherapy and psychological therapy (psychodynamic interpersonal therapy). Participants should be adults with a positive diagnosis of IBS, and they should be stratified into those with and without refractory IBS and then randomised to treatments. The primary outcome should be global improvement in IBS symptoms. Health related quality of life should also be measured. Adverse effects should be recorded. Study outcomes should be assessed at 12, 26 and 52 weeks after the start of therapy.

3. What factors contribute to refractory symptoms in IBS?

Why is this important?

Most individuals with IBS experience symptoms that are relatively short lived or only trouble them on an intermittent basis. Some people, however, develop chronic and severe symptoms

that are difficult to treat. There are relatively few prospective studies that have investigated this problem.

A large, prospective, population based cohort study is proposed, which would evaluate people in the community with IBS symptoms, according to measures of bowel symptomatology, physical symptom profile, psychological symptoms, childhood adversity, past history of psychiatric disorder, social supports, quality of life and other relevant potential predictors. Individuals would be re-evaluated 12 and 24 months later using similar measures. Baseline variables would be used to predict chronicity of symptoms, quality of life and healthcare utilisation at 12 months and at 24 months.

4. Relaxation and biofeedback

What is the effect of relaxation and biofeedback therapies on IBS symptoms and patient-related outcomes?

Why is this important?

Reviews of biofeedback and relaxation therapies suggest a positive effect on the control of IBS symptoms, but evidence is limited and not sufficient to make recommendations. Patient representation within the group supports this view, from a personal and anecdotal perspective.

Recent developments in computer-aided biofeedback methods merit investigation. A large randomised trial is proposed to compare relaxation therapy, computer-aided biofeedback therapy and attention control in primary care. Participants should be adults with a positive diagnosis of IBS, and they should be stratified into those with and without refractory IBS, and then randomised to treatments. The primary outcome should be global improvement in IBS symptoms. Health related quality of life should also be measured. Adverse effects should be recorded. Study outcomes should be assessed at 12, 26 and 52 weeks after the start of therapy. Qualitative data should be generated relating to how people with IBS perceive their IBS condition.

5. Herbal medicines

Are Chinese and non Chinese herbal medicines safe and effective as first-line therapy in the treatment of IBS, and which is the more effective and safer option?

Why this is important

Reviews of herbal medicines suggest a positive effect on the control of IBS symptoms, but evidence is limited and not sufficient to make recommendations (8 comparisons from the six trials provides heterogeneous data which are very difficult to interpret). A large randomised placebo controlled trial is proposed, comparing Chinese and non Chinese herbal medicine, single and multiple compounds, which should be available within the UK as standard preparations. Participants should be adults with a positive IBS diagnosis and should be

stratified by IBS type and then randomised to treatments. The primary outcome should be global improvement in IBS symptoms, with symptom scores being recorded using a validated scale. Health-related quality of life should also be measured, and adverse events recorded. Study outcomes should be assessed at 12, 26 and 52 weeks post-intervention.

13 IMPLEMENTATION OF THE GUIDELINE

The Healthcare Commission assesses the performance of NHS organisations in meeting core and developmental standards set by the Department of Health in 'Standards for better health', issued in July 2004. Implementation of clinical guidelines forms part of the developmental standard D2. Core standard C5 says that national agreed guidance should be taken into account when NHS organisations are planning and delivering care.

NICE has developed tools to help organisations implement this guidance (listed below). These are available on the NICE website (www.nice.org.uk/CG61).

- Slides highlighting key messages for local discussion.
- Costing tools:
  - Costing report to estimate the national savings and costs associated with implementation
  - Costing template to estimate the local costs and savings involved.
- Implementation advice on how to put the guidance into practice and national initiatives that support this locally.
- Audit criteria to monitor local practice.

14 RELATED NICE GUIDANCE

Published

Depression: Depression, management of depression in primary and secondary care. NICE clinical guideline 23 (2004). Available from www.nice.org.uk.

Referral for Suspected Cancer: Referral Guidelines for Suspected Cancer in Adults and Children. NICE clinical guideline 27 (2005). Available from www.nice.org.uk.

Physical Activity. NICE public health intervention guidance PH1002 (2006). Available from www.nice.org.uk.

15 UPDATE OF THE GUIDELINE

NICE clinical guidelines are updated as needed so that recommendations take into account important new information. We check for new evidence 2 and 4 years after publication, to decide whether all or part of the guideline should be updated. If important new evidence is published at other times, we may decide to do a more rapid update of some recommendations.

16 REFERENCES

[No authors listed] (177) Irritable bowel syndrome: practitioner awareness, patient education can limit utilization, *Disease Management Advisor,* 8(12):185-7.

[No authors listed] (2000) Irritable bowel syndrome and women's health, *National Women's Health Report,* 22(3):1-2.

Cochrane Handbook for Systematic Reviews of Interventions 4.2.5 [updated May 2005] (2007) in: Higgins J and Green S, (editors) *The Cochrane Library, Issue 3, 2005.* Chichester, UK: John Wiley & Sons, Ltd.,

Abrahamsson H (1982) Irritable bowel syndrome. Diagnosis, *Scandinavian Journal of Gastroenterology - Supplement,* 79:20-3.

Adeniji OA, Barnett CB, and Di Palma JA (2004) Durability of the diagnosis of irritable bowel syndrome based on clinical criteria, *Digestive Diseases and Sciences,* 49(4):572-4.

Agrawal A and Whorwell PJ (2006) Irritable bowel syndrome: Diagnosis and management, *British Medical Journal,* 332(7536):280-3.

Akehurst RL, Brazier JE, Mathers N, O'Keefe C, Kaltenthaler E, Morgan A, Platts M, and Walters SJ (2002) Health-related quality of life and cost impact of irritable bowel syndrome in a UK primary care setting, *Pharmacoeconomics,* 20(7):455-62.

Aller R, de Luis DA, Izaola O, la Calle F, del Olmo L, Fernandez L, Arranz T, and Gonzalez Hernandez JM (2004) Effects of a high-fiber diet on symptoms of irritable bowel syndrome: a randomized clinical trial, *Nutrition,* 20(9):735-7.

Allison MC, Sercombe J, and Pounder RE (1988) A double-blind crossover comparison of lidamidine, loperamide and placebo for the control of chronic diarrhoea, *Alimentary Pharmacology and Therapeutics,* 2(4):347-51.

Amery W, Duyck F, Polak J, and van den BG (1975) A multicentre double-blind study in acute diarrhoea comparing loperamide (R 18553) with two common antidiarrhoeal agents and a placebo, *Current Therapeutic Research, Clinical and Experimental,* 17(3):263-70.

Arthurs Y and Fielding JF (1983) Double blind trial of ispaghula/poloxamer in the Irritable Bowel Syndrome, *Irish Medical Journal,* 76(5):253.

Asp NG (1992) Resistant starch. Proceedings from the second plenary meeting of EURESTA: European FLAIR concerted action no. 11 on physiological implications of the consumption of resistant starch in man. Preface, *European Journal of Clinical Nutrition,* 46(SUPPL. 2):S1.

Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, Guyatt GH, Harbour RT, Haugh MC, Henry D, Hill S, Jaeschke R, Leng G, Liberati A, Magrini N, Mason J, Middleton P, Mrukowicz J, O'Connell D, Oxman AD, Phillips B, Schunemann HJ, Edejer TT, Varonen H, Vist GE, Williams JW, Jr., Zaza S, and GRADE Working Group (2004) Grading quality of evidence and strength of recommendations, *British Medical Journal,* 328(7454):1490.

Atkinson W, Sheldon TA, Shaath N, and Whorwell PJ (2004) Food elimination based on IgG antibodies in irritable bowel syndrome: a randomised controlled trial., *Gut,* 53(10):1459-64.

Attar A, Lemann M, Ferguson A, Halphen M, Boutron MC, Flourie B, Alix E, Salmeron M, Guillemot F, Chaussade S, Menard AM, Moreau J, Naudin G, and Barthet M (1999) Comparison of a low dose polyethylene glycol electrolyte solution with lactulose for treatment of chronic constipation, *Gut,* 44(2):226-30.

Babic Z, Simek M, Altabas K, Bilic A, and Maras A (1997) Irritable bowel syndrome, *Croatian Journal of Gastroenterology and Hepatology,* 6(3-4):55-9.

Badia X, Mearin F, Balboa A, Baro E, Caldwell E, Cucala M, Diaz-Rubio M, Fueyo A, Ponce J, Roset M, and Talley NJ (2002) Burden of illness in irritable bowel syndrome comparing Rome I and Rome II criteria, *Pharmacoeconomics,* 20(11):749-58.

Barbara G, Stanghellini V, Brandi G, Cremon C, Nardo GD, De Giorgio R, and Corinaldesi R (2005) Interactions between commensal bacteria and gut sensorimotor function in health and disease, *American Journal of Gastroenterology,* 100(11):2560-8.

Barbezat G, Poulton R, Milne B, Howell S, Fawcett JP, and Talley N (2002) Prevalence and correlates of irritable bowel symptoms in a New Zealand birth cohort, *New Zealand Medical Journal,* 115(1164):U220.

Barbezat GO, Clain JE, and Halter F (1979) A double-blind trial of loperamide in the treatment of chronic diarrhoea, *South African Medical Journal,* Suid-Afrikaanse Tydskrif Vir Geneeskunde. 55(13):502-3.

Barnes J (1996) When to investigate and treat IBS symptoms, *Practitioner,* 240(1560):184-7.

Bellini M, Tosetti C, Costa F, Biagi S, Stasi C, Del Punta A, Monicelli P, Mumolo MG, Ricchiuti A, Bruzzi P, and Marchi S (2005) The general practitioner's approach to irritable bowel syndrome: from intention to practice, *Digestive and Liver Disease,* 37(12):934-9.

Bellini M, Tosetti C, Stasi C, Biagi S, Costa F, Bruzzi P, and Marchi S (2006) The general practitioner's management of patients with a new diagnosis of irritable bowel syndrome, *Journal of Clinical Gastroenterology,* 40(1):87.

Bennett P and Wilkinson S (1985) A comparison of psychological and medical treatment of the irritable bowel syndrome, *British Journal of Clinical Psychology,* 24(Pt 3):215-6.

Bensoussan A (1998) Treatment of irritable bowel syndrome with Chinese herbal medicine: a randomized controlled trial, *Journal of the American Medical Association,* 280(18):1585-9.

Bergeron CM (1984) A comparison of cognitive stress management, progressive muscle relaxation, and biofeedback in the treatment of irritable bowel syndrome, *Dissertation Abstracts International,* 44(10-B):3186.

Berthelot J and Centonze V (1981) Etude controlee en double aveugle Duspatalin (Mebeverine) contre placebo, dans le traitement du colon irritable., *Gazette Medicale De France,* 88(16):2341-3.

Bertram S, Kurland M, Lydick E, Locke GR, III, and Yawn BP (2001) The patient's perspective of irritable bowel syndrome, *Journal of Family Practice,* 50(6):521-5.

Bi L and Triadafilopoulos G (2003) Exercise and gastrointestinal function and disease: an evidence-based review of risks and benefits, *Clinical Gastroenterology and Hepatology,* 1(5):345-55.

Bijkerk CJ, de Wit NJ, Stalman WAB, Knottnerus JA, Hoes AW, and Muris JWM (2003) Irritable bowel syndrome in primary care: The patient's and doctors' views on symptoms, etiology and management, *Canadian Journal of Gastroenterology,* 17(6):363-8.

Bittner AC, Croffut RM, and Stranahan MC (2005) Prescript-assist probiotic-prebiotic treatment for irritable bowel syndrome: A methodologically oriented, 2-week, randomized, placebo-controlled, double-blind clinical study, *Clinical Therapeutics,* 27(6):755-61.

Blanchard EB and Schwarz SP (1987) Adaptation of a multicomponent treatment for irritable bowel syndrome to a small-group format, *Biofeedback & Self Regulation.,* 12(1):63-9.

Blanchard EB and Radnitz C. (1987) Psychological changes associated with self-regulatory treatments of irritable bowel syndrome, *Biofeedback & Self Regulation.,* 12(1):31-7.

Blanchard EB, Schwarz SP, Suls JM, Gerardi MA, Scharff L, Greene B, Taylor AE, Berreman C, and Malamood HS (1992) Two controlled evaluations of multicomponent psychological treatment of irritable bowel syndrome, *Behaviour Research and Therapy,* 30(2):175-89.

Blanchard EB, Greene B, Scharff L, and Schwarz-McMorris SP (1993) Relaxation training as a treatment for irritable bowel syndrome, *Biofeedback & Self Regulation.,* 18(3):125-32.

Block J, Myren J, Larssen SE, and Larsen S (1983) [Trimipramin (Surmontil) and placebo in irritable colon syndrome. A double-blind study], *Tidsskrift for Den Norske Laegeforening,* 103(11):903-5.

Boerner D, Eberhardt R, Metz K, and Schick E (1988) Wirksamkeit ind vertraeglichkeit eines antidepressivums beim colon irritablie, *Therapiewoche,* 38:201-8.

Bogalo L and Moss-Morris R (2006) The Effectiveness of Homework Tasks in an Irritable Bowel Syndrome Cognitive Behavioural Self-Management Programme., *New Zealand Journal of Psychology,* 35(3):120-5.

Bommelaer G, Dorval E, Denis P, Czernichow P, Frexinos J, Pelc A, Slama A, and El Hasnaoui A (2002) Prevalence of irritable bowel syndrome in the French population according to the Rome I criteria, *Gastroenterologie Clinique Et Biologique,* 26(12):1118-23.

Bouhnik Y, Neut C, Raskine L, Michel C, Riottot M, Andrieux C, Guillemot F, Dyard F, and Flourie B (2004) Prospective, randomized, parallel-group trial to evaluate the effects of lactulose and polyethylene glycol-4000 on colonic flora in chronic idiopathic constipation, *Alimentary Pharmacology and Therapeutics,* 19(8):889-99.

Bowling A (2002) *Research Methods in Health*, 2nd Edition. Maidenhead: Open University Press.

Bozzani A (2002) Managing patients with irritable bowel syndrome in primary care: Review of the specific literature, *Journal of Functional Syndromes,* 2(1):40-2.

Brinkhaus B, Hentschel C, Von Keudell C, Schindler G, Lindner M, Stutzer H, Kohnen R, Willich SN, Lehmacher W, and Hahn EG (2005) Herbal medicine with curcuma and fumitory in the treatment of irritable bowel syndrome: a randomized, placebo-controlled, double-blind clinical trial, *Scandinavian Journal of Gastroenterology,* 40(8):936-43.

Burden S (2001) Dietary treatment of irritable bowel syndrome: Current evidence and guidelines for future practice, *Journal of Human Nutrition & Dietetics,* 14(3):231-41.

Cann PA, Read NW, Holdsworth CD, and Barends D (1984) Role of loperamide and placebo in management of irritable bowel syndrome (IBS), *Digestive Diseases and Sciences,* 29(3):239-47.

Carling L, Svedberg L-E, and Hulten S (1989) Short term treatment of the irritable bowel syndrome: A placebo-controlled trial of peppermint oil against hyoscyamine, *Opuscula Medica,* 34(3):55-7.

Casellas F, Lopez VJ, and Malagelada JR (2005) Perceived health status in celiac disease, *Revista Espanola De Enfermedades Digestivas,* 97(11):794-804.

Cash BD, Schoenfeld P, and Chey WD (2002) The utility of diagnostic tests in irritable bowel syndrome patients: a systematic review, *American Journal of Gastroenterology,* 97(11):2812-9.

Cash BD and Chey WD (2002) Irritable bowel syndrome: an evidence-based management approach: case study and commentary, *Journal of Clinical Outcomes Management,* 9(7):409-18.

Cash BD and Chey WD (2004) Irritable bowel syndrome: A systematic review, *Clinics in Family Practice,* 6(3):647-69.

Cash BD and Chey WD (2005) Diagnosis of irritable bowel syndrome, *Gastroenterology Clinics of North America,* 34(2):205-20.

Catassi C, Kryszak D, Louis-Jacques O, Duerksen DR, Hill I, Crowe SE, Brown AR, Procaccini NJ, Wonderly BA, Hartley P, Moreci J, Bennett N, Horvath K, Burk M, and Fasano A (2007) Detection of Celiac disease in primary care: a multicenter case-finding study in North America, *American Journal of Gastroenterology,* 102(7):1454-60.

Chapman ND, Grillage MG, Mazumder R, and Atkinson SN (1990) A comparison of mebeverine with high-fibre dietary advice and mebeverine plus ispaghula in the treatment of irritable bowel syndrome: an open, prospectively randomised, parallel group study, *British Journal of Clinical Practice,* 44(11):461-6.

Charapata C and Mertz H (2006) Physician knowledge of Rome symptom criteria for irritable bowel syndrome is poor among non-gastroenterologists, *Neurogastroenterology and Motility,* 18(3):211-6.

Chaussade S and Minic M (2003) Comparison of efficacy and safety of two doses of two different polyethylene glycol-based laxatives in the treatment of constipation. *Alimentary Pharmacology and Therapeutics,* 17(1):165-72.

Chey WD, Olden K, Carter E, Boyle J, Drossman D, and Chang L (2002) Utility of the Rome I and Rome II criteria for irritable bowel syndrome in U.S. women, *American Journal of Gastroenterology,* 97(11):2803-11.

Chinn S (2000) A simple method for converting an odds ratio to effect size for use in meta-analysis, *Statistics in Medicine,* 19(22):3127-31.

Christie AH, Culbert P, Guest JF, Christie AH, Culbert P, and Guest JF (2002) Economic impact of low dose polyethylene glycol 3350 plus electrolytes compared with lactulose in the management of idiopathic constipation in the UK, *Pharmacoeconomics,* 20(1):49-60.

Colwell LJ, Prather CM, Phillips SF, and Zinsmeister AR (1998) Effects of an irritable bowel syndrome educational class on health- promoting behaviors and symptoms, *American Journal of Gastroenterology,* 93(6):901-5.

Conboy LA, Wasserman RH, Jacobson EE, Davis RB, Legedza AT, Park M, Rivers AL, Morey EB, Nam BH, Lasagna L, Kirsch I, Lembo AJ, Kaptchuk TJ, and Kerr CE (2006) Investigating placebo effects in irritable bowel syndrome: a novel research design, *Contemporary Clinical Trials,* 27(2):123-34.

Cook IJ, Irvine EJ, Campbell D, Shannon S, Reddy SN, and Collins SM (1990) Effect of dietary fiber on symptoms and rectosigmoid motility in patients with irritable bowel syndrome. A controlled, crossover study, *Gastroenterology,* 98(1):66-72.

Corazziari E, Badiali D, Habib FI, Reboa G, Pitto G, Mazzacca G, Sabbatini F, Galeazzi R, Cilluffo T, Vantini I, Bardelli E, and Baldi F (1996) Small volume isosmotic polyethylene glycol electrolyte balanced solution (PMF-100) in treatment of chronic nonorganic constipation, *Digestive Diseases and Sciences,* 41(8):1636-42.

Corazziari E, Badiali D, Bazzocchi G, Bassotti G, Roselli P, Mastropaolo G, Luca MG, Galeazzi R, and Peruzzi E (2000) Long term efficacy, safety, and tolerabilitity of low daily doses of isosmotic polyethylene glycol electrolyte balanced solution (PMF-100) in the treatment of functional chronic constipation, *Gut,* 46(4):522-6.

Corbett CL, Palmer KR, and Holdsworth CD (1980) Effect of loperamide, codeine phosphate and diphenoxylate on urgency and incontinence in chronic diarrhoea, *Gut,* 21(Suppl 1-12):A924.

Cornett JWD, Aspeling RL, and Mallegol D (1977) A double blind comparative evaluation of loperamide versus diphenoxylate with atropine in acute diarrhea, *Current Therapeutic Research, Clinical and Experimental,* 21(5):629-37.

Corney RH, Stanton R, Newell R, Clare A, and Fairclough P (1991) Behavioural psychotherapy in the treatment of irritable bowel syndrome, *Journal of Psychosomatic Research,* 35(4-5):461-9.

Corrao G, Corazza GR, Bagnardi V, Brusco G, Ciacci C, Cottone M, Sategna GC, Usai P, Cesari P, Pelli MA, Loperfido S, Volta U, Calabro A, and Certo M (2001) Mortality in patients with coeliac disease and their relatives: a cohort study, *Lancet,* 358(9279):356-61.

Corsetti M and Tack J (2004) Are symptom-based diagnostic criteria for irritable bowel syndrome useful in clinical practice?, *Digestion,* 70(4):207-9.

Creed F, Fernandes L, Guthrie E, Palmer S, Ratcliffe J, Read N, Rigby C, Thompson D, Tomenson B, and North of England IBS Research Group. (2003) The cost-effectiveness of psychotherapy and paroxetine for severe irritable bowel syndrome. *Gastroenterology,* 124(2):303-17.

Cremonini F and Talley NJ (2004) Diagnostic and therapeutic strategies in the irritable bowel syndrome, *Minerva Medica,* 95(5):427-41.

Curtin F, Morabia A, Bernstein M, and Dederding J-P (1998) A population survey of bowel habits in urban Swiss men, *European Journal of Public Health,* 8(2):170-5.

Czalbert HJ, Neder M, and Feher K (1990) Experiences with colpermintherapy (Tillots-England) at patients of irritable colon syndrome, *Gyogyszereszet,* 34(5):251-3.

Dancey CP and Backhouse S (1993) Towards a better understanding of patients with irritable bowel syndrome, *Journal of Advanced Nursing,* 18(9):1443-50.

Dancey CP, Hutton-Young A, Moye S, and Devins GM (2002) Perceived stigma, illness intrusiveness and quality of life in men and women with irritable bowel syndrome, *Psychology, Health and Medicine,* 7(4):381-95.

Dapoigny M, Bellanger J, Bonaz B, Des Varannes SB, Bueno L, Coffin B, Ducrotte P, Flourie B, Lemann M, Lepicard A, and Reigneau O (2004) Irritable bowel syndrome in France: A common, debilitating and costly disorder, *European Journal of Gastroenterology and Hepatology,* 16(10):995-1001.

Davis K (2006) Randomised double-blind placebo-controlled trial of aloe vera for irritable bowel syndrome, *International Journal of Clinical Practice,* 60(9):1080-6.

De Giorgio R, Barbara G, Stanghellini V, Cremon C, Salvioli B, De Ponti F, and Corinaldesi R (2004) Diagnosis and therapy of irritable bowel syndrome, *Alimentary Pharmacology and Therapeutics,* 20 Suppl 2:10-22.

De Schryver AM, Keulemans YC, Peters HP, Akkermans LM, Smout AJ, De Vries WR, and Berge-Henegouwen GP (2005) Effects of regular physical activity on defecation pattern in middle-aged patients complaining of chronic constipation, *Scandinavian Journal of Gastroenterology,* 40(4):422-9.

Dear KL, Elia M, and Hunter JO (2005) Do interventions which reduce colonic bacterial fermentation improve symptoms of irritable bowel syndrome?, *Digestive Diseases and Sciences,* 50(4):758-66.

Delbecq AL, Van de Ven AH, and Gustafson DH (1986) *Group Techniques For Program Planning: A Guide to Nominal Group and Delphi Processes*, Middleton, Wis: Green Briar Press.

Department of Health (2006) *Reference Costs 2005-06*, London: Department of Health.

Dettmar PW and Sykes J (1998) A multi-centre, general practice comparison of ispaghula husk with lactulose and other laxatives in the treatment of simple constipation, *Current Medical Research and Opinion,* 14(4):227-33.

Dettmer A (1994) Loperamide oxide in the treatment of acute diarrhea in adults, *Clinical Therapeutics,* 16(6):972-80.

Dogan UB and Unal S (1996) Kruis scoring system and Manning's criteria in diagnosis of irritable bowel syndrome: is it better to use combined?, *Acta Gastroenterologica Belgica,* 59(4):225-8.

Dom J, Leyman R, Schuermans V, and Brugmans J (1974) Loperamide (R 18 553), a novel type of antidiarrheal agent. Part 8: Clinical investigation. Use of a flexible dosage schedule in a double-blind comparison of loperamide with diphenoxylate in 614 patients suffering from acute diarrhea, *Arzneimittel-Forschung,* 24(10):1660-5.

Dretzke J, Cummins C, Sandercock J, Fry-Smith A, Barrett T, and Burls A (2004) Autoantibody testing in children with newly diagnosed type 1 diabetes mellitus, *Health Technology Assessment (Winchester, England),* 8(22):iii-ixi.

Dreverman JW and Van der Poel AJ (1995) Loperamide oxide in acute diarrhoea: a double-blind, placebo-controlled trial. The Dutch Diarrhoea Trialists Group, *Alimentary Pharmacology and Therapeutics,* 9(4):441-6.

Drossman DA, Thompson WG, and Whitehead WE (1992) Approaching IBS with confidence, *Patient Care,* 26(13):175-8.

Drossman DA and Thompson WG (1992) The irritable bowel syndrome: review and a graduated multicomponent treatment approach, *Annals of Internal Medicine,* 116(12 Pt 1):1009-16.

Drossman DA, Toner BB, Whitehead WE, Diamant NE, Dalton CB, Duncan S, Emmott S, Proffitt V, Akman D, Frusciante K, Le T, Meyer K, Bradshaw B, Mikula K, Morris CB, Blackman CJ, Hu Y, Jia H, Li JZ, Koch GG, and Bangdiwala SI (2003) Cognitive-behavioral therapy versus education and desipramine versus placebo for moderate to severe functional bowel disorders, *Gastroenterology,* 125(1):19-31.

Drossman DA, Morris CB, Hu Y, Toner BB, Diamant N, Leserman J, Shetzline M, Dalton C, Bangdiwala SI, Drossman DA, Morris CB, Hu Y, Toner BB, Diamant N, Leserman J, Shetzline M, Dalton C, and Bangdiwala SI (2005) A prospective assessment of bowel habit in irritable bowel syndrome in women: defining an alternator, *Gastroenterology,* 128(3):580-9.

Drossmsn DA (1984) Diagnosis of the irritable bowel syndrome. A simple solution, *Gastroenterology,* 87(1):224-5.

Drummond MF and Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party, *British Medical Journal,* 313(7052):275-83.

Dubinsky MC, Johanson JF, Seidman EG, Ofman JJ, Dubinsky MC, Johanson JF, Seidman EG, and Ofman JJ (2002) Suspected inflammatory bowel disease--the clinical and economic impact of competing diagnostic strategies, *American Journal of Gastroenterology,* 97(9):2333-42.

Efskind PS, Bernklev T, and Vatn MH (1996) A double-blind placebo-controlled trial with loperamide in irritable bowel syndrome, *Scandinavian Journal of Gastroenterology,* 31(5):463-8.

Ehrenpreis ED (2004) Characterizing patients with IBS: how to make a confident diagnosis, *Family Practice Recertification,* 26(8):53-61.

El Serag HB, Olden K, Bjorkman D, El Serag HB, Olden K, and Bjorkman D (2002) Health-related quality of life among persons with irritable bowel syndrome: a systematic review, *Alimentary Pharmacology and Therapeutics,* 16(6):1171-85.

Ericsson CD, DuPont HL, Mathewson JJ, West MS, Johnson PC, and Bitsura JA (1990) Treatment of traveler's diarrhea with sulfamethoxazole and trimethoprim and loperamide, *Journal of the American Medical Association,* 263(2):257-61.

Fass R, Longstreth GF, Pimentel M, Fullerton S, Russak SM, Chiou CF, Reyes E, Crane P, Eisen G, McCarberg B, and Ofman J (2001) Evidence- and consensus-based practice guidelines for the diagnosis of irritable bowel syndrome, *Archives of Internal Medicine,* 161(17):2081-8.

Ferguson A, Culbert P, Gillett H, and Barras N (1999) New polyethylene glycol electrolyte solution for the treatment of constipation and faecal impaction, *Italian Journal of Gastroenterology and Hepatology,* 31 Suppl 3:S249-S252.

Fernandez C, Perez M, Amigo I, and Linares A (1998) Stress and contingency management in the treatment of irritable bowel syndrome, *Stress Medicine,* 14(1):31-42.

Fielding JF and Kehoe M (1984) Different dietary fibre formulations and the irritable bowel syndrome, *Irish Journal of Medical Science,* 153(5):178-80.

Forbes A, MacAuley S, and Chiotakakou-Faliakou E (2000) Hypnotherapy and therapeutic audiotape: effective in previously unsuccessfully treated irritable bowel syndrome? *International Journal of Colorectal Disease,* 15(5-6):328-34.

Forbes A, Jackson S, Walter C, Quraishi S, Jacyna M, and Pitcher M (2005) Acupuncture for irritable bowel syndrome: a blinded placebo-controlled trial, *World Journal of Gastroenterology,* 11(26):4040-4.

Fowell AJ, Thomas PW, Surgenor SL, and Snook JA (2006) The epidemiology of coeliac disease in East Dorset 1993-2002: an assessment of the 'coeliac iceberg', and preliminary evidence of case clustering, *QJM,* 99(7):453-60.

Fowlie S, Eastwood MA, and Prescott R (1992) Irritable bowel syndrome: assessment of psychological disturbance and its influence on the response to fibre supplementation, *Journal of Psychosomatic Research,* 36(2):175-80.

Francis CY, Duffy JN, Whorwell PJ, and Martin DF (1996) Does routine abdominal ultrasound enhance diagnostic accuracy in irritable bowel syndrome?, *American Journal of Gastroenterology,* 91(7):1348-50.

Francis CY and Whorwell PJ (1997) The irritable bowel syndrome, *Postgraduate Medical Journal,* 73(855):1-7.

Frigerio G, Beretta A, Orsenigo G, Tadeo G, Imperiali G, and Minoli G (1992) Irritable bowel syndrome. Still far from a positive diagnosis, *Digestive Diseases and Sciences,* 37(2):164-7.

Gade J and Thorn P (1989) Paraghurt for patients with irritable bowel syndrome. A controlled clinical investigation from general practice, *Scandinavian Journal of Primary Health Care,* 7(1):23-6.

Gaynes BN and Drossman DA (1999) The role of psychosocial factors in irritable bowel syndrome, *Best Practice and Research in Clinical Gastroenterology,* 13(3):437-52.

Gilbody JS, Fletcher CP, Hughes IW, and Kidman SP (2000) Comparison of two different formulations of mebeverine hydrochloride in irritable bowel syndrome, *International Journal of Clinical Practice,* 54(7):461-4.

Golechha AC, Chadda VS, Chadda S, Sharma SK, and Mishra SN (1982) Role of ispaghula husk in the management of irritable bowel syndrome (a randomized double-blind crossover study), *Journal of the Association of Physicians of India,* 30(6):353-5.

Gong Y-Y, Wen Y-H, and Qu T (2002) A study on the improvement of treatment effect to treat irritable bowel syndrome with psychological therapy, *Zhongguo Linchuang Kangfu,* 6(11):1706.

Griffith CJ (1994) Irritable bowel syndrome: pathophysiology, diagnosis, and management... recertification series, *Physician Assistant,* 18(11):25-6.

Grillage MG, Nankani JN, Atkinson SN, and Prescott P (1990) A randomised, double-blind study of mebeverine versus dicyclomine in the treatment of functional abdominal pain in young adults, *British Journal of Clinical Practice,* 44(5):176-9.

Gunn MC, Cavin AA, and Mansfield JC (2003) Management of irritable bowel syndrome, *Postgraduate Medical Journal,* 79(929):154-8.

Gwee K-A (2005) Irritable bowel syndrome in developing countries - A disorder of civilization or colonization? *Neurogastroenterology and Motility,* 17(3):317-24.

Hamilton-Miller JMT (2001) Probiotics in the management of irritable bowel syndrome: A review of clinical trials, *Microbial Ecology in Health & Disease,* 13(4):212-6.

Hamm LR, Sorrells SC, Harding JP, Northcutt AR, Heath AT, Kapke GF, Hunt CM, and Mangel AW (1999) Additional investigations fail to alter the diagnosis of irritable bowel syndrome in subjects fulfilling the Rome criteria, *American Journal of Gastroenterology,* 94(5):1279-82.

Hammer J and Talley NJ (1999) Diagnostic criteria for the irritable bowel syndrome, *American Journal of Medicine,* 107(5A):5S-11S.

Harford WV, Krejs GJ, Santa Ana CA, and Fordtran JS (1980) Acute effect of diphenoxylate with atropine (Lomotil) in patients with chronic diarrhea and fecal incontinence, *Gastroenterology,* 78(3):440-3.

Harvey RF, Mauad EC, and Brown AM (1987) Prognosis in the irritable bowel syndrome: a 5-year prospective study, *Lancet,* 1(8539):963-5.

Harvey RF, Hinton RA, Gunary RM, and Barry RE (1989) Individual and group hypnotherapy in treatment of refractory irritable bowel syndrome, *Lancet,* 1(8635):424-5.

Hatlebakk JG and Hatlebakk MV (2004) Diagnostic approach to suspected irritable bowel syndrome., *Best Practice and Research in Clinical Gastroenterology,* 18(4):735-46.

Haynes RB and Wilczynski NL (2004) Optimal search strategies for retrieving scientifically strong studies of diagnosis from Medline: analytical survey, *British Medical Journal,* 328(7447):1040.

Hebden JM, Blackshaw E, D'Amato M, Perkins AC, and Spiller RC (2002) Abnormalities of GI transit in bloated irritable bowel syndrome: effect of bran on transit and symptoms, *American Journal of Gastroenterology,* 97(9):2315-20.

Heymann-Monnikes I, Arnold R, Florin I, Herda C, Melfsen S, and Monnikes H (2000) The combination of medical treatment plus multicomponent behavioral therapy is superior to medical treatment alone in the therapy of irritable bowel syndrome, *American Journal of Gastroenterology,* 95(4):981-94.

Hin H, Bird G, Fisher P, Mahy N, and Jewell D (1999) Coeliac disease in primary care: case finding study, *British Medical Journal,* 318(7177):164-7.

Holten KB (2003) Irritable bowel syndrome: minimize testing, let symptoms guide treatment, *Journal of Family Practice,* 52(12):942-50.

House of Lords Select Committee on Science and Technology (2000) *Sixth Report (HL123): Complementary and Alternative Medicine*, London:

Hovdenak N (1987) Loperamide treatment of the irritable bowel syndrome, *Scandinavian Journal of Gastroenterology - Supplement,* 130:81-4.

Inauen W and Halter F (1994) Clinical efficacy, safety and tolerance of mebeverine slow release (200 mg) vs mebeverine tablets in patients with irritable bowel syndrome, *Drug Investigation,* 8(4):234-40.

Jaffe G (1977) A comparison of lomotil and imodium in acute non-specific diarrhoea, *Journal of International Medical Research,* 5(3):195-8.

Jalihal A and Kurian G (1990) Ispaghula therapy in irritable bowel syndrome: improvement in overall well-being is related to reduction in bowel dissatisfaction, *Journal of Gastroenterology and Hepatology,* 5(5):507-13.

Jeong H, Lee HR, Yoo BC, and Park SM (1993) Manning criteria in irritable bowel syndrome: its diagnostic significance, *Korean Journal of Internal Medicine,* 8(1):34-9.

Johnson KH and Millard PS (1996) Diagnosis of irritable bowel syndrome, *Journal of Family Practice,* 42(4):346-7.

Joint Formulary Committee (2007) *British National Formulary*, 53rd Edition. London: British Medical Association and Royal Pharmaceutical Society of Great Britain.

Jones J and Hunter D (1995) Consensus methods for medical and health services research, *British Medical Journal,* 311(7001):376-80.

Jones J, Boorman J, Cann P, Forbes A, Gomborone J, Heaton K, Hungin P, Kumar D, Libby G, Spiller R, Read N, Silk D, and Whorwell P (2000) British Society of Gastroenterology guidelines for the management of the irritable bowel syndrome, *Gut,* 47 Suppl 2:ii1-19.

Kajander K, Hatakka K, Poussa T, Farkkila M, and Korpela R (2005) A probiotic mixture alleviates symptoms in irritable bowel syndrome patients: a controlled 6-month intervention, *Alimentary Pharmacology and Therapeutics,* 22(5):387-94.

Keefer L and Blanchard EB (2001) The effects of relaxation response meditation on the symptoms of irritable bowel syndrome: results of a controlled treatment study, *Behaviour Research and Therapy,* 39(7):801-11.

Kennedy A, Robinson A, and Rogers A (2003) Incorporating patients' views and experiences of life with IBS in the development of an evidence based self-help guidebook, *Patient Education and Counseling,* 50(3):303-10.

Kennedy T, Jones R, Darnley S, Seed P, Wessely S, and Chalder T (2005) Cognitive behaviour therapy in addition to antispasmodic treatment for irritable bowel syndrome in primary care: randomised controlled trial, *British Medical Journal,* 331(7514):435.

Kennedy T, Chalder T, McCrone P, Darnley S, Knapp M, Jones R, and Wessely S (2006) Cognitive behavioural therapy in addition to antispasmodic therapy for irritable bowel syndrome in primary care: a randomised controlled trial, *Health Technology Assessment (Winchester, England),* 10(19)

Kienzle-Horn S, Vix J-M, Schuijt C, Peil H, Jordan CC, and Kamm MA (2006) Efficacy and safety of bisacodyl in the acute treatment of constipation: A double-blind, randomized, placebo-controlled study, *Alimentary Pharmacology and Therapeutics,* 23(10):1479-88.

Kienzle-Horn S, Vix JM, Schuijt C, Peil H, Jordan CC, and Kamm MA (2007) Comparison of bisacodyl and sodium picosulphate in the treatment of chronic constipation, *Current Medical Research and Opinion,* 23(4):691-9.

Kim HJ, Camilleri M, McKinzie S, Lempke MB, Burton DD, Thomforde GM, and Zinsmeister AR (2003) A randomized controlled trial of a probiotic, VSL#3, on gut transit and symptoms in diarrhoea-predominant irritable bowel syndrome, *Alimentary Pharmacology and Therapeutics,* 17(7):895-904.

Kim HJ, Vazquez Roque MI, Camilleri M, Stephens D, Burton DD, Baxter K, Thomforde G, and Zinsmeister AR (2005) A randomized controlled trial of a probiotic combination VSL# 3 and placebo in irritable bowel syndrome with bloating, *Neurogastroenterology and Motility,* 17(5):687-96.

Kim YJ and Ban DJ (2005) Prevalence of irritable bowel syndrome, influence of lifestyle factors and bowel habits in Korean college students, *International Journal of Nursing Studies,* 42(3):247-54.

Kruis W, Thieme C, Weinzierl M, Schussler P, Holl J, and Paulus W (1984) A diagnostic score for the irritable bowel syndrome. Its value in the exclusion of organic disease, *Gastroenterology,* 87(1):1-7.

Kruis W, Weinzierl M, Schussler P, and Holl J (1986) Comparison of the therapeutic effect of wheat bran, mebeverine and placebo in patients with the irritable bowel syndrome, *Digestion,* 34(3):196-201.

Kumar A, Kumar N, Vij JC, Sarin SK, and Anand BS (1987) Optimum dosage of ispaghula husk in patients with irritable bowel syndrome: correlation of symptom relief with whole gut transit time and stool weight, *Gut,* 28(2):150-5.

Kyosola K (1985) Positive diagnostic criteria for the irritable bowel syndrome, *Gastroenterology,* 89(1):235-6.

Lacy BE, Weiser K, Noddin L, Robertson DJ, Crowell MD, Parratt-Engstrom C, and Grau MV (2007) Irritable bowel syndrome: patients' attitudes, concerns and level of knowledge, *Alimentary Pharmacology and Therapeutics,* 25(11):1329-41.

Lambert JP, Brunt PW, Mowat NAG, Khin CC, Lai CKW, Morrison V, Dickerson JWT, and Eastwood MA (1991) The value of prescribed 'high-fibre' diets for the treatment of the irritable bowel syndrome, *European Journal of Clinical Nutrition,* 45(12):601-9.

Lavo B, Stenstam M, and Nielsen AL (1987) Loperamide in treatment of irritable bowel syndrome--a double-blind placebo controlled study, *Scandinavian Journal of Gastroenterology - Supplement,* 130:77-80.

Lea R, Hopkins V, Hastleton J, Houghton LA, and Whorwell PJ (2004) Diagnostic criteria for irritable bowel syndrome: utility and applicability in clinical practice, *Digestion,* 70(4):210-3.

Leahy ACB, Clayman C, Mason I, and Epstein O (1997) Dosed relaxation in resistant irritable bowel syndrome using gut directed biofeedback, *Gut,* 40 Suppl 1:A51.

Lech Y, Olesen KM, Hey H, Rask-Pedersen E, Vilien M, and Ostergaard O (1988) Treatment of irritable bowel syndrome with peppermint oil. A double-blind investigation with a placebo, *Ugeskrift for Laeger,* 150(40):2388-9.

Lee IK (1968) Comparative trial of Lomotil-with-neomycin and kaolin-and-morphine mixture in general practice, *British Journal of Clinical Practice,* 22(8):347-8.

Legorreta AP, Ricci J-F, Markowitz M, and Jhingran P (2002) Patients diagnosed with irritable bowel syndrome: Medical record validation of a claims-based identification algorithm, *Disease Management and Health Outcomes,* 10(11):715-22.

Lembo A (2004) Irritable bowel syndrome medications side effects survey, *Journal of Clinical Gastroenterology,* 38(9):776-81.

Leung WK, Wu JC, Liang SM, Chan LS, Chan FK, Xie H, Fung SS, Hui AJ, Wong VW, Che CT, and Sung JJ (2006) Treatment of diarrhea-predominant irritable bowel syndrome with traditional Chinese herbal medicine: a randomized placebo-controlled trial, *American Journal of Gastroenterology,* 101(7):1574-80.

Liu GZ (1997) [Treatment of acupuncture and moxibustion plus psychotherapy for irritable bowel syndrome], *Chinese Acupuncture and Moxibustion,* 10:611-2.

Liu JH, Chen GH, Yeh HZ, Huang CK, and Poon SK (1997) Enteric-coated peppermint-oil capsules in the treatment of irritable bowel syndrome: a prospective, randomized trial, *Journal of Gastroenterology,* 32(6):765-8.

Longstreth GF, Fox DD, Youkeles L, Forsythe AB, and Wolochow DA (1981) Psyllium therapy in the irritable bowel syndrome. A double-blind trial, *Annals of Internal Medicine,* 95(1):53-6.

Longstreth GF (1994) Irritable bowel syndrome and chronic pelvic pain, *Obstetrical and Gynecological Survey,* 49(7):505-7.

Longstreth GF and Drossman DA (2002) New developments in the diagnosis and treatment of irritable bowel syndrome, *Current Gastroenterology Reports,* 4(5):427-34.

Lucey MR, Clark ML, Lowndes J, and Dawson AM (1987) Is bran efficacious in irritable bowel syndrome? A double blind placebo controlled crossover study, *Gut,* 28(2):221-5.

Lustman F, Walters EG, Shroff NE, and Akbar FA (1987) Diphenoxylate hydrochloride (Lomotil(Reg.trademark)) in the treatment of acute diarrhoea, *British Journal of Clinical Practice,* 41(3):648-51.

Lustyk MKB, Jarrett ME, Bennett JC, and Heitkemper MM (2001) Does a physically active lifestyle improve symptoms in women with irritable bowel syndrome?, *Gastroenterology Nursing,* 24(3):129-37.

Lynch PM and Zamble E (1989) A controlled behavioral treatment study of Irritable Bowel Syndrome, *Behavior Therapy,* 20(4):509-23.

MacIntosh DG, Thompson WG, Patel DG, Barr R, and Guindi M (1992) Is rectal biopsy necessary in irritable bowel syndrome?, *American Journal of Gastroenterology,* 87(10):1407-9.

Madden JAJ and Hunter JO (2002) A review of the role of the gut microflora in irritable bowel syndrome and the effects of probiotics, *British Journal of Nutrition,* 88(SUPPL. 1):S67-S72.

Madisch A, Holtmann G, Plein K, and Hotz J (2004) Treatment of irritable bowel syndrome with herbal preparations: results of a double-blind, randomized, placebo-controlled, multi-centre trial, *Alimentary Pharmacology and Therapeutics,* 19(3):271-9.

Manning AP, Heaton KW, and Harvey RF (1977) Wheat fibre and irritable bowel syndrome. A controlled trial, *Lancet,* 2(8035):417-8.

Manning AP, Thompson WG, Heaton KW, and Morris AF (1978) Towards positive diagnosis of the irritable bowel, *British Medical Journal,* 2(6138):653-4.

Mascolo R and Saltzman JR (1998) Lactose intolerance and irritable bowel syndrome, *Nutrition Reviews,* 56(10):306-8.

Mason J, Nicolson D, and Wilson D (2002) Systematic Review Methods for National Guidelines (Unpublished Discussion Paper).

McIntyre A, Vincent RM, Perkins AC, and Spiller RC (1997) Effect of bran, ispaghula, and inert plastic particles on gastric emptying and small bowel transit in humans: The role of physical factors, *Gut,* 40(2):223-7.

Mearin F, Badia X, Balboa A, Baro E, Caldwell E, Cucala M, Diaz-Rubio M, Fueyo A, Ponce J, Roset M, and Talley NJ (2001) Irritable bowel syndrome prevalence varies enormously depending on the employed diagnostic criteria: comparison of Rome II versus previous criteria in a general population, *Scandinavian Journal of Gastroenterology,* 36(11):1155-61.

Mearin F, Baro E, Roset M, Badia X, Zarate N, Perez I, Mearin F, Baro E, Roset M, Badia X, Zarate N, and Perez I (2004) Clinical patterns over time in irritable bowel syndrome: symptom instability and severity variability, *American Journal of Gastroenterology,* 99(1):113-21.

Mearin F, Roset M, Badia X, Balboa A, Baro E, Ponce J, Diaz-Rubio M, Caldwell E, Cucala M, Fueyo A, and Talley NJ (2004) Splitting irritable bowel syndrome: from original Rome to Rome II criteria, *American Journal of Gastroenterology,* 99(1):122-30.

Medoff J, Katz S, Malik P, Pambianco D, Pruitt R, Poulos J, Rank J, and Rose M (2004) Open-label, dose-ranging pilot study of 4 weeks of low-dose therapy with sodium phosphate tablets in chronically constipated adults, *Clinical Therapeutics,* 26(9):1479-91.

Mein SM, Ladabaum U, Mein SM, and Ladabaum U (2004) Serological testing for coeliac disease in patients with symptoms of irritable bowel syndrome: a cost-effectiveness analysis, *Alimentary Pharmacology and Therapeutics,* 19(11):1199-210.

Miller V, Lea R, Agrawal A, and Whorwell PJ (2006) Bran and irritable bowel syndrome: The primary-care perspective, *Digestive and Liver Disease,* 38(10):737-40.

Mitchell SA, Mee AS, Smith GD, Palmer KR, and Chapman RW (2002) Alverine citrate fails to relieve the symptoms of irritable bowel syndrome: Results of a double-blind, randomized, placebo-controlled trial, *Alimentary Pharmacology and Therapeutics,* 16(6):1187-95.

Moreno-Osset E, Calvo B, Tomas-Ridocci M, Montero I, Minguez M, Mora F, and Benages A (1991) The irritable bowel syndrome: diagnostic strategies, *Italian Journal of Gastroenterology,* 23(8 Suppl 1):41-7.

Morgan T and Robson KM (2002) Irritable bowel syndrome: Diagnosis is based on clinical criteria, *Postgraduate Medicine,* 112(5):30-41.

Mortensen PB, Andersen JR, Arffmann S, and Krag E (1987) Short-chain fatty acids and the irritable bowel syndrome: the effect of wheat bran, *Scandinavian Journal of Gastroenterology,* 22(2):185-92.
Myren J, Lovland B, Larssen SE, and Larsen S (1984) Psychopharmacologic drugs in the treatment of the irritable bowel syndrome. A double blind study of the effect of trimipramine, *Annales De Gastroenterologie Et D'Hepatologie.,*(3):117-23.

Myren J, Lovland B, Larssen SE, and Larsen S (1984) A double-blind study of the effect of trimipramine in patients with the irritable bowel syndrome, *Scandinavian Journal of Gastroenterology.,*(6):835-43.

National Collaborating Centre for Mental Health (2004) *National Clinical Practice Guideline Number 23: Depression: Management of depression in primary and secondary care*, Leicester: British Psychological Society.

National Institute for Health and Clinical Excellence (2006) *Public Health Intervention Guidance no. 2: Four commonly used methods to increase physical activity: brief interventions in primary care, exercise referral schemes, pedometers and community-based exercise programmes for walking and cycling*, London: National Institute for Health and Clinical Excellence.

National Institute for Health and Clinical Excellence (2007) *The guidelines manual*, London: National Institute for Health and Clinical Excellence.

Neff DF and Blachard EB (1987) A multi-component treatment for irritable bowel syndrome, *Behavior Therapy,* 18(1):70-83.

Netten A and Curtis L (2006) *Unit Costs of Health and Social Care 2006*, University of Canterbury, Kent: Personal Social Services Research Unit.

Newcastle University (2007) *http://www.ncl.ac.uk/nnp/teaching/management/dynamic/index.html [Accessed 6th August 2007]*, Newcastle: Newcastle University.

NHS Health and Social Care Information Centre HC (2006) *Prescription Cost Analysis, England 2005*, London: NHS Health and Social Care Information Centre, Health CareStatistics.

Niec AM, Frankum B, and Talley NJ (1998) Are adverse food reactions linked to irritable bowel syndrome?, *American Journal of Gastroenterology,* 93(11):2184-90.

Niedzielin K, Kordecki H, and Birkenfeld B (2001) A controlled, double-blind, randomized study on the efficacy of Lactobacillus plantarum 299V in patients with irritable bowel syndrome, *European Journal of Gastroenterology and Hepatology,* 13(10):1143-7.

Nigam P, Kapoor KK, Rastog CK, Kumar A, and Gupta AK (1984) Different therapeutic regimens in irritable bowel syndrome, *Journal of the Association of Physicians of India,* 32(12):1041-4.

Niv E, Naftali T, Hallak R, and Vaisman N (2005) The efficacy of Lactobacillus reuteri ATCC 55730 in the treatment of patients with irritable bowel syndrome--a double blind, placebo-controlled, randomized study, *Clinical Nutrition,* 24(6):925-31.

Nobaek S, Johansson ML, Molin G, Ahrne S, and Jeppsson B (2000) Alteration of intestinal microflora is associated with reduction in abdominal bloating and pain in patients with irritable bowel syndrome, *American Journal of Gastroenterology,* 95(5):1231-8.

O'Leary C, Wieneke P, Buckley S, O'Regan P, Cronin CC, Quigley EM, and Shanahan F (2002) Celiac disease and irritable bowel-type symptoms, *American Journal of Gastroenterology,* 97(6):1463-7.

O'Mahony L, McCarthy J, Kelly P, Hurley G, Luo F, Chen K, O'Sullivan GC, Kiely B, Collins JK, Shanahan F, and Quigley EM (2005) Lactobacillus and bifidobacterium in irritable bowel syndrome: symptom responses and relationship to cytokine profiles, *Gastroenterology,* 128(3):541-51.

O'Sullivan MA, Mahmud N, Kelleher DP, Lovett E, and O'Morain CA (2000) Patient knowledge and educational needs in irritable bowel syndrome, *European Journal of Gastroenterology and Hepatology,* 12(1):39-43.

Odes HS and Madar Z (1991) A double-blind trial of a celandin, aloevera and psyllium laxative preparation in adult patients with constipation, *Digestion,* 49(2):65-71.

OECD (2006) *OECD Health Data 2006*, Paris: OECD.
Office of National Statistics (2006) *Interim Life Tables, Expectation of Life, England and Wales*, London: Office of National Statistics.

Olden KW (2003) The challenge of diagnosing irritable bowel syndrome, *Reviews in Gastroenterological Disorders,* 3 Suppl 3:S3-11.

Olesen M and Gudmand-Hoyer E (2000) Efficacy, safety, and tolerability of fructooligosaccharides in the treatment of irritable bowel syndrome, *American Journal of Clinical Nutrition,* 72(6):1570-5.

Ouyang H and Chen JD (2004) Review article: therapeutic roles of acupuncture in functional gastrointestinal disorders, *Alimentary Pharmacology and Therapeutics,* 20(8):831-41.

Oxman AD, Cook DJ, and Guyatt GH (1994) Users' guides to the medical literature: VI. How to use an overview, *Journal of the American Medical Association,* 272(17):1367-71.

Page JG and Dirnberger GM (1981) Treatment of the irritable bowel syndrome with Bentyl (dicyclomine hydrochloride), *Journal of Clinical Gastroenterology,* 3(2):153-6.

Paille F, Colombey N, Alleaume B, and Vicari F (1999) An open six-month study of the safety of Transipeg for treating constipation in community medicine, Journal of Clinical Research, 2:65-76.

Palmer KR, Corbett CL, and Holdsworth CD (1980) Double-blind cross-over study comparing loperamide, codeine and diphenoxylate in the treatment of chronic diarrhea, *Gastroenterology,* 79(6):1272-5.

Palsson OS, Turner MJ, Johnson DA, Burnett CK, and Whitehead WE (2002) Hypnosis treatment for severe irritable bowel syndrome: Investigation of mechanism and effects on symptoms, *Digestive Diseases and Sciences,* 47(11):2605-14.

Parisi G, Bottona E, Carrara M, Cardin F, Faedo A, Goldin D, Marino M, Pantalena M, Tafner G, Verdianelli G, Zilli M, and Leandro G (2005) Treatment effects of partially hydrolyzed guar gum on symptoms and quality of life of patients with irritable bowel syndrome. A multicenter randomized open trial, *Digestive Diseases and Sciences,* 50(6):1107-12.

Parisi GC, Zilli M, Miani MP, Carrara M, Bottona E, Verdianelli G, Battaglia G, Desideri S, Faedo A, Marzolino C, Tonon A, Ermani M, and Leandro G (2002) High-fiber diet supplementation in patients with irritable bowel syndrome (IBS): a multicenter, randomized, open trial comparison between wheat bran diet and partially hydrolyzed guar gum (PHGG), *Digestive Diseases and Sciences,* 47(8):1697-704.

Paterson WG, Thompson WG, Vanner SJ, Faloon TR, Rosser WW, Birtwhistle RW, Morse JL, and Touzel TA (1999) Recommendations for the management of irritable bowel syndrome in family

practice. IBS Consensus Conference Participants, *Canadian Medical Association Journal,* 161(2):154-60.

Payne A and Blanchard EB (1995) A controlled comparison of cognitive therapy and self-help support groups in the treatment of irritable bowel syndrome, *Journal of Consulting and Clinical Psychology,* 63(5):779-86.

Pelemans W and Vantrappen F (1976) A double blind crossover comparison of loperamide with diphenoxylate in the symptomatic treatment of chronic diarrhea, *Gastroenterology,* 70(6):1030-4.

Pimentel M, Chow EJ, and Lin HC (2000) Eradication of small intestinal bacterial overgrowth reduces symptoms of irritable bowel syndrome, *American Journal of Gastroenterology,* 95(12):3503-6.

Pimentel M, Chow EJ, and Lin HC (2003) Normalization of lactulose breath testing correlates with symptom improvement in irritable bowel syndrome. a double-blind, randomized, placebo-controlled study, *American Journal of Gastroenterology,* 98(2):412-9.

Poynard T, Couturier D, Frexinos J, Bommelaer G, Hernandez M, Dapoigny M, Buscail L, Benand-Agostini H, Chaput JC, and Rheims N (1992) French experience of Manning's criteria in the irritable bowel syndrome, *European Journal of Gastroenterology and Hepatology,* 4(9):747-52.

Prior A and Whorwell PJ (1987) Double blind study of ispaghula in irritable bowel syndrome, *Gut,* 28(11):1510-3.

Quah HM, Ooi BS, Seow-Choen F, Sng KK, and Ho KS (2006) Prospective randomized crossover trial comparing fibre with lactulose in the treatment of idiopathic chronic constipation, *Techniques in Coloproctology,* 10(2):111-4.

Quartero AO, Meineche-Schmidt V, Muris J, Rubin G, and de Wit N (2007) Bulking agents, antispasmodic and antidepressant medication for the treatment of irritable bowel syndrome., *Cochrane Database of Systematic Reviews,* 2005, Issue 2. Art. No.: CD003460. DOI: 10.1002/14651858.CD003460.pub2.

Quigley EMM (2007) Bacterial flora in irritable bowel syndrome: Role in pathophysiology, implications for management, *Chinese Journal of Digestive Diseases,* 8(1):2-7.

Radnitz CL and Blanchard EB (1989) A 1- and 2- year follow-up study of bowel sound biofeedback as a treatment for irritable bowel syndrome, *Biofeedback & Self Regulation.,* 14(4):333-8.

Rajagopalan M, Kurian G, and John J (1998) Symptom relief with amitriptyline in the irritable bowel syndrome, *Journal of Gastroenterology and Hepatology,* 13(7):738-41.

Rao KP, Gupta S, Jain AK, Agrawal AK, and Gupta JP (363) Evaluation of Manning's criteria in the diagnosis of irritable bowel syndrome, *Journal of the Association of Physicians of India,* 41(6):357-8.

Rao SSC, Welcher K, Zimmerman B, and Stumbo P (1998) Is coffee a colonic stimulant?, *European Journal of Gastroenterology and Hepatology,* 10(2):113-8.

Rees GA, Trevan M, and Davies GJ (1994) Dietary fibre modification and the symptoms of irritable bowel syndrome - A review, *Journal of Human Nutrition & Dietetics,* 7(3):179-89.

Reid G (2001) *Regulatory and clinical aspects of dairy probiotics. Joint FAO/WHO Expert Consultation on Evaluation of Health and Nutritional Properties of Probiotics in Food Including Powder Milk with Live Lactic Acid Bacteria. Cordoba (Argentina), 1-4 Oct 2001*, Rome: Italy.

Ringel Y and Drossman DA (2001) Psychosocial Factors in Functional Gastrointestinal Disorders: Toward a More Comprehensive Understanding and Approach to Treatment, *Medscape,* http://www.medscape.com/viewarticle/418547 [Accessed 9th August 2007]

Ritchie JA and Truelove SC (1979) Treatment of irritable bowel syndrome with lorazepam, hyoscine butylbromide, and ispaghula husk, *British Medical Journal,* 1(6160):376-8.

Roberts L, Wilson S, Singh S, Roalfe A, and Greenfield S (2006) Gut-directed hypnotherapy for irritable bowel syndrome: piloting a primary care-based randomised controlled trial, *British Journal of General Practice,* 56(523):115-21.

Robinson A, Lee V, Kennedy A, Middleton L, Rogers A, Thompson DG, and Reeves D (2006) A randomised controlled trial of self-help interventions in patients with a primary care diagnosis of irritable bowel syndrome, *Gut,* 55(5):643-8.

Rogers A, Lee V, and Kennedy A (2007) Continuity and change?: Exploring reactions to a guided self-management intervention in a randomised controlled trial for IBS with reference to prior experience of managing a long term condition, *Trials [Electronic Resource],* 8, 2007. Article Number

Rothstein RD (2000) Irritable bowel syndrome, *Medical Clinics of North America,* 84(5):1247-57.

Rouse M, Chapman N, Mahapatra M, Grillage M, Atkinson SN, and Prescott P (1991) An open, randomised, parallel group study of lactulose versus ispaghula in the treatment of chronic constipation in adults, *British Journal of Clinical Practice,* 45(1):28-30.

Saggioro A (2004) Probiotics in the treatment of irritable bowel syndrome, *Journal of Clinical Gastroenterology,* 38(6 Suppl):S104-S106.

Saito YA, Locke GR, Talley NJ, Zinsmeister AR, Fett SL, and Melton LJ, III (2000) A comparison of the Rome and Manning criteria for case identification in epidemiological investigations of irritable bowel syndrome, *American Journal of Gastroenterology,* 95(10):2816-24.

Saito YA, Talley NJ, Melton J, Fett S, Zinsmeister AR, and Locke GR (2003) The effect of new diagnostic criteria for irritable bowel syndrome on community prevalence estimates, *Neurogastroenterology and Motility,* 15(6):687-94.

Sanders DS, Carter MJ, Hurlstone DP, Pearce A, Ward AM, McAlindon ME, and Lobo AJ (2001) Association of adult coeliac disease with irritable bowel syndrome: a case-control study in patients fulfilling ROME II criteria referred to secondary care, *Lancet,* 358(9292):1504-8.

Sanders DS, Patel D, Stephenson TJ, Ward AM, McCloskey EV, Hadjivassiliou M, and Lobo AJ (2003) A primary care cross-sectional study of undiagnosed adult coeliac disease, *European Journal of Gastroenterology and Hepatology,* 15(4):407-13.

Sanjoaquin MA, Appleby PN, Spencer EA, and Key TJ (2004) Nutrition and lifestyle in relation to bowel movement frequency: A cross-sectional study of 20 630 men and women in EPIC-Oxford, *Public Health Nutrition,* 7(1):77-83.

Schafer E and Ewe K (1990) [The treatment of irritable colon. Efficacy and tolerance of buscopan plus, buscopan, paracetamol and placebo in ambulatory patients with irritable colon], *Fortschritte Der Medizin,* 108(25):488-92.

Schaffstein W, Panijel M, and Luttecke K (1990) Comparative safety and efficacy of trimebutine versus mebeverine in the treatment of irritable bowel syndrome. A multicenter double-blind study, *Current Therapeutic Research, Clinical and Experimental,* 47(1):136-45.

Schneider A, Enck P, Streitberger K, Weiland C, Bagheri S, Witte S, Friederich HC, Herzog W, and Zipfel S (2006) Acupuncture treatment in irritable bowel syndrome, *Gut,* 55(5):649-54.

Schuster MM (1991) Diagnostic evaluation of the irritable bowel syndrome, *Gastroenterology Clinics of North America,* 20(2):269-78.

Schuster MM (2001) Defining and diagnosing irritable bowel syndrome., *American Journal of Managed Care,* 7(8 Suppl):S246-S251.

Scottish Nutrition and Diet Resources Initiative (2004) *Irritable Bowel Syndrome (IBS) Your Diet Can Help [Available from: http://www.caledonian.ac.uk/sndri/pdf/IrritableBowelSyndrome.pdf]*, Glasgow: Caledonian University.

Shrivastava RK and Siegel H (1984) The role of tricyclics and benzodiazepine compounds in the treatment of irritable gut syndrome and peptic ulcer disease, *Psychopharmacology Bulletin,* 20(4):616-21.

Skoog SM and Bharucha AE (2004) Dietary fructose and gastrointestinal symptoms: A review, *American Journal of Gastroenterology,* 99(10):2046-50.

Smith RC (1992) Diagnosing the irritable bowel syndrome, *Annals of Internal Medicine,* 117(12):1056-7.

Snook J and Shepherd HA (1994) Brain supplementation in the treatment of irritable bowel syndrome, *Alimentary Pharmacology and Therapeutics,* 8(5):511-4.

Soltoft J, Krag B, Gudmand-Hoyer E, Kristensen E, and Wulff HR (1976) A double-blind trial of the effect of wheat bran on symptoms of irritable bowel syndrome, *Lancet,* 1(7954):270-2.

Spiegel BM, DeRosa VP, Gralnek IM, Wang V, Dulai GS, Spiegel BMR, DeRosa VP, Gralnek IM, Wang V, and Dulai GS (2004) Testing for celiac sprue in irritable bowel syndrome with predominant diarrhea: a cost-effectiveness analysis, *Gastroenterology,* 126(7):1721-32.

Steinhart MJ, Wong PY, and Zarr ML (1981) Therapeutic usefulness of amitriptyline in spastic colon syndrome, *International Journal of Psychiatry in Medicine,* 11(1):45-57.

Steinmann B, Gitzelmann R, and Van den Berghe G (2007) 'Disorders of Fructose Metabolism', in: Scriver CR, (editor) *The Metabolic Basis of Inherited Disease. Vol 1.* New York; London: McGraw-Hill, 1511.

Suleiman S, Sonnenberg A, Suleiman S, and Sonnenberg A (2001) Cost-effectiveness of endoscopy in irritable bowel syndrome, *Archives of Internal Medicine,* 161(3):369-75.

Symons P, Jones MP, and Kellow JE (1992) Symptom provocation in irritable bowel syndrome. Effects of differing doses of fructose-sorbitol, *Scandinavian Journal of Gastroenterology,* 27(11):940-4.

Tabas G, Beaves M, Wang J, Friday P, Mardini H, and Arnold G (2004) Paroxetine to treat irritable bowel syndrome not responding to high-fiber diet: a double-blind, placebo-controlled trial., *American Journal of Gastroenterology,* 99(5):914-20.

Talley NJ, Phillips SF, Melton LJ, Mulvihill C, Wiltgen C, and Zinsmeister AR (1990) Diagnostic value of the Manning criteria in irritable bowel syndrome, *Gut,* 31(1):77-81.

Talley NJ (2003) When to conduct testing in patients with suspected irritable bowel syndrome, *Reviews in Gastroenterological Disorders,* 3 Suppl 3:S18-S24.

Taneja I, Deepak KK, Poojary G, Acharya IN, Pandey RM, and Sharma MP (2004) Yogic versus conventional treatment in diarrhea-predominant irritable bowel syndrome: a randomized control study, *Applied Psychophysiology and Biofeedback,* 29(1):19-33.

Tanum L and Malt UF (1996) A new pharmacologic treatment of functional gastrointestinal disorder. A double-blind placebo-controlled study with mianserin, *Scandinavian Journal of Gastroenterology,* 31(4):318-25.

Tarpila S, Tarpila A, Grohn P, Silvennoinen T, and Lindberg L (2004) Efficacy of ground flaxseed on constipation in patients with irritable bowel syndrome, *Current Topics in Nutraceuticals Research,* 2(2):119-25.

Thomas B (2001) 'Disorders of the colon: Irritable Bowel Synrome', in: Thomas B, (editor) *Manual of Dietetic Practice.* Oxford: Blackwell Scientific Publications, 398-400.

Thomas BJ (1992) British Diabetic Association's discussion paper on the role of 'diabetic' foods, *Diabetic Medicine,* 9(3):300-6.

Thompson WG, Dotevall G, Drossman DA, Heaton KW, and Kruis W (1989) Irritable bowel syndrome: Guidelines for the diagnosis, *Gastroenterology International,* 2(2):92-5.

Thompson WG (1997) Gender differences in irritable bowel symptoms, *European Journal of Gastroenterology and Hepatology,* 9(3):299-302.

Tijtgat GN, Meuwissen SG, and Huibregtse K (1975) Loperamide in the symptomatic control of chronic diarrhoea. Double-blind placebo-controlled study, *Annals of Clinical Research,* 7(5):325-30.

Tkachuk GA, Graff LA, Martin GL, and Bernstein CN (2003) Randomized controlled trial of cognitive-behavioral group therapy for irritable bowel syndrome in a medical setting, *Journal of Clinical Psychology in Medical Settings,* 10(1):57-69.

Tolliver BA, Herrera JL, and DiPalma JA (1994) Evaluation of patients who meet clinical criteria for irritable bowel syndrome, *American Journal of Gastroenterology,* 89(2):176-8.

Tovey P (2002) A single-blind trial of reflexology for irritable bowel syndrome, *British Journal of General Practice,* 52(474):19-23.

Tripathi BM, Misra NP, and Gupta AK (1983) Evaluation of tricyclic compound (trimipramine) vis-a-vis placebo in irritable bowel syndrome. (Double blind randomised study), *Journal of the Association of Physicians of India,* 31(4):201-3.

Tsuchiya J, Barreto R, Okura R, Kawakita S, Fesce E, and Marotta F (2004) Single-blind follow-up study on the effectiveness of a symbiotic preparation in irritable bowel syndrome, *Chinese Journal of Digestive Diseases,* 5(4):169-74.

Tynes LL and Gibson RL (1999) Irritable bowel syndrome: overview of diagnosis and treatment, *Journal of the Louisiana State Medical Society,* 151(2):76-81.

UK Council for Psychotherapy (UKCP) (1992) *Hypno-Psychotherapy Section [http://www.psychotherapy.org.uk/hypno_psychotherapy.html]*, London: UK Council for Psychotherapy.

Van Outryve M, Mayeur S, Meeus MA, Rosillon D, Hendrickx B, and Ceuppens M (1995) A double-blind crossover comparison study of the safety and efficacy of mebeverine with mebeverine sustained release in the treatment of irritable bowel syndrome, *Journal of Clinical Pharmacy and Therapeutics,* 20(5):277-82.

Vanner SJ, Depew WT, Paterson WG, DaCosta LR, Groll AG, Simon JB, and Djurfeldt M (1999) Predictive value of the Rome criteria for diagnosing the irritable bowel syndrome., *American Journal of Gastroenterology,* 94(10):2912-7.

Verhaegen H, De Cree J, and Schuermans V (1974) Loperamide (R 18 553), a novel type of antidiarrheal agent. Part 7: Clinical investigation. Efficacy and safety of loperamide in patients with severe chronic diarrhea, *Arzneimittel-Forschung,* 24(10):1657-60.

Vesa TH, Seppo LM, Martea PR, Sahi T, and Korpela R (1998) Role of irritable bowel syndrome in subjective lactose intolerance, *American Journal of Clinical Nutrition,* 67(4):710-05.

Vij JG, JR, and KN (1991) Effect of antidepressant drug (doxepin) on irritable bowel syndrome patients, *Indian Journal of Psychiatry,* 33:243-6.

Villagrasa M, Boix J, Humbert P, and Quer JC (1991) Aleatory clinical study comparing otilonium bromide with a fiber-rich diet in the treatment of irritable bowel syndrome, *Italian Journal of Gastroenterology,* 23(8 Suppl 1):67-70.

Vollmer A and Blanchard EB (1998) Controlled comparison of individual versus group cognitive therapy for irritable bowel syndrome, *Behavior Therapy,* 29(1):19-33.

Wang G, Li TQ, Wang L, Xia Q, Chang J, Zhang Y, Wan MH, Guo J, Cheng Y, Huang X, and Zhang RM (2006) Tong-xie-ning, a Chinese herbal formula, in treatment of diarrhea-predominant irritable bowel syndrome: a prospective, randomized, double-blind, placebo-controlled trial, *Chinese Medical Journal,* 119(24):2114-9.

Watson AR and Bowling TE (2005) Irritable bowel syndrome: diagnosis and symptom management, *British Journal of Community Nursing,* 10(3):118-22.

West J, Logan RF, Smith CJ, Hubbard RB, and Card TR (2004) Malignancy and mortality in people with coeliac disease: population based cohort study, *British Medical Journal,* 329(7468):716-9.

Whorwell PJ, Prior A, and Faragher EB (1984) Controlled trial of hypnotherapy in the treatment of severe refractory irritable-bowel syndrome, *Lancet,* 2(8414):1232-4.

Whorwell PJ, Altringer L, Morel J, Bond Y, Charbonneau D, O'Mahony L, Kiely B, Shanahan F, and Quigley EM (2006) Efficacy of an encapsulated probiotic Bifidobacterium infantis 35624 in women with irritable bowel syndrome, *American Journal of Gastroenterology,* 101(7):1581-90.

Wiklund IK, Fullerton S, Hawkey CJ, Jones RH, Longstreth GF, Mayer EA, Peacock RA, Wilson IK, and Naesdal J (2003) An irritable bowel syndrome-specific symptom questionnaire: development and validation, *Scandinavian Journal of Gastroenterology,* 38(9):947-54.

Wilhelmsen I (2000) The role of psychosocial factors in gastrointestinal disorders, *Gut,* 47(Suppl 4):73-5.

Wolf S (1981) The psyche and the stomach. A historical vignette, *Gastroenterology,* 80:605-14.

Wulkow R, Vix JM, Schuijt C, Peil H, Kamm MA, and Jordan C (2007) Randomised, placebo-controlled, double-blind study to investigate the efficacy and safety of the acute use of sodium picosulphate in patients with chronic constipation, *International Journal of Clinical Practice,* 61(6):944-50.

Yadav SK, Jain AK, Tripathi SN, and Gupta JP (1989) Irritable bowel syndrome: Therapeutic evaluation of indigenous drugs, *Indian Journal of Medical Research,* 90:496-503.

Zastrow C and Navarre R (1977) Nominal Group - New Tool for Making Social-Work Education Relevant, *Journal of Education for Social Work,* 13(1):112-8.

Work Smart Session - MRCP Part 1

Time taken: 3 hrs 46 mins 41 secs

Question: 59 of 100

An 81-year-old frail man admitted with a stroke becomes increasingly drowsy after receiving nasogastric (NG) feeding for five days.

Which biochemical abnormality is the most likely cause of his drowsiness?

(Please select 1 option)

- ○ Hyperglycaemia
- ○ Hypermagnesaemia
- ○ Hypernatraemia
- ○ Hypocalcaemia
- ○ Hypophosphataemia

Submit answer | Skip question | Tag Question | Remove question

Questions Set : REF4968 - Windows Internet Explorer
http://my.onexamination.com/Assessment/Questions.aspx
Favorites Suggested Sites Get More Add-ons
Hotmail - dr.zahir200... Questions Set : RE... how to take a screens... Learn how to make a ... How to Take a Screen... How to Take a Screen...
Page Safety Tools

(Please select 1 option)

○	In the absence of anaemia transferrin is 80% saturated with iron
○	Levels are elevated in haemochromatosis
○	Levels are elevated in patients on the oral contraceptive pill ← This is the correct answer
○	Transferrin binds ferrous iron
◉	Transferrin levels fall during pregnancy ✕ Incorrect answer selected

Pregnancy and the oral contraceptive pill (OCP) both increase transferrin levels. Iron is carried in the blood bound to transferrin. Fe^{2+} (ferrous iron) is oxidised to Fe^{3+} (ferric iron) by caeruloplasmin to bind to transferrin which is about one third saturated with iron.

The saturation of transferrin (plasma iron concentration/TIBC x 100) is used as a measure of iron stores. A value below 16% is indicative of iron deficiency.

The transferrin level and the TIBC rise in iron deficiency. Pregnancy and the OCP both increase transferrin levels; whereas transferrin and TIBC fall in iron overload, percentage saturation is increased in haemochromatosis.

Next question Tag Question Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Internet | Protected Mode: On 125%

Work Smart Session - MRCP Part 1

Time taken:

Question: 1 of 19

Which one of the following drugs is associated with hypersensitivity reactions?

(Please select 1 option)

- Atazanavir
- Lamivudine
- Nevirapine
- Tenofovir
- Zidovudine

Submit answer | Skip question | Tag Question | Remove question

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 14 mins 3 secs

Question: 10 of 19

A 34-year-old homosexual Caucasian man developed jaundice two months after taking a combination of antiretroviral drugs.

He admitted that he had had several episodes of unprotected sex with several casual male partners. His liver function showed raised bilirubin with normal transaminases and alkaline phosphatase.

What is the most likely cause of his jaundice?

(Please select 1 option)

- ○ Acute hepatitis B
- ○ Alcoholic hepatitis
- ○ Atazanavir
- ○ Efavirenz
- ○ Nevirapine

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

A 34-year-old homosexual Caucasian man developed jaundice two months after taking a combination of antiretroviral drugs.

He admitted that he had had several episodes of unprotected sex with several casual male partners. His liver function showed raised bilirubin with normal transaminases and alkaline phosphatase.

What is the most likely cause of his jaundice?

(Please select 1 option)

○	Acute hepatitis B
○	Alcoholic hepatitis
○	Atazanavir ← This is the correct answer
◉	Efavirenz ✕ Incorrect answer selected
○	Nevirapine

Atazanavir causes hyperbilirubinaemia with normal transaminases and alkaline phosphatase (mimicking Gilbert's syndrome).

Acute hepatitis B is unlikely with normal trasaminases and alkaline phosphatase.

A mild to moderate rise in trasaminases and alkaline phosphatase occurs in alcoholic hepatitis.

Efavirenz can cause acute hepatitis with raised levels of transaminases.

Nevirapine causes acute hepatitis where transaminases are raised several fold.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 16 mins 29 secs

Question: 11 of 19

Which one of the following antiretrovirals is likely to cause increased pigmentation of the skin in a black African patient?

(Please select 1 option)

- Didanosine
- Efavirenz
- Emtricitabine
- Nevirapine
- Stavudine

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Question: 11 of 19

Which one of the following antiretrovirals is likely to cause increased pigmentation of the skin in a black African patient?

(Please select 1 option)

◉	Didanosine ✕ Incorrect answer selected
○	Efavirenz
○	Emtricitabine ← This is the correct answer
○	Nevirapine
○	Stavudine

Emtricitabine causes hyperpigmentation of skin including palmar creases in 8% of black patients.

Didanosine and stavudine cause mitochondrial toxicity, hence peripheral neuropathy, pancreatitis and hyperlactataemia.

Efavirenz causes CNS toxicity.

Nevirapine causes acute hepatitis and skin rash.

Reference:
Levin J. Evaluation of hyperpigmentation in HIV infected patients receiving emtricitabine (FTC, Emtriva), International AIDS conference, Rio de Janeiro, Brazil, July 24-27, 2005.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 17 mins 8 secs

Question: 12 of 19

Which of the following is a sign of immunodeficiency in the mouth?

(Please select 1 option)

○	Gingivitis
○	Herpes labialis
○	Leucoplakia
○	Oral hairy leucoplakia
○	Oral wart

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Question: 12 of 19

Which of the following is a sign of immunodeficiency in the mouth?

(Please select 1 option)

○	Gingivitis
○	Herpes labialis
○	Leucoplakia
◉	Oral hairy leucoplakia ✓ Correct
○	Oral wart

Oral hairy leucoplakia is a sign of immunodefiency. It is due to reactivation of Epstein-Barr virus infection.

Gingivitis is not a sign of immunodefiency.

Leucoplakia is not a sign of immunodefiency but it is a precancerous lesion.

Herpes labialis is due to herpes simplex infection, which causes 'cold sores' in immunocompetent patients and chronic herpes labialis in immunocompromised patients.

Oral warts can occur in healthy people. They are due to HPV infection usually due to benign types, 6 and 11.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 17 mins 45 secs

Question: 13 of 19

A 32-year-old African woman with HIV presents with a two week history of greenish, frothy, itchy vaginal discharge.

What is the most likely cause of her discharge?

(Please select 1 option)

○	*Candida albicans* infection
○	*Chlamydia* infection
○	Foreign body
○	Gonorrhoea infection
○	*Trichomonas vaginalis* infection

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Question: 13 of 19

A 32-year-old African woman with HIV presents with a two week history of greenish, frothy, itchy vaginal discharge.

What is the most likely cause of her discharge?

(Please select 1 option)

○	*Candida albicans* infection
○	*Chlamydia* infection
○	Foreign body
○	Gonorrhoea infection
◉	*Trichomonas vaginalis* infection ✓ Correct

Trichomonas vaginalis causes itchy, frothy, greenish vaginal discharge.

Candida albicans causes a white, curdy, itchy vaginal discharge.

Chlamydia and gonorrhoea do not cause itchy, frothy vaginal discharge and both can be asymptomatic.

Foreign body causes foul smelling vaginal discharge.

Further reading:
United Kingdom National Guideline on the Management of *Trichomonas vaginalis* (2007) (pdf) BASHH

Next question

Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 19 mins 1 secs

Question: 14 of 19

A 51-year-old homosexual Caucasian HIV positive man developed multiple violaceous painless lesions on his trunk.

Which one of the following is the most likely cause of his skin lesions?

(Please select 1 option)

○	Cytomegalovirus (CMV)
○	Human herpes virus 8 (HHV8)
○	Human herpes virus 10 (HHV 10)
○	Human papilloma virus 16 (HHV 16)
○	Pox virus

Submit answer | Skip question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 20 mins 25 secs

Question: 14 of 19

A 51-year-old homosexual Caucasian HIV positive man developed multiple violaceous painless lesions on his trunk.

Which one of the following is the most likely cause of his skin lesions?

(Please select 1 option)

○	Cytomegalovirus (CMV)
◉	Human herpes virus 8 (HHV8) ✓ Correct
○	Human herpes virus 10 (HHV 10)
○	Human papilloma virus 16 (HHV 16)
○	Pox virus

Multiple violaceous painless lesions are typical of Kaposi's sarcoma in Caucasians. It is associated with HHV 8.

CMV and HHV 10 do not cause multiple violaceous painless lesions.

HPV 16 is an oncogenic virus which causes squamous cell carcinomas.

Pox virus causes molluscum contagiosum.

Next question

Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 20 mins 25 secs

Question: 15 of 19

A 35-year-old HIV positive African woman presented with weakness of both legs and double incontinence.

CSF showed increased protein and neutrophils with normal glucose.

What is the most likely cause of her weakness?

(Please select 1 option)

- CMV polyradiculomyelopathy
- Guillain-Barré syndrome
- Herpes virus encephalitis
- HIV encephalopathy
- Toxoplasma encephalitis

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

A 35-year-old HIV positive African woman presented with weakness of both legs and double incontinence.

CSF showed increased protein and neutrophils with normal glucose.

What is the most likely cause of her weakness?

(Please select 1 option)

○	CMV polyradiculomyelopathy ← This is the correct answer
◉	Guillain-Barré syndrome ✕ Incorrect answer selected
○	Herpes virus encephalitis
○	HIV encephalopathy
○	Toxoplasma encephalitis

Symptoms are suggestive of polyradicularmyelopathy (weakness of legs with involvement of sphincters).

Increased neutrophils are found in CMV polyradiculomyelopathy but not in Guillain-Barré syndrome.

HIV encephalopathy usually causes confusion and memory loss. It does not involve sphincters.

Guillain-Barré syndrome causes polyradiculopathy, explaining all her symptoms, but with normal cell counts and raised protein in the CSF.

Herpes simplex encephalitis causes fever, headache, confusion and deteriorating level of consciousness.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 22 mins 36 secs

Question: 16 of 19

A 48-year-old African man with HIV was prescribed a combination of antiretroviral therapy. He developed increased diffuse pigmentation of the nails in both hands and toes.

What is the most likely cause of the increased pigmentation of the nails?

(Please select 1 option)

- Efavirenz
- Lamivudine
- Nevirapine
- Tenofovir
- Zidovudine

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

(Please select 1 option)

○	Efavirenz
○	Lamivudine
○	Nevirapine
◉	Tenofovir ✕ Incorrect answer selected
○	Zidovudine ← This is the correct answer

Zidovudine causes increased pigmentation of the nails in black patients.

Efavirenz causes central nervous system toxicity not hyperpigmentation.

Lamivudine does not normally cause hyperpigmentation of nails but it can occasionally cause hyperpigmentation of the skin in black people.

Nevirapine does not cause hyperpigmentation of skin but can cause acute hepatitis and skin rash.

Tenofovir can cause proximal tubular damage hence Fanconi-like syndrome.

Reference:

Furth PA, Kazakis AM. Nail pigmentation changes associated with azidothymidine (zidovudine). Ann Intern Med. 1987 Sep; 107(3): 350.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 24 mins

Question: 17 of 19

A 39-year-old Caucasian man with symptomatic HIV disease developed multiple painless umbilicated papular lesions on his face.

What is the most likely cause of his skin lesions?

(Please select 1 option)

○	Cytomegalovirus (CMV)
○	Epstein Barr virus (EBV)
○	Human herpes virus (HHV) 8
○	Human papilloma virus (HPV 16)
○	Pox virus

Submit answer | Skip question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

(Please select 1 option)

○	Cytomegalovirus (CMV)
○	Epstein Barr virus (EBV)
○	Human herpes virus (HHV) 8
◉	Human papilloma virus (HPV 16) ✕ Incorrect answer selected
○	Pox virus ← This is the correct answer

Multiple painless umbilicated papular lesions are typical of molluscum contagiosum and it is caused by pox virus.

CMV does not cause painless papular lesions.

EBV causes Burkitt's lymphoma, non-Hodgkin's lymphoma and primary brain lymphomas.

HHV 8 is strongly associated with Kaposi's sarcoma.

HPV 16 is associated with squamous cell carcinomas in cervix, penis, anus and oral cavity.

Reference:

Bain S, Yoganathan K. Physical Signs for the General Practitioner. Case 51. Molluscum contagiosum. Dental update. 2008; 68.

Yoganathan K, Patel RN, Maitland N, McManus TJ, Calman FM, Pozniak A. Carcinoma of the penis in a HIV positive patient. Genitourin Med.1995 Feb; 71 (1): 41-2.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 25 mins 12 secs

Question: 18 of 19

A 46-year-old homosexual HIV positive man presents with a two week history of weakness of his right arm and leg.

Examination reveals right hemiparesis and left cerebellar signs. CT scan shows white matter lesions in left cerebellar region and left temporoparietal area. There is no midline shift or surrounding oedema.

Which one of the following is most likely to be found in his cerebrospinal fluid (CSF)?

(Please select 1 option)

- Positive cytomegalovirus (CMV) PCR
- Positive Epstein-Barr virus (EBV) PCR
- Positive herpes simplex virus (HSV) PCR
- Positive human herpes virus (HHV) 8 PCR
- Positive JC PCR

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Which one of the following is most likely to be found in his cerebrospinal fluid (CSF)?

(Please select 1 option)

○	Positive cytomegalovirus (CMV) PCR
○	Positive Epstein-Barr virus (EBV) PCR
○	Positive herpes simplex virus (HSV) PCR
○	Positive human herpes virus (HHV) 8 PCR
◉	Positive JC PCR ✓ Correct

Multifocal lesions in left cerebellar and temporoparietal white matter areas without any mass effect or surrounding oedema are most likely to be due to progressive multifocal leucoencephalopathy (PML).

JC virus causes PML in immunocompromised patients especially when the CD4 count is below 100 cells/mm^3.

CMV polymerase chain reaction (PCR) may be found in CMV encephalitis. It is clinically not a typical feature of CMV encephalitis.

Positive EBV PCR indicates primary brain lymphoma where CT scan often shows significant mass effect with surrounding oedema.

HSV PCR may be found in HSV encephalitis which commonly affects temporal lobes in patients with good CD4 count.

HHV 8 PCR is usually associated with Kaposi's sarcoma.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 26 mins 43 secs

Question: 19 of 19

Which of the following is characteristic of Bartter's syndrome?

(Please select 1 option)

○	Diarrhoea
○	Hyperkalaemia
○	Metabolic acidosis
○	Secondary hyperaldosteronism
○	Reduced renal concentrating ability

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

	Metabolic acidosis
◉	Secondary hyperaldosteronism ✓ Correct
	Reduced renal concentrating ability

Bartter's syndrome is a rare form of renal potassium wasting characterised by hypokalaemia, normotension, and elevated renin and aldosterone levels.

It is occasionally autosomal recessive.

There is hyperplasia of the juxtaglomerular apparatus in most cases.

It is postulated that the primary defect is in chloride reabsorption in the ascending limb, resulting in sodium chloride excessively presented to the distal tubule, with sodium reabsorption in exchange for potassium, resulting in urinary sodium wasting.

There is secondary stimulation of prostaglandin synthesis, which activates the renin angiotensin aldosterone system which exacerbates the renal potassium wasting.

Younger children typically present with

- growth failure
- muscle weakness
- constipation
- polyuria
- dehydration.

Older children typically present with

The potassium is <2.5 mmol/l, there is metabolic alkalosis, and hyperammonaemia with hyperaldosteronism.

There are high levels of urinary potassium and chloride.

The high urinary chloride level is helpful in distinguishing it from similar presentations which have low urinary chloride levels, such as

- liquorice, laxative, or diuretic use

It is postulated that the primary defect is in chloride reabsorption in the ascending limb, resulting in sodium chloride excessively presented to the distal tubule, with sodium reabsorption in exchange for potassium, resulting in urinary sodium wasting.

There is secondary stimulation of prostaglandin synthesis, which activates the renin angiotensin aldosterone system which exacerbates the renal potassium wasting.

Younger children typically present with

- growth failure
- muscle weakness
- constipation
- polyuria
- dehydration.

Older children typically present with

The potassium is <2.5 mmol/l, there is metabolic alkalosis, and hyperammonaemia with hyperaldosteronism.

There are high levels of urinary potassium and chloride.

The high urinary chloride level is helpful in distinguishing it from similar presentations which have low urinary chloride levels, such as

- liquorice, laxative, or diuretic use
- persistent vomiting or diarrhoea
- pyelonephritis
- diabetes insipidus.

Oral potassium and indomethacin may be used.

Finish

Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Which one of the following drugs is associated with hypersensitivity reactions?

(Please select 1 option)

○	Atazanavir
○	Lamivudine
◉	Nevirapine ✓ Correct
○	Tenofovir
○	Zidovudine

Nevirapine can cause acute hepatitis and skin rash as a part of hypersensitive reaction especially when the CD4 count is over 250 cells/ml in women and over 400 cells/ml in men. Nevirapine should not be prescribed in those conditions.

Atazanavir causes hyperbilirubinaemia and rarely renal stones.

Lamivudine does not cause hypersensitivity reaction.

Tenofovir causes proximal tubular damage.

Zidovudine causes bone marrow suppression.

Reference:

Danino S, Yoganathan K, Jones P, Banner T. Urolithiasis in an HIV infected patient - a link with atazanavir? 2007; BHIVA spring meeting, Edinburgh.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 mins 45 secs

Question: 2 of 19

A 36-year-old Caucasian woman was successfully treated for *Pneumocystis jirovecii* pneumonia (PCP).

She was re-admitted with acute breathlessness with left-sided chest pain ten days after her discharge from the hospital. Examination revealed that she was hypoxic and found to have diminished breath sounds on the left side of chest.

What is the most likely cause of her recent admission?

(Please select 1 option)

- Acute myocardial infarction
- Acute pericarditis
- Acute pulmonary embolism
- Left lobar pneumonia
- Pneumothorax

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

A 36-year-old Caucasian woman was successfully treated for *Pneumocystis jirovecii* pneumonia (PCP).

She was re-admitted with acute breathlessness with left-sided chest pain ten days after her discharge from the hospital. Examination revealed that she was hypoxic and found to have diminished breath sounds on the left side of chest.

What is the most likely cause of her recent admission?

(Please select 1 option)

○	Acute myocardial infarction
○	Acute pericarditis
○	Acute pulmonary embolism
○	Left lobar pneumonia
◉	Pneumothorax ✓ Correct

Pneumothorax is a well-known complication of PCP. An acute history of chest pain with breathlessness and diminished breath sounds is typical of pneumothorax.

Diminished breath sounds are not a feature of acute myocardial infarction or acute pericarditis.

Acute pulmonary embolism should be considered due to her recent admission but diminished breath sounds are not a feature.

There are no signs of consolidation to consider lobar pneumonia.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 4 mins 26 secs

Question: 3 of 19

Which one of the following cutaneous lesions is associated with HIV infection?

(Please select 1 option)

○	Leucoplakia
○	Lichen planus
○	Lichen sclerosus
○	Plasma cell balanitis
○	Psoriasis

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 6 mins 4 secs

Question: 3 of 19

Which one of the following cutaneous lesions is associated with HIV infection?

(Please select 1 option)

◉	Leucoplakia ✕ Incorrect answer selected
○	Lichen planus
○	Lichen sclerosus
○	Plasma cell balanitis
○	Psoriasis ← This is the correct answer

It occurs in 2-4% of healthy people. If pre-existing psoriasis flares up for no apparent reason or middle-aged people develop psoriasis for the first time, one should exclude underlying HIV infection in those patients.

Leucoplakia is a pre-cancerous lesion whereas oral hairy leucoplakia is a sign of immunodefiency in an HIV positive patient.

Lichen planus, lichen sclerosus and plasma cell balanitis are not associated with HIV infection.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 6 mins 4 secs

Question: 4 of 19

Which one of the following is an AIDS defining illness?

(Please select 1 option)

- Anal canal warts
- Extra genital molluscum contagiosum
- Multidermatomal shingles
- Oesophageal candidiasis
- Oral candidiasis

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 6 mins 45 secs

Question: 4 of 19

Which one of the following is an AIDS defining illness?

(Please select 1 option)

○	Anal canal warts
○	Extra genital molluscum contagiosum
○	Multidermatomal shingles
○	Oesophageal candidiasis ← This is the correct answer
◉	Oral candidiasis ✕ Incorrect answer selected

Any opportunistic infections or opportunistic malignancies are AIDS defining illnesses.

Oesophageal candidiasis is an AIDS defining illness but oral candidiasis is not.

Anal warts are not an opportunistic infection.

Extra genital molluscum contagiosum is also not an opportunistic infection but frequently occurs in symptomatic HIV positive patients.

Multidermatomal shingles is not an opportunistic infection but if it occurs in a young person HIV infection needs to be excluded.

Next question | Tag Question | Remove question

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 6 mins 45 secs

Question: 5 of 19

A 31-year-old African man presented with a history of fever, night sweats, shortness of breath and weight loss for two months. His chest radiograph showed a moderately severe left pleural effusion only. He consented to an HIV test which was positive.

What is the most likely cause of pleural effusion?

(Please select 1 option)

○	Hodgkin's lymphoma
○	Pleural tuberculosis
○	*Pneumocystis jirovecii* pneumonia (PCP)
○	Pulmonary aspergillosis
○	Pulmonary Kaposi's sarcoma

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

(Please select 1 option)

○	Hodgkin's lymphoma
◉	Pleural tuberculosis ✓ Correct
○	*Pneumocystis jirovecii* pneumonia (PCP)
○	Pulmonary aspergillosis
○	Pulmonary Kaposi's sarcoma

Pleural tuberculosis is the most likely cause in an HIV positive African man with a two month history of weight loss. His pleural effusion is due to pleural tuberculosis (extra pulmonary tuberculosis).

Hodgkin's lymphoma can cause pleural effusion due to pleural involvement but it is often associated with mediastinal mass. His chest radiograph showed only pleural effusion. Non-Hodgkin's lymphoma (not Hodgkin's lymphoma) is commonly associated with these patients.

PCP does not cause pleural effusion. It typically causes bilateral reticular shadows from the hila without any hilar lymph node enlargement or pleural effusion.

Pulmonary aspergillosis shows infiltrative lesions but it does not typically cause pleural effusion.

Pulmonary Kaposi's sarcoma can cause pleural effusion by involving the pleura, but it often causes coarse irregular nodular lesions in the lungs.

Reference:
El-Gadi SM, Banks J, Yoganathan K. Kaposi sarcoma presenting as severe haemoptysis. Genitourin Med. 1997 Dec; 73(6): 575-6.

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 8 mins 4 secs

Question: 6 of 19

A 28-year-old man with HIV presents with a five day history of feeling unwell. He is a heavy smoker.

A chest radiograph showed right upper lobe consolidation. His CD4 count was 468 cells/mm^3. HIV RNA level was 90,678 copies/ml. He is not on any antiretroviral treatment.

What is the most likely diagnosis?

(Please select 1 option)

- Bronchial carcinoma
- Invasive pulmonary aspergillosis
- Pulmonary tuberculosis
- *Pneumocystis jiroveci* pneumonia (PCP)
- Streptococcal pneumonia

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

copies/ml. He is not on any antiretroviral treatment.

What is the most likely diagnosis?

(Please select 1 option)

○	Bronchial carcinoma
○	Invasive pulmonary aspergillosis
◉	Pulmonary tuberculosis ✕ Incorrect answer selected
○	*Pneumocystis jiroveci* pneumonia (PCP)
○	Streptococcal pneumonia ← This is the correct answer

This is typical of community-acquired pneumonia. One should think of common infections rather than any opportunistic infections in HIV patients with good CD4 counts. (More than 400 cells/mm^3 is not immunocompromised.)

It is not a typical history for bronchial carcinoma as the history was short and radiographic changes were not typical of bronchial carcinoma.

Invasive pulmonary aspergillosis is unlikely in a patient with good CD4 count. Pulmonary tuberculosis typically causes cavitating lesions in a patient with a good CD4 count.

PCP commonly occurs in patients with CD4 count of less than 200 cells/mm^3 and chest radiograph shows bilateral infiltrates from the hila without any effusion or lymphadenopathy.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 11 mins 9 secs

Question: 7 of 19

Which one of the following is an oncogenic virus?

(Please select 1 option)

- Hepatitis A
- Human papilloma virus 6 (HPV 6)
- Human papilloma virus 11 (HPV 11)
- Human papilloma virus 16 (HPV 16)
- Varicella zoster virus (VZV)

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Which one of the following is an oncogenic virus?

(Please select 1 option)

○	Hepatitis A
○	Human papilloma virus 6 (HPV 6)
○	Human papilloma virus 11 (HPV 11)
◉	Human papilloma virus 16 (HPV 16) ✓ Correct
○	Varicella zoster virus (VZV)

HPV 16 is oncogenic and causes squamous cell carcinomas in the oral cavity, cervix, anus and penis.

Hepatitis A is not an oncogenic virus, as it does not cause chronic infection or cancer.

HPV 6 and 11 typically cause the majority of benign warts.

VZV causes chicken pox and herpes zoster.

Reference:

Yoganathan K, Patel RN, Maitland N, McManus TJ, Calman FM, Pozniak A. Carcinoma of the penis in an HIV positive patient. Genitourin Med.1995 Feb; 71 (1): 41-2.

Further reading:

United Kingdom National Guideline on the Management of Ano-genital Warts, 2007 (pdf)

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 11 mins 34 secs

Question: 8 of 19

A 34-year-old Thai lady presented with a left hemiparesis of two weeks duration.

HIV antibody test was positive. CT scan of the head showed multiple ring-enhanced lesions.

What is the most likely cause of her weakness?

(Please select 1 option)

○	Amoebic brain abscesses
○	Cerebral toxoplasmosis
○	Herpes simplex encephalitis
○	Primary brain lymphoma
○	Progressive multifocal leucoencephalopathy

Submit answer | Skip question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

(Please select 1 option)

○	Amoebic brain abscesses
◉	Cerebral toxoplasmosis ✓ Correct
○	Herpes simplex encephalitis
○	Primary brain lymphoma
○	Progressive multifocal leucoencephalopathy

Cerebral toxoplasmosis is the most likely diagnosis. Multiple ring-enhanced lesions are commonly seen in patients with cerebral toxoplasmosis, though solitary ring enhanced lesions are seen in 25% of patients on CT scan. MRI scan is more sensitive in identifying small lesions than CT scan.

Amoebic brain abscesses are not the most likely cause in this patient.

Multiple ring-enhanced lesions are not seen in patients with herpes simplex encephalitis.

Primary brain lymphoma causes a significant mass effect with surrounding oedema.

Progressive multifocal leucoencephalopathy causes multifocal white matter lesions without any mass effect or surrounding oedema.

Reference:
Yoganathan K., A brain tumour in an intravenous drug abuser. Accepted for publication in International Journal of General Medicine, February 2009.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd. All rights reserved. Terms and conditions Privacy policy

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 12 mins 20 secs

Question: 9 of 19

A 47-year-old Portuguese ex-intravenous drug abuser presented with a two week history of right hemiparesis.

He was found to have hepatitis B and C infection. His absolute lymphocyte count was 0.6×10^{9}. CT of the head showed multiple ring-enhanced lesions.

What would be your next best course of action?

(Please select 1 option)

- Manage him conservatively with physiotherapy
- Refer him to a neurosurgeon for urgent brain biopsy
- Refer him to a stroke specialist
- Request an HIV antibody test
- Start thrombolysis treatment

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

What would be your next best course of action?

(Please select 1 option)

○	Manage him conservatively with physiotherapy
○	Refer him to a neurosurgeon for urgent brain biopsy
○	Refer him to a stroke specialist
◉	Request an HIV antibody test ✓ Correct
○	Start thrombolysis treatment

This man was already infected with two blood-borne viruses (hepatitis B and C). His absolute lymphocyte count was low. CT scan showed multiple ring-enhanced lesions, which were suggestive of cerebral toxoplasmosis.

Therefore, testing HIV is the next best course of action. Finding multiple ring-enhanced lesions on CT scan needs further investigations.

Managing conservatively with physiotherapy is not an appropriate course of action.

CT scan is not typical of brain tumour, hence referring him for urgent brain biopsy is not the best course of action.

Thrombolysis treatment should not be started, as the CT scan was not typical of ischaemic stroke.

Reference:

Yoganathan K. A brain tumour in an intravenous drug abuser. Accepted for publication in International Journal of General Medicine in February 2009.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd. All rights reserved. Terms and conditions Privacy policy

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken:

Question: 1 of 100

The blood product with the highest risk of transmission of a bacterial infection related to transfusion is:

(Please select 1 option)

- **A** Cryoprecipitate
- **B** fresh frozen plasma
- **C** factor VIII concentrates
- **D** packed red cells
- **E** platelets

Submit answer | Skip question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 12 mins 47 secs

Question: 10 of 100

A young man with haemophilia conceives with his wife and attends requesting information.

He asks about the chances of his offspring being affected by haemophilia.

Which of the following statements is correct?

(Please select 1 option)

- A daughter will have a 50% chance of being a carrier
- A son has a 50% chance of being a carrier
- A son will not be affected
- There is a 100% chance that a daughter will be affected
- There is a 50% chance that a son will be affected

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 3 hrs 33 mins 56 secs

Question: 100 of 100

A patient with end stage renal disease is receiving haemodialysis and erythropoietin.

Which of the following does erythropoietin therapy cause?

(Please select 1 option)

○	Benign intracranial hypertension
○	Hypotension
○	Myositis
○	Osteoporosis
○	Seizures

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Shop

○	Myositis
○	Osteoporosis
◉	Seizures ✓ Correct

Hypertension is a frequent problem associated with erythropoietin and may induce seizures.

A particular symptom is the onset of sudden stabbing migraine-like headache and should raise awareness to the possibility of hypertensive crisis.

Other adverse effects of treatment with erythropoietin include:

- hyperkalaemia in uraemic patients

- increased packed cell volume (PCV) (especially with misuse by normal individuals)

- thrombocythaemia

- shunt thrombosis

- induction of iron deficiency

- skin rashes

- urticaria and

- flu-like illness.

Finish | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 15 mins

Question: 10 of 100

A young man with haemophilia conceives with his wife and attends requesting information.

He asks about the chances of his offspring being affected by haemophilia.

Which of the following statements is correct?

(Please select 1 option)

○	A daughter will have a 50% chance of being a carrier
○	A son has a 50% chance of being a carrier
○	A son will not be affected ← This is the correct answer
○	There is a 100% chance that a daughter will be affected
◉	There is a 50% chance that a son will be affected ✕ Incorrect answer selected

Haemophilia is inherited in an X-linked recessive fashion.

All daughters of this family will be carriers, as they would inherit an X-chromosome from their father. They will however be protected from the disease by their normal X-chromosome.

A son of this partnership would inherit a Y-chromosome from the father, and would thus not be affected.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 15 mins

Question: 11 of 100

Which of the following statements regarding thrombocytosis is correct?

(Please select 1 option)

○	Erythropoietin is the key hormone in the regulation of megakaryocyte differentiation
○	May occur as a response to exercise
○	Occurs exclusively in essential thrombocythaemia
○	Secondary thrombocytosis is an indication for hydroxycarbamide therapy
○	The most common cause is essential thrombocythaemia

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 16 mins 25 secs

Question: 11 of 100

Which of the following statements regarding thrombocytosis is correct?

(Please select 1 option)

- Erythropoietin is the key hormone in the regulation of megakaryocyte differentiation
- May occur as a response to exercise ✓ Correct
- Occurs exclusively in essential thrombocythaemia
- Secondary thrombocytosis is an indication for hydroxycarbamide therapy
- The most common cause is essential thrombocythaemia

The most common cause of thrombocytosis is a reactive thrombocytosis.

Thrombocythaemia may occur in any of the myeloproliferative disorders, particularly polycythaemia rubra vera (PRV).

Thrombopoietin is the key hormone in the regulation of megakaryocyte differentiation.

Secondary thrombocytosis does not place the patient at risk for haemostatic or cardiovascular events.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 16 mins 25 secs

Question: 12 of 100

A 70-year-old woman is on multiple medications for various conditions and she is found to have a macrocytic anaemia with a low serum B_{12}.

Which of the following medications is a possible cause of the B_{12} deficiency?

(Please select 1 option)

- Amiodarone
- Ezetimibe
- Metformin
- Nicotinic acid
- Sodium valproate

Submit answer | Skip question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 17 mins 8 secs

Question: 12 of 100

A 70-year-old woman is on multiple medications for various conditions and she is found to have a macrocytic anaemia with a low serum B_{12}.

Which of the following medications is a possible cause of the B_{12} deficiency?

(Please select 1 option)

○	Amiodarone
○	Ezetimibe
◉	Metformin ✓ Correct
○	Nicotinic acid
○	Sodium valproate

Metformin can lead to reduced B_{12} absorption but this is not usually a clinical problem.

"The clinician must be aware of the possibility of metformin-associated B_{12} deficiency in users who suffer cognitive impairment, peripheral neuropathy, subacute combined degeneration of the cord or anaemia." Age Ageing. 2006 Mar;35(2):200-1

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 17 mins 8 secs

Question: 13 of 100

A 40-year-old lady presents with a swollen right calf. She has a history of mental health problems and is on a number of medications.

Which of the following treatments increases the risk of thromboembolism?

(Please select 1 option)

- Antipsychotics
- Benzodiazepines
- Monoamine oxidase inhibitors
- Selective serotonin reuptake inhibitors
- Tricyclic antidepressants

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 17 mins 52 secs

Question: 13 of 100

A 40-year-old lady presents with a swollen right calf. She has a history of mental health problems and is on a number of medications.

Which of the following treatments increases the risk of thromboembolism?

(Please select 1 option)

◉	Antipsychotics ✓ Correct
○	Benzodiazepines
○	Monoamine oxidase inhibitors
○	Selective serotonin reuptake inhibitors
○	Tricyclic antidepressants

The oral contraceptive and antipsychotics are possible causes of thromboembolism.

Next question

Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 17 mins 52 secs

Question: 14 of 100

Which of the following conditions would be expected to be associated with a raised leukocyte alkaline phosphatase (LAP) score?

(Please select 1 option)

- Chronic myeloid leukaemia
- Infectious mononucleosis
- Myelofibrosis
- Pernicious anaemia
- Thrombocytopaenic purpura

Submit answer | Skip question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

○	Chronic myeloid leukaemia
○	Infectious mononucleosis
◉	Myelofibrosis ✓ Correct
○	Pernicious anaemia
○	Thrombocytopaenic purpura

The LAP score aids in the differential diagnosis of chronic myelocytic leukaemia (CML) versus leukaemoid reaction.

It also aids in the evaluation of:

- polycythaemia vera
- myelofibrosis with myeloid metaplasia, and
- paroxysmal nocturnal haemoglobinuria.
-
- Low scores have been associated with CML, paroxysmal nocturnal haemoglobinuria (PNH), thrombocytopaenic purpura, and hereditary hypophosphatasia.
-
- High scores have been seen in polycythaemia vera, myelofibrosis, aplastic anaemia, mongolism, hairy cell leukaemia, leukaemoid reactions, and neutrophilia either physiological or secondary to infection.
-
- It is also increased in Hodgkin disease. Read more

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 18 mins 30 secs

Question: 15 of 100

In idiopathic thrombocytopaenic purpura there are antibodies directed at which of the following?

(Please select 1 option)

- ADP receptor
- Antithrombin III
- ATP receptor
- Glycoprotein IIb/IIIa complex
- Platelet-activating factor

Submit answer | Skip question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 19 mins 31 secs

Question: 15 of 100

In idiopathic thrombocytopaenic purpura there are antibodies directed at which of the following?

(Please select 1 option)

○	ADP receptor
○	Antithrombin III
○	ATP receptor
◉	Glycoprotein IIb/IIIa complex ✓ Correct
○	Platelet-activating factor

In many cases of idiopathic thrombocytopaenic purpura, the cause is not actually idiopathic but autoimmune, with antibodies against platelets being detected in approximately 80% of patients.

Most often these antibodies are against platelet membrane glycoproteins IIb-IIIa or Ib-IX, and are of the IgG type.

The coating of platelets with IgG renders them susceptible to opsonisation and phagocytosis by splenic macrophages.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 19 mins 31 secs

Question: 16 of 100

A 32-year-old lady on holiday presented with a swollen left calf. She says that she has 'factor V Leiden mutation'.

Which one of the following is the most appropriate description of the pathophysiology of this mutation?

(Please select 1 option)

- Activated protein C resistance
- Antithrombin deficiency
- Protein C deficiency
- Protein S deficiency
- Prothrombin mutation

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Question: 16 of 100

A 32-year-old lady on holiday presented with a swollen left calf. She says that she has 'factor V Leiden mutation'.

Which one of the following is the most appropriate description of the pathophysiology of this mutation?

(Please select 1 option)

◉	Activated protein C resistance ✓ Correct
○	Antithrombin deficiency
○	Protein C deficiency
○	Protein S deficiency
○	Prothrombin mutation

In the normal person, factor V functions as a co-factor to allow factor X to generate the active form of an enzyme called thrombin.

Thrombin in turn cleaves fibrinogen to fibrin, which polymerises to form the dense meshwork that makes up the majority of a clot. Activated protein C (aPC) is a natural anticoagulant that acts to limit the extent of clotting by cleaving and degrading factor V.

Factor V Leiden is an autosomal dominant condition in which the coagulation factor cannot be destroyed by aPC. Mutation of the gene encoding factor Va single nucleotide substitution of adenine for guanine changes the protein's 506th amino acid from arginine to glutamine.

Since this amino acid is normally the cleavage site for aPC, the mutation prevents efficient inactivation of factor V. When factor V remains active, it facilitates overproduction of thrombin leading to excess fibrin generation and excess clotting.

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 21 mins 4 secs

Question: 17 of 100

Burkitt lymphoma is associated with a mutation of which of the following genes?

(Please select 1 option)

- BCL-6 gene
- BCR-ABL gene
- Cyclin D1 gene
- MYC gene
- RAR-alpha gene

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 21 mins 41 secs

Question: 17 of 100

Burkitt lymphoma is associated with a mutation of which of the following genes?

(Please select 1 option)

- BCL-6 gene
- BCR-ABL gene
- Cyclin D1 gene
- MYC gene ✓ Correct
- RAR-alpha gene

Burkitt lymphoma is a monoclonal proliferation of B lymphocytes which results (approximately 90% of the cases) from chromosome translocations that involve the Myc gene.

A chromosome translocation means that a chromosome is broken which allows it to associate with parts of other chromosomes. The classic chromosome translocation in Burkitt lymphoma involves chromosome 8, the site of the MYC gene.

Next question

Tag Question

Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 21 mins 41 secs

Question: 18 of 100

A 45-year-old man is diagnosed with acute promyelocytic leukaemia.

Which of the following chromosomal translocations is associated with this type of leukaemia?

(Please select 1 option)

○	t(8;9)
○	t(8;21)
○	t(9:22)
○	t(15;17)
○	t(17;22)

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 22 mins 14 secs

Question: 18 of 100

A 45-year-old man is diagnosed with acute promyelocytic leukaemia.

Which of the following chromosomal translocations is associated with this type of leukaemia?

(Please select 1 option)

○	t(8;9)
◉	t(8;21) ✕ Incorrect answer selected
○	t(9:22)
○	t(15;17) ← This is the correct answer
○	t(17;22)

Acute promyelocytic leukaemia is characterised by a chromosomal translocation involving the retinoic acid receptor-alpha gene on chromosome 17 (RARA).

In 95% of cases, retinoic acid receptor-alpha (RARA) gene on chromosome 17 is involved in a reciprocal translocation with the promyelocytic leukaemia gene (PML) on chromosome 15.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 22 mins 14 secs

Question: 19 of 100

A 16-year-old boy with easy bruising and excessive bleeding from a tooth extraction is found to have von Willebrand's disease.

He is due to have further dental extractions and DDAVP is prescribed.

What is the mechanism of action of DDAVP in von Willebrand's disease?

(Please select 1 option)

○	Acts as a substitute carrier for factor VIII
○	Inhibits breakdown of von Willebrand's factor
○	Prevents renal excretion of von Willebrand's factor
○	Stimulates release of von Willebrand's factor from endothelial cells
○	Turns on the gene associated with von Willebrand's factor production

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 23 mins 58 secs

Question: 19 of 100

A 16-year-old boy with easy bruising and excessive bleeding from a tooth extraction is found to have von Willebrand's disease.

He is due to have further dental extractions and DDAVP is prescribed.

What is the mechanism of action of DDAVP in von Willebrand's disease?

(Please select 1 option)

○	Acts as a substitute carrier for factor VIII
○	Inhibits breakdown of von Willebrand's factor
◉	Prevents renal excretion of von Willebrand's factor ✕ Incorrect answer selected
○	Stimulates release of von Willebrand's factor from endothelial cells ← This is the correct answer
○	Turns on the gene associated with von Willebrand's factor production

DDAVP may be given to increase the amount of the von Willebrand factor long enough for surgery or dental procedures to be performed.

DDAVP can provide a 2- to 5-fold increase in plasma von Willebrand factor and factor VIII concentrations.

It induces cyclic adenosine monophosphate (cAMP)-mediated vWF secretion by a direct effect on endothelial cells.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 mins 38 secs

Question: 1 of 100

The blood product with the highest risk of transmission of a bacterial infection related to transfusion is:

(Please select 1 option)

○	**A** Cryoprecipitate
○	**B** fresh frozen plasma
○	**C** factor VIII concentrates
◉	**D** packed red cells ✕ Incorrect answer selected
○	**E** platelets ← This is the correct answer

Since platelets are stored at room temperature (22℃), the risk of bacterial contamination is highest in this blood product (option e). In contrast packed red cells are stored at an average of 4℃ (option a) while fresh frozen plasma as well as cryoprecipitate are stored at - 20℃. Factor VIII concentrates are heat inactivated freeze dried products with a minimal risk of bacterial contamination.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 mins 38 secs

Question: 2 of 100

A pre transfusion sample shows that a patient has blood group O. This means that:

(Please select 1 option)

- **A** the red cells have absent A /B antigen and plasma has anti A & anti B antibodies
- **B** the red cells have A /B antigen but no antibodies in the plasma
- **C** the red cells may have any antigen but plasma has anti A & anti B antibodies
- **D** the red cells have antigen A and plasma has anti B antibodies
- **E** the red cells have antigen B and plasma has A antibodies

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 23 mins 58 secs

Question: 20 of 100

Interferon alpha immunotherapy is used as treatment of which for the following conditions?

(Please select 1 option)

- Acute lymphoblastic leukaemia
- Acute myeloid leukaemia
- Burkitt's lymphoma
- Hairy cell leukaemia
- Myelodysplastic syndrome

Submit answer | Skip question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 29 mins 5 secs

Question: 20 of 100

Interferon alpha immunotherapy is used as treatment of which for the following conditions?

(Please select 1 option)

◉	Acute lymphoblastic leukaemia ✗ Incorrect answer selected
○	Acute myeloid leukaemia
○	Burkitt's lymphoma
○	Hairy cell leukaemia ← This is the correct answer
○	Myelodysplastic syndrome

"Interferon-alpha is an immune system hormone which is very helpful to a relatively small number of patients, and somewhat helpful to most patients. Most commonly, the drug helps stabilize the disease or produce a slow, minor improvement. The typical dosing schedule injects 3 million units of Interferon-alpha (not pegylated versions) three times a week, although the original protocol began with six months of daily injections." Wikipedia: Hairy Cell Leukaemia

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 29 mins 5 secs

Question: 21 of 100

A 60-year-old lady with bruising is investigated and found to have the following full blood count:

Haemoglobin	13 x10 g/dL	(11.5-16.5)
White cell count	6.3 $x10^9$/L	(4-11 $x10^9$)
Platelet count	15 $x10^9$/L	(150-400 $x10^9$)

She refuses to give consent to a bone marrow biopsy.

What is the most appropriate management plan?

(Please select 1 option)

- Intravenous immunoglobulin
- No treatment
- Oral prednisolone
- Platelet transfusion
- Splenectomy

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

White cell count	6.3 x10^{9}/L	(4-11 x10^{9})
Platelet count	15 x10^{9}/L	(150-400 x10^{9})

She refuses to give consent to a bone marrow biopsy.

What is the most appropriate management plan?

(Please select 1 option)

○	Intravenous immunoglobulin
○	No treatment
○	Oral prednisolone ← This is the correct answer
◉	Platelet transfusion ✗ Incorrect answer selected
○	Splenectomy

This lady most likely has idiopathic thrombocytopenic purpura.

The history should highlight any drug causes (not mentioned here) and a blood film would help exclude leukaemia.

A bone marrow examination is useful especially in the older person.

Platelet transfusion would not be helpful without treating the underlying cause.

No treatment is often an option but this lady is older and has bruising.

Given the circumstances the best management plan is to treat with steroid.

Next question

Remove Tag | Remove question

Work Smart Session - MRCP Part 1

Time taken: 30 mins 22 secs

Question: 22 of 100

A 45-year-old lady is found to have thymoma.

Which one of the following conditions is associated with thymoma?

(Please select 1 option)

○	Acute lymphocytic leukaemia
○	Acute myeloid leukaemia
○	Myelofibrosis
○	Pure red cell aplasia
○	Thrombocythaemia

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 30 mins 57 secs

Question: 22 of 100

A 45-year-old lady is found to have thymoma.

Which one of the following conditions is associated with thymoma?

(Please select 1 option)

○	Acute lymphocytic leukaemia
○	Acute myeloid leukaemia
○	Myelofibrosis
◉	Pure red cell aplasia ✓ Correct
○	Thrombocythaemia

"Originally, thymoma was cited as the primary cause of acquired pure red cell aplasia. However, subsequent studies revealed that thymomas caused only 2 of 37 cases of pure red cell aplasia. Conversely, only 7% of patients with thymomas had pure red cell aplasia. T-cell mediated erythroid rejection is considered the mechanism for the production of pure red cell aplasia in patients with thymomas. This is supported by evidence that a subgroup of T cells in B-cell chronic lymphocytic leukemia is responsible for pure red cell aplasia." eMedicine: Pure Red Cell Aplasia

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 30 mins 57 secs

Question: 23 of 100

A 65-year-old lady with a history of recurrent DVT. She has been weaned off her warfarin and started on intravenous heparin prior to cardiac bypass for ischaemic heart disease. She seems to require very high doses of heparin to achieve adequate anticoagulation especially during surgery.

Which of the following conditions would explain her thrombophilia and her heparin resistance?

(Please select 1 option)

- Activated protein C resistance
- Antithrombin III deficiency
- Lupus anticoagulant
- Protein C deficiency
- Protein S deficiency

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 32 mins 36 secs

Question: 23 of 100

A 65-year-old lady with a history of recurrent DVT. She has been weaned off her warfarin and started on intravenous heparin prior to cardiac bypass for ischaemic heart disease. She seems to require very high doses of heparin to achieve adequate anticoagulation especially during surgery.

Which of the following conditions would explain her thrombophilia and her heparin resistance?

(Please select 1 option)

○	Activated protein C resistance
◉	Antithrombin III deficiency ✓ Correct
○	Lupus anticoagulant
○	Protein C deficiency
○	Protein S deficiency

"Cardiac surgery produces a unique activation of coagulation due to the presence of the cardiopulmonary bypass (CPB) circuit. Whilst not yet fully elucidated, the mechanisms of activation of coagulation during CPB may involve activation of fX by the tissue factor-mediated pathway within the pericardial cavity, in addition to direct generation of fXa on the surface of monocytes by Cathepsin G, a substance released from activated monocytes. The inhibition of fXa in these situations involves the AT-dependent mechanism of action of heparin." British Journal of Anaesthesia, 2002, Vol. 88, No. 4 467-469

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 32 mins 36 secs

Question: 24 of 100

A previously well 75-year-old lady presented with tiredness and a mildly raised lymphocyte count on her full blood count. A blood film reports '*Smudge cells seen. Is this lady known to have Chronic Lymphocytic Leukaemia?*'

What is the most appropriate next investigation to confirm this lady's diagnosis?

(Please select 1 option)

- ○ Bone marrow aspirate
- ○ Bone marrow trephine
- ○ Immunophenotyping
- ○ Serum immunoglobulins
- ○ Ultrasound scan

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 34 mins 51 secs

Question: 24 of 100

A previously well 75-year-old lady presented with tiredness and a mildly raised lymphocyte count on her full blood count. A blood film reports '*Smudge cells seen. Is this lady known to have Chronic Lymphocytic Leukaemia?*'

What is the most appropriate next investigation to confirm this lady's diagnosis?

(Please select 1 option)

○	Bone marrow aspirate
○	Bone marrow trephine
◉	Immunophenotyping ✓ Correct
○	Serum immunoglobulins
○	Ultrasound scan

"A definitive diagnosis of CLL is based on the combination of a lymphocytosis and characteristic lymphocyte morphology and immunophenotype." British Committee for Standards in Haematology Guideline for CLL diagnosis 2005

The other tests are additional investigations all used in the workup of CLL.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 36 mins 15 secs

Question: 25 of 100

A 28-year-old man presented with recurrent nose bleeds and iron deficiency anaemia. A chest x ray found a shadow over the right lung base and auscultation in this area revealed a bruit.

Which of the following is the most likely diagnosis?

(Please select 1 option)

○	Ehlers-Danlos syndrome
◉	Hereditary haemorrhagic telangiectasia ✓ Correct
○	Idiopathic thrombocytopaenic purpura
○	von Willebrand's disease
○	Wegener's granulomatosis

This is hereditary haemorrhagic telangiectasia (Osler-Weber-Rendu syndrome) characterised by bleeding from telangiectasia on mucuous membranes such as the nose, mouth and gastrointestinal (GI) tract.

Clinical examination reveals telangiectasia on the skin.

Arteriovenous malformation (AVM) may be seen in the lung (as in this case) or brain.

Hereditary Hemorrhagic Telangiectasia Foundation International

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 36 mins 15 secs

Question: 26 of 100

A 25-year-old man presented with an enlarged inguinal lymph node with night sweats and the most likely clinical diagnosis is Hodgkin's lymphoma.

A biopsy has been taken.

Which of the following findings on histology is associated with the best prognosis in Hodgkin's disease?

(Please select 1 option)

- Lymphocyte depleted
- Lymphocyte predominant
- Mixed cellularity
- Nodular sclerosing
- Reed-Sternberg cells

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Question: 26 of 100

A 25-year-old man presented with an enlarged inguinal lymph node with night sweats and the most likely clinical diagnosis is Hodgkin's lymphoma.

A biopsy has been taken.

Which of the following findings on histology is associated with the best prognosis in Hodgkin's disease?

(Please select 1 option)

○	Lymphocyte depleted
◉	Lymphocyte predominant ✓ Correct
○	Mixed cellularity
○	Nodular sclerosing
○	Reed-Sternberg cells

Hodgkin's disease is characterised by Reed-Sternberg cells and this is therefore not a prognostic feature.

Nodular sclerosing is the most common finding and has a good prognosis.

Mixed cellularity also has good prognosis; lymphocyte depleted has the worst.

The best prognosis is with lymphocyte predominant histology.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 37 mins 7 secs

Question: 27 of 100

A 16-year-old boy presents with a haemarthrosis that developed in his left knee following an injury in the garden.

His investigations show:

Platelet count	260 x10^9/l	(150-400)
Prothrombin time	13 s	(11.5-15.5)
Activated partial thromboplastin time	80 s	(30-40)
Factor VIII	110 IU/dl	(50-150)

Which of the following is the most likely diagnosis?

(Please select 1 option)

- Antiphospholipid syndrome
- Antithrombin III deficiency
- Haemophilia A
- Haemophilia B
- von Willebrand's disease

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Shop

Factor VIII	110 IU/dl	(50-150)

Which of the following is the most likely diagnosis?

(Please select 1 option)

- Antiphospholipid syndrome
- Antithrombin III deficiency
- Haemophilia A
- Haemophilia B ✓ Correct
- von Willebrand's disease

An elevated activated partial thromboplastin time (APTT) could be due to

- Treatment with heparin
- Haemophilia
- von Willebrand's disease
- Antiphospholipid syndrome.

A normal factor VIII would suggest haemophilia B where there is lack of factor IX.

A prolonged APTT can be seen in von Willebrand's disease but factor VIII activity would be low.

The presentation is not consistent with antiphospholipid syndrome and would also, typically, be associated with thrombocytopenia.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 39 mins 7 secs

Question: 28 of 100

A 20-year-old man presented to hospital two days after returning from visiting his family in Bangladesh.

Within a day of his return to the United Kingdom he suddenly developed profuse watery diarrhoea. He says there had been an outbreak of diarrhoea in his family's village in the week before his return.

Stool culture revealed a growth of *Vibrio cholerae*.

Which one of the following blood types is associated with the greatest susceptibilty to severe cholera?

(Please select 1 option)

- Blood Group A
- Blood Group AB
- Blood Group B
- Blood Group O
- Rhesus -ve

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 41 mins 18 secs

Question: 28 of 100

A 20-year-old man presented to hospital two days after returning from visiting his family in Bangladesh.

Within a day of his return to the United Kingdom he suddenly developed profuse watery diarrhoea. He says there had been an outbreak of diarrhoea in his family's village in the week before his return.

Stool culture revealed a growth of *Vibrio cholerae*.

Which one of the following blood types is associated with the greatest susceptibilty to severe cholera?

(Please select 1 option)

◉	Blood Group A ✕ Incorrect answer selected
○	Blood Group AB
○	Blood Group B
○	Blood Group O ← This is the correct answer
○	Rhesus -ve

"Individuals with blood group O are more susceptible than other individuals to severe cholera, although the mechanism underlying this association is unknown." Infect Immun. 2005 Nov; 73(11): 7422-7.

Next question

Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 41 mins 18 secs

Question: 29 of 100

Which of the following is the mechanism of action of warfarin?

(Please select 1 option)

- Activation of gamma-glutamyl carboxylase
- Chelation of calcium
- Inhibition of activated factor X
- Inhibition of vitamin K-dependent carboxylase
- Inhibition of vitamin K epoxide reductase

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 41 mins 51 secs

Question: 29 of 100

Which of the following is the mechanism of action of warfarin?

(Please select 1 option)

○	Activation of gamma-glutamyl carboxylase
○	Chelation of calcium
○	Inhibition of activated factor X
○	Inhibition of vitamin K-dependent carboxylase
◉	Inhibition of vitamin K epoxide reductase ✓ Correct

The vitamin K epoxide is in turn recycled back to vitamin K and vitamin K hydroquinone by another enzyme, the vitamin K epoxide reductase (VKOR).

Warfarin inhibits epoxide reductase (specifically the VKORC1 subunit), thereby diminishing available vitamin K and vitamin K hydroquinone in the tissues which inhibits the carboxylation activity of the glutamyl carboxylase.

When this occurs, the coagulation factors are no longer carboxylated at certain glutamic acid residues, and are incapable of binding to the endothelial surface of blood vessels, and are thus biologically inactive. (Wikipedia - warfarin)

Next question | Tag Question | Remove question

Show tools

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 3 mins 8 secs

Question: 2 of 100

A pre transfusion sample shows that a patient has blood group O. This means that:

(Please select 1 option)

◉	**A** the red cells have absent A /B antigen and plasma has anti A & anti B antibodies ✓ Correct
○	**B** the red cells have A /B antigen but no antibodies in the plasma
○	**C** the red cells may have any antigen but plasma has anti A & anti B antibodies
○	**D** the red cells have antigen A and plasma has anti B antibodies
○	**E** the red cells have antigen B and plasma has A antibodies

Option A is blood group O as it has no A or B antigen but has the corresponding antibodies. Option B represent blood group AB while option D and E represent groups A and B respectively. Option C does not represent any blood group.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 3 mins 8 secs

Question: 3 of 100

A patient on a medical ward received a transfusion 48 hours ago for symptomatic anaemia on background of chronic renal disease and obstructive airways disease. He gives a history of previous transfusions in the last year. The patient has now actually dropped his Hb by 2g/L compared to his pretansfusion level and reports a dark coloured urine. The LDH and bilirubin are elevated. The is most likely to represent:

(Please select 1 option)

- **A** acute hepatitis as an infective complication
- **B** acute haemolytic transfusion reaction
- **C** delayed haemolytic transfusion reaction
- **D** non haemolytic febrile transfusion reaction
- **E** transfusion related graft versus host disease

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Question: 30 of 100

A 24-year-old female student presented with fever and rigors for two days, fatigue, headache especially retro-orbital and diarrhoea. In particular she complained of a weakness of the left side of her face and drooping of the lip.

She had recently returned from a sabbatical in Uganda four weeks previously.

She was febrile (39.9°C), had a mild left facial nerve palsy, lymphadenopathy in her axillae and groin and she had an erythematous, maculopapular rash.

Laboratory investigations showed:

Haemoglobin	12.0 g/dl (11.5-16.5)
WBC	3.0 $x10^9$/l (4-11 $x10^9$)
Platelets	150 $x10^9$/l (150-400 $x10^9$)
Blood film	Lymphopaenia, some atypical lymphocytes seen

Which of the following is the most likely diagnosis?

(Please select 1 option)

- Acute HIV infection (seroconversion illness)
- Dengue fever
- Infectious mononucleosis
- Typhoid fever
- Viral hepatitis

(Please select 1 option)

◉	Acute HIV infection (seroconversion illness) ✓ Correct
○	Dengue fever
○	Infectious mononucleosis
○	Typhoid fever
○	Viral hepatitis

Acute human immunodeficiency virus (HIV) seroconversion illness should be suspected where there has been a risk of exposure.

The symptoms and signs are often vague but the clinical presentation here is consistent. The median time from exposure to presentation is 25 days.

More than three quarters of patients who become infected with HIV develop symptoms consistent with primary HIV infection.

Symptoms typically appear a few days to a few weeks after exposure to HIV, and generally include several of the following:

- Fever
- Rash, often erythematous maculopapular
- Fatigue
- Pharyngitis
- Generalised lymphadenopathy
- Urticaria
- Myalgia/arthralgia
- Anorexia
- Mucocutaneous ulceration
- Headache, retro-orbital pain
- Neurologic symptoms, e.g.
    - aseptic meningitis
    - radiculitis
    - myelitis.

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 43 mins 53 secs

Question: 31 of 100

A 35-year-old lady presented with left-sided weakness.

She has a young family with a 5-year-old son and a 2-year-old daughter. Previously she had two spontaneous abortions. After the birth of her last child she developed a deep vein thrombosis (DVT) and received three months of anticoagulation with warfarin.

On examination she has left-sided weakness with pyramidal signs. A CT head scan showed a right middle cerebral artery territory infarct.

Which of the following is the most likely diagnosis?

(Please select 1 option)

- Hypertension
- Kawasaki syndrome
- Patent foramen ovale
- Systemic lupus erythematosus
- Thrombotic thrombocytopaenic purpura

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 44 mins 54 secs

Question: 31 of 100

A 35-year-old lady presented with left-sided weakness.

She has a young family with a 5-year-old son and a 2-year-old daughter. Previously she had two spontaneous abortions. After the birth of her last child she developed a deep vein thrombosis (DVT) and received three months of anticoagulation with warfarin.

On examination she has left-sided weakness with pyramidal signs. A CT head scan showed a right middle cerebral artery territory infarct.

Which of the following is the most likely diagnosis?

(Please select 1 option)

○	Hypertension
○	Kawasaki syndrome
○	Patent foramen ovale
◉	Systemic lupus erythematosus ✓ Correct
○	Thrombotic thrombocytopaenic purpura

This patient has a prothrombotic tendency suggestive of the lupus anticoagulant with recurrent abortions, previous DVT and now she has developed a left hemiparesis.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 44 mins 54 secs

Question: 32 of 100

A 26-year-old man presents with dark urine, especially in the early morning. Further investigations show that he has haemoglobinuria and haemolytic anaemia.

A diagnosis of paroxysmal nocturnal hemoglobinuria (PNH) is made.

What is the likely mechanism underlying this condition?

(Please select 1 option)

- Aberrant fusion of two genes
- Impaired protein degradation
- Over-expression of cellular oncogene
- Post-translational modification
- Telomere shortening

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 45 mins 55 secs

Question: 32 of 100

A 26-year-old man presents with dark urine, especially in the early morning. Further investigations show that he has haemoglobinuria and haemolytic anaemia.

A diagnosis of paroxysmal nocturnal hemoglobinuria (PNH) is made.

What is the likely mechanism underlying this condition?

(Please select 1 option)

○	Aberrant fusion of two genes
○	Impaired protein degradation
○	Over-expression of cellular oncogene
◉	Post-translational modification ✓ Correct
○	Telomere shortening

Post-translational modification by the GPI glycolipid anchor is essential for the surface expression of many membrane proteins.

Defect of GPI biosynthesis due to somatic mutation in the haematopoietic stem cell is the basis for an acquired genetic disease, paroxysmal nocturnal haemoglobinuria.

The other mechanisms are associated with various other diseases.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Question: 33 of 100

A 22-year-old male presents with episodic nausea and abdominal pain although he has maintained a normal weight. The symptoms have been attributed to irritable bowel syndrome. There are no abnormalities on examination.

Blood tests were performed which reveal:

Haemoglobin	12.2 g/dl	(13.0-18.0)
MCV	92 fl	(80-96)
White cell count	6.5 x 10^9/l	(4-11)
Platelets	310 x 10^9/l	(150-400)
Reticulocytes	5%	(0.5-2.4)
Bilirubin	42 µmol/l	(1-22)
AST/ALP	Normal	
Coombs' test	Negative	
Haptoglobin	Undetectable	

Which of the following is the likely diagnosis?

(Please select 1 option)

- Acute intermittent porphyria
- Dubin-Johnson syndrome
- Gilbert's syndrome
- Hereditary spherocytosis
- Viral hepatitis

- Shop

White cell count	6.5 x 10^9/l	(4-11)
Platelets	310 x 10^9/l	(150-400)
Reticulocytes	5%	(0.5-2.4)
Bilirubin	42 µmol/l	(1-22)
AST/ALP	Normal	
Coombs' test	Negative	
Haptoglobin	Undetectable	

Which of the following is the likely diagnosis?

(Please select 1 option)

- ◉ Acute intermittent porphyria ✕ Incorrect answer selected
- ○ Dubin-Johnson syndrome
- ○ Gilbert's syndrome
- ○ Hereditary spherocytosis ← This is the correct answer
- ○ Viral hepatitis

This patient has an elevated bilirubin concentration and elevated reticulocyte count suggesting haemolysis.

The most likely explanation would be hereditary spherocytosis which could be confirmed on blood film. This too explains the symptoms - nausea and abdominal pains suggesting gallstones, which are common even in mild disease.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Question: 34 of 100

A 78-year-old female who is on warfarin for atrial fibrillation presents with melaena.

Her blood pressure is 90/60 mmHg and heart rate is 100 bpm.

Investigations show:

Haemoglobin	9 g/l	(12-16)
MCV	87 fl	(83-95)
INR	7.2	(<1.4)

A PR examination confirms melaena.

Which is the best option for correcting the coagulopathy?

(Please select 1 option)

- FFP
- IV vitamin K
- Stop warfarin
- Stop warfarin and give IV vitamin K
- Stop warfarin and give IV vitamin K and prothrombin complex concentrate

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Shop

INR	7.2	(<1.4)

A PR examination confirms melaena.

Which is the best option for correcting the coagulopathy?

(Please select 1 option)

○	FFP
○	IV vitamin K
○	Stop warfarin
○	Stop warfarin and give IV vitamin K
◉	Stop warfarin and give IV vitamin K and prothrombin complex concentrate ✓ Correct

This patient is hypotensive and tachycardic with melaena suggesting a major bleeding episode on warfarin.

In these circumstances current guidelines suggest stopping warfarin, giving IV vitamin K, and either fresh frozen plasma (FFP) or prothrombin complex concentrate.

Local guidelines will be available and if in doubt consult with the haematologist on call. FFP may not completely reverse the effects of warfarin so it may now be preferable to consider prothrombin complex concentrate (PCC) if available.

The rate of fatal haemorrhage in patients receiving warfarin approaches 1%. It is therefore essential that knowledge regarding the reversal of warfarin coagulation is serviceable.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 49 mins 48 secs

Question: 35 of 100

A 70-year-old male is diagnosed with multiple myeloma and is treated with melphalan and prednisolone.

Which of the following when added to this chemotherapeutic regime would be expected to improve survival?

(Please select 1 option)

- Cyclosporin
- Interferon alpha
- Methotrexate
- Simvastatin
- Thalidomide

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 50 mins 14 secs

Question: 35 of 100

A 70-year-old male is diagnosed with multiple myeloma and is treated with melphalan and prednisolone.

Which of the following when added to this chemotherapeutic regime would be expected to improve survival?

(Please select 1 option)

○	Cyclosporin
○	Interferon alpha
◉	Methotrexate ✕ Incorrect answer selected
○	Simvastatin
○	Thalidomide ← This is the correct answer

Significant improvements in survival may be expected through the addition of thalidomide to standard chemotherapeutic regimes.

Studies suggest a significant improvement at both two years and five years with thalidomide.

NEJM 2006; 367:825-31.

Lancet 2006 354:1021-1-30

Next question

Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 50 mins 14 secs

Question: 36 of 100

A 12-year-old boy was diagnosed with haemophilia A.

His uncle from the mother's side also has the same condition although his mother is well. The parents of the boy are worried about their next child suffering with the same condition.

What is the chance of the next child having the disease?

(Please select 1 option)

○	0%
○	25%
○	50%
○	75%
○	100%

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Question: 36 of 100

A 12-year-old boy was diagnosed with haemophilia A.

His uncle from the mother's side also has the same condition although his mother is well. The parents of the boy are worried about their next child suffering with the same condition.

What is the chance of the next child having the disease?

(Please select 1 option)

○	0%
○	25% ← This is the correct answer
◉	50% ✗ Incorrect answer selected
○	75%
○	100%

Haemophilia is an X linked recessive disease.

The mother is the carrier of the disease.

There will be 50% chance of her sons having the disease and there is a 50% chance of her daughters being carriers.

The sex of the next child it is not mentioned in this question. The overall chance of the next child having the disease will be 25% and phenotypically normal child will be 75%.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Question: 37 of 100

A 23-year-old footballer was prescribed ibuprofen by his GP for a sprained ankle. Several hours later he felt very unwell and was passing dark urine.

The peripheral blood film shows many schistocytes.

The laboratory results show:

Haemoglobin	<9 g/dL (13.0-18.0)
WBC	7 $x10^9$/L (4-11 $x10^9$) with normal differentials
Platelets	450 $x10^9$/L (150-400 $x10^9$)
Reticulocyte count	5% (0.5-2.4)
Bilirubin	40 mol/L (1-22)

What is the most likely cause for his presentation?

(Please select 1 option)

- Allergic reaction
- Autoimmune haemolytic anaemia
- Glucose-6-phosphate dehydrogenase deficiency
- Paroxysmal nocturnal haemoglobinuria
- Pyruvate kinase deficiency

Submit answer | Skip question | Tag Question | Remove question

Platelets	450 x10^{9}/L (150-400 x10^{9})
Reticulocyte count	5% (0.5-2.4)
Bilirubin	40 mol/L (1-22)

What is the most likely cause for his presentation?

(Please select 1 option)

- ○ Allergic reaction
- ○ Autoimmune haemolytic anaemia
- ◉ Glucose-6-phosphate dehydrogenase deficiency ✓ Correct
- ○ Paroxysmal nocturnal haemoglobinuria
- ○ Pyruvate kinase deficiency

This is a case of intravascular haemolysis with haemoglobinuria.

The patient has a history of taking ibuprofen which is an oxidant and causes haemolysis in patients with G-6-PD deficiency.

Oxidative stressors can be infectious agents, drugs, chemicals and certain legumes. In G-6-PD deficient patients, oxidative stress exposes interior sulfhydryl groups that are oxidised and cannot be reduced, leading to irreversible denaturation of the haemoglobin with Heinz body formation.

Schistocytes are red blood cell fragments that result from membrane damage. They are sometimes referred to as "bite cells".

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 53 mins 25 secs

Question: 38 of 100

What is the mechanism of action of low molecular weight heparin?

(Please select 1 option)

- Activation of plasminogen
- Chelation of calcium
- Inhibition of activated factor X
- Inhibition of antithrombin
- Inhibition of vitamin K-dependent carboxylase

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 53 mins 59 secs

Question: 38 of 100

What is the mechanism of action of low molecular weight heparin?

(Please select 1 option)

○	Activation of plasminogen
○	Chelation of calcium
○	Inhibition of activated factor X ← This is the correct answer
◉	Inhibition of antithrombin ✕ Incorrect answer selected
○	Inhibition of vitamin K-dependent carboxylase

The shorter chain low molecular weight (LMW) fractions of heparin inhibit activated factor X but have less effect on thrombin (and on coagulation in general) than the high molecular weight (HMW) species.

Next question

Remove Tag

Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 53 mins 59 secs

Question: 39 of 100

Which of the following is most likely to be reversible following venesection in a 45-year-old male with haemochromatosis?

(Please select 1 option)

- Arthropathy
- Cardiomyopathy
- Cirrhosis
- Diabetes mellitus
- Hypopituitarism

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 55 mins 15 secs

Question: 39 of 100

Which of the following is most likely to be reversible following venesection in a 45-year-old male with haemochromatosis?

(Please select 1 option)

○	Arthropathy
◉	Cardiomyopathy ✓ Correct
○	Cirrhosis
○	Diabetes mellitus
○	Hypopituitarism

Disorders that are potentially reversible in haemochromatosis include the dermal pigmentation and cardiomyopathy.

Similarly there are improvements in liver function tests.

However, diabetes, cirrhosis, hypogonadism and arthropathy are usually irreversible.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Question: 3 of 100

A patient on a medical ward received a transfusion 48 hours ago for symptomatic anaemia on background of chronic renal disease and obstructive airways disease. He gives a history of previous transfusions in the last year. The patient has now actually dropped his Hb by 2g/L compared to his pretansfusion level and reports a dark coloured urine. The LDH and bilirubin are elevated. The is most likely to represent:

(Please select 1 option)

○	**A** acute hepatitis as an infective complication
○	**B** acute haemolytic transfusion reaction
◉	**C** delayed haemolytic transfusion reaction ✓ Correct
○	**D** non haemolytic febrile transfusion reaction
○	**E** transfusion related graft versus host disease

This case is an example of delayed haemolytic transfusion reaction which occurs 24 hrs after the transfusion (hence option c as explained further). This happens in a patient who has been previously immunized by transfusions or pregnancy. The antibodies are not detectable initially but becomes obvious as a secondary immune response to the antigen exposure during the transfusion occurs. A haemoglobin level, blood film, LDH, direct antiglobulin test, renal profile, serum bilirubin, haptoglobin and urinalysis for haemoglobinuria should be checked. The group and antibody screen should be repeated. A transfusion associated graft versus host disease and an acute hepatitis is unlikely given the time frame - both would be expected to occur in a week or two (hence not options a or e). This is also not an acute hemolysis which would be expected to occur during the transfusion (hence not option b). Given the rise in Bilirubin and LDH this is a haemolytic reaction (hence not option d).

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 4 mins 56 secs

Question: 4 of 100

The blood used for an exchange transfusion in a neonate should fulfil these criteria:

(Please select 1 option)

- **A** any blood less than 5 days old
- **B** any Plasma reduced whole blood in CPD
- **C** plasma reduced whole blood in CPD which is irradiated
- **D** plasma reduced whole blood in CPD less than 5 days old and irradiated
- **E** plasma reduced whole blood in CPD less than 5 days old , irradiated and Rh group should be same as the neonate

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 55 mins 15 secs

Question: 40 of 100

A patient who received total body irradiation for the treatment of Hodgkin's lymphoma develops graft versus hostdDisease (GVHD).

Which of the following blood products is likely to have caused this?

(Please select 1 option)

- Cryoprecipitate
- FFP
- Frozen deglycerolised red blood cells
- Immunoglobulin
- Packed red blood cells

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

(Please select 1 option)

◉	Cryoprecipitate ✕ Incorrect answer selected
○	FFP
○	Frozen deglycerolised red blood cells
○	Immunoglobulin
○	Packed red blood cells ← This is the correct answer

Graft versus host disease (GVHD) occurs when donor lymphocytes engraft in a susceptible recipient.

Products implicated in cases of transfusion associated (TA)-GVHD include:

- Non-irradiated whole blood
- Packed red blood cells
- Platelets
- Granulocytes and
- Fresh non-frozen plasma.

The following have not been implicated:

- Frozen deglycerolized red blood cells
- Fresh frozen plasma and
- Cryoprecipitate.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 56 mins 26 secs

Question: 41 of 100

A 28-year-old pregnant woman is being treated for a deep vein thrombosis with unfractionated heparin.

A recent blood test shows:

Haemoglobin	9.8 g/dl	(11.5-16.5)
White cell count	9.5 x 10^9/l	(4-11)
Platelets	35 x 10^9/l	(150-400)

What would be the best course of action for this woman?

(Please select 1 option)

- Change to hirudin
- Change to low molecular weight heparin
- Change to warfarin
- Danaparoid
- No change in treatment and observe

Submit answer | Skip question | Tag Question | Remove question

A recent blood test shows:

Haemoglobin	9.8 g/dl	(11.5-16.5)
White cell count	9.5 x 10^9/l	(4-11)
Platelets	35 x 10^9/l	(150-400)

What would be the best course of action for this woman?

(Please select 1 option)

- Change to hirudin
- Change to low molecular weight heparin ✕ Incorrect answer selected
- Change to warfarin
- Danaparoid ← This is the correct answer
- No change in treatment and observe

This patient appears to have heparin-induced thrombocytopaenia (HIT). When HIT is suspected, heparin treatment should be discontinued and alternative anticoagulation should be started.

The heparinoid danaparoid appears to be the drug of choice for acute treatment and prophylaxis because of its low placental permeability.

Hirudin should only be used when either cross-reactivity with heparin-induced antibodies or cutaneous allergy against heparinoids are observed.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 57 mins 36 secs

Question: 42 of 100

A patient with AML develops jaundice and spiking pyrexia three weeks into induction chemotherapy.

The patient remained pyrexial after seven days of intravenous antibiotics.

What is the likely diagnosis?

(Please select 1 option)

○	CMV
○	Fungal infection
○	Hepatic leukaemic deposits
○	Miliary TB
○	Toxoplasmosis

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 58 mins 19 secs

Question: 42 of 100

A patient with AML develops jaundice and spiking pyrexia three weeks into induction chemotherapy.

The patient remained pyrexial after seven days of intravenous antibiotics.

What is the likely diagnosis?

(Please select 1 option)

◉	CMV ✓ Correct
○	Fungal infection
○	Hepatic leukaemic deposits
○	Miliary TB
○	Toxoplasmosis

The most likely cause for the persisting pyrexia plus hepatitis in this immunocompromised patient treated with appropriate antibiotics would be a *Cytomegalovirus* (CMV) infection.

Fungal infection would not be expected to cause the jaundice but again may be responsible for the pyrexia.

TB would be most unlikely and hepatic infiltration would not be expected to produce this pyrexia.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 58 mins 19 secs

Question: 43 of 100

A patient presents with acute promyelocytic leukaemia (APL).

What is the likely mechanism underlying leukaemogenesis?

(Please select 1 option)

- Aberrant fusion of 2 genes
- Impaired protein degradation
- Over expression of cellular oncogene
- Post-translational modification
- Telomere shortening

Submit answer | Skip question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 58 mins 50 secs

Question: 43 of 100

A patient presents with acute promyelocytic leukaemia (APL).

What is the likely mechanism underlying leukaemogenesis?

(Please select 1 option)

◉	Aberrant fusion of 2 genes ✓ Correct
○	Impaired protein degradation
○	Over expression of cellular oncogene
○	Post-translational modification
○	Telomere shortening

In APL one of the retinoic acid receptor genes, RARA, is fused to PML in the great majority of patients as a result of the chromosomal translocation t(15; 17).

Next question

Remove Tag

Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Question: 44 of 100

A 61-year-old who has smoked for 40 years presents with thoracic back pain.

His investigations reveal:

Haemoglobin	11.1 g/dL (13.0-18.0)
Urea	9.3 mmol/L (2.5-7.5)
Creatinine	298 µmol/L (60-110)
Calcium	3.67 mmol/L (2.2-2.6)
Albumin	30 g/L (37-49)
Total protein	97 g/L (61-76)
Thoracic spine x ray	Collapse of T8

Which investigation would confirm the diagnosis?

(Please select 1 option)

- ○ Bone marrow aspirate
- ○ Creatinine clearance
- ○ CXR
- ○ ESR
- ○ PTH

Submit answer | Skip question | Tag Question | Remove question

Albumin	30 g/L (37-49)
Total protein	97 g/L (61-76)
Thoracic spine x ray	Collapse of T8

Which investigation would confirm the diagnosis?

(Please select 1 option)

- (●) Bone marrow aspirate ✓ Correct
- ( ) Creatinine clearance
- ( ) CXR
- ( ) ESR
- ( ) PTH

This man has myeloma. The smoking is a red herring.

Myeloma typically presents with back pain often associated with pathological fractures.

He is mildly anaemic, there is renal impairment and hypercalcaemia, with a raised total protein secondary to a paraproteinaemia.

Bone marrow examination would reveal increased plasma cells (greater than 4% and usually greater than 30%). The erythrocyte sedimentation rate will be raised, but the bone marrow aspirate would confirm the diagnosis irrefutably.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 14 secs

Question: 45 of 100

A 27-year-old woman presented with a history of sudden onset right-sided weakness and dysphasia lasting eight hours. She had returned to the United Kingdom from Australia two days previously.

There was no significant past medical history and physical examination was normal. Chest x ray, ECG and a CT head scan were all normal.

Which one of the following investigations is most likely to reveal the underlying cause of this episode?

(Please select 1 option)

- Carotid Doppler ultrasonography
- Cerebral angiography
- MRI of head
- Transoesophageal echocardiography
- Transthoracic echocardiography

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

A 27-year-old woman presented with a history of sudden onset right-sided weakness and dysphasia lasting eight hours. She had returned to the United Kingdom from Australia two days previously.

There was no significant past medical history and physical examination was normal. Chest x ray, ECG and a CT head scan were all normal.

Which one of the following investigations is most likely to reveal the underlying cause of this episode?

(Please select 1 option)

○	Carotid Doppler ultrasonography
○	Cerebral angiography
○	MRI of head
◉	Transoesophageal echocardiography ✓ Correct
○	Transthoracic echocardiography

The history here suggests a lower limb deep vein thrombosis with peripheral embolus through a patent foramen ovale, leading to a left sided cerebrovascular event.

This is termed the paradoxical embolus so-called because a thromboembolus arising from the venous circulation can end up in the systemic circulation.

Transoesophageal echocardiography is the investigation of choice to investigate for a patent foramen ovale, although transthoracic echocardiography with contrast may be an alternative.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Question: 46 of 100

A 73-year-old man presented with a two week history of breathlessness and easy bruising.

Investigations show:

Haemoglobin	6.9 g/dL (13.0-18.0)
White cell count	0.4 x 10^9/L (4-11)
Platelet count	9 x 10^9/L (150-400)

Bone marrow aspirate all cellular elements reduced.

Which drug is the most likely cause of these abnormalities?

(Please select 1 option)

- Acyclovir
- Amiloride
- Amoxicillin
- Paracetamol
- Trimethoprim

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Investigations show:

Haemoglobin	6.9 g/dL (13.0-18.0)
White cell count	0.4 x 10^9/L (4-11)
Platelet count	9 x 10^9/L (150-400)

Bone marrow aspirate all cellular elements reduced.

Which drug is the most likely cause of these abnormalities?

(Please select 1 option)

- ○ Acyclovir
- ○ Amiloride
- ○ Amoxicillin
- ○ Paracetamol
- ◉ Trimethoprim ✓ Correct

There is a pancytopenia and marrow aspirate shows reduction in production of all cellular elements.

Trimethoprim is the drug most likely of these five to cause depression of haematopoiesis as this picture would be particularly unusual with paracetamol, amiloride acyclovir and amoxicillin.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

A 70-year-old female presents with a three month history of exertional dyspnoea and chest pain. She admitted to a poor diet, some vague abdominal pains and having lost 7 kg in weight.

Examination revealed pallor, patches of vitiligo on her arms and trunk, ankle oedema and a palpable spleen.

Investigations revealed:

Haemoglobin	5 g/dL (11.5-16.5)
MCV	105 fL (80-96)
White cell count	2 $x10^9$/L (4-11 $x10^9$)
Platelet count	50 $x10^9$/L (150-400 $x10^9$)
Bilirubin	40 µmol/L (1-22)
ALT	60 U/L (1-31)
AST	40 U/L (5-35)
LDH	1000 U/L (10-250)

Which one of the following is the most likely diagnosis?

(Please select 1 option)

- Aplastic anaemia
- Autoimmune haemolytic anaemia
- Dietary folate deficiency
- Pernicious anaemia
- Sideroblastic anaemia

Which one of the following is the most likely diagnosis?

(Please select 1 option)

○	Aplastic anaemia
○	Autoimmune haemolytic anaemia
○	Dietary folate deficiency
◉	Pernicious anaemia ✓ Correct
○	Sideroblastic anaemia

There is pancytopenia with anaemia being more significant. The anaemia is macrocytic.

Lactate dehydrogenase (LDH) is very high with some derangement of liver function tests (LFTs). Aplastic anaemia would cause pancytopenia but not a raised LDH.

Autoimmune haemolysis and sideroblastic anaemia would not cause pancytopenia.

Folate deficiency and pernicious anaemia would both cause the above results - the LDH is elevated due to ineffective erythropoiesis and likewise the deranged LFTs.

Pernicious anaemia is more likely given the history of other autoimmune disease.

Of note, with such a low haemoglobin one would expect a much higher mean corpuscular volume (MCV); but sometimes when the deficiency is severe, the red cell anisopoikilocytosis causes a lower MCV.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Question: 48 of 100

A 75-year-old male presents with a two month history of dyspnoea, weight loss and generalised lethargy. Past medical history included a previous left-sided hemiparesis due to stroke for which he took aspirin and perindopril.

Examination revealed residual left sided hemiparesis together with a pale and slightly jaundiced appearance.

Investigations show:

Haemoglobin	5 g/dL (13.0-18.0)
MCV	109 fL (80-96)
White cell count	2 $x10^9$/L (4-11 $x10^9$)
Platelets	45 $x10^9$/L (150-400 $x10^9$)

- Urinalysis: Increased urobilinogen

What is the next most appropriate investigation?

(Please select 1 option)

- Bone marrow aspirate
- Direct antiglobulin test
- Endoscopy
- Serum haptoglobins
- Vitamin B_{12} concentration

Submit answer | Skip question | Tag Question | Remove question

Platelets	45 x10^9/L (150-400 x10^9)

- Urinalysis: Increased urobilinogen

What is the next most appropriate investigation?

(Please select 1 option)

◉	Bone marrow aspirate ✕ Incorrect answer selected
○	Direct antiglobulin test
○	Endoscopy
○	Serum haptoglobins
○	Vitamin B_{12} concentration ← This is the correct answer

In this situation, serum B_{12} estimation is the correct choice. With a pancytopenic picture and raised mean corpuscular volume (MCV), the most appropriate step is to check the B_{12} and folate.

The other choices are considered only after the basic assays.

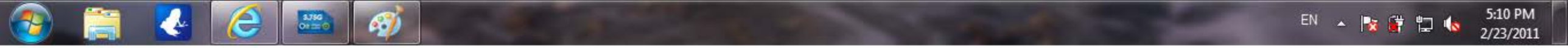
Haemolysis does not explain the low WCC, nor the thrombocytopenia.

A haptoglobin only adds weight to a diagnosis of haemolysis, and a RBC-labelled scan would add greater sensitivity to the diagnosis of haemolysis.

The mild jaundice is typical of megaloblastic anaemia (vitamin B12 or folate deficiency) because of increased destruction of red cell precursors in the bone marrow.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A


EN
5:10 PM
2/23/2011

(Please select 1 option)

○	Affinity maturation of the B-cell receptor is an important process initiated during the primary immune response
◉	IgD are surface receptors of B-lymphocytes ✗ Incorrect answer selected
○	In normal individuals T- lymphocytes with T-cell receptors (TCR) that recognise auto-antigens are all deleted to prevent autoimmunity ← This is the correct answer
○	TCRs with different antigen specificities can be co-expressed on a single T lymphocytes
○	The antigen specificity of the T-cell receptor is generated during development

T- and B-lymphocytes express receptors on their surface that recognise antigen in a specific manner. Each individual lymphocyte expresses a single type of receptor with unique specificity (except dual specificity T-cells - see below).

The receptor on the B-lymphocyte is membrane bound immunoglobulin (IgM and IgD isotype) and recognises particulate antigen, whilst the TCR is a heterodimer that recognises peptide fragments presented by MHC molecules.

The antigen specificity of T- and B- cells is generated during development by recombination of gene segments encoding the variable domains (antigen recognition domains) of immune receptors. These gene recombinations are random and maturing lymphocytes that express auto-reactive receptors which are then deleted or rendered anergic. These processes take place in the thymus (T-lymphocytes) and in the bone marrow (B-lymphocytes).

However, not all autoreactive lymphocytes are deleted during development. In the case of T-lymphocytes, not all proteins are expressed in the thymus, and those that are present only in the periphery or at certain stages of development will encounter mature T-cells that can respond to them. Thus, autoreactive T-cells exist in the periphery and other mechanisms are responsible for the protection of the body against autoimmunity.

Affinity maturation refers to the process of progressive development of immunoglobulin with higher affinity to the antigen. This occurs in the germinal centres of lymphoid organs during the evolution of the humoral response and is accomplished by hypermutation of the variable region genes. T-cells with dual specificities have been reported although their function is unknown.

Next question | Tag Question | Remove question

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 6 mins 23 secs

Question: 4 of 100

The blood used for an exchange transfusion in a neonate should fulfil these criteria:

(Please select 1 option)

○	**A** any blood less than 5 days old
○	**B** any Plasma reduced whole blood in CPD
○	**C** plasma reduced whole blood in CPD which is irradiated
○	**D** plasma reduced whole blood in CPD less than 5 days old and irradiated ← This is the correct answer
◉	**E** plasma reduced whole blood in CPD less than 5 days old , irradiated and Rh group should be same as the neonate ✕ Incorrect answer selected

An exchange transfusion requires blood which is plasma reduced whole blood, irradiated and less than 5 days old (hence option d and not a, b or c). The Rh group should be compatible with the mother, not the neonate, to avoid haemolytic transfusion reaction in the neonate due to maternal Rh antibodies (hence not option e).

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 6 mins 23 secs

Question: 5 of 100

The minimum dataset for identifying a patient and a sample for purpose of a blood transfusion request is:

(Please select 1 option)

- **A** the full name and gender
- **B** the full name, gender, date of birth, address and patient identity number
- **C** the full name , gender and patient identity number
- **D** the full name, gender, address and patient identity number
- **E** the full name, gender, previous blood grouping details, address and patient identity number

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 14 mins 49 secs

Question: 50 of 100

A 17-year-old male with glucose-6-phosphate dehydrogenase (G6PD) deficiency presents with tiredness and is noticed to be jaundiced. These features have developed since he developed a mild chest infection one week ago.

Which one of the following is the most likely haematological finding?

(Please select 1 option)

○	Haemoglobinuria
○	Low mean cell volume
○	Positive direct antiglobulin test
○	Reduced reticulocyte count
○	Spherocytes present on blood film

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 15 mins 44 secs

Question: 50 of 100

A 17-year-old male with glucose-6-phosphate dehydrogenase (G6PD) deficiency presents with tiredness and is noticed to be jaundiced. These features have developed since he developed a mild chest infection one week ago.

Which one of the following is the most likely haematological finding?

(Please select 1 option)

◉	Haemoglobinuria ✓ Correct
○	Low mean cell volume
○	Positive direct antiglobulin test
○	Reduced reticulocyte count
○	Spherocytes present on blood film

G6PD deficiency is a red cell enzymopathy that can lead to acute intravascular haemolysis after exposure to certain drugs, infection etc.

You would therefore get haemoglobinuria but would not get a positive direct antiglobulin test. The mean corpuscular volume (MCV) and reticulocyte count would be high due to haemolysis.

There is a form of G6PD deficiency where there is a chronic low level haemolysis where there are spherocytes seen - but the clinical information points to intravascular haemolysis after an infection.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Question: 51 of 100

A 50-year-old woman with a long history of alcohol abuse is prescribed phenytoin for epilepsy.

Examination was normal except for a liver edge.

Her full blood count reveals:

Haemoglobin	10.0 g/dL (11.5-16.5)
MCV	122 fL (80-96)
White cell count	2.2 $x10^9$/L (4-11 $x10^9$)
Platelet count	85 $x10^9$/L (150-400 $x10^9$)

What is the most likely explanation for these results?

(Please select 1 option)

- Alcoholic liver disease
- Aplastic anaemia
- Folic acid deficiency
- Hypothyroidism
- Vitamin C deficiency

Submit answer | Skip question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

MCV	122 fL (80-96)
White cell count	2.2 x10^{9}/L (4-11 x10^{9})
Platelet count	85 x10^{9}/L (150-400 x10^{9})

What is the most likely explanation for these results?

(Please select 1 option)

- Alcoholic liver disease
- Aplastic anaemia
- Folic acid deficiency ✓ Correct
- Hypothyroidism
- Vitamin C deficiency

Folic acid deficiency would give all these results. In addition she has good reason to be folate deficient - drinks a considerable amount and is on anticonvulsants.

Alcoholic liver disease on its own would not make you leucopenic.

Hypothyroidism would cause a raised mean corpuscular volume (MCV) but not the other parameters.

Scurvy does not cause this picture.

Aplastic anaemia could cause this haematological picture but the clinical scenario leads you towards folic acid deficiency.

Next question

Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 16 mins 51 secs

Question: 52 of 100

A 75-year-old male is admitted with tiredness and lethargy and is found to have an enlarged right supraclavicular mass.

Past medical history reveals that he had developed acrocyanosis six months previously and two months ago had been admitted with a chest infection for which he was treated with co-amoxiclav.

Investigations reveal:

- Blood film red cell auto-agglutination
- Direct antiglobulin test positive
- Cold agglutinin test positive.

What is the most likely diagnosis?

(Please select 1 option)

- Bronchial carcinoma
- Drug-induced haemolysis
- *Mycoplasma pneumoniae* infection
- Non-Hodgkin's lymphoma (NHL)
- Paroxysmal cold haemoglobinuria (PCH)

Submit answer | Skip question | Tag Question | Remove question

○	Bronchial carcinoma
○	Drug-induced haemolysis
○	*Mycoplasma pneumoniae* infection
◉	Non-Hodgkin's lymphoma (NHL) ✓ Correct
○	Paroxysmal cold haemoglobinuria (PCH)

The results are consistent with an autoimmune haemolytic screen caused by a cold antibody. Drug induced haemolysis does not give these results.

Bronchial Ca can give rise to an autoimmune haemolytic process but the antibody is usually warm - you do not get red cell agglutination or a postive cold agglutinin test.

PCH is a rare syndrome of acute intravascular haemolysis after exposure to cold caused by the Donath-Landsteiner antibody. It typically follows a viral illness or syphilis and is usually self limiting.

The results and clinical description of acrocyanosis are consistent with a cold auto antibody (cold autoimmune haemolytic anaemia).

The antibody attaches to the RBCs in the peripheral circulation where the blood is cold, causing agglutination of the RBCs in the small vessels leading to the acrocyanosis.

It is an IgM Ab that can fix complement and cause both intra- and extravascluar haemolysis. It can be a primary phenomenon (idiopathic cold haemagglutinin disease) or secondary to infection, for example, *Mycoplasma pneumoniae* or Epstein-Barr virus (EBV) or secondary to lymphoma.

The acrocyanosis developed before the chest infection, and in view of the lymphadenopathy, then NHL is the likely cause.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 19 mins 2 secs

Question: 53 of 100

A 25-year-old female with a history of type 1 von Willebrand's (vWBD) disease is referred for an opinion. She is to have a cervical cone biopsy and the admitting team are concerned about her clotting.

You find that she has a past history menorrhagia and has had two dental extractions as an adolescent that were uncomplicated.

What is the most useful test to assess her bleeding tendency?

(Please select 1 option)

◉	Activated partial thromboplastin time
○	Bleeding time
○	Plasma factor VIII activity
○	Platelet aggregation
○	Prothrombin time

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Question: 53 of 100

A 25-year-old female with a history of type 1 von Willebrand's (vWBD) disease is referred for an opinion. She is to have a cervical cone biopsy and the admitting team are concerned about her clotting.

You find that she has a past history menorrhagia and has had two dental extractions as an adolescent that were uncomplicated.

What is the most useful test to assess her bleeding tendency?

(Please select 1 option)

◉	Activated partial thromboplastin time ✕ Incorrect answer selected
○	Bleeding time
○	Plasma factor VIII activity ← This is the correct answer
○	Platelet aggregation
○	Prothrombin time

In Type I vWBD the prothrombin time (PT) and platelet aggregation will be normal.

Bleeding time, activated partial thromboplastin time (APTT) and FVIIIc are likely to be abnormal.

The bleeding time would be a good screening test, but as we already know she has Type I vWBD it will not give a quantitative measurement of her bleeding tendency.

Similarly APTT will not be that useful.

The most useful test in practice is to do the VWB antigen and activity(RICOF); But you would also do FVIIIc as this is also low in vWD.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Question: 54 of 100

A 62-year-old male attends the Emergency Department with a severe nose bleed. He is known to have alcoholic cirrhosis.

His investigations reveal:

Haemoglobin	10.9 g/dl	(13.0-18.0)
White cell count	5 x 10^9/l	(4-11)
Platelet count	60 x 10^9/l	(150-400)
Prothrombin time	17.5 s	(11.5-15.5)
APPT	42 s	(30-40)
Fibrinogen	0.7 g/l	(1.8-5.4)

What is the most appropriate blood product for this patient?

(Please select 1 option)

- Cryoprecipitate
- Factor VIII
- Platelets
- Prothrombin complex concentrate
- Whole blood

Submit answer | Skip question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

APPT	42 s	(30-40)
Fibrinogen	0.7 g/l	(1.8-5.4)

What is the most appropriate blood product for this patient?

(Please select 1 option)

○	Cryoprecipitate ← This is the correct answer
○	Factor VIII
○	Platelets
◉	Prothrombin complex concentrate ✗ Incorrect answer selected
○	Whole blood

The most significant abnormality is the low fibrinogen. Therefore the best product to correct the fibrinogen out of those given is cryoprecipitate.

To correct a coagulopathy you need to aim for:

- Fibrinogen >1.0 g/l
- Platelets >50 $x10^9$/l
- PT and APTT <1.5 upper range of normal

So from the results you can see the most significant abnormality is the low fibrinogen.

The platelets are low and activated partial thromboplastin time/prothrombin time (APTT/PT) prolonged but not really sufficient to cause bleeding.

Next question

Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Question: 55 of 100

A 72-year-old male presents with a five day history of cough, dyspnoea and fever.

His chest x ray shows a left basal consolidation.

His full blood count shows:

Haemoglobin	11 g/dL (13.0-18.0)
White cell count	30 $x10^9$/L (4-11 $x10^9$)
Neutrophils	10 $x10^9$/L (1.5-7 $x10^9$)
Lymphocytes	20 $x10^9$/L (1.5-4 $x10^9$)
Monocytes	1 $x10^9$/L (0-0.8 $x10^9$)
Eosinophils	0.4 $x10^9$/L (0.04-0.4 $x10^9$)
Basophils	0.1 $x10^9$/L (0-0.1 $x10^9$)

Which one of the following is the most appropriate test to establish the diagnosis?

(Please select 1 option)

- ○ Bone marrow aspirate
- ○ Bone marrow cytogenetics
- ○ CT abdomen
- ○ Immunophenotyping of white cells
- ○ Sputum cytology and AFB

Monocytes	1 x10⁹/L (0-0.8 x10⁹)
Eosinophils	0.4 x10⁹/L (0.04-0.4 x10⁹)
Basophils	0.1 x10⁹/L (0-0.1 x10⁹)

Which one of the following is the most appropriate test to establish the diagnosis?

(Please select 1 option)

- ○ Bone marrow aspirate
- ○ Bone marrow cytogenetics
- ○ CT abdomen
- ◉ Immunophenotyping of white cells ✓ Correct
- ○ Sputum cytology and AFB

Apart from the mild neutrophilia which could be explained by the infection the significant abnormality on the FBC is the lymphocyte count. Such a high lymphocyte count could be suggestive of a lymphoproliferative disorder such as chronic lymphocytic leukaemia. The best way to diagnose these is immunophenotyping of the blood - non-invasive and will give a diagnosis.

The patient may have lymphadenopathy or splenomegaly which would show on CT but no diagnosis can be made from this.

A bone marrow is invasive and the BM is sometimes not involved in low grade lymphoproliferative disorders and similarly there may be no cytogenetic abnormality.

The FBC is not suggestive of TB or malignancy, therefore sputum examination would not be useful.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 27 mins 37 secs

Question: 56 of 100

A 69-year-old male presents with tiredness and dyspnoea and is diagnosed with acute myeloid leukaemia.

Which of the following is the most important prognostic factor?

(Please select 1 option)

- A. Elevated lactate dehydrogenase activity
- B. Karyotype of bone marrow
- C. Monocytic morphology
- D. Number of blasts in bone marrow
- E. White cell count at diagnosis

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 28 mins 47 secs

Question: 56 of 100

A 69-year-old male presents with tiredness and dyspnoea and is diagnosed with acute myeloid leukaemia.

Which of the following is the most important prognostic factor?

(Please select 1 option)

○	A. Elevated lactate dehydrogenase activity
○	B. Karyotype of bone marrow ← This is the correct answer
○	C. Monocytic morphology
○	D. Number of blasts in bone marrow
◉	E. White cell count at diagnosis ✕ Incorrect answer selected

A, C, and D have no prognostic value.

White cell count at diagnosis is however important, but most important is the karyotype of bone marrow, as this result stratifies patients into lower risk, standard risk and poor risk, which has prognostic significance.

Next question

Remove Tag
Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 28 mins 47 secs

Question: 57 of 100

A 30-year-old female presents to the antenatal clinic with her first pregnancy.

During the interview she reports that she has been entirely well but her sister had suffered a deep vein thrombosis in her second pregnancy. A thrombophilia screen shows that she is heterozygous for factor V Leiden (FVL).

Which is the most appropriate action for this patient?

(Please select 1 option)

○	She should be informed to seek medical attention if she becomes aware of calf swelling or pain
○	She should be treated with aspirin 75 mg daily
◉	She should be treated with prophylactic low molecular weight heparin
○	She should be treated with prophylactic unfractionated heparin
○	She should receive warfarin

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 29 mins 57 secs

Question: 57 of 100

A 30-year-old female presents to the antenatal clinic with her first pregnancy.

During the interview she reports that she has been entirely well but her sister had suffered a deep vein thrombosis in her second pregnancy. A thrombophilia screen shows that she is heterozygous for factor V Leiden (FVL).

Which is the most appropriate action for this patient?

(Please select 1 option)

○	She should be informed to seek medical attention if she becomes aware of calf swelling or pain ← This is the correct answer
○	She should be treated with aspirin 75 mg daily
◉	She should be treated with prophylactic low molecular weight heparin ✕ Incorrect answer selected
○	She should be treated with prophylactic unfractionated heparin
○	She should receive warfarin

Although she is heterozygous for factor V Leiden, she has not had a previous thrombotic event.

There is no need to anticoagulate her throughout pregnancy. However she is at increased risk - pregnant and FVL - and should be very alert to the symptoms and signs of a thrombotic event.

There is no evidence of benefit from aspirin to reduce her thrombotic risk.

Next question

Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 29 mins 57 secs

Question: 58 of 100

A 40-year-old man presents with bleeding gums and ease of bruising. His only medication is omeprazole for dyspepsia.

Investigations show:

Haemoglobin	12.5 g/dL (13.0-18.0)
MCV	90 fL (80-96)
Platelets	20 $x10^9$/L (150-400 $x10^9$)
Prothrombin time	13.5s (11.5-15.5)

- Blood film: occasional giant platelets

What is the most likely diagnosis?

(Please select 1 option)

- ○ Amegakaryocytic thrombocytopenia
- ○ Disseminated intravascular coagulation
- ○ Drug-induced thrombocytopenia
- ○ Immune thrombocytopenia
- ○ Thrombotic thrombocytopenic purpura

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

What is the most likely diagnosis?

(Please select 1 option)

○	Amegakaryocytic thrombocytopenia
○	Disseminated intravascular coagulation
◉	Drug-induced thrombocytopenia ✗ Incorrect answer selected
○	Immune thrombocytopenia ← This is the correct answer
○	Thrombotic thrombocytopenic purpura

The only abnormality is the very low platelet count.

The bone marrow is still working as there are giant platelets seen on film, which you see when there is peripheral consumption of the platelets.

The large platelets are a sign that the bone marrow is churning them out prematurely to keep up with demand.

With disseminated intravascular coagulation the prothrombin time would be prolonged.

With thrombotic thrombocytopenic purpura the haemoglobin would be low- as haemolysis is a feature.

Drug-induced thrombocytopenia in itself is an immune mechanism, and while lansoprazole can cause a reduction in platelet count, it is not classically a drug you associate with drug induced thrombocytopenia.

Immune thrombocytopenia is very common and would give this very low platelet count, and by choosing this answer it covers drug induced thrombocytopenia as well.

Next question

Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 31 mins 28 secs

Question: 59 of 100

A 30-year-old male presents with episodic jaundice and anaemia and has been diagnosed with glucose-6-phosphate dehydrogenase (G6PD) deficiency.

On further testing his wife has normal plasma G6PD activity.

What is the risk of their children developing this condition?

Which one of the following statements is correct?

(Please select 1 option)

- ○ 50% of their children will be affected, irrespective of gender
- ○ All their children will be affected
- ○ All their daughters will be affected
- ○ All their sons will be affected
- ○ None of their children will be affected

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

deficiency.

On further testing his wife has normal plasma G6PD activity.

What is the risk of their children developing this condition?

Which one of the following statements is correct?

(Please select 1 option)

○	50% of their children will be affected, irrespective of gender
○	All their children will be affected
◉	All their daughters will be affected ✕ Incorrect answer selected
○	All their sons will be affected
○	None of their children will be affected ← This is the correct answer

G6PD is X linked - therefore females are carriers, and are not usually affected, unless there is inactivation of their X chromosome, Males are affected.

Males will pass on the 'bad' X chromosome to their daughters so that they become carriers, and as said above they are not usually affected. Males pass on their Y chromosomes to any sons, therefore they will not be affected.

In the question the male is affected, but as the female has normal levels of the enzyme, we are assuming she is not a carrier (although strictly she could be a carrier and have normal levels).

The male will pass on the X chromosome to any daughters, who will not be affected, as they will have a 'good' X from the mothers, and the father will pass on the Y chromosome to his sons, who will not be affected.

Next question

Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 7 mins 13 secs

Question: 5 of 100

The minimum dataset for identifying a patient and a sample for purpose of a blood transfusion request is:

(Please select 1 option)

○	**A** the full name and gender
○	**B** the full name, gender, date of birth, address and patient identity number ← This is the correct answer
◉	**C** the full name , gender and patient identity number ✕ Incorrect answer selected
○	**D** the full name, gender, address and patient identity number
○	**E** the full name, gender, previous blood grouping details, address and patient identity number

Given that maximum errors and near misses occur because of mislabelling or mistaken identity of patient or the sample a minimum data set is prescribed for transfusion requests. This involves recording the full name, gender, date of birth, address (in some areas) and patient identity number (option b). Previous blood grouping details are not required and missing elements of this minimum dataset is not acceptable in th transfusion service (options a,c d and e)

Next question

Remove Tag

Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 7 mins 13 secs

Question: 6 of 100

Which of the following infusion times would be appropriate during the transfusion of a blood product in a stable patient:

(Please select 1 option)

○	**A** A platelet transfusion should be given over 90 minutes
○	**B** A Packed cell transfusion should be given over 20 minutes
○	**C** A platelet transfusion should be given over 60 minutes
○	**D** A packed cell transfusion should be given over 90 minutes
○	**E** A Platelet transfusion over 120 minutes

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 32 mins 32 secs

Question: 60 of 100

A 29-year-old female presents with acute right-sided weakness.

She has one child aged four years and had two spontaneous abortions in the past. After the birth of her child she developed a DVT and required three months' anticoagulation with warfarin.

Examination revealed a right hemiparesis. A CT head scan showed a left middle cerebral artery territory infarct.

What is the most likely finding on echocardiography?

(Please select 1 option)

- Atrial septal defect
- Bicuspid aortic valve
- Left atrial myxoma
- Normal appearances
- Ventricular septal defect

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Question: 60 of 100

A 29-year-old female presents with acute right-sided weakness.

She has one child aged four years and had two spontaneous abortions in the past. After the birth of her child she developed a DVT and required three months' anticoagulation with warfarin.

Examination revealed a right hemiparesis. A CT head scan showed a left middle cerebral artery territory infarct.

What is the most likely finding on echocardiography?

(Please select 1 option)

○	Atrial septal defect
○	Bicuspid aortic valve
○	Left atrial myxoma
◉	Normal appearances ✓ Correct
○	Ventricular septal defect

This patient has a prothrombotic tendency suggestive of the lupus anticoagulant with recurrent abortions, previous deep vein thrombosis (DVT) and now she has developed a left hemiparesis.

This has occurred off warfarin and it is highly unlikely to be due to any right to left transference of clot.

It is more likely to be due to spontaneous infarct related to the thrombophilia and her heart is likely to be normal.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 33 mins 15 secs

Question: 61 of 100

A 53-year-old woman presents with a six month history of recurrent facial and tongue swelling.

She associated the attacks with consuming certain food additives and with contact with some cosmetics and cleaning fluids. Her only regular medication was hormone replacement therapy.

Investigations reveal:

Total serum IgE	145 kU/L (0-120)
Serum C3	105 mg/dL (65-190)
Serum C4	35 mg/dL (15-50)

What is the most likely diagnosis?

(Please select 1 option)

- ○ C1 esterase inhibitor deficiency
- ○ Chemical intolerance
- ○ Food allergy
- ○ Idiopathic angioedema
- ○ Mastocytosis

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

medication was hormone replacement therapy.

Investigations reveal:

Total serum IgE	145 kU/L (0-120)
Serum C3	105 mg/dL (65-190)
Serum C4	35 mg/dL (15-50)

What is the most likely diagnosis?

(Please select 1 option)

- C1 esterase inhibitor deficiency
- Chemical intolerance
- Food allergy ✓ Correct
- Idiopathic angioedema
- Mastocytosis

The history suggests atopy which is confirmed by the mildly elevated IgE concentration and normal C4 and C3 concentrations.

Hereditary or acquired angioedema is unlikely given the normal C4 and the history occurs late. Also the patient herself has noticed a link with food - food allergy is usually easier to diagnosis in adults.

The cosmetics (chemical intolerance) are unlikely and the clinical history does not fit mastocytosis.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Question: 62 of 100

A 71-year-old man presents with a tender left calf and has a background history of headaches, tiredness and dizziness. He is a smoker of 20 cigarettes daily and drinks 45 units of alcohol weekly.

On examination he was plethoric, had a blood pressure of 186/102 mmHg and has a swollen, hot tender and erythematous left calf. Dopplers confirm the presence of a deep vein thrombosis.

Investigations reveal:

Haemoglobin	19 g/dl	(13-18)
Haematocrit	0.58	(0.40-0.52)
White cell count	12.5 x 10^9/l	(4-11)
Platelet count	500 x 10^9/l	(150-400)

Which one of the following is the most appropriate investigation to establish the diagnosis?

(Please select 1 option)

- Abdominal ultrasound scan
- Arterial blood gases
- Bone marrow trephine
- Leucocyte alkaline phosphatase score
- Red blood cell mass

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

White cell count	12.5 x 10^9/l	(4-11)
Platelet count	500 x 10^9/l	(150-400)

Which one of the following is the most appropriate investigation to establish the diagnosis?

(Please select 1 option)

- Abdominal ultrasound scan
- Arterial blood gases
- Bone marrow trephine
- Leucocyte alkaline phosphatase score
- Red blood cell mass ✓ Correct

The most significant abnormality is the raised haemoglobin and haematocrit suggesting polycythaemia, which in the presence of all the other features suggests secondary polycythaemia.

Therefore, the most useful and appropriate investigation will be red cell mass studies which will distinguish between true and relative polycythaemia.

Further investigations will then be dictated by the the results of this initial test; an ultrasound scan (USS) bone marrow et cetera, and blood gases may be needed after the initial red cell mass studies.

The leucocyte alkaline phosphatase score is rather outdated and seldom performed.

The raised WCC and platelet count would suggest that this is primary polycythaemia not apparent polycythaemia but red blood cell mass is still the best answer.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 48 mins 1 secs

Question: 63 of 100

A 75-year-old woman receives two units of packed red cells following a hip replacement. One week later her haemoglobin concentration had fallen by 4 g/l.

Which one of the following would be most likely to indicate a delayed transfusion reaction?

(Please select 1 option)

- **A** Conjugated hyperbilirubinaemia
- **B** Elevated D-dimer concentration
- **C** Haemoglobinuria
- **D** Haemosiderinuria
- **E** Positive direct antiglobulin test

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 55 mins 10 secs

Question: 63 of 100

A 75-year-old woman receives two units of packed red cells following a hip replacement. One week later her haemoglobin concentration had fallen by 4 g/l.

Which one of the following would be most likely to indicate a delayed transfusion reaction?

(Please select 1 option)

○	**A** Conjugated hyperbilirubinaemia
○	**B** Elevated D-dimer concentration
◉	**C** Haemoglobinuria ✕ Incorrect answer selected
○	**D** Haemosiderinuria
○	**E** Positive direct antiglobulin test ← This is the correct answer

The features suggest immune haemolysis with direct antiglobulin test (DAT) being diagnostic.

A. Is inappropriate as it is unconjugated bilirubin that is raised in haemolysis.

B, **C** and **D.** Are not going to be diagnostic of an immune haemolytic transfusion reaction.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 55 mins 10 secs

Question: 64 of 100

A 30-year-old woman presents with jaundice and her investigations reveal:

Haemoglobin	9.0 g/dl	(11.5-16.5)
Reticulocyte count	180 x 10^9/l	(25-85)
Serum bilirubin	50 µmol/l	(1-22)

Her blood film reveals the presence of spherocytes.

Which of the following is the next most useful investigation?

(Please select 1 option)

- Abdominal ultrasound scan
- Direct antiglobulin test
- Glucose-6-phosphate dehydrogenase activity
- Haemoglobin electrophoresis
- Red cell osmotic fragility

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Question: 64 of 100

A 30-year-old woman presents with jaundice and her investigations reveal:

Haemoglobin	9.0 g/dl	(11.5-16.5)
Reticulocyte count	180 x 10^9/l	(25-85)
Serum bilirubin	50 µmol/l	(1-22)

Her blood film reveals the presence of spherocytes.

Which of the following is the next most useful investigation?

(Please select 1 option)

- Abdominal ultrasound scan
- Direct antiglobulin test ✓ Correct
- Glucose-6-phosphate dehydrogenase activity
- Haemoglobin electrophoresis
- Red cell osmotic fragility

The results given indicate a haemolytic anaemia of which spherocytes are typical and given the age of the patient the most likely cause is immune.

Therefore the most useful test is the direct antiglobulin test.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 57 mins 31 secs

Question: 65 of 100

Which of the following statements is most true regarding polycythaemia rubra vera (PRV)?

(Please select 1 option)

- PRV is often associated with hypertension and smoking
- PRV is usually associated with a high haemoglobin, but with neutropenia and thrombocytopenia
- PRV may be characterised by a raised packed cell volume (PCV) and decreased plasma volume
- The diagnosis of PRV is based on a high red cell mass, normal oxygen saturations and splenomegaly
- Venesection treatment will improve long term survival rates

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 58 mins 29 secs

Question: 65 of 100

Which of the following statements is most true regarding polycythaemia rubra vera (PRV)?

(Please select 1 option)

○	PRV is often associated with hypertension and smoking
○	PRV is usually associated with a high haemoglobin, but with neutropenia and thrombocytopenia
○	PRV may be characterised by a raised packed cell volume (PCV) and decreased plasma volume
◉	The diagnosis of PRV is based on a high red cell mass, normal oxygen saturations and splenomegaly ✓ Correct
○	Venesection treatment will improve long term survival rates

The diagnosis of PRV is based on a high red cell mass, normal oxygen saturations and splenomegaly.

A decreased plasma volume causing a raised PCV is known as apparent or spurious polycythaemia. This may be associated with hypertension or smoking.

PRV is usually associated with a raised haemoglobin and often with a high platelet count and white cell count.

Venesection will lessen the rates of thrombotic complications but there is no evidence that venesection improves long term survival rates.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 58 mins 29 secs

Question: 66 of 100

A 50-year-old female presents with acute chest pain and dyspnoea.

Examination reveals bilateral ankle oedema with 24 hour urine protein assessment showing 8g/d (<0.2).

Which is the most likely explanation for these findings?

(Please select 1 option)

- Factor V Leiden
- Reduced antithrombin III activity
- Reduced concentration of von Willebrand's factor
- Reduced factor VIII
- Reduced fibrinogen concentration

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 15 secs

Question: 66 of 100

A 50-year-old female presents with acute chest pain and dyspnoea.

Examination reveals bilateral ankle oedema with 24 hour urine protein assessment showing 8g/d (<0.2).

Which is the most likely explanation for these findings?

(Please select 1 option)

○	Factor V Leiden
◉	Reduced antithrombin III activity ✓ Correct
○	Reduced concentration of von Willebrand's factor
○	Reduced factor VIII
○	Reduced fibrinogen concentration

This patient has developed nephrotic syndrome and appears to have had a thromboembolic event.

The suggestion is that she has had nephritic syndrome before developing the thromboembolism.

Deranged coagulation associated with nephrotic syndrome is a consequence of AT III deficiency, increased fibrinogen and increased factor VIIIc.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 15 secs

Question: 67 of 100

A 21-year-old man with non-Hodgkin's lymphoma and haemolytic anaemia is assessed for splenectomy.

When should Pneumovax vaccine be administered?

(Please select 1 option)

- One month after surgery
- One month before surgery
- One week after surgery
- One week before surgery
- Perioperatively

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 1 mins 12 secs

Question: 67 of 100

A 21-year-old man with non-Hodgkin's lymphoma and haemolytic anaemia is assessed for splenectomy.

When should Pneumovax vaccine be administered?

(Please select 1 option)

○	One month after surgery
◉	One month before surgery ✓ Correct
○	One week after surgery
○	One week before surgery
○	Perioperatively

The vaccine should be given a minimum of two weeks before elective splenectomy in order to ensure an optimal antibody response.

In emergency splenectomy the patient should be immunised as soon as possible after recovery from the operation and before discharge from hospital.

Unvaccinated patients splenectomised some time earlier should be vaccinated at the first opportunity.

Vaccination is delayed for at least six months after immunosuppressive chemotherapy or radiotherapy during which time prophylactic antibiotics should be given.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 1 mins 12 secs

Question: 68 of 100

Which of the following statements regarding disseminated intravascular coagulation (DIC) is most correct?

(Please select 1 option)

- DIC is associated with an elevated D-dimer
- DIC is associated with rising fibrinogen levels
- DIC is associated with a rising platelet count
- Normal clotting parameters effectively exclude a diagnosis of DIC
- Removal of the underlying cause of the DIC will lead to resolution of the manifestations of DIC

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 1 mins 55 secs

Question: 68 of 100

Which of the following statements regarding disseminated intravascular coagulation (DIC) is most correct?

(Please select 1 option)

◉	DIC is associated with an elevated D-dimer ✓ Correct
○	DIC is associated with rising fibrinogen levels
○	DIC is associated with a rising platelet count
○	Normal clotting parameters effectively exclude a diagnosis of DIC
○	Removal of the underlying cause of the DIC will lead to resolution of the manifestations of DIC

DIC is caused by the enhanced and abnormally sustained generation of thrombin, and is associated with elevated products of fibrin breakdown, one of these being D-dimer.

Treatment of the underlying cause , for example, sepsis, does not always lead to resolution of the condition, and recombinant human activated protein C has been shown to be effective in reducing mortality from DIC in patients with sepsis.

DIC is associated with a falling platelet count and decreased fibrinogen, but the clotting factors may be normal, especially when one considers that the acute phase response may shorten the activated partial thromboplastin time (APTT) and increase fibrinogen.

For an excellent review see BMJ 2003;327:974-7.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 1 mins 55 secs

Question: 69 of 100

A 32-year-old man was prescribed an oral antibiotic for a urinary tract infection.

Two days later he noticed that his urine was increasingly dark in colour.

Investigations revealed:

Haemoglobin	8.5g/dL (13.0-18.0)
Reticulocytes	147 $x10^9$/L (25-85 $x10^9$)

Blood film: marked anisopoikilocytosis and bite cells.

What is the most likely diagnosis?

(Please select 1 option)

- A. Acute myeloid leukaemia
- B. Autoimmune haemolytic anaemia
- C. Haemoglobin H disease
- D. Hereditary spherocytosis
- E. Paroxysmal cold haemoglobinuria

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

	A. Acute myeloid leukaemia
	B. Autoimmune haemolytic anaemia ← This is the correct answer
	C. Haemoglobin H disease
◉	D. Hereditary spherocytosis ✕ Incorrect answer selected
	E. Paroxysmal cold haemoglobinuria

I think that this is a dificult question!

Paroxysmal cold haemoglobinuria (PCH) is a rare type of autoimmune haemolytic anaemia (AIHA) occurring primarily in children.

The classic symptom of PCH is a sudden onset of haemoglobinuria following exposure to cold, even for a few minutes. Symptoms may occur minutes to hours following exposure to cold. Haemoglobinuria is not always present because in some persons with PCH the autoantibody level is not high enough to cause intravascular haemolysis. PCH is usually of abrupt onset in the setting of an infectious disease.

Given the patient's age and the specific history in this case the diagnosis is unlikely to be PCH.

If the diagnosis were hereditary spherocytosis then the blood film would show spherocytes.

In haemoglobin H disease the typical inclusions can be demonstrated in erythrocytes stained with brilliant cresyl blue and a chronic microcytic, hypochromic anaemia would be present.

Haemolytic anaemia may be precipitated by sulfonamides and also by penicillins.

This gentleman may have been treated with trimethoprim or a penicillin which then caused AIHA with the typical blood film.

I feel that the most appropriate answer to this question is B, given the patient's age, the lack of history of exposure to cold, and the history which is given of antibiotic prescription.

Next question | Tag Question | Remove question

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 8 mins 34 secs

Question: 6 of 100

Which of the following infusion times would be appropriate during the transfusion of a blood product in a stable patient:

(Please select 1 option)

○	**A** A platelet transfusion should be given over 90 minutes
○	**B** A Packed cell transfusion should be given over 20 minutes
○	**C** A platelet transfusion should be given over 60 minutes
◉	**D** A packed cell transfusion should be given over 90 minutes ✓ Correct
○	**E** A Platelet transfusion over 120 minutes

In a stable patient red cell packs may be transfused over 90-120 minutes while a platelet transfusion should not take more than 20-30 minutes (hence option d). Rapid infusion of red cells or fresh frozen plasma may be required in acutely bleeding patient but not in this patient who is stable (hence not a,b,c and e).

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 8 mins 34 secs

Question: 7 of 100

A 17-year-old girl with mild von Willebrand's disease is scheduled for dental extraction. A previous dental extraction resulted in bleeding that had required two unit transfusion.

What is the most appropriate treatment prior to dental surgery?

(Please select 1 option)

- Cryoprecipitate
- DDAVP
- Fresh frozen plasma
- High purity factor VIII concentrate
- Recombinant factor VIII concentrate

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Question: 70 of 100

You are called to the Emergency Department to assess a 21-year-old student who has presented with bloody diarrhoea.

The diarrhoea started two weeks previously and was associated with increasing nausea and malaise and mild swelling of the lower limbs. She was having difficulty passing urine. She had eaten steak from the local butcher at a friend's barbeque the day before developing diarrhoea.

On examination she was pale with evidence of petechiae over her legs. Her face appeared puffy. Blood pressure was 160/95 mmHg. She was apyrexial but had a tachycardia and crackles on inspiration at both lung bases. There was an old appendicectomy scar in the right iliac fossa.

Investigations showed:

Haemoglobin	8.5 g/dl	(11.5-16.5)
White cell count	13.2 x 10^9/l	(4-11)
Neutrophils	9.5 x 10^9/l	(1.5-7)
Platelets	35 x 10^9/l	(150-400)
PT	12 s	(11.5-15.5)
APTT	34 s	(30-40)
Fibrinogen	4 g/l	(1.8-5.4)
Serum sodium	139 mmol/l	(137-144)
Serum potassium	6.1 mmol/l	(3.5-4.9)
Serum urea	40 mmol/l	(2.5-7.5)
Serum creatinine	411 µmol/l	(60-110)
Serum albumin	27 g/l	(37-49)
Dipstick urine	Blood ++ Protein +	

What is the single most important next investigation to determine the diagnosis?

Investigations showed:

Haemoglobin	8.5 g/dl	(11.5-16.5)
White cell count	13.2 x 10^9/l	(4-11)
Neutrophils	9.5 x 10^9/l	(1.5-7)
Platelets	35 x 10^9/l	(150-400)
PT	12 s	(11.5-15.5)
APTT	34 s	(30-40)
Fibrinogen	4 g/l	(1.8-5.4)
Serum sodium	139 mmol/l	(137-144)
Serum potassium	6.1 mmol/l	(3.5-4.9)
Serum urea	40 mmol/l	(2.5-7.5)
Serum creatinine	411 µmol/l	(60-110)
Serum albumin	27 g/l	(37-49)
Dipstick urine	Blood ++ Protein +	

What is the single most important next investigation to determine the diagnosis?

(Please select 1 option)

- ASO titres
- Renal tract ultrasound
- Stool culture
- Transthoracic echocardiogram
- Urine microscopy

What is the single most important next investigation to determine the diagnosis?

(Please select 1 option)

○	ASO titres
○	Renal tract ultrasound
◉	Stool culture ✓ Correct
○	Transthoracic echocardiogram
○	Urine microscopy

This patient has haemolytic uraemic syndrome (HUS).

It typically presents with a triad of

- Acute renal failure (ARF)
- Microangiopathic haemolytic anaemia
- Thrombocytopaenia with normal clotting.

HUS is a complication of infection with verocytotoxin producing *Escherichia coli* usually of the serotype 0157:H7.

Toxins produced in the intestine enter the blood and bind to endothelial cells in target organs. Endothelial cell damage leads to platelet and fibrin deposition with resultant fragmentation of circulating red blood cells and microvascular occlusion.

The syndrome has also been reported after infections with coxsackie, echovirus and *Shigella*.

HUS is characterised by the sudden onset of haemolytic anaemia with fragmentation of red blood cells, thrombocytopaenia and acute renal failure after a prodromal illness of acute gastroenteritis often with bloody diarrhoea.

Clinical signs include increasing pallor, haematuria, oliguria and purpura. Jaundice is occasionally seen. Hypertension may be present.

Typical results show an anaemia, thrombocytopaenia, and often a neutrophilia. Blood film shows fragmented erythrocytes.

HUS is characterised by the sudden onset of haemolytic anaemia with fragmentation of red blood cells, thrombocytopaenia and acute renal failure after a prodromal illness of acute gastroenteritis often with bloody diarrhoea.

Clinical signs include increasing pallor, haematuria, oliguria and purpura. Jaundice is occasionally seen. Hypertension may be present.

Typical results show an anaemia, thrombocytopaenia, and often a neutrophilia. Blood film shows fragmented erythrocytes.

Urea and electrolytes are typical of acute renal failure. There is normal coagulation and fibrinogen.

Neurological complications include

- Stroke, seizure and coma occur in 25% of patients
- Rarely pancreatitis
- Pleural and pericardial effusions.

Approximately 5% of patients will develop end stage renal failure.

Long term renal sequelae range from proteinuria to chronic renal failure.

Therapy is supportive with

- correction of anaemia
- correction of uraemia by early dialysis
- strict fluid balance
- treatment of hypertension.

Major differential diagnosis is

1. Sepsis with DIC - presents with abnormalities of clotting parameters.
2. TTP - thrombotic thrombocytopaenic purpura presents with microangiopathic haemolytic anaemia, thrombocytopaenic purpura, neurologic abnormalities, fever, and renal disease.

Renal abnormalities tend to be more severe in HUS.

Although once considered variants of a single syndrome, recent evidence suggests that the pathogenesis of TTP and HUS is different. Patients with TTP lack a plasma protease that is responsible for the breakdown of von Willebrand factor (vWF) multimers and these accumulate in the plasma. The activity of this protease is normal in patients with HUS.

Until the test for vWF protease activity becomes available, differentiation between HUS and TTP is based on the presence of central nervous system involvement in TTP and the more severe renal involvement in HUS.

In HUS 90% of patients are children and a history of prodromal diarrhoeal illness is more common.

The therapy of choice for TTP is plasma exchange with fresh frozen plasma.

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 10 mins 46 secs

Question: 71 of 100

A 42-year-old man presented with tiredness, breathlessness and nose bleeds for three weeks. On examination there were several bruises on his arms and legs, 2 cm splenomegaly and fundal haemorrhages.

Investigations revealed:

Haemoglobin	7.2 g/dl	(13.0-18.0)
White cell count	13.8 $x10^9$/l	(4-11)
Platelet count	24 $x10^9$/l	(150-400)
Blood film	White cells predominantly myeloblasts and promyelocytes	

Which one of the following investigations would be of most prognostic value?

(Please select 1 option)

- ○ Bone marrow trephine biopsy
- ○ Cerebrospinal fluid examination
- ○ Cytochemistry
- ○ Cytogenic karyotype
- ○ Immunophenotyping

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Haemoglobin	7.2 g/dl	(13.0-18.0)
White cell count	13.8 $x10^9$/l	(4-11)
Platelet count	24 $x10^9$/l	(150-400)
Blood film	White cells predominantly myeloblasts and promyelocytes	

Which one of the following investigations would be of most prognostic value?

(Please select 1 option)

- Bone marrow trephine biopsy
- Cerebrospinal fluid examination ✗ Incorrect answer selected
- Cytochemistry
- Cytogenic karyotype ← This is the correct answer
- Immunophenotyping

Cytogenetic evaluation of malignant haematological cells may have important implications for the prognosis and treatment options in acute myelogenous leukaemia (AML).

For example t(8;21) confers a good prognosis in adult AML, and about 70% of patients in this low-risk group can be cured with intensive chemotherapy alone, radiotherapy being reserved for patients who relapse.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 14 mins 59 secs

Question: 72 of 100

A 69-year-old woman presented with an ulcer over the left ankle, which had developed over the previous nine months. She had a history of right deep vein thrombosis (DVT) five years previously.

On examination she had a superficial slough-based ulcer, 6 cm in diameter, over the medial malleolus with no evidence of cellulitis.

Which one of the following is the most appropriate next investigation?

(Please select 1 option)

○	Ankle-brachial pressure index
○	Bacteriological swab of the ulcer
○	Bilateral lower limb arteriogram
○	Right leg venogram
○	Venous duplex ultrasound scan

Submit answer | Skip question | Remove question

- Shop

(Please select 1 option)

◉	Ankle-brachial pressure index ✓ Correct
○	Bacteriological swab of the ulcer
○	Bilateral lower limb arteriogram
○	Right leg venogram
○	Venous duplex ultrasound scan

It has been reported that venous ulcerations are the most common type of ulcer affecting the lower extremities. The probable underlying cause of venous congestion, which may promote ulceration, is venous insufficiency.

The treatment of venous ulceration is control of oedema, treating any infection, and compression. However, compressive dressings or devices should not be applied if the arterial circulation is impaired.

It is thus important to identify any arterial disease, and ankle-brachial pressure index is a simple way of doing this. One may then progress to lower limb arteriogram if indicated.

There is no clinical sign of infection, and although a bacterial swab would help to rule out pathogens within the ulcer, arterial insufficiency is the more important issue.

If there is a clinical suspicion of DVT then duplex (or rarely a venogram) is indicated to decide on the indication for warfarin.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 16 mins 12 secs

Question: 73 of 100

A 70-year-old male is admitted with haematemesis. He is currently being treated with warfarin for atrial fibrillation and his INR returns as 10 (<1.4).

Which of the following is the most appropriate immediate treatment of his INR?

(Please select 1 option)

○	Cryoprecipitate
○	Fresh frozen plasma
○	Intravenous vitamin K
○	Oral vitamin K
○	Recombinant Factor VIII concentrate

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 16 mins 49 secs

Question: 73 of 100

A 70-year-old male is admitted with haematemesis. He is currently being treated with warfarin for atrial fibrillation and his INR returns as 10 (<1.4).

Which of the following is the most appropriate immediate treatment of his INR?

(Please select 1 option)

○	Cryoprecipitate
◉	Fresh frozen plasma ✓ Correct
○	Intravenous vitamin K
○	Oral vitamin K
○	Recombinant Factor VIII concentrate

This patient has had a bleed related to a grossly elevated international normalised ratio (INR). Consequently the INR needs correction as rapidly as is possible.

Vitamin K will correct the INR over a few days, whereas fresh frozen plasma will correct the bleeding time rapidly.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Question: 74 of 100

An 84-year-old woman presented with tiredness.

On examination, she was anaemic but had no palpable splenomegaly.

Investigations revealed a haemoglobin of 9.7 g/dL (11.5-16.5). She was commenced on oral iron therapy for one month and her haemoglobin remained unchanged.

Further investigations revealed:

MCV	102 fL (80-96)
Blood film	Marked anisopoikilocytosis
Serum ferritin	70 µg/L (15-300)
Vitamin B_{12}	280 ng/L (160-760)
Red cell folate	230 µg/L (160-640)
Serum urea	9.1 mmol/L (2.5-7.5)
Serum creatinine	150 µmol/L (60-110)

What is the most likely diagnosis?

(Please select 1 option)

- **A** Anaemia due to renal disease
- **B** Aplastic anaemia
- **C** Hypothyroidism
- **D** Iron deficiency anaemia
- **E** Sideroblastic anaemia

http://my.onexamination.com/Assessment/Que
Search-results Web Search
onexamination.com

Blood film	Marked anisopoikilocytosis
Serum ferritin	70 µg/L (15-300)
Vitamin B_{12}	280 ng/L (160-760)
Red cell folate	230 µg/L (160-640)
Serum urea	9.1 mmol/L (2.5-7.5)
Serum creatinine	150 µmol/L (60-110)

What is the most likely diagnosis?

(Please select 1 option)

- **A** Anaemia due to renal disease
- **B** Aplastic anaemia
- **C** Hypothyroidism ✗ Incorrect answer selected
- **D** Iron deficiency anaemia
- **E** Sideroblastic anaemia ← This is the correct answer

Idiopathic sideroblastic anaemia is a member of the myelodysplastic syndromes.

In this condition the red blood cells are normal or macrocytic and there is anisocytosis and poikilocytosis on the peripheral films.

This is not iron deficiency anaemia as the ferritin is normal and a microcytic anaemia would be expected.

A normochromic normocytic anaemia is expected in renal disease (epo deficiency).

Hypothyroidism may cause a slight elevation of mean corpuscular volume but no anisopoikilocytosis is evident.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Question: 75 of 100

A 42-year-old female presents with tiredness.

Her investigations reveal:

Haemoglobin	7.8 g/dL (11.5-16.5)
MCV	72 fL (80-96)
White cell count	7.6 $x10^9$/L (4-11 $x10^9$)
Platelet count	350 $x10^9$/L (150-400 $x10^9$)
Serum ferritin	8 µg/L (15-300)

She was commenced on oral iron therapy and one month later her haemoglobin concentration was 8.0 g/dL (11.5-16.5).

What is the most likely cause of the failure of her haemoglobin to respond to this treatment?

(Please select 1 option)

- Coeliac disease
- Folate deficiency
- Inadequate dosage of iron
- Poor compliance with therapy
- Sideroblastic anaemia

Serum ferritin	8 µg/L (15-300)

She was commenced on oral iron therapy and one month later her haemoglobin concentration was 8.0 g/dL (11.5-16.5).

What is the most likely cause of the failure of her haemoglobin to respond to this treatment?

(Please select 1 option)

- ○ Coeliac disease
- ○ Folate deficiency
- ○ Inadequate dosage of iron
- ◉ Poor compliance with therapy ✓ Correct
- ○ Sideroblastic anaemia

The most likely explanation for the failure of an iron deficiency anaemia to respond to iron therapy in a menstruant female is poor compliance.

It is likely that the dose that this patient is prescribed would be adequate and if not some response would still be expected.

There is no evidence of a concomitant folate deficiency as suggested by the blood picture, which would also argue against coeliac disease.

Similarly, there is no evidence to suggest a sideroblastic anaemia where a raised mean corpuscular volume (MCV) and increased ferritin may be expected.

Next question | Tag Question | Remove question

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 23 mins 58 secs

Question: 76 of 100

Which of the following statements concerning iron metabolism is correct?

(Please select 1 option)

○	Approximately 0.1% of body iron circulates in the plasma
○	Approximately 90% of dietary iron is absorbed in the intestine
○	The main route of excretion is the liver
○	The serum ferritin concentration is reduced characteristically following surgery
○	The transferrin content of intestinal mucosal cells is high when body iron stores are high

Submit answer | Skip question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Question: 76 of 100

Which of the following statements concerning iron metabolism is correct?

(Please select 1 option)

○	Approximately 0.1% of body iron circulates in the plasma ← This is the correct answer
◉	Approximately 90% of dietary iron is absorbed in the intestine ✕ Incorrect answer selected
○	The main route of excretion is the liver
○	The serum ferritin concentration is reduced characteristically following surgery
○	The transferrin content of intestinal mucosal cells is high when body iron stores are high

Approximately 4 mg of iron circulate within the plasma with a total body iron store of 3-4 g (2500 mg in the RBCs, 500 mg in liver, 500 mg in macrophages and about 500 mg in muscle).

From an intake of approximately 6 mg/1000 kcal of dietary iron only 15% is bioavailable.

The majority of iron contained within the RBCs is metabolised and re-utilised but 1 mg per day is lost through the gut.

Ferritin, the plasma protein responsible for binding iron, is an acute phase reactant protein and increases in inflammatory conditions following surgery.

Transferrin is a glycoprotein responsible for internal iron exchange and the content within mucosal cells is naturally low in haemochromatosis with high saturation.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 26 mins 30 secs

Question: 77 of 100

A 19-year-old man with glucose-6-phosphate dehydrogenase deficiency wishes to travel to Africa.

Which one of the following should he be advised to avoid?

(Please select 1 option)

- Ibuprofen
- Loperamide
- Mefloquine
- Primaquine
- Yellow fever vaccine

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 26 mins 55 secs

Question: 77 of 100

A 19-year-old man with glucose-6-phosphate dehydrogenase deficiency wishes to travel to Africa.

Which one of the following should he be advised to avoid?

(Please select 1 option)

○	Ibuprofen
○	Loperamide
○	Mefloquine
◉	Primaquine ✓ Correct
○	Yellow fever vaccine

G6PD deficiency is inherited in an X linked fashion and predisposes red blood cells to haemolysis.

Drugs recognised to predispose to acute haemolysis in G6PD deficiency include antimalarials such as primaquine, sulphonamides, nitrofurantoin and nalidixic acid.

Next question

Tag Question

Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Whilst being investigated for infertility, a 30-year-old woman is noted to have some bruising on her limbs with a palpable spleen on abdominal examination.

Investigations reveal:

Haemoglobin	10.0 g/dL (11.5-16.5)
White cell count	110 $x10^9$/L (4-11 $x10^9$)
Neutrophils	60 $x10^9$/L (1.5-7 $x10^9$)
Lymphocytes	2 $x10^9$/L (1.5-4 $x10^9$)
Monocytes	0.8 $x10^9$/L (0-0.8 $x10^9$)
Eosinophils	0.3 $x10^9$/L (0.04-0.4 $x10^9$)
Basophils	0.7 $x10^9$/L (0-0.1 $x10^9$)
Myelocytes	40 $x10^9$/L
Myeloblasts	4 $x10^9$/L
Platelet count	900 $x10^9$/L (150-400 $x10^9$)

What is the most likely diagnosis?

(Please select 1 option)

- ○ Acute myeloid leukaemia
- ○ Acute promyelocytic leukaemia
- ○ Chronic myeloid leukaemia
- ○ Essential thrombocythaemia
- ○ Myelofibrosis

Eosinophils	0.3 x10^9/L (0.04-0.4 x10^9)
Basophils	0.7 x10^9/L (0-0.1 x10^9)
Myelocytes	40 x10^9/L
Myeloblasts	4 x10^9/L
Platelet count	900 x10^9/L (150-400 x10^9)

What is the most likely diagnosis?

(Please select 1 option)

- ○ Acute myeloid leukaemia
- ○ Acute promyelocytic leukaemia
- ◉ Chronic myeloid leukaemia ✓ Correct
- ○ Essential thrombocythaemia
- ○ Myelofibrosis

The features of this blood film are anaemia, thrombocytosis, neutrophilia with roughly 55% neutrophils, 40% myelocytes with less than 5% blast cells.

This is typical of chronic myeloid leukaemia which usually has associated tender splenomegaly. Usually the Philadelphia chromosome is present in 95% of cases.

Acute leukaemia is defined as blast cells constituting over 30% of cell type present.

Chronic myeloid leukaemia often ends in acute blastic transformation after a mean duration of approximately four years.

Next question | Tag Question | Remove question

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 29 mins 7 secs

Question: 79 of 100

An 80-year-old woman has a three month history of progressive numbness and unsteadiness of her gait.

On examination, there is a mild spastic paraparesis, with brisk knee reflexes, ankle reflexes are present with reinforcement, extensor plantars, sensory loss in the legs with a sensory level at T10, impaired joint position sense in the toes, and loss of vibration sense below the iliac crests.

Investigations were as follows:-

Haemoglobin	12.2 g/dL (12-16)
MCV	95 fL (80-96)

What is the most likely diagnosis?

(Please select 1 option)

- Anterior spinal artery occlusion
- Dorsal meningioma
- Multiple sclerosis
- Subacute combined degeneration of the cord
- Tabes dorsalis

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Question: 79 of 100

An 80-year-old woman has a three month history of progressive numbness and unsteadiness of her gait.

On examination, there is a mild spastic paraparesis, with brisk knee reflexes, ankle reflexes are present with reinforcement, extensor plantars, sensory loss in the legs with a sensory level at T10, impaired joint position sense in the toes, and loss of vibration sense below the iliac crests.

Investigations were as follows:-

Haemoglobin	12.2 g/dL (12-16)
MCV	95 fL (80-96)

What is the most likely diagnosis?

(Please select 1 option)

○	Anterior spinal artery occlusion
○	Dorsal meningioma ← This is the correct answer
○	Multiple sclerosis
○	Subacute combined degeneration of the cord
◉	Tabes dorsalis ✕ Incorrect answer selected

The presence of a sensory loss at T10 indicates a thoracic myelopathy.

Subacute combined degeneration of the cord is unlikely as the haemoglobin concentration and mean corpuscular volume (MCV) are normal.

Anterior spinal artery occlusion is unlikely as the history is progessive and chronic.

Next question

Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Question: 7 of 100

A 17-year-old girl with mild von Willebrand's disease is scheduled for dental extraction. A previous dental extraction resulted in bleeding that had required two unit transfusion.

What is the most appropriate treatment prior to dental surgery?

(Please select 1 option)

○	Cryoprecipitate
◉	DDAVP ✓ Correct
○	Fresh frozen plasma
○	High purity factor VIII concentrate
○	Recombinant factor VIII concentrate

DDAVP is the choice treatment for mild von Willebrand disease, which would include type I, and the majority of type II; although there is some controversy in type II B as it is thought that DDAVP can exacerbate thrombocytopenia that can accompany this type of von Willebrand's.

It is of no use in type III - severe von Willebrand's disease. The history tells us that she has mild disease.

You would not use cryoprecipitate or fresh frozen plasma in these patients in this era, due to potential viral transmission risk from blood products.

For severe disease you would use a Von Willebrand factor concentrate, not factor VIII concentrate.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 9 mins 51 secs

Question: 8 of 100

Which of the following haematological disorders is inherited as an autosomal recessive condition?

(Please select 1 option)

- Antithrombin III deficiency
- Protein C deficiency
- Glucose-6-phosphate dehydrogenase deficiency
- Pyruvate kinase deficiency
- Acute intermittent porphyria

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Question: 80 of 100

A 55-year-old male presents with anorexia and weight loss of 12 months duration. Over this year he has had two deep vein thromboses (DVTs) and had the last whilst his INR was 2 (less than 1.4).

He remains on long term warfarin therapy with an INR above 2.6. Examination reveals that he is pigmented and has a postural drop in his blood pressure of 15 mmHg.

Investigations are as follows:

Sodium	131 mmol/l	(137-144)
Potassium	5.0 mmol/l	(3.5-4.9)
INR	3.0	(<1.4)

A short Synacthen test reveals a baseline cortisol concentration at time 0 of 120 nmol/l which rises to 155 nmol/l after 30 minutes (normal response greater than 550 nmol/l).

Which single diagnosis would explain this patient's illness?

(Please select 1 option)

- ○ Addison's disease
- ○ Antiphospholipid syndrome
- ○ Autoimmune polyendocrine syndrome (Schmidt's disease)
- ○ Pituitary infarction
- ○ Protein S deficiency

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

(Please select 1 option)

○	Addison's disease
◉	Antiphospholipid syndrome ✓ Correct
○	Autoimmune polyendocrine syndrome (Schmidt's disease)
○	Pituitary infarction
○	Protein S deficiency

With a history of recurrent DVT and confirmed hypoadrenalism, this patient is likely to have the antiphospholipid syndrome. Antiphospholipid syndrome is a primary diagnosis or may co-exist with systemic lupus erythematosus.

Anticardiolipin antibodies or lupus anticoagulant may be present.

It is associated with arterial and venous thrombosis and has a predilection for the adrenal veins causing adrenal infarction with consequent hypoadrenalism.

Addison's disease is an autoimmune phenomenon and is not associated with DVT.

The pigmentation (due to increased adrenocorticotropic hormone [ACTH] in hypoadrenalism) would exclude pituitary infarction as the cause of the hypoadrenalism.

Hypoadrenalism is not associated with protein S deficiency.

Autoimmune polyendocrine syndrome is associated with

- Hypothyroidism
- Type 1 diabetes
- Addison's disease.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 56 mins 17 secs

Question: 81 of 100

A 41-year-old African man has a history of multiple episodes of sudden onset of severe abdominal pain and back pain lasting for hours. Each time this happens, his peripheral blood smear demonstrates numerous sickled erythrocytes.

A haemoglobin electrophoresis shows 94% Hgb S, 5% Hgb F, and 1% Hgb A2.

He now has increasing pain in his right groin radiating to the anterior aspect of the thigh and to the knee. His temperature was 38°C and examination of his hip revealed pain on internal rotation. A radiograph reveals irregular bony destruction of the femoral head.

The most likely organism to be responsible for these findings is?

(Please select 1 option)

- ○ *Candida albicans*
- ○ *Clostridium perfringens*
- ○ Group B *Streptococcus*
- ○ *Salmonella* species
- ○ *Yersinia pestis*

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 59 mins 20 secs

Question: 81 of 100

A 41-year-old African man has a history of multiple episodes of sudden onset of severe abdominal pain and back pain lasting for hours. Each time this happens, his peripheral blood smear demonstrates numerous sickled erythrocytes.

A haemoglobin electrophoresis shows 94% Hgb S, 5% Hgb F, and 1% Hgb A2.

He now has increasing pain in his right groin radiating to the anterior aspect of the thigh and to the knee. His temperature was 38°C and examination of his hip revealed pain on internal rotation. A radiograph reveals irregular bony destruction of the femoral head.

The most likely organism to be responsible for these findings is?

(Please select 1 option)

○	*Candida albicans*
○	*Clostridium perfringens*
○	Group B *Streptococcus*
◉	*Salmonella* species ✓ Correct
○	*Yersinia pestis*

Salmonella osteomyelitis is seen in patients with sickle cell anemia. Other organisms that are frequent causes for osteomyelitis with sickle cell anemia include *Staphylococcus aureus* and Gram negatives such as *Klebsiella*.

Why *Salmonella* species predominate in patients with sickle cell disease instead of *Staphylococcus aureus* is a matter of debate. Etiology of Osteomyelitis Complicating Sickle Cell Disease. Pediatrics 1998;101;296-297

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 59 mins 20 secs

Question: 82 of 100

Which of the following statements is true of sickle cell disease?

(Please select 1 option)

○	A painful shoulder joint will respond to intra-articular corticosteroid injection
○	Oral iron supplements are required
○	Symptoms of anaemia are usually limiting when Hb equals 8 g/dl
○	There is often an inability to concentrate urine
○	The spleen is frequently enlarged

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Which of the following statements is true of sickle cell disease?

(Please select 1 option)

○	A painful shoulder joint will respond to intra-articular corticosteroid injection
○	Oral iron supplements are required
○	Symptoms of anaemia are usually limiting when Hb equals 8 g/dl
◉	There is often an inability to concentrate urine ✓ Correct
○	The spleen is frequently enlarged

There is a tendancy to iron overload in sickle cell disease and therefore iron therapy is not usually indicated.

The spleen is decreased in size after six months of age.

Blood transfusion is not indicated since anaemia is usually only symptomatic below 7g/dl - oxygen is released more readily from erythrocytes.

Intra-articular steroids should be avoided.

Bone disease in sickle cell disease consists of aseptic necrosis, acute infarction and osteomyelitis so steroids will be harmful.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 3 hrs 39 secs

Question: 83 of 100

Which of the following is a feature of hereditary haemorrhagic telangiectasia?

(Please select 1 option)

○	A good response to oestrogen therapy
○	Cerebral arteriovenous malformations
○	GI haemorrhage is the usual presenting feature
○	Telangiectasia of the mucous membranes, but not the skin
○	Tendency of lesions to become less obvious with age

Submit answer | Skip question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

◉	Cerebral arteriovenous malformations ✓ Correct
○	GI haemorrhage is the usual presenting feature
○	Telangiectasia of the mucous membranes, but not the skin
○	Tendency of lesions to become less obvious with age

Hereditary Haemorrhagic Telangiectasia (HHT) is a multisystem vascular dysplasia characterised by the presence of multiple arteriovenous malformations (AVMs) that lack intervening capillaries and result in direct connections between arteries and veins. Small AVMs, called telangiectases, close to the surface of skin and mucous membranes often rupture and bleed.

The most common clinical manifestations are spontaneous and recurrent epistaxis and multiple telangiectases, which commonly appear on the lips, face, tongue or hands in adulthood. A minority of individuals with HHT have symptomatic GI bleeding, which most commonly begins after age 50 years. Large AVMs often cause symptoms when they occur in the brain or lung; complications from bleeding or shunting may be sudden and catastrophic.

In HHT there may also be pulmonary AVMs.

Epistaxis, not gastrointestinal (GI) haemorrhage, is the usual presenting feature.

Lesions become more obvious with age and affect mucous membranes as well as skin.

Oestrogen therapy is sometimes advocated but the effect, if any, is small.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 3 hrs 4 mins 18 secs

Question: 84 of 100

Which of the following conditions is most likely to be associated with thrombocytopaenia?

(Please select 1 option)

○	Haemophilia A
○	Hereditary haemorrhagic telangiectasia
○	Pernicious anaemia
○	Porphyria
○	Uraemia

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 3 hrs 4 mins 42 secs

Question: 84 of 100

Which of the following conditions is most likely to be associated with thrombocytopaenia?

(Please select 1 option)

○	Haemophilia A
○	Hereditary haemorrhagic telangiectasia
◉	Pernicious anaemia ✓ Correct
○	Porphyria
○	Uraemia

Pernicious anaemia is usually a megaloblastic anaemia but may also be associated with a pancytopaenia.

The platelet count is usually normal in chronic renal failure but there is a platelet function abnormality.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 3 hrs 4 mins 42 secs

Question: 85 of 100

Which of the following public health measures would reduce the incidence of iron deficiency anaemia?

(Please select 1 option)

○	Continuing breast feeding until a year of age.
○	Delaying the introduction of mixed feeding until 9 months of age.
○	Giving 0.5mg per day of elemental iron to all preterm babies.
○	Giving young children tea rather than fruit juice.
○	Using doorstep cow's milk from 6 months of age.

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Which of the following public health measures would reduce the incidence of iron deficiency anaemia?

(Please select 1 option)

◉	Continuing breast feeding until a year of age. ✓ Correct
○	Delaying the introduction of mixed feeding until 9 months of age.
○	Giving 0.5mg per day of elemental iron to all preterm babies.
○	Giving young children tea rather than fruit juice.
○	Using doorstep cow's milk from 6 months of age.

The following would achieve primary prevention of iron deficiency anaemia:

- Provision of adequate iron supplements for premature and low birth weight infants in adequate dosage (2mg/kg of elemental iron per day)
- Not using unmodified doorstep milk in the first year of life. Although breast milk has a low iron concentration, the relative bioavailability is much higher than from modified or unmodified cow's milk
- Not giving young children tea (this reduced iron's bioavailability)
- Use of follow-on or ordinary infant formulae in the second half of the first year of life
- Weaning on to mixed feeding by 6 months of age
- Iron supplementation for all children in high risk groups.

Copyright © 2002 Dr Colin Melville

Next question | Tag Question | Remove question

Work Smart Session - MRCP Part 1

Time taken: 3 hrs 5 mins 48 secs

Question: 86 of 100

Which of the following is a proto-oncogene?

(Please select 1 option)

○	The BCRabI translocation (Philadelphia chromosome)
○	The N-Myc gene
○	The retinoblastoma gene
○	The WT1 (first Wilm's tumour) gene
○	The WT2 (second Wilm's tumour) gene

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

◉	The N-Myc gene ✓ Correct
○	The retinoblastoma gene
○	The WT1 (first Wilm's tumour) gene
○	The WT2 (second Wilm's tumour) gene

Oncogenes are endogenous human deoxyribonucleic acid (DNA) sequences that arise from normal genes called proto-oncogenes.

Proto-oncogenes are normally expressed in many cells, particularly during fetal development, and are thought to play an important regulatory role in cell growth and development.

Alterations in the proto-oncogene can activate an oncogene, which produces unregulated gene activity, contributing directly to tumourogenesis.

Oncogene alterations are important causes of:

- Rhabdomyosarcomas (ras oncogene)
- Burkitt's lymphoma (C-myc is translocated intact from its normal position on chromosome 8 to chromosome 14)
- Neuroblastoma (N-myc proto-oncogene is seen in a proportion of patients with poor prognosis).

They should be contrasted with tumour suppressor genes. In this situation, the genes normally down regulate cell growth, and require inactivation to allow malignant growth. Examples include retinoblastoma.

Copyright © 2002 Dr Colin Melville

A 68-year-old man complained of tiredness and lethargy.

On examination there was 2 cm hepatomegaly and 7 cm splenomegaly.

Investigations show

Haemoglobin	17.4 g/dL (13.0-18.0)
White cell count	39.4 $x10^9$/L (4-11 $x10^9$)
White cell differential:	
Neutrophils	22.2 $x10^9$/L (1.5-7 $x10^9$)
Lymphocytes	1.1 $x10^9$/L (1.5-4 $x10^9$)
Monocytes	1.0 $x10^9$/L (0-0.8 $x10^9$)
Eosinophils	0.4 $x10^9$/L (0.04-0.4 $x10^9$)
Basophils	2.1 $x10^9$/L (0-0.1 $x10^9$)
Metamyelocytes	1.2 $x10^9$/L
Myelocytes	10.9 $x10^9$/L
Myeloblasts	1.3 $x10^9$/L
Nucleated RBC	3 per 100 rbc
Platelet count	585 $x10^9$/L (150-400 $x10^9$)

What is the most likely diagnosis?

(Please select 1 option)

- ○ Acute myeloid leukaemia
- ○ Chronic myeloid leukaemia (CML)
- ○ Essential thrombocythaemia
- ○ Myelofibrosis

Haemoglobin	17.4 g/dL (13.0-18.0)
White cell count	39.4 $x10^9$/L (4-11 $x10^9$)
White cell differential:	
Neutrophils	22.2 $x10^9$/L (1.5-7 $x10^9$)
Lymphocytes	1.1 $x10^9$/L (1.5-4 $x10^9$)
Monocytes	1.0 $x10^9$/L (0-0.8 $x10^9$)
Eosinophils	0.4 $x10^9$/L (0.04-0.4 $x10^9$)
Basophils	2.1 $x10^9$/L (0-0.1 $x10^9$)
Metamyelocytes	1.2 $x10^9$/L
Myelocytes	10.9 $x10^9$/L
Myeloblasts	1.3 $x10^9$/L
Nucleated RBC	3 per 100 rbc
Platelet count	585 $x10^9$/L (150-400 $x10^9$)

What is the most likely diagnosis?

(Please select 1 option)

- ○ Acute myeloid leukaemia
- ○ Chronic myeloid leukaemia (CML)
- ○ Essential thrombocythaemia
- ○ Myelofibrosis
- ○ Primary proliferative polycythaemia (rubra vera)

Submit answer | Skip question | Tag Question | Remove question

Eosinophils	0.4 x10^9/L (0.04-0.4 x10^9)
Basophils	2.1 x10^9/L (0-0.1 x10^9)
Metamyelocytes	1.2 x10^9/L
Myelocytes	10.9 x10^9/L
Myeloblasts	1.3 x10^9/L
Nucleated RBC	3 per 100 rbc
Platelet count	585 x10^9/L (150-400 x10^9)

What is the most likely diagnosis?

(Please select 1 option)

- ○ Acute myeloid leukaemia
- ◉ Chronic myeloid leukaemia (CML) ✓ Correct
- ○ Essential thrombocythaemia
- ○ Myelofibrosis
- ○ Primary proliferative polycythaemia (rubra vera)

The presentation is typical with vague symptoms of malaise and splenomegaly.

The blood film also shows the typical high white cell count and there are all stages of myeloid cell maturation present in the peripheral blood with the metamyelocytes suggesting CML.

Thrombocythaemia is also seen in CML.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Question: 88 of 100

A 35-year-old woman with a history of recurrent anaemia was noted to have target cells and Howell-Jolly bodies on a blood film examination.

Investigations revealed:

Haemoglobin	7.0 g/dL (11.5-16.5)
MCV	77 fL (80-96)
MCH	26.2 pg (28-32)
Serum B12	140 µg/L (160-760)
Red cell folate	95 µg/L (160-640)
Serum ferritin	10 µg/L (15-300)

What disease specific antibody is most likely to be present?

(Please select 1 option)

- Antiendomysial
- Antigastric parietal cell
- Antiglutamic acid decarboxylase
- Anti-intrinsic factor
- Antimitochondrial

Submit answer | Skip question | Tag Question | Remove question

What disease specific antibody is most likely to be present?

(Please select 1 option)

◉	Antiendomysial ✓ Correct
○	Antigastric parietal cell
○	Antiglutamic acid decarboxylase
○	Anti-intrinsic factor
○	Antimitochondrial

The patient has hyposplenism as suggested by the blood film and a mixed anaemia.

Coeliac disease could therefore fit the above picture with antiendomysial antibodies being the most appropriate selection from the above list.

- Antimitochonrial antibodies are seen in PBC
- Anti-gastric and anti intrinsic Abs are seen in pernicious anaemia
- Anti-GAD abs are found in auto-immune DM.

Screening for coeliac disease should include high-risk groups such as anaemia (iron or folate deficiency), hyposplenism, reduced bone density and infertility.

"Anti-endomysial IgA antibodies are extremely specific markers for CD and for dermatitis herpetiformis. These antibodies are directed to a component of the gut endomysium (connective tissue surrounding smooth muscle fibers of the gut)." (Further reading)

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd. All rights reserved. Terms and conditions Privacy policy A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 3 hrs 12 mins 30 secs

Question: 89 of 100

A 75-year-old man has a history of chronic lymphocytic leukaemia. He has had treatment with several courses of chemotherapy and has now been admitted to hospital with pneumonia. His past medical history revealed that he had suffered several previous upper respiratory tract infections over the previous six months.

Which of the following components of his immune system is likely to be deficient?

(Please select 1 option)

- Complement
- Immunoglobulin G
- Macrophages
- Mast cells
- T lymphocytes

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 3 hrs 14 mins 8 secs

Question: 89 of 100

A 75-year-old man has a history of chronic lymphocytic leukaemia. He has had treatment with several courses of chemotherapy and has now been admitted to hospital with pneumonia. His past medical history revealed that he had suffered several previous upper respiratory tract infections over the previous six months.

Which of the following components of his immune system is likely to be deficient?

(Please select 1 option)

◉	Complement ✕ Incorrect answer selected
○	Immunoglobulin G ← This is the correct answer
○	Macrophages
○	Mast cells
○	T lymphocytes

Chronic lymphocytic leukaemia (CLL) is commonly complicated by panhypogammaglobulinaemia.

Although intravenous immunoglobulin prevents recurrent infections it does not prolong survival.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

(Please select 1 option)

○	Antithrombin III deficiency
○	Protein C deficiency
○	Glucose-6-phosphate dehydrogenase deficiency
◉	Pyruvate kinase deficiency ✓ Correct
○	Acute intermittent porphyria

Anti-thrombin 3 (AT3) is a plasma inhibitor protein that blocks the enzymatic activity of some serine proteases coagulation factors. The activity of this inhibitor in increased by heparin.

AT3 is synthesised by the liver, is not vitamin K dependent, and can be consumed during disseminated intravascular coagulation (DIC). Normal newborns have a reduced activity. Congenital AT3 deficiency is an autosomal dominant. Treatment of thrombotic events in these patients may be difficult.

Protein C is an inhibitor that, once activated, inhibits clot formation and enhances fibrinolysis. It is liver synthesised and vitamin K dependent. Protein C is converted to an active enzyme by a thrombin-thrombomodulin complex on the endothelial cell surface.

Activated protein C inhibits a plasminogen activator inhibitor, which results in enhanced fibrinolysis, and, with protein S as a co-factor, inhibits the clotting of the activated factors 5 and 8 by limited proteolysis. Activated protein C thus controls the conversion of factor 10 to 10a and prothrombin to thrombin.

Congenital deficiency is an autosomal dominant trait. Acquired deficiency may occur in association with infection.

Glucose-6-phosphate dehydrogenase deficiency is the most important disease of the pentose phosphate pathway, and is responsible for two clinical syndromes:

- An episodic haemolytic anaemia induced by infections or certain drugs
- A spontaneous chronic non-spherocytic haemolytic anaemia.

- An episodic haemolytic anaemia induced by infections or certain drugs
- A spontaneous chronic non-spherocytic haemolytic anaemia.

The deficiency is X linked, and heterozygous females are resistant to falciparum infections. There are a large number of abnormal alleles causing disease of vastly different severity.

Pyruvate kinase deficiency is a rare congenital haemolytic anaemia inherited as an autosomal recessive. Generation of adenosine triphosphate (ATP) within the red cell is impaired, resulting in an abnormally high concentration of 2,3,DPG in the red cell, which inhibits the enzymes of the pentose phosphate pathway.

Clinical manifestations vary from severe neonatal haemolysis, to a mild, well compensated haemolysis first noted in adulthood.

Acute intermittent porphyria is an autosomal dominant disorder resulting from partial porphobilinogen deaminase deficiency in the cytosol of all tissues including erythrocytes. Clinical expression of the disease is linked to environmental or acquired factors such as

- nutritional status
- drugs
- steroids
- chemicals.

The major abnormality is of the peripheral, autonomic or central nervous system (CNS).

Major symptoms are abdominal pain, nausea, vomiting, constipation or diarrhoea. In severe cases the urine develops a port wine colour due to the high content of porphobilin, an auto-oxidation product of PBG.

Hypertension and neuropathy are common, with muscle weakness, cranial nerve abnormality and seizures.

© 2002 Dr Colin Melville

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 11 mins 46 secs

Question: 9 of 100

Which of the following statements concerning abnormalities of the haemoglobin molecule is true?

(Please select 1 option)

- **A** Alpha thalassaemia is due to a deficiency of beta-chain production
- **B** HbS is caused by a single base mutation on the beta-chain
- **C** Genes for the alpha and beta chains are located on the same chromosome
- **D** In thalassaemia, persistence of HbF is an adverse prognostic sign
- **E** Oligonucleotide probes may assist in the diagnosis of haemoglobinopathies in adolescents

Submit answer | Skip question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 3 hrs 14 mins 8 secs

Question: 90 of 100

In porphyria, which of the following is least likely to precipitate an acute attack?

(Please select 1 option)

- Aspirin
- Menstruation
- Phenytoin
- Starvation
- Thiopentone

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 3 hrs 14 mins 54 secs

Question: 90 of 100

In porphyria, which of the following is least likely to precipitate an acute attack?

(Please select 1 option)

○	Aspirin ← This is the correct answer
○	Menstruation
○	Phenytoin
◉	Starvation ✕ Incorrect answer selected
○	Thiopentone

Porphyria is a group of diseases characterised by excess production and excretion of porphyrins and their precursors.

They are caused by enzyme defects within the haem metabolic pathway.

Stress, infection, pregnancy, menstruation, starvation and certain drugs may precipitate acute attacks.

Definite precipitants include sulphonamides, barbiturates and phenytoin.

Drugs unsafe in porphyria

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 3 hrs 14 mins 54 secs

Question: 91 of 100

In sickle cell disease, which of the following is correct?

(Please select 1 option)

○	Exchange transfusions prior to major surgery on HbSS patients aims to lower the HbS concentration to 60%
○	It is caused by the substitution of glutamic acid by valine at position 4 on the beta chain of haemoglobin
○	The erythrocytes of haemoglobin AS patients can sickle at a PO_2 of 5 to 6 kPa (40 ? 50 mmHg)
○	The erythrocytes of haemoglobin SC patients may sickle at a PO_2 of 4 kPa (30 mmHg)
○	The Sickledex test involves adding a reagent to blood which allows the nature of the haemoglobinopathy to be determined

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Questions
- Scores
- Community
- Help
- Shop

(Please select 1 option)

○	Exchange transfusions prior to major surgery on HbSS patients aims to lower the HbS concentration to 60%
◉	It is caused by the substitution of glutamic acid by valine at position 4 on the beta chain of haemoglobin ✕ Incorrect answer selected
○	The erythrocytes of haemoglobin AS patients can sickle at a PO_2 of 5 to 6 kPa (40 ? 50 mmHg)
○	The erythrocytes of haemoglobin SC patients may sickle at a PO_2 of 4 kPa (30 mmHg) ← This is the correct answer
○	The Sickledex test involves adding a reagent to blood which allows the nature of the haemoglobinopathy to be determined

Sickle cell disease in a haemoglobinopathy is caused by the substitution of glutamic acid by valine at position 6 (from the N-terminal) of the beta chain.

It is inherited as an autosomal gene, heterozygous (HbAS) and homozygous (HbSS) forms exist.

A low partial pressure of oxygen (PO_2) causes HbS to polymerise and precipitate resulting in sickling of the erythrocyte. HbSS patients sickle at PO_2 of 5 ? 6 kPa and HbAS patients sickle at PO_2 of 2.5 - 4 kPa.

A mild disease is produced when heterozygotes for HbS combine with other haemoglobins, for example, haemoglobin C, thus creating HbSC. Sickling occurs at around 4 kPa.

Diagnosis of sickle cell disease requires the detection of HbS.

The Sickledex test involves the addition of reagent to blood; turbidity confirming the presence of HbS, but it gives no information on other haemoglobins.

Haemoglobin electrophoresis is the only investigation that determines the nature of the haemoglobinopathy.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 3 hrs 16 mins 26 secs

Question: 92 of 100

A 45-year-old Chinese man is found incidentally to have a severely hypochromic and microcytic blood picture, with Hb11.2g/dl. He is asymptomatic.

Which of the following is the most discriminatory investigation?

(Please select 1 option)

- Barium enema
- Bone marrow biopsy
- Gastroscopy
- Haemoglobin electrophoresis
- Ham test

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 3 hrs 17 mins 23 secs

Question: 92 of 100

A 45-year-old Chinese man is found incidentally to have a severely hypochromic and microcytic blood picture, with Hb11.2g/dl. He is asymptomatic.

Which of the following is the most discriminatory investigation?

(Please select 1 option)

○	Barium enema
○	Bone marrow biopsy
○	Gastroscopy
◉	Haemoglobin electrophoresis ✓ Correct
○	Ham test

Thalassaemia trait is a common, usually asymptomatic abnormality.

Red cells are hypochromic and microcytic, but iron and ferritin stores are normal.

Haemoglobin electrophoresis shows raised HbA2 (greater than 3.5%) and raised HbF (normally consisting predominantly of HbA with trace of HbF and HbA2).

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Question: 93 of 100

A 26-year-old woman presented at 35 weeks of pregnancy with profuse vaginal bleeding. She had suffered two previous miscarriages.

She had a pulse of 95 beats per minute, blood pressure of 110/84 mmHg and no fetal heart sounds were audible.

Investigations revealed:

Haemoglobin	9.8 g/dl	
Platelets	66 x 10^9/l	
Prothrombin time	21 sec	(11.5-15.5)
APTT	52 sec	(30-40)
Fibrinogen	0.5 g/l	(2-4)

What is the most appropriate next step in management?

(Please select 1 option)

- Antithrombin III infusion
- Fibrinogen replacement infusion (cryoprecipitate)
- Intravenous heparin
- Platelet transfusion
- Transfusion of two units group O Rhesus D negative blood

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Fibrinogen	0.5 g/l	(2-4)

What is the most appropriate next step in management?

(Please select 1 option)

- Antithrombin III infusion
- Fibrinogen replacement infusion (cryoprecipitate) ✓ Correct
- Intravenous heparin
- Platelet transfusion
- Transfusion of two units group O Rhesus D negative blood

The clinical picture is disseminated intravascular coagulation.

When bleeding is the major problem, the aim is to maintain the prothrombin and activated thromboplastin time at a ratio of 1.5 times of the control and the fibrinogen level above 1 g/l.

Platelet transfusion is recommended if the count is less than 50×10^9/l.

Anaemia is not very severe so in this case fibrinogen replacement would be the appropriate first choice with blood transfusion an addition if bleeding continues and patient develops hypovolaemic shock.

Reference:
Oxford Textbook of Medicine

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 3 hrs 23 mins 13 secs

Question: 94 of 100

A 23-year-old male presents with a deep vein thrombosis (DVT). He has no past medical history but his mother has suffered from deep vein thromboses.

Which of the following is likely to be found on haematological assessment?

(Please select 1 option)

- Antithrombin deficiency
- Factor V (FV) Leiden mutation
- Lupus anticoagulant
- Protein C deficiency
- Protein S deficiency

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

(Please select 1 option)

◉	Antithrombin deficiency ✓ Correct
○	Factor V (FV) Leiden mutation
○	Lupus anticoagulant
○	Protein C deficiency
○	Protein S deficiency

Antithrombin deficiency is an autosomal dominant (AD) condition present in 0.02-1.1% of the population and is found in 4% of subjects who present with a thromboembolism.

Factor V Leiden is a possibility, although it seems less likely as the inheritance pattern seems more likely to be AD.

Similarly as the son had a DVT this would be far less likely with FV Leiden than antithrombin (AT) III, as thrombosis is more often precipitated in females on the oral contraceptive pill (OCP).

See Simioni P, Sanson BJ, Prandoni P, et al. Thromb Haemost 1999 Feb;81(2):198-202, who show that "The annual incidences of total and spontaneous venous thromboembolic events in carriers of AT, PC or PS defects (n=181) were 1.01% and 0.40%, respectively, as compared to 0.10% and 0.04% in non-carriers, respectively (relative risks both 10.6). In carriers of Factor V Leiden (n= 224), the annual incidences of total and spontaneous venous thromboembolism were 0.28% and 0.11%, respectively, as compared to 0.09% and 0.04% in non-carriers, respectively (relative risks 2.8 and 2.5)."

See also "Risk of a first venous thrombotic event in carriers of a familial thrombophilic defect. The European Prospective Cohort on Thrombophilia (EPCOT)." J Thromb Haemost. 2005 Mar;3(3):459-64

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 3 hrs 23 mins 47 secs

Question: 95 of 100

Heinz bodies in red blood cells in haemolytic anaemia are present in which of the following?

(Please select 1 option)

- *Clostridium welchii* septicaemia
- Cold agglutinin disease
- Glucose 6 phosphate dehydrogenase deficiency
- Paroxysmal nocturnal haemoglobinuria
- Post splenectomy

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 3 hrs 24 mins 20 secs

Question: 95 of 100

Heinz bodies in red blood cells in haemolytic anaemia are present in which of the following?

(Please select 1 option)

○	*Clostridium welchii* septicaemia
○	Cold agglutinin disease
◉	Glucose 6 phosphate dehydrogenase deficiency ✓ Correct
○	Paroxysmal nocturnal haemoglobinuria
○	Post splenectomy

Heinz bodies are oxidised denatured Hb.

Post splenectomy causes

- Target cells
- Pappenheimer bodies (siderotic granules) and
- Howell-Jolly bodies (DNA remnants).

Next question

Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 3 hrs 24 mins 20 secs

Question: 96 of 100

Folic acid metabolism can be affected by which of the following?

(Please select 1 option)

- Brufen
- Penicillin
- Pyrimethamine
- Tetracycline
- Vitamin B12

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Question: 96 of 100

Folic acid metabolism can be affected by which of the following?

(Please select 1 option)

○	Brufen
○	Penicillin
○	Pyrimethamine ← This is the correct answer
○	Tetracycline
◉	Vitamin B12 ✕ Incorrect answer selected

Drugs which inhibit dihydrofolate reductase are

- Methotrexate
- Pyrimethamine and
- Trimethoprim.

Drugs which interfere with absorption/storage of folate are

- Phenytoin
- Primidone
- Oral contraceptives.

Next question

Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 3 hrs 25 mins

Question: 97 of 100

A 20-year-old Caucasian student returns from Ghana with a spiking temperature and nocturnal sweats. She has 0.5% of red blood cells infected with *Plasmodium falciparum*.

Select one of the following answers relating to quinine therapy in this case.

(Please select 1 option)

○	Glucose levels should be monitored in those being treated with quinine
○	Pregnancy is a contraindication for quinine
○	Quinine is contraindicated in those taking mefloquine prophylactically
○	Quinine must always be given parenterally initially
○	The dose of quinine should be reduced in liver impairment

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 3 hrs 29 mins 56 secs

Question: 97 of 100

A 20-year-old Caucasian student returns from Ghana with a spiking temperature and nocturnal sweats. She has 0.5% of red blood cells infected with *Plasmodium falciparum*.

Select one of the following answers relating to quinine therapy in this case.

(Please select 1 option)

◉	Glucose levels should be monitored in those being treated with quinine ✓ Correct
○	Pregnancy is a contraindication for quinine
○	Quinine is contraindicated in those taking mefloquine prophylactically
○	Quinine must always be given parenterally initially
○	The dose of quinine should be reduced in liver impairment

Severe malaria is indicated by more than 1% of RBC infected.

Hypoglycaemia is an important side-effect of quinine therapy and should be monitored in those having intravenous quinine.

Intravenous infusion of quinine is reserved for severe or cerebral malaria (most deaths from *M. falciparum* occur in first 96 hours of starting treatment).

The initial dose should **not** be reduced in those severely ill with renal/hepatic impairment.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 3 hrs 29 mins 56 secs

Question: 98 of 100

Are the following true concerning anti-neutrophilic cytoplasmic autoantibodies?

(Please select 1 option)

- ANCA positive glomerulonephritis characteristically causes nephrotic syndrome
- Cause neutropenia in SLE
- Increased in systemic lupus erythematosus (SLE)
- Positive only in Wegener's syndrome associated with renal disease
- Present in inflammatory bowel disease

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 3 hrs 31 mins 45 secs

Question: 98 of 100

Are the following true concerning anti-neutrophilic cytoplasmic autoantibodies?

(Please select 1 option)

○	ANCA positive glomerulonephritis characteristically causes nephrotic syndrome
○	Cause neutropenia in SLE
○	Increased in systemic lupus erythematosus (SLE)
○	Positive only in Wegener's syndrome associated with renal disease
◉	Present in inflammatory bowel disease ✓ Correct

Eighty five percent of untreated subjects with Wegener's will have circulating anti-neutrophil cytoplasmic antibody (cANCA) and those with limited disease are less likely to have positive serology.

Perinuclear anti-neutrophil cytoplasmic antibody (pANCA) is present in approximately 70% with ulcerative colitis and less than 20% of Crohn's patients.

Neither p nor c-ANCA is typical of SLE.

Initial renal damage causes proteinuria (focal proliferative glomerulonephritis) but renal function can deteriorate rapidly with development of acute focal necrotising glomerulonephritis.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 3 hrs 31 mins 45 secs

Question: 99 of 100

A 56-year-old female presents at the general practitioner with weakness.

A full blood count (FBC) reveals a haemoglobin concentration of 10.5 g/dL (11.5-16.5) and a mean cell volume (MCV) of 104 fL (80-96), but no other abnormality.

Which of the following may account for this?

(Please select 1 option)

- Hormone replacement therapy (HRT)
- Scurvy
- Thyrotoxicosis
- Ulcerative colitis
- Zollinger-Ellison syndrome

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Question: 99 of 100

A 56-year-old female presents at the general practitioner with weakness.

A full blood count (FBC) reveals a haemoglobin concentration of 10.5 g/dL (11.5-16.5) and a mean cell volume (MCV) of 104 fL (80-96), but no other abnormality.

Which of the following may account for this?

(Please select 1 option)

○	Hormone replacement therapy (HRT)
○	Scurvy ← This is the correct answer
○	Thyrotoxicosis
○	Ulcerative colitis
◉	Zollinger-Ellison syndrome ✕ Incorrect answer selected

Bear in mind this patient's symptoms and her FBC.

She has weakness and in association with a mild anaemia (do not really think that this would cause the weakness) and her increased MCV a vitamin C deficiency is most probable. Vitamin C deficiency is associated with a macrocytosis and slight anaemia.

HRT is more likely to be associated with iron (Fe) deficiency anaemia as is Zollinger-Ellison syndrome and ulcerative colitis.

Hypothyroidism is associated with macrocytosis.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 12 mins 47 secs

Question: 9 of 100

Which of the following statements concerning abnormalities of the haemoglobin molecule is true?

(Please select 1 option)

○	**A** Alpha thalassaemia is due to a deficiency of beta-chain production
○	**B** HbS is caused by a single base mutation on the beta-chain ← This is the correct answer
○	**C** Genes for the alpha and beta chains are located on the same chromosome
○	**D** In thalassaemia, persistence of HbF is an adverse prognostic sign
◉	**E** Oligonucleotide probes may assist in the diagnosis of haemoglobinopathies in adolescents ✕ Incorrect answer selected

A Alpha thalassaemia is due to abnormalities of the alpha chain. Persistence of HbF has survival advantages in severely affected subjects.

C Alpha is located on 16, beta on 11.

E Hb electrophoresis are used in the adult, rather than oligonucleotide probes as used in the fetus.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

GIG CYMRU NHS WALES
Bwrdd Iechyd Prifysgol Caerdydd a'r Fro
Cardiff and Vale University Health Board

Ysbyty Athrofaol Cymru
University Hospital of Wales

Canolfan Gwybodaeth Meddyginiaethau Cymru
Welsh Medicines Information Centre

Eich cyf/Your ref:
Ein cyf/Our ref:
Welsh Health Telephone Network: 1872
Llinell uniongychol/Direct Line:

Gweinyddiad/Administration: 029 2074 4298
Cyfarwyddwr/ Director: 029 2074 2796

Bocs 134
Adran Fferylliaeth
Ysbyty Athrofaol Cymru
Parc Y Mynydd Bychan
Caerdydd CF14 4XW

Box No 134
Pharmacy Department
University Hospital of Wales
Heath Park
Cardiff CF14 4XW

Ymholiadau/Enquiries: 029 2074 2251/2979/3877
Ffacs/Fax: 029 2074 3879

Telephone: 029 2074 3877 or 029 2074 2251
Fax: 029 2074 3879

August 2010

Dear Sir/Madam

Please find enclosed a 2010 version of the Porphyria safe list. I would like to point out some additions and amendments to the list. If you require any further advice please do not hesitate to contact the centre.

A D D I T I O N S

Amisulpride	HCG
Amlodipine	Nifedipine
Atomoxetine	Sulpiride
Felodipine	Tramadol

A M E N D M E N T S

Ciprofloxacin Ofloxacin Levofloxacin	These are removed as individual medicines and replaced by their group name, Quinolones
Bezafibrate Fenofibrate Gemfibrozil	These are removed as individual medicines and replaced by their group name, Fibrates

Yours sincerely

Alana Adams (Mrs)
Senior Information Pharmacist
Welsh Medicines Information Centre

Drugs that are considered to be **SAFE** for use in the acute porphyrias

This safe list provides guidance on first choice medication, it is not intended to be comprehensive. **For information on medication not listed or if you wish to confirm the safety of any drug, please contact the Welsh Medicines Information Centre (WMIC) by telephone (029 2074 3877) or by fax (029 2074 3879), or alternatively use www.drugs-porphyria.org. We are unable to accept enquiries via email.**

Please note that some drugs may be included under their group name and not their individual drug name.

Abciximab	Desflurane	**Ibuprofen**	Phenylephrine
ACE Inhibitors[1]	Desloratadine	Imipenem	Pipotiazine
Acetazolamide	Dextran	Immunoglobulins	Pramipexole
Acetylcysteine	Dextromethorphan	Indometacin	Prazosin
Aciclovir	Diamorphine	Insulin	Pregabalin
Adenosine	Diazoxide	Iodine based contrast media[5]	Prilocaine
Adrenaline	Dicycloverine	Iron	Primaquine
Alfentanil	Digoxin	Isoflurane	Procaine
Alimemazine	Dihydrocodeine	Isosorbide mononitrate	Prochlorperazine
Allopurinol	Dimercaprol	Ispaghula	Proguanil
Almotriptan	Dimeticone	**Ketoprofen**	Promazine
Alteplase	Diphenhydramine	Ketotifen	Promethazine
Aluminium salts	Diphenoxylate	**Labetalol**	Propantheline
Amiloride	Dipyridamole	Lactulose	Propofol[7]
Aminoglycosides	Distigmine	Leflunomide	Propylthiouracil
Amisulpride	Dobutamine	Levetiracetam	Pseudoephedrine
Amlodipine	Domperidone	Levomepromazine	**Quinine**
Amphotericin	Dopamine	Levothyroxine sodium	Quinolones[8]
Articaine	Doxazosin	Lidocaine[6]	**Ranitidine**
Aspirin	**Epinephrine**	Lithium	Rosuvastatin
Atomoxetine	Epoetin and analogues	Loperamide	**Salbutamol**
Atovaquone	Eprosartan	Loratadine	Senna
Atropine	Eptifibatide	Lorazepam	Sodium acid phoshate
Azithromycin	Etanercept	**Magnesium sulphate**	Sodium bicarbonate
Baclofen	Ethambutol	Mefloquine	Sodium fusidate
Balsalazide	Etherified starches	Meloxicam	Sodium picosulfate
Barium sulphate	Ezetimibe	Meropenem	Streptokinase
Bendroflumethiazide	**Famciclovir**	Mesalazine	Sulindac
Beta blockers	Felodipine	Metformin	Sulpiride
Bisacodyl	Fenbufen	Methadone	Suxamethonium
Bisphosphonates	Fentanyl	Methylphenidate	**Tazocin**
Bumetanide	Fexofenadine	Midazolam[7]	Teicoplanin
Bupivacaine	Fibrates[2]	Monoclonal antibodies	Temazepam
Buprenorphine	Flucytosine	Morphine	Terazosin
Calcitonin	Flumazenil	Muscle relaxants non-depolarising	Tetracosactide
Calcium carbonate	Fluoxetine	Mycophenolate salts	Tirofiban
Candesartan	Fluphenazine	**Naftidrofuryl**	Tramadol
Carbimazole	Flurbiprofen	Naloxone	Tranexamic acid
Caspofungin	FSH	Naproxen	Triamterene
Cephalosporins	Furosemide	Neostigmine	Trifluoperazine
Chloral hydrate	Ganciclovir	Nicotine replacement therapy	**Urokinase**
Chloroquine	**Gabapentin**	Nifedipine	**Vaccines**[9]
Chlorphenamine	G-CSF	Nitrous oxide	Valaciclovir
Chlorpromazine	Glipizide	Nystatin	Valganciclovir
Ciclosporin	Glucagon	**Octreotide**	Valsartan
Cimetidine	Glucosamine	Olanzapine	Vancomycin
Clobazam	Glucose	Omeprazole	Venlafaxine
Clomifene	Glyceryl trinitrate	Ondansetron	Vigabatrin
Clonazepam	Glycopyrronium	Orlistat	Vitamins
Clozapine	Gonadorelin (LHRH) and-	Oseltamivir	**Warfarin**
Co-amoxiclav	-analogues[3,4]	Oxytocin	**Zanamivir**
Codeine phosphate	Granisetron	**Paracetamol**	Zinc preparations
Colchicine	**Haloperidol**	Paraldehyde	Zopiclone
Colestipol	HCG	Penicillamine	
Colestyramine	Heparin	Penicillins	
Corticosteroids	Heparins-low molecular weight	Pentamidine	
Cyclopenthiazide	Hydrochlorothiazide	Pethidine	**Prepared August 2010**
Desferrioxamine	Hyoscine hydrobromide	Phentolamine	**Review August 2011**

1. Imidapril has not been classified
2. Ciprofibrate has not been classified and should not be used
3. An acute attack has been reported within the first 15 days of treatment with gonadorelin (LHRH) and analogues.
4. For more detailed information contact WMIC
5. Includes Gastrograffin
6. Intravenous doses should be avoided
7. Clinical safety has not been assessed for continuous use of these preparations
8. Nalidixic acid is unsafe and should not be used
9. An acute attack has been reported following yellow fever vaccine, caution should be observed when using any live vaccine in adults.
10. All topical preparations (including topical antifungals) are considered safe

Anti-emetics
Domperidone
Granisetron
Hyoscine hydrobromide
Ondansetron
Prochlorperazine
Promazine

Antihistamines
Alimemazine
Chlorphenamine
Desloratadine
Diphenhydramine
Fexofenadine
Ketotifen
Loratadine
Promethazine

Antibacterial agents
Aminoglycosides
Azithromycin
Cephalosporins
Co-amoxiclav
Imipenem
Meropenem
Penicillins
Pentamidine
Quinolones[8]
Sodium fusidate
Tazocin
Teicoplanin
Vancomycin

Antivirals/Antifungals[10]
Aciclovir
Amphotericin
Caspofungin
Famciclovir
Flucytosine
Ganciclovir
Nystatin
Oseltamivir
Valaciclovir
Valganciclovir
Zanamivir

Malaria Prophylaxis
Atovaquone
Chloroquine
Mefloquine
Proguanil

Immunisations
Immunoglobulins
Vaccines[9]

Corticosteroids + other immunosuppressants
Ciclosporin
Corticosteroids
Monoclonal antibodies

Cardiovascular agents
Abciximab
ACE Inhibitors[1]
Adenosine
Alteplase
Amiloride
Amlodipine
Bendroflumethiazide
Beta blockers
Bumetanide
Candesartan
Cyclopenthiazide
Diazoxide
Digoxin
Dipyridamole
Dobutamine
Dopamine
Doxazosin
Eprosartan
Eptifibatide
Felodipine
Furosemide
Glyceryl trinitrate
Heparin
Heparins-low molecular--weight
Hydrochlorothiazide
Isosorbide mononitrate
Labetalol
Naftidrofuryl
Nifedipine
Prazosin
Streptokinase
Terazosin
Tirofiban
Triamterene
Urokinase
Valsartan
Warfarin

Lipid lowering agents
Colestipol
Colestyramine
Ezetimibe
Fibrates[2]
Rosuvastatin

Antidepressants
Fluoxetine
Venlafaxine

Antipsychotics
Amisulpride
Chlorpromazine
Clozapine
Fluphenazine
Haloperidol
Olanzapine
Pipotiazine
Sulpiride
Trifluoperazine

Anticonvulsants
Clobazam
Clonazepam
Gabapentin
Levetiracetam
Paraldehyde
Pregabalin
Vigabatrin

Analgesics
Alfentanil
Aspirin
Buprenorphine
Codeine phosphate
Dextromethorphan
Diamorphine
Dihydrocodeine
Fenbufen
Fentanyl
Flurbiprofen
Ibuprofen
Indometacin
Ketoprofen
Meloxicam
Methadone
Morphine
Naproxen
Paracetamol
Pethidine
Sulindac
Tramadol

Drugs used in Anaesthesia[4]
Adrenaline
Atropine
Desflurane
Epinephrine
Isoflurane
Muscle relaxants non-depolarising
Neostigmine
Nitrous oxide
Phentolamine
Propofol[7]
Suxamethonium

Local Anaesthetics[10]
Articaine
Bupivacaine
Lidocaine[6]
Prilocaine
Procaine

Miscellaneous
Acetazolamide
Acetylcysteine
Allopurinol
Almotriptan
Aluminium salts
Atomoxetine
Baclofen
Balsalazide
Barium sulphate
Bisacodyl
Bisphosphonates
Calcitonin
Calcium carbonate
Carbimazole
Chloral hydrate
Cimetidine
Clomifene
Colchicine
Desferrioxamine
Dextran
Dicycloverine
Dimercaprol
Dimeticone
Diphenoxylate
Distigmine
Epoetin and analogues
Etanercept
Ethambutol
Etherified starches
Flumazenil
FSH
G-CSF
Glipizide
Glucagon
Glucosamine
Glucose
Glycopyrronium
Gonadorelin (LHRH) and--analogues[3,4.]
HCG
Insulin
Iodine based contrast media[5]
Iron
Ispaghula
Lactulose
Leflunomide
Levomepromazine
Levothyroxine sodium
Lithium
Loperamide
Lorazepam
Magnesium sulphate
Mesalazine
Metformin
Methylphenidate
Midazolam[7]
Mycophenolate salts
Naloxone
Nicotine replacement therapy
Octreotide
Omeprazole
Orlistat
Oxytocin
Penicillamine
Phenylephrine
Pramipexole
Primaquine
Propantheline
Propylthiouracil
Pseudoephedrine
Quinine
Ranitidine
Salbutamol
Senna
Sodium acid phosphate
Sodium bicarbonate
Sodium picosulfate
Temazepam
Tetracosactide
Tranexamic acid
Vitamins
Zinc preparations
Zopiclone

See overpage for explanation of footnotes

This list was produced jointly by staff of the WMIC and Dr Mike Badminton, Director Cardiff Porphyria Service, Department of Medical Biochemistry and Immunology, University Hospital of Wales. It is based on the best information available to us at the time of compilation. Inclusion of a drug does not guarantee that it will be safe in all circumstances.

For medication not listed please contact the Welsh Medicines Information Centre (WMIC) by telephone or by fax

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken:

Question: 1 of 1

A 25-year-old man presented with an enlarged inguinal lymph node with night sweats and the most likely clinical diagnosis is Hodgkin's lymphoma.

A biopsy has been taken.

Which of the following findings on histology is associated with the best prognosis in Hodgkin's disease?

(Please select 1 option)

- Lymphocyte depleted
- Lymphocyte predominant
- Mixed cellularity
- Nodular sclerosing
- Reed-Sternberg cells

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Question: 1 of 1

A 25-year-old man presented with an enlarged inguinal lymph node with night sweats and the most likely clinical diagnosis is Hodgkin's lymphoma.

A biopsy has been taken.

Which of the following findings on histology is associated with the best prognosis in Hodgkin's disease?

(Please select 1 option)

○	Lymphocyte depleted
◉	Lymphocyte predominant ✓ Correct
○	Mixed cellularity
○	Nodular sclerosing
○	Reed-Sternberg cells

Hodgkin's disease is characterised by Reed-Sternberg cells and this is therefore not a prognostic feature.

Nodular sclerosing is the most common finding and has a good prognosis.

Mixed cellularity also has good prognosis; lymphocyte depleted has the worst.

The best prognosis is with lymphocyte predominant histology.

Finish | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken:

Question: 1 of 100

A 58-year-old female with type 2 diabetes is admitted with diarrhoea and vomiting. She has noticed small amounts of blood in her stools. The vomiting had commenced one day after a meal of chicken and chips.

The patient's type 2 diabetes is treated with diet alone. Stool cultures taken by the GP reveal *Campylobacter jejuni*.

Which of the following is the most appropriate therapy?

(Please select 1 option)

- Amoxicillin
- Cefaclor
- IV fluids
- Metronidazole
- Trimethoprim

Submit answer | Skip question | Tag Question | Remove question

Work Smart Session - MRCP Part 1

Time taken: 11 mins 58 secs

Question: 10 of 100

A 30-year-old schoolteacher is admitted with headache, photophobia and neck stiffness.

His temperature is 39.0°C, pulse rate 120 beats/min and he has no skin rash or focal neurological signs. His Glasgow coma scale is 15/15.

A CT scan shows no contraindication to lumbar puncture. CSF is obtained and Gram stain shows gram-positive cocci, subsequent culture confirms a pneumococcal meningitis.

What chemoprophylaxis should be offered to his pupils?

(Please select 1 option)

- Azithromycin
- Ceftriaxone
- Ciprofloxacin
- No chemoprophylaxis required
- Rifampicin

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 30 mins 35 secs

Question: 100 of 100

Two strains of *Escherichia coli* are isolated and both are resistant to ampicillin.

Strain A retains its resistance to ampicillin when grown from multiple generations in the absence of ampicillin.

However strain B loses its resistance when grown in the absence of ampicillin.

Which of the following best explains the loss of antibiotic resistance in strain B?

(Please select 1 option)

○	Changes in the bacterial DNA gyrase
○	Downregulation of the resistance gene
○	Loss of a plasmid containing the resistance gene
○	Mutations in the resistance gene
○	Transposition of another sequence into the resistance gene

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd. All rights reserved. Terms and conditions. Privacy policy.

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Two strains of *Escherichia coli* are isolated and both are resistant to ampicillin.

Strain A retains its resistance to ampicillin when grown from multiple generations in the absence of ampicillin.

However strain B loses its resistance when grown in the absence of ampicillin.

Which of the following best explains the loss of antibiotic resistance in strain B?

(Please select 1 option)

○	Changes in the bacterial DNA gyrase
○	Downregulation of the resistance gene
◉	Loss of a plasmid containing the resistance gene ✓ Correct
○	Mutations in the resistance gene
○	Transposition of another sequence into the resistance gene

Bacteria develop resistance to antibiotics by gaining genes that encode for particular proteins that offer protection to the organism.

Sometimes this is by mutation and other times the gene may be acquired from another bacterial species.

The genes are usually found in plasmids - circular segments of DNA separate from the bacterial chromosome.

Plasmids can easily spread from one bacteria to another - a sort of resistance package that bacteria can share.

Finish | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd. All rights reserved. Terms and conditions Privacy policy

Question: 10 of 100

A 30-year-old schoolteacher is admitted with headache, photophobia and neck stiffness.

His temperature is 39.0°C, pulse rate 120 beats/min and he has no skin rash or focal neurological signs. His Glasgow coma scale is 15/15.

A CT scan shows no contraindication to lumbar puncture. CSF is obtained and Gram stain shows gram-positive cocci, subsequent culture confirms a pneumococcal meningitis.

What chemoprophylaxis should be offered to his pupils?

(Please select 1 option)

○	Azithromycin
○	Ceftriaxone
○	Ciprofloxacin
○	No chemoprophylaxis required ← This is the correct answer
◉	Rifampicin ✕ Incorrect answer selected

Chemoprophylaxis is not normally indicated for close contacts of those with pneumococcal meningitis.

Chemoprophylaxis with rifampicin, ceftriaxone, ciprofloxacin or azithromycin is used for meningococcal meningitis.

Close contacts of *Haemophilus influenzae* meningitis should receive rifampicin; children under two years should be vaccinated.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 12 mins 54 secs

Question: 11 of 100

A 23-year-old female presents 16 weeks into her pregnancy with a vaginal discharge.

Further investigation confirms infection with *Chlamydia trachomatis*.

Which of the following is the most appropriate treatment for this patient?

(Please select 1 option)

- Ciprofloxacin
- Co-trimoxazole
- Doxycyline
- Erythromycin
- Metronidazole

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

National Guideline on the Diagnosis and Treatment of Gonorrhoea in Adults 2005

Commissioned by: Clinical Effectiveness Group, BASHH (British Association for Sexual Health and HIV).

Aetiology.

Gonorrhoea is the clinical disease resulting from infection with the Gram-negative diplococcus *Neisseria gonorrhoeae.* The primary sites of infection are the mucous membranes of the urethra, endocervix, rectum, pharynx and conjunctiva. Transmission is by direct inoculation of infected secretions from one mucous membrane to another.

Clinical features.

Symptoms. [1-4]

Men:

- urethral infection commonly causes urethral discharge (>80%) and/or dysuria (>50%).
- urethral infection can be asymptomatic (<10%).
- rectal infection in homosexual men is usually asymptomatic but may cause anal discharge (12%) or perianal/anal pain or discomfort (7%).
- pharyngeal infection is usually asymptomatic (>90%).

Women:

- infection at the endocervix is frequently asymptomatic (up to 50%).
- increased or altered vaginal discharge is the most common symptom (up to 50%).
- lower abdominal pain may be present (up to 25%).
- urethral infection may cause dysuria (12%) but not frequency.
- gonorrhoea is a rare cause of intermenstrual bleeding or menorrhagia.
- rectal infection more frequently develops by transmucosal spread of infected genital secretions than from anal intercourse and is usually asymptomatic.
- pharyngeal infection is usually asymptomatic (>90%).

Neisseria gonorrhoeae may co-exist with other genital mucosal pathogens, notably *Trichomonas vaginalis, Candida albicans* and *Chlamydia trachomatis.* If symptoms are present, they may be attributable to the co-infecting pathogen.

Signs. [1, 2]

Men:

- a mucopurulent or purulent urethral discharge is commonly evident.
- rarely, epididymal tenderness/swelling or balanitis may be present.

Women:

- mucopurulent endocervical discharge and easily induced endocervical bleeding (<50%). [Note: mucopurulent endocervical discharge is not a sensitive predictor of cervical infection (<50%).]
- pelvic/lower abdominal tenderness (<5%).
- commonly, no abnormal findings are present on examination.

Complications.

Transluminal spread of *N. gonorrhoeae* may occur from the urethra or endocervix to involve the epididymis and prostate in men (1% or less) and the endometrium and pelvic organs in women (probably <10%). Haematogenous dissemination may also occur from infected mucous membranes, resulting in skin lesions, arthralgia, arthritis and tenosynovitis. Disseminated gonococcal infection is uncommon (<1%).

Diagnosis.

- The diagnosis is established by the identification of *N. gonorrhoeae* at an infected site.
- Culture offers a readily available, specific, sensitive and cheap diagnostic test that readily allows confirmatory identification and antimicrobial susceptibility testing. It is currently the method of first choice for use in genitourinary medicine clinics in the UK. Selective culture media containing antimicrobials are recommended to reduce contamination [5] (recommendation level B).
- Alternative tests include nucleic amplification tests (NAATs) and nucleic acid hybridization tests. NAATs are more sensitive than culture and can also be used as diagnostic/screening tests on non-invasively collected specimens (urine and self-taken vaginal swabs). Comparisons between NAATs and culture suggest the sensitivity of NAATs exceeds 90% for genital sites, whilst the sensitivity of culture may be less than 75% for endocervical swabs [6]. This probably indicates that NAATs are less affected than culture by inadequacies in collection and transport of specimens. The TMA assay (APTIMA Combo 2) and SDA assay (BD ProbeTec-SDA) are more sensitive in women than the PCR assay [7]. There are currently no NAATs which are licensed for use with rectal or pharyngeal samples, although studies suggest that the sensitivity of NAATs at non-genital sites exceeds 90% [8] whereas the sensitivity of culture can be less than 60% for rectal swabs [8] and less than 50% for pharyngeal swabs [8, 9]. Caution is required in interpretation of positive results as the specificity of NAATs is not 100% [10, 11]. Confirmation of a NAAT positive result by culture is advisable (recommendation level C).
- Rapid diagnostic tests can be performed to facilitate immediate diagnosis and treatment. Microscopy (x1000) of gram stained genital specimens allows direct visualization of *N. gonorrhoeae* as monomorphic gram negative diplococci within polymorphonuclear leukocytes. In men, microscopy of urethral smears is more sensitive in symptomatic (90-95%) than in asymptomatic (50-75%) patients [1]. In women, microscopy of gram stained endocervical smears is more sensitive than urethral smears (37-50% vs 20%) [2]. Microscopy is not appropriate for pharyngeal specimens.

Specimen collection.

Men: routinely from the urethra; rectal and/or oropharyngeal tests when symptomatic at these sites and as indicated by sexual activity. A first pass urine provides an alternative urethral specimen for testing with a NAAT.

Women: routinely from endocervix if speculum examination performed and from the urethra; rectal and oropharyngeal tests when symptomatic at these sites, when a sexual partner has gonorrhoea and when indicated by the sexual history. Urine or a self-taken vaginal swab provide suitable alternative specimens as screening tests using a NAAT (note: the PCR assay has poor sensitivity on female urine [7]).

- Direct plating of genital samples and use of transport media with prompt laboratory plating both give acceptable results [5, 12] (evidence level IV).

- The use of endocervical samples alone will identify 90-95 % of women with gonococcal infection [2, 13].
- Data is lacking on the sensitivity of a single set of tests from anogenital sites to identify infection with *N. gonorrhoeae*. To confidently exclude infection in patients who attend within three days of sexual contact with a confirmed case of gonorrhoea, a second set of tests should be considered if epidemiological treatment with effective antimicrobial therapy is not given [12] (evidence level IV, recommendation level C).

Management.

General Advice.

- Referral to a GU Medicine Department for management is strongly encouraged.
- Patients should be given a detailed explanation of their condition with particular emphasis on the long-term implications for the health of themselves and their partner(s). This should be reinforced with clear and accurate written information.
- Patients should be advised to avoid unprotected sexual intercourse until they and their partner(s) have completed treatment.

Further Investigation.

- Screening for coincident sexually transmitted infections should routinely be performed in patients with or at risk of gonorrhoea (evidence level III, recommendation level C).

Treatment.

Indications for therapy:

- a positive rapid diagnostic test,
- a positive culture for *N. gonorrhoeae*,
- a positive nucleic acid test - confirmation of the diagnosis by culture is recommended prior to or at the time of treatment [11] (recommendation grade C).
- on epidemiological grounds, if a recent sexual partner has confirmed gonococcal infection,

Recommended treatments [3, 14-20.]

Uncomplicated anogenital infection in adults:

- Ceftriaxone 250mg IM as a single dose. (grade A recommendation)
  or
- Cefixime 400mg oral as a single dose. (grade A recommendation)
  or
- Spectinomycin* 2g IM as a single dose. (grade A recommendation)

- *N. gonorrhoeae* has shown the capacity to develop reduced sensitivity and resistance to many classes of antimicrobials. Published trials of gonorrhoea treatment reflect clinical efficacy in a past era of antimicrobial sensitivity. Surveillance data for 2004 shows significant levels of *N. gonorrhoeae* resistance to penicillin (11.2%), tetracyclines (44.5%) and ciprofloxacin (14.1%) in the UK [21-23]. Most resistant infections are acquired in the UK.

- Antimicrobial therapy should take account of local patterns of antimicrobial sensitivity to *N. gonorrhoeae*. The chosen regimen should eliminate infection in at least 95% of those presenting in the local community [12].

Alternative regimens - may be used when an infection is known to be sensitive to these antimicrobials or where the regional prevalence of resistance to them is less than 5%:

- Ciprofloxacin 500mg orally as a single dose. (grade A recommendation)
  or
- Ofloxacin 400mg orally as a single dose. (grade A recommendation).
  or
- Ampicillin 2g or 3g plus probenecid* 1g orally as a single dose, (grade B recommendation),

- Other single dose cephalosporin regimes, notably Cefotaxime 500mg IM as a single dose. (grade A recommendation)
  or Cefoxitin 2g IM as a single dose plus probenecid* 1g oral.

- Cefpodoxime is an alternative oral third generation cephalosporin that as a single dose of 200mg is licensed for the treatment of uncomplicated gonorrhoea [24]. Published trial data is limited, but in view of its short half-life, less favourable pharmokinetics than cefixime and suboptimal efficacy against pharyngeal infection, it cannot be recommended (recommendation C).

- Clinicians using alternative regimens are recommended to regularly review local antimicrobial sensitivity testing with microbiology colleagues.

- The alternative treatment regimens listed do not comprise all effective treatment regimens, but reflect clinical practice in the UK.

- High dose azithromycin (2.0g as a single dose) has shown acceptable efficacy in clinical trials, but is associated with a high gastrointestinal intolerance [25]. The emergence of azithromycin resistant *N. gonorrhoeae* has been reported and clinical efficacy does not always correlate with *in-vitro* sensitivity testing [26-27]. Azithromycin is not a recommended treatment for gonorrhoea.

β lactam allergy.

- Spectinomycin* 2g IM as a single dose.
  or
- Ciprofloxacin 500mg orally as a single dose when the infection is known or anticipated to be quinolone sensitive.

Pregnancy and Breastfeeding.

- Pregnant women should not be treated with quinolone or tetracycline antimicrobials.

  Recommended Regimes [28-30]

  - Ceftriaxone 250mg IM as a single dose. (grade A recommendation)

  or

  - Cefixime 400mg oral as a single dose. (grade A recommendation)

  or

  - Spectinomycin* 2g IM as a single dose. (grade A recommendation).

or

- Amoxycilin 3g or Ampicillin 2g or 3g plus probenecid* 1g orally as a single dose, where regional prevalence of penicillin resistant *N. gonorrhoeae* is ≤5%. (grade B recommendation).

Pharyngeal infection.

Recommended treatments [15, 31]

- Ceftriaxone 250mg IM as a single dose (grade B recommendation)

or

- Ciprofloxacin 500mg orally as a single dose if *N. gonorrhoeae* known to be quinolone sensitive (grade B recommendation)

or

- Ofloxacin 400mg orally as a single dose if *N. gonorrhoeae* known to be quinolone sensitive. (grade B recommendation).

- Single dose treatments using ampicillin or spectinomycin have a poor efficacy in eradicating gonococcal infection of the pharynx [15] (evidence level II).

*There may be problems with the availability of these drugs in the UK.

Co-infection with *Chlamydia trachomatis*

Genital infection with *C. trachomatis* commonly accompanies genital gonococcal infection (up to 20% of men and 40% of women with gonorrhoea). Screening for *C. trachomatis* should routinely be performed on adults with gonorrhoea or treatment given to eradicate possible co-infection [3, 12, 14]. Combining effective antimicrobial therapy against *C. trachomatis* with single dose therapy for gonococcal infection is particularly appropriate when there is doubt that a patient will return for follow up evaluation.

Sexual partners.

Partner notification should be pursued in all patients identified with gonococcal infection, preferably by a trained health adviser in GU Medicine. Action and outcomes should be documented [32]. Male patients with symptomatic urethral infection should notify all partners with whom they had sexual contact within the preceding 2 weeks or their last partner if longer ago. Patients with infection at other sites or asymptomatic infection should notify all partners within the preceding 3 months. Sexual partners should be treated for gonorrhoea preferably after evaluation for sexually acquired infection. (recommendation level C)

Follow up.

Patients should be assessed after treatment (recommendation C):

- to confirm compliance with treatment,
- to ensure resolution of symptoms,
- to enquire about adverse reactions,
- to re-take the sexual history to explore the possibility of re-infection,
- to pursue partner notification and health promotion.

A microbiological test of cure is not routinely necessary when the infection has been treated with a recommended directly observed therapy, the infection is fully

sensitive to the antimicrobial administered, symptoms have resolved and there is no risk of re-infection. (evidence level III, recommendation C) [33-34]. If a patient is symptomatic after treatment, has received a suboptimal treatment, a resistant strain is identified or there is a possibility of reinfection, test of cure with culture is recommended (recommendation C). Pregnancy does not diminish treatment efficacy. All treatments are less effective at eradicating pharyngeal infection [31] and test of cure is recommended following treatment of infection at this site (recommendation C). If a test of cure is performed, culture tests should be performed at least 72 hours after completion of antimicrobial therapy [5] and NAATs tests two weeks after therapy [35]. Infection identified after treatment more commonly indicates reinfection rather than treatment failure [4, 34].

Auditable Outcome Measures.

- At least 95% of cases of genital gonorrhoea should be cured by first line therapy [12].
- All patients with gonorrhoea should be screened for genital infection with *Chlamydia trachomatis* or receive presumptive treatment for this infection.
- All patients identified with genital gonorrhoea should have at least one documented interview with a health adviser in GU Medicine or other health professional trained in partner notification and their action documented.
- All patients identified with gonorrhoea should receive written information about sexually transmitted infections and their prevention.
- For every case of gonorrhoea, at least 0.6 sexual partners should be verified as having been satisfactorily managed within four weeks. This rate of management of sexual partners may be unachievable in departments in some large cities and a lower rate may need to be locally determined [36].

Acknowledgments.
I wish to thank the following for their valuable contributions to this Guideline: Mark FitzGerald, Keith Radcliffe, Jonathan Ross, Cathy Ison, Jan Clarke, Jackie Sherrard, and the many members of BASHH who made comments during the web-based consultation and on 22 October 2004 at the BASHH OGM in London. .

Author and Centre.
Chris Bignell
Nottingham City Hospital NHS Trust

Membership of the CEG.
Clinical Effectiveness Group: Chairman, Keith Radcliffe; Imtyaz Ahmed-Jushuf; David Daniels (Chairman, BASHH National Audit Group); Mark FitzGerald; Guy Rooney (Royal College of Physicians representative); Jan Welch.

Conflict of Interest.
None.

Evidence Base.

Cochrane Library
The Cochrane Library 2004 Issue 2 (Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effectiveness, and Cochrane Controlled Trials Register) was searched using the textword 'gonorrhoea' and all entries considered.

MEDLINE
A MEDLINE search of published articles in any language for the years 1990-2004 (August) using the subject headings 'gonorrhea' and 'Neisseria gonorrheae'. The sub-headings focused on were: clinical trials, drug therapy, diagnosis, epidemiology, prevention and control, and therapy. All entries in the English language or with abstracts in English were viewed because of the paucity of 'clinical trials' or 'reviews'. Comprehensive reviews of therapy for gonorrhoea that have employed MEDLINE search strategies are published and include trials up to 1993.

References.

1. Sherrard J, Barlow D. Gonorrhoea in men: clinical and diagnostic aspects. Genitourin Med 1996; **72:** 422-426.

2. Barlow D, Phillips I. Gonorrhoea in women: diagnostic, clinical and laboratory aspects. Lancet 1978; **i:** 761-764.

3. Sexually Transmitted Diseases (STD): Netherlands Guidelines 1997.

4. Lewis DA, Bond M, Butt KD, Smith CP, Shafi MS, Murphy SM. A one-year survey of gonococcal infection seen in the genitourinary medicine department of a London district general hospital. Int J STD AIDS 1999; **10**: 588-594.

5. Jephcott AE. Microbiological diagnosis of gonorrhoea. Genitourin Med 1997; **73:** 245-252.

6. Van Dyck E, Ieven M, Pattyn S, Van Damme L, Laga M. Detection of Chlamydia trachomatis and Neisseria gonorrhoeae by enzyme immunoassay, culture and three nucleic acid amplification tests. J Clin Microbiol 2001; **39**: 1751-1756.

7. Cook RL, Hutchison SL, Østergaard L, Braithwaite RS, Ness RB. Systematic Review: Non-invasive testing for *Chlamydia trachomatis* and *Neisseria goorrhoeaea.* Ann Intern Med 2005; **142**: 914-925.

8. Young H, Manavi K McMillam A. Evaluation of ligase chain reaction for the non-cultural detection of rectal and pharyngeal gonorrhoea in men who have sex with men. Sex Trans Infect 2003; **79**: 484-486.

9. Page-Shafer K, Graves A, Kent C, Bals JE, Zapitz VM, Klausner JD. Increased sensitivity of DNA amplification testing for the detection of pharyngeal gonrrhoea in men who have sex with men. Clinical Infectious Diseases 2002; **34**: 173-176.

10. Palmer H, Mallinson H, Wood RL, Herring AJ. Evaluation of the specificities of five DNA amplification methods for the detection of *Neisseria gonorrhoeae*. J Clin Microbiol 2003; **41**: 835-837.

11. Katz AR, Effler PV, Ohye RG, et al. False-positive gonorrhoea test results with a nucleic amplification test: the impact of low prevalence on positive predictive value. Clin Infect Dis 2004; 38: 814-819.

12. FitzGerald M, Bedford C. National standards for the management of gonorrhoea. Int J STD AIDS 1996; **7**: 298-300.

13. Ghanem M, Radcliffe K, Allan P. The role of urethral samples in the diagnosis of gonorrhoea in women. Int J STD AIDS 2004; **15**: 45-47.

14. Centers for Disease Control and Prevention. Sexually transmitted disease treatment guidelines 2002. MMWR 2002; **51** (No. RR-6): 36-42.

15. Bignell CJ. Antibiotic treatment of gonorrhoea - clinical evidence for choice. Genitourin Med 1996; **72:** 315-320.

16. Echols RM, Heyd A, O' Keeffe BJ, Schacht P. Single-dose ciprofloxacin for the treatment of uncomplicated gonorrhoea: a worldwide summary. Sex Trans Dis 1994; **21:** 345-352.

17. Korting HC, Kollman M. Effective single dose treatment of uncomplicated gonorrhoea. Int J of STD AIDS 1994; **5:** 239-243.

18. Moran JS, Zenilman JM. Therapy for gonoccocal infections: options in 1989. Rev Infect Dis 1990; **12** (suppl 6): S633-644.

19. Moran JS, Levine WC. Drugs of choice for the treatment of uncomplicated gonococcal infections. Clin Infect Dis 1995; **20** (suppl 1): S47-65.

20. Moran JS. Ciprofloxacin for gonorrhea - 250mg or 500mg? Sex Trans Dis 1996; **23:** 165-167.

21. HPA. GRASP The Gonococcal Resistance to Antimicrobials Surveillance Programme – Annual Report 2004. London: Health Protection Agency, August 2005. Available at: http://www.hpa.org.uk/infections/topics_az/hiv_and_sti/sti-gonorrhoea/publications/GRASP_2004_Annual_Report.pdf.

22. Fenton KA, Ison CA, Johnson AP, Rudd E, Soltani M, Martin I, et al. Ciprofloxacin resistance in Neisseria gonorrhoeae in England and Wales in 2002. Lancet 2003: **361**: 1867-69.

23. Forsyth A, Moyes A, Young H. Increased ciprofloxacin resistance in gonococci isolated in Scotland. Lancet 2000; **356**: 1984-5.

24. Novak E, Paxton LM, Tubbs HJ, Turner LF, Keck CW, Yatsu J. Orally administered cefpodoxime proxetil for the treatment of uncomplicated gonococcal urethritis in males: a dose –response study. Antimicrob Agents Chemther 1992; **36**: 1764-1765.

25. Handsfield HH, Dalu ZA, Martin DH, et al. Multicenter trial of single-dose azithromycin vs ceftriaxone in the treatment of uncomplicated gonorrhoea. Sex Trans Dis 1994; **21**: 107-111.

26. Young H, Moyes A, McMillan A. Azithromycin and erythromycin resistant *Neisseria gonorrhoeae* following treatment with azithromycin. Int J STD AIDS 1997; **8**: 299-302.

27. Tapsall JW, Schultz TR, Limnios EA, Donovan B, Lum G, Mulhall BP. Failure of azithromycin therapy in gonorrhoea and discorrelation with laboratory parameters. Sex Trans Dis 1998; **25**:505-508.

28. Brocklehurst P. Interventions for treating gonorrhoea in pregnancy. Cochrane Library, Issue 3, 2003.Oxford: Update Software.

29. Cavenee MR, Farris JR, Spalding TR, Barnes DL, Castaneda YS, Wendel GD. Treatment of gonorrhea in pregnancy. Obstet Gynecol 1993; **81:** 33-38.

30. Ramus RM, Sheffield JS, Mayfield JA, Wendel GD. A randomised trial that compared oral cefixime and intramuscular ceftriaxone for the treatment of gonorrhoea in pregnancy. Am J Obstet Gynecol 2001;**185**:629-32.

31. Moran JS. Treating uncomplicated Neisseria gonorrhoeae infections: is the anatomic site of infection important? Sex Trans Dis 1995; **22:** 39-47.

32. Fitzgerald M, Thirlby D, Bell G, Bedford C. National standards for contact tracing in gonorrhoea. Int J STD AIDS 1996; **7**: 301.

33. Holland TM, Hussey J, Pattman RS, Sankar KN, Faldon CM. Audit of gonorrhoea test of cure at the genitourinary medicine department in Newcastle upon Tyne, UK. Int J STD AIDS 2003; **14**: 630-631.

34. Komolafe AJ, Sugunendran H, Corkill JE. Gonorrhoea: test of cure for sensitive bacteria? Use of genotyping to disprove treatment failure. Int J STD AIDS 2004; **15**: 212.

35. Bachmann LH, Desmond RA, Stephens J, Hughes A, Hook EW 3rd. Duration of persistence of gonococcal DNA detected by ligase chain reaction in men and women following recommended therapy for uncomplicated gonorrhoea. J Clin Microbiol 2002; **40**: 3596-601.

36. Low N, Welch J, Radcliffe K. Developing national outcome standards for the management of gonorrhoea and genital chlamydia in genitourinary medicine clinics. Sex Transm Infect 2004; **80**: 223-229.

(Please select 1 option)

○	Ciprofloxacin
○	Co-trimoxazole
○	Doxycyline
◉	Erythromycin ✓ Correct
○	Metronidazole

C. trachomatis infection is common in pregnancy and is associated with adverse fetal outcome including:

- spontaneous miscarriage
- premature rupture of membranes and
- intrauterine growth retardation (IUGR).

Appropriate treatment is with macrolides such as erythromycin or azithromycin, Erythromycin has an established safety profile in pregnancy whereas at present the BNF states that azithromycin should be used with caution. Azithromycin is becoming more widely used as WHO guidelines now recommend its use as it has advantages over erythromycin such as a lower side effect profile and a single one-off dose treatment which results in increased compliance. Local guidelines should be consulted. Of the options provided here, erythromycin is the most appropriate.

Both doxycycline and ciprofloxacin are contraindicated in pregnancy.

Further reading:
2006 UK National Guideline for the Management of Genital Tract Infection with *Chlamydia trachomatis* (pdf)

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 15 mins 32 secs

Question: 12 of 100

An 18-year-old male presented with a two week history of dysuria and purulent penile discharge.

Gram stain of a urethral swab showed Gram-negative intracellular diplococci.

What specific treatment should he receive?

(Please select 1 option)

- Cefixime
- Cephradine
- Ciprofloxacin
- Co-amoxiclav
- Crystalline penicillin

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

An 18-year-old male presented with a two week history of dysuria and purulent penile discharge.

Gram stain of a urethral swab showed Gram-negative intracellular diplococci.

What specific treatment should he receive?

(Please select 1 option)

○	Cefixime ← This is the correct answer
○	Cephradine
◉	Ciprofloxacin ✕ Incorrect answer selected
○	Co-amoxiclav
○	Crystalline penicillin

Neisseria gonorrhoeae occurs in young adults and is often preceded by a migratory tendonitis or arthritis.

Gram-stain is positive in 25% and culture positive in 50%.

Current UK guidlelines recommend first-line treatment with either cefotaxime, cefixime or spectinomycin may be given (as a stat dose).

Fluoroquinolones are no longer used as first-line treatment due to the high rate of resistance.

Further reading:
National Guideline on the Diagnosis and Treatment of Gonorrhoea in Adults 2005 (pdf)

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 16 mins 30 secs

Question: 13 of 100

A 45-year-old HIV-seropositive man attended the outpatient clinic for the results of a fasting serum lipid test.

He had been diagnosed with HIV disease two years previously and was started on highly active antiretroviral therapy. One year after commencing antiretrovirals, his CD4 count had risen from 10 cells/mm^3 to 120 cells/mm^3 with an undetectable viral load.

His current medications consisted of zidovudine, lamivudine, lopinavir, aciclovir, fluconazole and co-trimoxazole.

Fasting lipid profile revealed:

Serum cholesterol	4.1 mmol/l	(<5.2)
Serum triglyceride	18.2 mmol/l	(0.45-1.69)

Which of the following medications is most likely to be responsible for these results?

(Please select 1 option)

- Co-trimoxazole
- Fluconazole
- Lamivudine
- Lopinavir
- Zidovudine

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd. All rights reserved. Terms and conditions. Privacy policy.

○	Co-trimoxazole
○	Fluconazole
○	Lamivudine
◉	Lopinavir ✓ Correct
○	Zidovudine

Lipodystrophy, lipoatrophy and alterations in serum lipid values have been observed in patients with human immunodeficiency virus (HIV) disease taking highly active antiretroviral therapy.

Elevated serum lipid levels have been associated with premature coronary artery disease.

Hypertriglyceridaemia is also thought to contribute to central fat deposition, and insulin resistance that is also seen in these patients.

Abnormalities of serum lipid levels are likely to be multifactorial in patients with HIV disease, but appear much commoner in patients taking protease inhibitors.

Isolated hypertriglyceridaemia can occur in HIV disease in the absence of protease inhibitors, but extremely high serum triglycerides have been documented in some patients treated with these drugs.

If the elevation in lipid levels is modest, measures such as dietary modification and exercise may be tried first. Omega-3 fish oils may also be beneficial in reducing modestly-elevated serum triglycerides.

In refractory cases, or where there is extreme isolated hypertriglyceridaemia, a fibrate should be used.

In addition, patients with HIV disease may also have elevated serum lipid levels due to familial hyperlipidaemia.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 18 mins 36 secs

Question: 14 of 100

A 57-year-old woman develops a blistering rash around the midriff and is diagnosed with *Herpes zoster*. She is treated with acyclovir.

Which of the following is responsible for the activation of acyclovir?

(Please select 1 option)

- Integrase
- Polymerase
- Protease
- Reverse transcriptase
- Thymidine kinase

Submit answer | Skip question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 19 mins 16 secs

Question: 14 of 100

A 57-year-old woman develops a blistering rash around the midriff and is diagnosed with *Herpes zoster*. She is treated with acyclovir.

Which of the following is responsible for the activation of acyclovir?

(Please select 1 option)

○	Integrase
◉	Polymerase ✗ Incorrect answer selected
○	Protease
○	Reverse transcriptase
○	Thymidine kinase ← This is the correct answer

This is a variation on the acyclovir theme.

Acyclovir acts through inhibition of viral deoxyribonucleic acid (DNA) polymerase but it is a pro-hormone and first requires phosphorylation by thymidine kinase.

Next question

Remove Tag

Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 19 mins 16 secs

Question: 15 of 100

A 57-year-old woman develops a blistering rash around the midrif and is diagnosed with herpes zoster. She is treated with acyclovir.

Through inhibition of which of the following does acyclovir function?

(Please select 1 option)

- Integrase
- Polymerase
- Protease
- Reverse transcriptase
- Thymidine kinase

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 19 mins 43 secs

Question: 15 of 100

A 57-year-old woman develops a blistering rash around the midrif and is diagnosed with herpes zoster. She is treated with acyclovir.

Through inhibition of which of the following does acyclovir function?

(Please select 1 option)

○	Integrase
◉	Polymerase ✓ Correct
○	Protease
○	Reverse transcriptase
○	Thymidine kinase

Acyclovir is a synthetic purine nucleotide analogue and as such is a specific inhibitor of herpesvirus DNA polymerase.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 19 mins 43 secs

Question: 16 of 100

A 47-year-old man presents with progressive right hand swelling two days after being bitten by a dog.

On examination there is a puncture wound with pus over the dorsum of the hand, cellulitis, ascending lymphangitis and tender axillary lymphadenopathy.

What is the most appropriate antibiotics therapy in this case?

(Please select 1 option)

- Benzylpenicillin and flucloxacillin
- Ceftriaxone
- Ciprofloxacin
- Co-amoxiclav
- Erythromycin

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Question: 16 of 100

A 47-year-old man presents with progressive right hand swelling two days after being bitten by a dog.

On examination there is a puncture wound with pus over the dorsum of the hand, cellulitis, ascending lymphangitis and tender axillary lymphadenopathy.

What is the most appropriate antibiotics therapy in this case?

(Please select 1 option)

◉	Benzylpenicillin and flucloxacillin ✕ Incorrect answer selected
○	Ceftriaxone
○	Ciprofloxacin
○	Co-amoxiclav ← This is the correct answer
○	Erythromycin

Only 15-20% of dog bites become infected, and providing the wound is appropriately cleaned and not considered at risk (for example, crush or deep wounds) then antibiotic prophylaxis may not be required.

However, this patient has an infected wound, and infective organisms include *Pasteurella* spp, *Staph. aureus* and anaerobes like *Corynebacterium*.

The most appropriate antibiotic therapy in dog bites associated with cellulitis would be co-amoxiclav.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 20 mins 51 secs

Question: 17 of 100

A 27-year-old pop singer presented with a two month history of loose motions and weight loss. He underwent an HIV antibody test and was found to be positive.

The presence of which of the following diseases indicates a diagnosis of AIDS?

(Please select 1 option)

- Brucellosis
- Glandular fever
- Lyme disease
- Oral candidiasis
- Pulmonary tuberculosis

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

http://my.onexamination.com/Assessment/Que
Questions Set : REF19971

Oral candidiasis

Pulmonary tuberculosis ✓ Correct

AIDS defining diseases are:

- Cytomegalovirus disease (other than liver, spleen, or nodes)
- *Cytomegalovirus retinitis* (with loss of vision)
- Encephalopathy, HIV-related
- *Herpes simplex*: chronic ulcer(s) (>1 month's duration); or bronchitis, pneumonia, or oesophagitis
- Histoplasmosis, disseminated or extrapulmonary
- Isosporiasis, chronic intestinal (>1 month's duration)
- Kaposi's sarcoma
- Lymphoma, Burkitt's (or equivalent term)
- Lymphoma, primary, of brain
- *Mycobacterium avium* complex or *M. kansasii*, disseminated or extrapulmonary
- *Mycobacterium tuberculosis*, any site (pulmonary or extrapulmonary)
- Mycobacterium, other species or unidentified species, disseminated or extrapulmonary
- *Pneumocystis carinii* pneumonia
- Pneumonia, recurrent
- Progressive multifocal leukoencephalopathy
- Salmonella septicaemia, recurrent
- Toxoplasmosis of brain
- Wasting syndrome due to HIV.

Further reading:
Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents (pdf) (Centers for Disease Control and Prevention)

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 21 mins 36 secs

Question: 18 of 100

An elderly woman who had her right first metatarsal amputated two weeks previously for diabetic gangrene, presented with right foot pain, rash and fever. There were features of inflammation around the amputated area.

Which one of the following investigations would you like to order to confirm the diagnosis?

(Please select 1 option)

- Bone scan
- CT scan
- Indium-labelled leukocyte scanning
- MRI scan
- Right foot x ray

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Which one of the following investigations would you like to order to confirm the diagnosis?

(Please select 1 option)

◉	Bone scan ✕ Incorrect answer selected
○	CT scan
○	Indium-labelled leukocyte scanning
○	MRI scan ← This is the correct answer
○	Right foot x ray

Plain radiography of chronic osteomyelitis typically shows patchy osteopenia or frank bone destruction, loss of definition of the cortex, areas of sclerosis, or periosteal reaction with new bone formation. These changes take many weeks to develop fully.

For more rapid clarification of diagnosis however, specialised imaging is needed.

Computed tomography (CT) scanning may be able to identify cortical erosion that has been missed on plain films and can demonstrate sequestra within bone.

There is a lack of sensitivity early in the disease. White cell isotope scanning is widely used but there is a lack of consensus on the utility of various tests.

Conventional three-phase technetium bone scans are sensitive but non-specific. Specificity may be increased by the addition of indium-labelled leukocyte scanning.

Magnetic resonance imaging (MRI) is the standard and best method for diagnostic imaging of osteomyelitis. It can detect intra- and extraosseous oedema, abscesses, dead bone, and sinus tracts. It can distinguish active from inactive infection.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 23 mins 23 secs

Question: 19 of 100

A group of construction workers presented to the emergency department with diarrhoea, flushing, sweating and a hot mouth. They fell ill minutes after eating lunch in the staff canteen. They admitted that they had eaten tuna fish and wine.

What is the likely cause of food poisoning?

(Please select 1 option)

○	*Clostridium perfringens*
○	Heavy metal
○	Mushroom
○	Scrombotoxin
○	*Staphylococcus aureus*

Submit answer | Skip question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 24 mins 42 secs

Question: 19 of 100

A group of construction workers presented to the emergency department with diarrhoea, flushing, sweating and a hot mouth. They fell ill minutes after eating lunch in the staff canteen. They admitted that they had eaten tuna fish and wine.

What is the likely cause of food poisoning?

(Please select 1 option)

○	*Clostridium perfringens*
○	Heavy metal
○	Mushroom
◉	Scrombotoxin ✓ Correct
○	*Staphylococcus aureus*

Scrombotoxin food poisoning is caused by the ingestion of foods that contain high levels of histamine and possibly other vasoactive amines and compounds.

Histamine and other amines are formed by the growth of certain bacteria and the subsequent action of their decarboxylase enzymes on histidine and other amino acids in food, either during the production of a product such as Swiss cheese or by spoilage of foods such as fishery products, particularly tuna or mahi mahi.

Incubation period is 10-60 minutes.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

The patient's type 2 diabetes is treated with diet alone. Stool cultures taken by the GP reveal *Campylobacter jejuni*.

Which of the following is the most appropriate therapy?

(Please select 1 option)

○	Amoxicillin
○	Cefaclor
◉	IV fluids ✓ Correct
○	Metronidazole
○	Trimethoprim

Campylobacter is a leading cause of diarrhoeal illness, often caused by ingestion of undercooked meat harbouring the pathogen. It is also a major cause of traveller's diarrhoea.

The use of antibiotic therapy for the management of *Campylobacter* infection in adults is controversial. Antibiotic of choice in this infection is erythromycin, though ciprofloxacin and tetracycline may also be appropriate.

However, appropriate fluid replacement and anti-emetics are initially indicated - most units advocate no antibiotic treatment.

Work Smart Session - MRCP Part 1

Time taken: 3 mins 9 secs

Question: 2 of 100

Which of the following statements is true about immunological reactions?

(Please select 1 option)

- Angio-neurotic oedema is the most severe form of type I reaction
- Deficiencies in the terminal components of complement increase the risk of meningococcal disease
- Graves' disease is caused by a type IV reaction
- Serum sickness is caused by a type II reaction
- Urticaria usually responds to cimetidine

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 24 mins 42 secs

Question: 20 of 100

Which of the following is correct concerning oseltamivir?

(Please select 1 option)

- It is a direct viral cytotoxic agent
- It is administered via an inhaler
- It is a haemaglutinase inhibitor
- It is effective if administered within 72 hours of symptoms of flu
- It is of value in prophylaxis against influenza

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

2007 UK National Guideline on the Management of Non-gonococcal Urethritis

Updated Dec 2008

British Association for Sexual Health and HIV

Clinical Effectiveness Group

Scope and purpose

The main objective is to reduce the number of sexually transmitted infections (STIs) and the complications that can arise in people either presenting with signs and symptoms of an STI, or undergoing investigation for possible infection.

Specifically, this guideline offers recommendations on the diagnostic tests, treatment regimens and health promotion principles needed for the effective management of Non-Gonoccocal Urethritis (NGU),covering, the management of the initial presentation, as well as how to prevent transmission and future infection.

It is aimed primarily at people aged 16 years or older (see specific guidelines for those under 16) presenting to health care professionals, working in departments offering level 3 care in STI management (see national strategy[1]) within the United Kingdom. However, the principles of the recommendations should be adopted across all levels (levels 1 and 2 may need to develop, where appropriate, local care pathways).

The recommendation of this guideline may not be appropriate for use in all clinical situations. Decisions to follow these recommendations must be based on the professional judgement of the clinician and consideration of individual patient circumstances and available resources.

Stakeholder involvement

The document was reviewed by the Bacterial Special Interest Group and the Clinical Effectiveness Group of BASHH, and their comments incorporated. It was subsequently circulated for comments by the BASHH membership for three months.

What is new?

- No need to do a urethral smear in asymptomatic men.
- First line treatment for NGU is Azithromycin 1 g orally as a single dose
- The follow-up interview can be performed by telephone

- Persistent/recurrent NGU occurs in 10-20% of patients.
- A urethral smear should only be performed on follow-up if the patient is symptomatic.
- Any treatment for persistent/recurrent NGU should cover *Mycoplasma genitalium* and *Trichomonas vaginalis*.
- In persistent / recurrent cases, Moxifloxacin is no longer recommended as a 1st line therapy due to recent safety concerns from the UK Medicines and Healthcare products Regulatory Agency[84]. It is now placed as a 2nd line therapy (see main text)
- The 1st line treatment for persistent /recurrent NGU is

  Azithromycin 500mg stat, then 250mg daily for next 4 days, plus

  Metronidazole 400mg twice daily for 5 days

  OR

  Erythromycin 500mg four times daily for 3 weeks, plus

  Metronidazole 400mg twice daily for 5 days
- The two-glass urine test should be abandoned.

Introduction

Urethritis, or inflammation of the urethra, is a multifactorial condition which can be sexually acquired. It is characterised by discharge and/or dysuria but may be asymptomatic. The diagnosis of urethritis is confirmed by demonstrating an excess of polymorphonuclear leucocytes (PMNLs) in the anterior urethra. This is usually assessed using a urethral smear, but a first-pass urine specimen (FPU) can also be used. Urethritis is described as either gonococcal, when *Neisseria gonorrhoeae* is detected, or non-gonococcal (NGU) when it is not. The term non-specific urethritis (NSU) applies to non-gonococcal non-chlamydial NGU and to avoid confusion should be avoided. Mucopurulent cervicitis is the female equivalent with approximately 40% of cases being due to infection with *Chlamydia trachomatis.* [2]

There are a number of uncertainties with NGU. Urethral inflammation can occur without a known pathogen being isolated in the majority of patients even using more sensitive detection methods [3-6]. Conversely 8-37% of men infected with either *C. trachomatis* or *Mycoplasma genitalium* will have not have the diagnostic criteria on Gram stain of the urethral exudates. [5;7-10] Limiting tests to men with discharge or dysuria increases isolation of *C. trachomatis* or
M. genitalium to up to 50%.[5;11;12] In a further 3-20% an undiagnosed *C. trachomatis* or
M. genitalium is found in the partner if he/she is tested.[5;13-16] Finally inter-observer and intra-observer error, especially in samples with low grade inflammation (5-20 PMNL/hpf), make diagnostic consistency difficult. [17;18]

Aetiology

The prevalence of the common organisms associated with NGU is listed in table 1.

The commonest organisms implicated are *C. trachomatis* and *M. genitalium* with the latter perhaps causing more symptoms.[5;19] The isolation rates of common organisms in more recent studies using modern diagnostic tests is shown in table 2.

- Chlamydia is more likely to be isolated in younger patients than *M. genitalium*[20] and the two organisms rarely coexist in the same individual. [4]
- In 30-80% of the cases with NGU neither *C. trachomatis* nor *M. genitalium* is detected. [3-6;10;21-24]
- The isolation of *Trichomonas vaginalis* is dependent on the prevalence of the organism in the community, being more common in non-white ethnic groups, and greatly increased with the use of more sensitive polymerase chain reaction assays. [25]. *T. vaginalis* isolation is greater in men >30 years [26].
- The exact role of ureaplasmas in NGU has been controversial due to the conflicting observations in clinical studies. Ureaplasmas are ubiquitous micro-organisms which have recently been divided into two biovars: *U. urealyticum* biovar 2 may account for 5-10% of cases of acute NGU. [27]
- A urinary tract infection may account for 6.4% (95% CI 1.5% - 11.3%) of cases, although there is only one study evaluating this. [28]
- Adenoviruses may account for perhaps 2-4% of symptomatic patients and is often associated with a conjunctivitis. [24;29]
- Herpes simplex viruses types 1 and 2 are less commonly associated with NGU (2-3%)[24;30]

- *N. meningitidis*, *Haemophilus sp.*, *Candida sp*., urethral stricture and foreign bodies have been reported in a few cases and probably account for a small proportion of NGU[31].
- Asymptomatic urethritis, without an observable discharge, may have a different aetiology from symptomatic urethritis, with *C. trachomatis*[32-34] and *M. genitalium* being detected less frequently[22;35], and at lower quantities[36;37]. There is also a possible association of asymptomatic NGU with bacterial vaginosis. [38;39]

It is assumed that the aetiological agents of sexually acquired male NGU could potentially cause genital tract inflammation in women, in particular pelvic inflammatory disease (PID). This is undoubted with chlamydial and gonococcal infection and possible with *M. genitalium*[4;40-42]but remains to be substantiated for pathogen-negative NGU. Asymptomatic chlamydia-negative NGU was reported in male partners of women with PID, [43] but *M. genitalium* was not tested for in that study.

Clinical features*

SYMPTOMS

- Urethral discharge
- Dysuria
- Penile irritation
- Nil

SIGNS

- Urethral discharge. This may not have been noticed by the patient or may only be present on urethral massage.
- Normal examination

Examining the FPU for casts is of little additional value (IV)

COMPLICATIONS

- Epididymo-orchitis
- Sexually acquired reactive arthritis / Reiter's syndrome

These are infrequent, occurring in fewer than 1% of cases though incomplete forms may be more common.

Diagnosis

The diagnosis of urethritis must be confirmed by demonstrating PMNLs in the anterior urethra. This can be by means of:

(i) A Gram stained urethral smear containing >=5 PMNL per high-power (x1000) microscopic field (averaged over five fields with greatest concentration of PMNLs) [32] *and/or*

(ii) A Gram stained preparation from a centrifuged sample of a first passed urine (FPU) specimen, containing >=10 PMNL per high-power (x1000) microscopic field (averaged over five fields with greatest concentration of PMNLs).

- Either test can be used: both tests will identify cases missed by the other test [34]
- The quality of the smear is heavily dependent on how the smear is taken and there is both inter- and intra-observer variation. [17;18]
- Either a 5 mm plastic loop or cotton-tipped swab can be used and should be introduced about 1 cm into the urethra. There are no published data comparing the two but the former is probably less traumatic to the patient (IV).
- Positive leucocyte esterase activity on dipstick on FPU specimen correlates with NGU and the detection of chlamydia [21] and is considered diagnostic by some authorities. [44] However, it does not have adequate sensitivity to be considered a reliable rapid diagnostic test for acute

NGU[45;46]. Moreover its positive predictive value for *C trachomatis* in asymptomatic patients is poor.[21]

- There is controversy as to the need to perform microscopy in asymptomatic patients. [8;47] Treatment will be delayed in up to 30% of those infected with *C. trachomatis* who are asymptomatic[8;14;16;48]. Also a single nucleic acid amplification test (NAAT) may miss up to 3% of men with urethral chlamydia [49] and will miss 5-6% of asymptomatic men infected with *M. genitalium*. [7;8;13] It is however, unclear if microscopy would identify a substantial proportion of these patients, nor is *M. genitalium* currently proven to cause serious pathology (such as pelvic inflammatory disease). On the other hand, omitting microscopy in asymptomatic men will prevent diagnosing 77-87% of men as having a sexually transmitted infection in whom neither of the above organisms will be isolated[10;13]. Indeed, relying on microscopy alone will miss up to 37% of *C. trachomatis* and up to 23% *of M. genitalium* urethral infections. [6;10;20;22] There is, therefore, little justification in performing urethral microscopy in asymptomatic men (IIb). It does of course remain an important test in symptomatic men for the diagnosis of gonococcal urethritis.
- While a leucocyte esterase test (1+ = positive) has variable sensitivity in diagnosing urethritis it has a high negative predictive value (>96-8%), similar to that of a urethral smear, in asymptomatic men for the detection of *N. gonorrhoeae* and *C. trachomatis* and thus probably *M. genitalium*. [21;45] However its positive predictive value for chlamydia in asymptomatic men is low (5.1-23.3%). [21] It therefore has little place in routine practice though its good negative predictive value may be useful in population screening for *C. trachomatis*. [21]
- Physical examination of asymptomatic men does not result in an increased diagnosis of urethral pathogens [5]

- The sensitivity of the smear test, but probably not the FPU[50] is affected by the period since last passing urine. The optimum time to ensure a definite diagnosis in a symptomatic man is not known. 2-4 hours is conventional.
- Symptomatic patients, in whom no discharge or urethritis is detected, could either be retested having held their urine overnight, (IV) or given empirical treatment (IV). With the latter choice empirical treatment to the partner(s) would be indicated.

Investigations

- All patients attending should have a test for *N. gonorrhoeae*. If a NAAT is used for

N. gonorrhoeae a positive test should be confirmed by culture. [see BASHH gonorrhoea guidelines].

- *C. trachomatis* should also be sought (see BASHH guideline on chlamydia). It should be noted that even a NAAT will miss between 3%[49] and 10% of infections [51-53].
- Commercial testing for *M. genitalium* is not available and the place of such tests in routine clinical practice, once they become available, needs to be determined.
- An MSU should be taken if a urinary tract infection is suspected. Such as, for example, if the patient complains of severe dysuria, haematuria (microscopic or macroscopic), nocturia, urinary frequency, urgency, or has not been sexually exposed. In one study using a dipstick incorporating nitrite and leucocyte esterase tests had a sensitivity and specificity for urinary tract infection of 83 and 90% respectively. [28]
- The traditional two-glass test adds little to the diagnosis and should be abandoned [IV].

Management

GENERAL ADVICE

The following should be discussed and clear written information provided:

- An explanation of the causes of NGU, including non-infective causes, and possible short term and long term implications for the health of the patient and his partner.
- The side-effects of treatment and the importance of complying fully with it.
- The importance of their sex partner(s) being evaluated and treated
- Advice to abstain from sexual intercourse, or if that is not acceptable, the consistent use of condoms, until he has completed therapy and his partner(s) have been treated. [IV]
- Advice on safer sex
- The importance of complying with any follow-up arrangements made.

Treatment

Treatment should be initiated as soon as the diagnosis is made and without waiting for the results of tests for chlamydia and cultures for *N. gonorrhoeae*. Ideally, treatment should be effective (microbiological cure rate for *C. trachomatis* >95%), easy to take (not more than twice daily), with a low side-effect profile, and cause minimal interference with daily lifestyle**.** However assessing treatment efficacy is problematic, as no pathogen is identifiable in over 60% of cases, and the inflammatory process may not reflect persistent infection [31] It is important to note that the inflammatory exudate may persist for an unknown length of time even when the putative organism has been eliminated. [54]

Tetracyclines are generally effective against *C. trachomatis* though sporadic reports of treatment failure have been reported. [55]While in

general treatments that are effective against *C. trachomatis* appear to be also effective in NGU, tetracyclines in the doses used do not consistently eradicate *M. genitalium*[56-58] and this may also be the case with azithromycin 1g stat [57;58] (see below).

RECOMMENDED REGIMENS (GRADE OF RECOMMENDATION A)

- Azithromycin 1g orally in a single dose (Ib)

  or

- Doxycycline 100 mg twice a day orally for 7 days (Ib)

ALTERNATIVE REGIMENS (A)

- Erythromycin 500mg twice daily for 14 days (Ib)

  or

- Ofloxacin 200mg twice a day or 400mg once a day for 7 days (Ib)

COMPLIANCE WITH THERAPY

Single dose therapy has the advantage of improved compliance although azithromycin has not been shown to be more effective in clinical studies than doxycycline.

Sexual contacts/partners

All sexual partners at risk should be assessed and offered epidemiological treatment, maintaining patient confidentiality. The duration of "look back" is arbitrary; 4 weeks is suggested for symptomatic men (IIb).

- If *C. trachomatis* or *N. gonorrhoeae* are detected it is important to ensure that all sexual partner(s) potentially at risk have been notified (see relevant guidelines).
- Details of all contacts should be obtained at the first visit. Consent should also be obtained so that if *C. trachomatis* or *N. gonorrhoeae* are detected subsequently and the index patient does not reattend, he can be contacted and/or provider referral can be initiated for sexual contacts (IV).
- Female contacts of men with chlamydial urethritis should be treated regardless of the results of tests for chlamydia (Ib).

There is no direct evidence of treatment benefit to partners of men with chlamydia-negative NGU. There are, however, a number of issues which may influence decision making.

a. NGU cohort studies have looked at the effect on response of urethritis and have produced conflicting conclusions. [59]

b. There are reports of patients with persistent or recurrent urethritis being cured only after their sexual partner received appropriate treatment. [60]

c. Even newer NAATs may miss 3-10% of chlamydia-positive individuals.

d. There is also discordance in the isolation of chlamydia between partners.[16;61]

e. *C. trachomatis* can clear without treatment from the cervices of women[62;63], though much less frequently from the urethras of men. [64]

f. Finally, [65-67]*M. genitalium* accounts for approximately 20% of cases and probably causes disease in women. [4;42]

In the absence of randomised prospective studies it would be prudent to treat partners of microorganism-negative NGU concurrently to potentially reduce female morbidity (IV).

Follow-up for patients with NGU

Follow up is important in order to assess compliance with therapy – particularly in
chlamydia-positive patients. The follow up interview can be performed by phone. Patients who remain symptomatic, who have not completed their medication or who have had unprotected sexual intercourse with an untreated partner should be asked to return to the clinic and re-treated with appropriate contact tracing. (IV)

Persistent/recurrent NGU

This is empirically defined as persistent or recurrent symptomatic urethritis occurring 30-90 days following treatment of acute NGU [68] and occurs in 10-20% of patients. [68-71]There is no consensus of opinion for either the diagnosis or the management of this condition. Its aetiology is probably multifactorial. [31;59;68] *M. genitalium* may be implicated in 20-40% [58;68]. Tetracyclines, two weeks of erythromycin or a single dose of azithromycin do not reliably eradicate this organism[56;58]. In a randomised study of 398 men azithromycin 1g resulted in failure in 16% and doxycycline 100mgs bd for seven days in 64% of those who returned for follow-up.[57] In an open Scandinavian study azithromycin 500 mgs stat followed by 250 mg daily for the next 4 days cured all of 19 patients [58]. A role for *U. urealyticum* in chronic NGU has also been suggested. [72]. Although this organism may also exhibit tetracycline resistance the therapeutic implications remain unclear. Any treatment of chronic NGU should cover *M. genitalium* [73] and *T. vaginalis* which are not covered by standard therapy (IV).

The only randomised controlled trial for chronic NGU showed that erythromycin for three weeks is better than placebo[74] but did not test for *M. genitalium,* nor include partners.

As there is no evidence that female partners of men with persistent/recurrent NGU are at increased risk of pelvic inflammatory disease, they do not need to be retreated if treated appropriately at first. However, in view of the emerging evidence that both doxycycline and azithromycin can fail to eradicate *M. genitalium* in men, it is likely that this is also the case in women and this is therefore an area where further research is needed.

DIAGNOSIS OF PERSISTENT/RECURRENT NGU

- Avoiding routine test of cure in NGU will avoid creating a "patient" in an otherwise asymptomatic individual.

MANAGEMENT OF PERSISTENT/RECURRENT NGU

- Ensure that the patient has completed the initial course of therapy and that reinfection is not a possible cause.
- Only treat if patient has definite symptoms of urethritis, or physical signs on examination. Reassure asymptomatic patients that no further test or treatment is necessary.

RECOMMENDED REGIMENS - (C)

Patient symptomatic or an observable discharge present[56;68;74-76]

- **1st line**

  Azithromycin 500mg stat then 250mg for the next 4 days (IIIb)

  plus Metronidazole 400 mg twice daily for 5 days (IV)

OR

Erythromycin 500 mg four times daily for 3 weeks [74](Ib)

plus Metronidazole 400mg twice daily for 5 days (IV)

- **2nd line**

  Moxifloxacin 400mg orally once daily for 10 days (IIIb)[77]

  plus Metronidazole 400mg twice daily for 5 days (IV)

NB: In persistent / recurrent cases, Moxifloxacin is no longer recommended as a 1st line therapy due to recent safety concerns (an increased risk of life threatening liver reactions and other serious risks) from the UK Medicines and Healthcare products Regulatory Agency[84]. It is now placed as a 2nd line therapy.

CONTINUING SYMPTOMS

There is only limited evidence on how best to manage patients who either remain symptomatic following a second course of treatment or who have frequent recurrences after treatment.

- Urological investigation is usually normal unless the patient has urinary flow problems[75] and is not recommended.
- Chronic abacterial prostatitis (see guideline on prostatitis) and psychosexual causes

should be considered in the differential diagnosis. [74-76]

- For men with persistent or recurrent urethritis, there is currently no evidence that retreatment of an appropriately treated sexual partner is beneficial (see above).

Auditable outcome measures

- Symptomatic men should be offered microscopy of a Gram-stained urethral smear or first void urine (100%).
- Men with NGU should be offered treatment with a recommended antibiotic regimen (100%).

Acknowledgements

We wish to thank the following for their valuable contributions to this guideline: Anona Blackwell; Patrick Horner; Colm O'Mahony; Keith Radcliffe.

Author and centre

Dr Mohsen Shahmanesh, Department of Genitourinary Medicine, Whittall Street Clinic, Birmingham UK.

Membership of the CEG

Clinical Effectiveness Group: Keith Radcliffe (Chairman); Imtyaz Ahmed-Jushuf ; David Daniels ; Mark FitzGerald ; Neil Lazaro; Gillian McCarthy; Guy Rooney.

Conflict of interests

None.

Rigor of development

MEDLINE searches for 1970 to present using MeSH headings "urethritis" including all documents and subheadings. Additional searches were conducted using MeSH headings "Non-gonococcal urethritis", "nongonococcal urethritis", " non-specific urethritis", "NGU", "NSU", "Chlamydia trachomatis" "Mycoplasma genitalium".
The Cochrane library for 1970 to the present using keywords "Non-gonococcal urethritis", "nongonococcal urethritis", "non-specific urethritis", "NGU", "NSU". Hand search conference proceedings – BASHH (MSSVD), ISSTDR

This document is an update of the original article :

Horner PJ, Shahmanesh M. National guideline for the management of non-gonococcal urethritis. *Sex Transm Inf* 1999;75 (Supp 1):S9-S12. Updated 2002, http://www.bashh.org/guidelines/2002/ngu_0901c.pdf

Table 1. Prevalence of the most common pathogens isolated from patients with NGU

Micro-organism	**Prevalence**	**Reference**
C. trachomatis	11-43%	[5;6;10;13;16;21;22;24;34;78]
M. genitalium	9-25%	[3-5;13;19;20;22;24;34;34;34;79;80]
Adenoviruses	2-4%	[24;29}]
T. vaginalis	1- 20%	[25;78;81-83]
Herpes simplex virus	2-3%	[24;30]

Table 2. Individual isolation rates (percent) of more common organisms in recent studies.

Study	*Nature*	*CT*	*Mg*	*TV*	*Other*	*No pathogen*
Bradshaw 2006[24]	Only symptomatic	20	9	1	7	63
Falk 2004[5]	>10 PMN/hpf	22.5	12.5			65
Angarius 2005[13]		7.4	8.3			84.3
Giesler 2005[10]		27	Not done			73
Marazzo 2000[2]		17	Not done			83
Leung 2006[19]	Urethritis	20.9	10.9			65

Reference List

(1) The national strategy for sexual health. 2001. Department of Health (UK).
Ref Type: Pamphlet

(2) Marrazzo JM. Mucopurulent cervicitis: no longer ignored, but still misunderstood. [Review] [99 refs]. Infectious Disease Clinics of North America 2005; 19(2):333-349.

(3) Deguchi T, Maeda S. Mycoplasma genitalium: another important pathogen of nongonococcal urethritis. [Review] [100 refs]. Journal of Urology 2002; 167(3):1210-1217.

(4) Jensen JS. *Mycoplasma genitalium*: the aetiological agent of urethritis and other sexually transmitted diseases. Journal of the European Academy of Dermatology & Venereology 2004; *18*:1-11.

(5) Falk L, Fredlund H, Jensen JS. Symptomatic urethritis is more prevalent in men infected with Mycoplasma genitalium than with Chlamydia trachomatis. Sex Transm Infect 2004; 80(4):289-293.

(6) Haddow LJ, Bunn A, Copas AJ, Gilson R, Prince M, Ridgway GL et al. Polymorph count for predicting non-gonococcal urethral infection: a model using Chlamydia trachomatis diagnosed by ligase chain reaction. Sex Transm Infect 2004; 80(3):198-200.

(7) Foo C, Browne R, Boag F. Retrospective review of the correlation of symptoms, signs and microscopy with the diagnosis of Chlamydia trachomatis in men. International Journal of STD & AIDS 2004; 15(5):319-321.

(8) Horner PJ. Should we still be testing for asymptomatic non-specific urethritis in departments of genitourinary medicine? International Journal of STD & AIDS 2005; 16:273-277.

(9) *Mycoplasma genitalium* is associated with urethritis, in particular those with a urethral discharge. 2002.

(10) Geisler WM, Yu S, Hook EW, III. Chlamydial and gonococcal infection in men without polymorphonuclear leukocytes on Gram

stain: implications for diagnostic approach and management. Sexually Transmitted Diseases 2005; 32(10):630-634.

(11) Horner P, Gilroy C, Thomas B, Naidoo R, Olof M, Taylor-Robinson D. Association of *Mycoplasma genitalium* with acute non-gonococcal urethritis. Lancet 342, 582-585. 1993.
Ref Type: Generic

(12) Bradshaw CS, Morton AN, Hocking J, Garland SM, Morris MB, Moss LM et al. High recurrence rates of bacterial vaginosis over the course of 12 months after oral metronidazole therapy and factors associated with recurrence.[see comment]. Journal of Infectious Diseases 2006; 193(11):1478-1486.

(13) Anagrius C, Lore B, Jensen JS. Mycoplasma genitalium: prevalence, clinical significance, and transmission. Sex Transm Infect 2005; 81(6):458-462.

(14) Manavi K, McMillan A, Young H, Manavi K, McMillan A, Young H. Genital infection in male partners of women with chlamydial infection. International Journal of STD & AIDS 2006; 17(1):34-36.

(15) McCathie R, Carlin E. Does partner notification of men with asymptomatic non-gonococcal urethritis identify chlamydia positive women? International Journal of STD & AIDS 2006; 18(9):606-609.

(16) Tait IA, Hart CA. Chlamydia trachomatis in non-gonococcal urethritis patients and their heterosexual partners: routine testing by polymerase chain reaction. Sex Transm Infect 2002; 78(4):286-288.

(17) Wilcox JR, Adler MW, Belsey EM. Observer variation in the interpretation of Gram stained urethral smear. British Journal of Venereal Diseases 1981; 57:134-136.

(18) Smith R, Copas AJ, Prince M, George B, Walker AS, Sadiq ST. Poor sensitivity and consistency of microscopy in the diagnosis of low grade non-gonococcal urethritis. Sex Transm Infect 2003; 79(6):487-490.

(19) Leung A, Eastick K, Haddon L, Horne K, Aduja D, Horner PJ. *Mycolpasma genatalium* is associated with symptomatic urethritis. International Journal of STD & AIDS 2005; 17(5):285-288.

(20) Jensen JS, Bjornelius E, Dohn B, Lidbrink P. Comparison of first void urine and urogenital swab specimens for detection of Mycoplasma genitalium and Chlamydia trachomatis by polymerase chain reaction in patients attending a sexually transmitted disease clinic. Sexually Transmitted Diseases 2004; 31(8):499-507.

(21) Marrazzo JM, Whittington WL, Celum CL, Handsfield HH, Clark A, Cles L et al. Urine-based screening for Chlamydia trachomatis in men attending sexually transmitted disease clinics.[erratum appears in Sex Transm Dis 2001 Jul;28(7):429]. Sexually Transmitted Diseases 2001; 28(4):219-225.

(22) Mena L, Wang X, Mroczkowski TF, Martin DH. Mycoplasma genitalium infections in asymptomatic men and men with urethritis attending a sexually transmitted diseases clinic in New Orleans. Clinical Infectious Diseases 2002; 35(10):1167-1173.

(23) Horner PJ, Thomas B, Gilroy CB, Egger M, Taylor-Robinson D. Do all men attending departments of genitourinary medicine need to be screened for non-gonococcal urethritis?[see comment]. International Journal of STD & AIDS 2002; 13(10):667-673.

(24) Bradshaw CS, Tabrizi SN, Read TR, Garland SM, Hopkins CA, Moss LM et al. Etiologies of nongonococcal urethritis: bacteria, viruses, and the association with orogenital exposure.[see comment]. Journal of Infectious Diseases 2006; 193(3):336-345.

(25) Schwebke JR, Lawing LF. Improved detection by DNA amplification of Trichomonas vaginalis in males. Journal of Clinical Microbiology 2002; 40(10):3681-3683.

(26) Joyner JL, Douglas JM, Jr., Ragsdale S, Foster M, Judson FN. Comparative prevalence of infection with Trichomonas vaginalis among men attending a sexually transmitted diseases clinic.[see comment]. Sexually Transmitted Diseases 2000; 27(4):236-240.

(27) Povlsen K, Bjornelius E, Lidbrink P, Lind I. Relationship of Ureaplasma urealyticum biovar 2 to nongonococcal urethritis. European Journal of Clinical Microbiology & Infectious Diseases 2002; 21(2):97-101.

(28) Leung A, Horner P. Urinary tract infection in patients with acute non-gonococcal urethritis. International Journal of STD & AIDS 2003; 13(12):801-804.

(29) Tabrizi SN, Ling AE, Bradshaw CS, Fairley CK, Garland SM, Tabrizi SN et al. Human adenoviruses types associated with non-gonococcal urethritis. Sexual Health 2007; 4(1):41-44.

(30) Srugo I, Steinberg J, Madeb R, Gershtein R, Elias I, Tal J et al. Agents of non-gonococcal urethritis in males attending an Israeli clinic for sexually transmitted diseases.[see comment]. Israel Medical Association Journal: Imaj 2003; 5(1):24-27.

(31) Shahmanesh M. Problems with non-gonococcal urethritis. International Journal of STD and AIDS 1994; 5:390-399.

(32) Swartz SL, Kraus SJ, Herrmann KL, Stargel MD, Brown WJ, Allen SD. Diagnosis and etiology of nongonococcal urethritis. Journal of Infectious Diseases 1978; 138(4):445-454.

(33) Rietmeijer CA, Judson FN, Van Hensbroek MB, Ehret JM, Douglas JM, Jr. Unsuspected Chlamydia trachomatis infection in heterosexual men attending a sexually transmitted diseases clinic: evaluation of risk factors and screening methods. Sexually Transmitted Diseases 1991; 18(1):28-35.

(34) Janier M, Lassau F, Casin I, Grillot P, Scieux C, Zvaro A et al. Male urethritis with and without discharge: a clinical and microbiological study. Sexually Transmitted Diseases 1995; 22:244-252.

(35) Iser P, Read TH, Tabrizi S, Bradshaw C, Lee D, Horvarth L et al. Symptoms of non-gonococcal urethritis in heterosexual men: a case control study. Sex Transm Infect 2005; 81(2):163-165.

(36) Dupin N, Bijaoui G, Schwarzinger M, Ernault P, Gerhardt P, Jdid R et al. Detection and quantification of Mycoplasma genitalium in male patients with urethritis. Clinical Infectious Diseases 2003; 37(4):602-605.

(37) Jensen JS, Bjornelius E, Dohn B, Lidbrink P. Use of TaqMan 5' nuclease real-time PCR for quantitative detection of Mycoplasma genitalium DNA in males with and without urethritis who were attendees at a sexually transmitted disease clinic. Journal of Clinical Microbiology 2004; 42(2):683-692.

(38) Keane FEA, Thomas B, Whitaker L, Renton A, Taylor-Robinson D. An association between non-gonococcal urethritis and bacterial

vaginosis and the implications for patients and their sexual partners. Genitourinary Medicine 1997; 73:373-377.

(39) Arumainayagam JT, De Silva Y, Shahmanesh M. Anaerobic vaginosis: study of male sexual partners. International Journal of STD & AIDS 1991; 2(2):102-104.

(40) Simms I, Eastick K, Mallinson H, Thomas K, Gokhale R, Hay P et al. Associations between Mycoplasma genitalium, Chlamydia trachomatis and pelvic inflammatory disease. Journal of Clinical Pathology 2003; 56(8):616-618.

(41) Ross J. Pelvic Inflammatory Disease: how should it be managed. Current Opinion in Infectious Diseases 2003; 14:37-41.

(42) Ross JDC, Jensen JS. Mycoplasma genitalium as a sexually transmitted infection: implications for screening, testing, and treatment. Sex Transm Infect 2006; 82(4):269-271.

(43) Kamwendo F, Johansson E, Moi H, Forslin L, Danielsson D. Gonorrhea, genital chlamydial infection, and nonspecific urethritis in male partners of women hospitalized and treated for acute pelvic inflammatory disease. Sexually Transmitted Diseases 1993; 20:143-146.

(44) Centers for Disease Control and Prevention. 1998 guidelines for the treatment of sexually transmitted diseases. MMWR 1998; 47(1):11.

(45) Patrick DM, Rekart ML, Knowles L. Unsatisfactory performance of the leukocyte esterase test of first voided urine for rapid diagnosis of urethritis. Genitourinary Medicine 1994; 70(3):187-190.

(46) Fraser PA, Teasdale J, Gan KS, Eglin R, Scott SC, Lacey CJ. Neutrophil enzymes in urine for the detection of urethral infection in men. Genitourinary Medicine 1995; 71(3):176-179.

(47) O'Mahony C. View from the frontline. International Journal of STD & AIDS 2004; 15(7):498.

(48) Marcos AR. The incidence of sexually related conditions in asymptomatic vesus symptomatic patients. International Journal of STD & AIDS 2007; 18:610-612.

(49) Chernesky MA, Martin DH, Hook EW, Willis D, Jordan J, Wang S et al. Ability of new APTIMA CT and APTIMA GC assays to detect Chlamydia trachomatis and Neisseria gonorrhoeae in male urine and

urethral swabs. Journal of Clinical Microbiology 2005; 43(1):127-131.

(50) Chernesky M, Jang D, Chong S, Sellors J, Mahony J. Impact of urine collection order on the ability of assays to identify Chlamydia trachomatis infections in men. Sexually Transmitted Diseases 2003; 30(4):345-347.

(51) Sugunendran H, Birley HD, Mallinson H, Abbott M, Tong CY. Comparison of urine, first and second endourethral swabs for PCR based detection of genital Chlamydia trachomatis infection in male patients. Sex Transm Infect 2001; 77(6):423-426.

(52) Johnson RE, Green TA, Schachter J, Jones RB, Hook EW, III, Black CM et al. Evaluation of nucleic acid amplification tests as reference tests for Chlamydia trachomatis infections in asymptomatic men. Journal of Clinical Microbiology 2000; 38(12):4382-4386.

(53) Van Der PB, Ferrero DV, Buck-Barrington L, Hook E, III, Lenderman C, Quinn T et al. Multicenter evaluation of the BDProbeTec ET System for detection of Chlamydia trachomatis and Neisseria gonorrhoeae in urine specimens, female endocervical swabs, and male urethral swabs. Journal of Clinical Microbiology 2001; 39(3):1008-1016.

(54) Lomas DA, Natin D, Stockley RA, Shahmanesh M. Chemotactic activity of urethral secretions in men with urethritis and the effect of treatment. Journal of Infectious Diseases 1993; 167(1):233-236.

(55) Wang SA, Papp JR, Stamm WE, Peeling RW, Martin DH, Holmes KK. Evaluation of antimicrobial resistance and treatment failure for Chlamydia trachomatis: A meeting report. Journal of Infecticious Diseases 2005; 191:917-923.

(56) Falk L, Fredlund H, Jensen JS. Tetracycline treatment does not eradicate Mycoplasma genitalium. Sex Transm Infect 2003; 79(4):318-319.

(57) Mroczkowsky TF, Mena L, Nsuami M, Martin DH. A randomized comparison of azithromycin and doxycycline for the treatment of *Mycoplasma genitalium* (MG) positive urethritis. 16th Biennial Meeting of the International Society of Sexually Transmitted Disease (ISSTDR), Amsterdam, The Netherlands 2005;304-305.

(58) Wikstrom A, Jensen JS. Mycoplasma genitalium: a common cause of persistent urethritis among men treated with doxycycline. Sex Transm Infect 2006; 82(4):276-279.

(59) Bowie WR, Alexander ER, Stimson JB, Floyd JF, Holmes KK. Therapy for nongonococcal urethritis: double-blind randomized comparison of two doses and two durations of minocycline. Annals of Internal Medicine 1981; 95(3):306-311.

(60) Ford DK, Henderson E. Non-gonococcal urethritis due to T-mycoplasma (Ureaplasma urealyticum) serotype 2 in a conjugal sexual partnership. British Journal of Venereal Diseases 1976; 52(5):341-342.

(61) Clad A, Prillwitz J, Hintz KC, Mendel R, Flecken U, Schulte-Monting J et al. Discordant prevalence of chlamydia trachomatis in asymptomatic couples screened using urine ligase chain reaction. European Journal of Clinical Microbiology & Infectious Diseases 2001; 20(5):324-328.

(62) Morre SA, van den Brule AJ, Rozendaal L, Boeke AJ, Voorhorst FJ, de Blok S et al. The natural course of asymptomatic Chlamydia trachomatis infections: 45% clearance and no development of clinical PID after one-year follow-up. International Journal of STD & AIDS 2002; 13 Suppl 2:12-18.

(63) Molano M, Meijer CJLM, Weiderpass E, Arslan A, Posso H, Franceschi S et al. The natural cpurse of Chlamydia trachomatis infection in asymptomatic columbian women: a 5-year follow-up study. Journal of Infecticious Diseases 2005; 191:907-916.

(64) van den Brule AJ, Munk C, Winther JF, Kjaer SK, Jorgensen HO, Meijer CJ et al. Prevalence and persistence of asymptomatic Chlamydia trachomatis infections in urine specimens from Danish male military recruits. International Journal of STD & AIDS 2002; 13 Suppl 2:19-22.

(65) Lin JS, Donegan SP, Heeren TC, Greenberg M, Flaherty EE, Haivanis R et al. Transmission of Chlamydia trachomatis and Neisseria gonorrhoeae among men with urethritis and their female sex partners. Journal of Infectious Diseases 1998; 178(6):1707-1712.

(66) Quinn TC, Gaydos C, Shepherd M, Bobo L, Hook EW, III, Viscidi R et al. Epidemiologic and microbiologic correlates of Chlamydia

trachomatis infection in sexual partnerships. JAMA 1996; 276(21):1737-1742.

(67) Singh G, Blackwell A. Morbidity in male partners of women who have chlamydial infection before termination of pregnancy. Lancet 1994; 344(8934):1438.

(68) Horner P, Thomas B, Gilroy C, Egger M, Taylor-Robinson D. The role of *Mycoplasma genitalium* and U*reaplasma urealyticum* in acute and chronic non-gonococcal urethritis. Journal of Infectious Diseases 2000.

(69) Horner PJ, Cain D, McClure M, Thomas BJ, Gilroy C, Ali M et al. Association of antibodies to Chlamydia trachomatis heat-shock protein 60 kD with chronic nongonococcal urethritis. Clinical Infectious Diseases 1997; 24(4):653-660.

(70) Munday PE. Persistent and recurrent non-gonococcal urethritis. In: Taylor-Robinson D, editor. Clinical problems in sexually transmited diseses. Dordrecht: Martinun Nijhoff; 1985. 15-34.

(71) Hay PE, Thomas B, Gilchrist C, Palmer HM, Gilroy C, Taylor-Robinson D. A reappraisal of chlamydial and non-chlamydial urethritis. International Journal of STD and AIDS 3, 191-195. 1992. Ref Type: Generic

(72) Horner P, Thomas B, Gilroy CB, Egger M, Taylor-Robinson D. Role of Mycoplasma genitalium and Ureaplasma urealyticum in acute and chronic nongonococcal urethritis. Clinical Infectious Diseases 2001; 32(7):995-1003.

(73) Taylor-Robinson D, Gilroy CB, Thomas BJ, Hay PE. Mycoplasma genitalium in chronic non-gonococcal urethritis. International Journal of STD & AIDS 2004; 15(1):21-25.

(74) Hooton T, Wong ES, Barnes RC, Roberts PL, Stamm W. Erythromycin for persistent or recurrent non-gonococcal urethritis: a randomized, placebo-controlled trial. Annals of Internal Medicine 1990; 113(1):21-26.

(75) Krieger JN, Hooton TM, Brust PJ, Holmes KK, Stamm WE. Evaluation of chronic urethritis. Defining the role for endoscopic procedures. Archives of Internal Medicine 1988; 148(3):703-707.

(76) Wong ES, Hooton TM, Hill CC, McKevitt M, Stamm WE. Clinical and microbiological features of persistent or recurrent nongonococcal urethritis in men. Journal of Infectious Diseases 1988; 158(5):1098-1101.

(77) Bradshaw CS, Jensen JS, Tabrizi SN, Read TR, Garland SM, Hopkins CA et al. Azithromycin failure in Mycoplasma genitalium urethritis. Emerging Infectious Diseases 2006; 12(7):1149-1152.

(78) Wendel KA, Erbelding EJ, Gaydos CA, Rompalo AM. Use of urine polymerase chain reaction to define the prevalence and clinical presentation of Trichomonas vaginalis in men attending an STD clinic. Sex Transm Infect 2003; 79(2):151-153.

(79) Taylor-Robinson D, Jensen JS, Fehler G, Radebe F, Ballard RC. Observations on the microbiology of urethritis in black South African men. International Journal of STD & AIDS 2002; 13(5):323-325.

(80) Taylor-Robinson D. Mycoplasma genitalium -- an up-date. [Review] [66 refs]. International Journal of STD & AIDS 2002; 13(3):145-151.

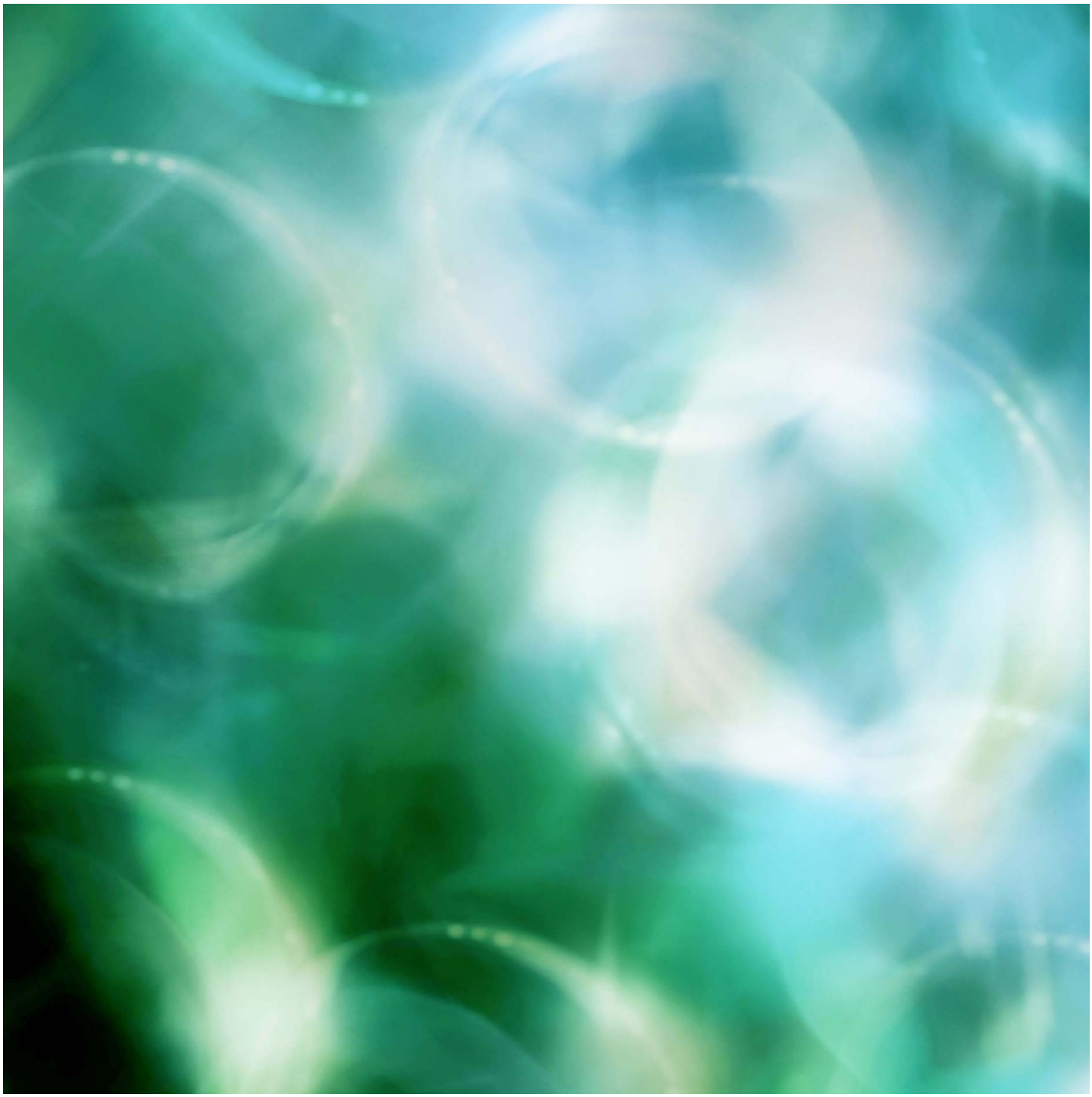
(81) KriegerJ.N.M. Consider Diagnosis and Treatment of Trichomoniasis in Men.[Editorial]. Sexually Transmitted Diseases 2000; 27(4):241-242.

(82) Price MA, Zimba D, Hoffman IF, Kaydos-Daniels SC, Miller WC, Martinson F et al. Addition of treatment for trichomoniasis to syndromic management of urethritis in Malawi: a randomized clinical trial. Sexually Transmitted Diseases 2003; 30(6):516-522.

(83) Schwebke JR, Hook EW, III. High rates of Trichomonas vaginalis among men attending a sexually transmitted diseases clinic: implications for screening and urethritis management. Journal of Infectious Diseases 2003; 188(3):465-468.

(84) Medicines and Healthcare products Regulatory Agency: Drug Safety Update Vol 2 , Issue 1. August 2008 http://www.mhra.gov.uk/Publications/Safetyguidance/DrugSafetyUpdate/CON023078

Guidance for gonorrhoea testing in England and Wales



Expert group

	Representing	Affiliation
Sarah Alexander	Health Protection Agency	Sexually Transmitted Bacteria Reference Laboratory, Centre for Infections
Chris Bignell	British Association of Sexual Health & HIV (BASHH)	Nottingham University Hospitals, NHS Trust
Fiona Boag	British Association of Sexual Health & HIV	Chelsea & Westminster Hospital
Jan Clarke	National Chlamydia Screening Advisory Group	Dept GU Medicine, Leeds General Infirmary
Mark Fitzgerald	Clinical Effectiveness Group, BASHH	Dept GU Medicine, Musgrove Park Hospital, Somerset
Gwenda Hughes	Health Protection Agency	STI Surveillance, Centre for Infections
Catherine Ison (Chair)	Health Protection Agency	STBRL, Centre for Infections
Kay Orton	Department of Health	Department of Health
Sue Skidmore	National Chlamydia Screening Programme	Shrewsbury and Telford NHS Hospital Trust
Shylaja Thomas	Health Protection Agency	Public Health Specialist Registrar. Eastern Region Public Health Training Programme

Introduction

The isolation of the causative organism, *Neisseria gonorrhoeae*, has been the 'gold standard' for the diagnosis of gonorrhoea for many years and can have a high sensitivity and specificity, but the organism is intolerant of problems with transportation or isolation methods resulting in a reduced sensitivity. In recent years, a number of factors have driven a change towards molecular detection using nucleic acid amplification tests (NAATs), including:

- A greater tolerance of NAATs to inadequacies in specimen collection or storage, compared to culture.
- Increasing pressure on genitourinary medicine (GUM) clinics to reduce waiting times and so increase throughput of patients.
- Desire to screen for sexually transmitted infections in non-GUM settings, particularly in young people under 25 years, as part of the National Chlamydia Screening Programme roll-out.
- Dual detection of *N. gonorrhoeae* and *Chlamydia trachomatis*.
- High sensitivity and specificity of NAATs and faster turnaround times for results, compared to culture.
- Use of non-invasive specimens with NAATs, which facilitates screening in both GUM and non-GUM settings.

However, there has been confusion over the correct algorithm for incorporating molecular testing in different settings and this document has been produced by an expert group to provide evidence-based guidance. It is also supported by a paired laboratory standard method which gives technical advice (1).

The document provides:

- **Key points**, giving relevant background information.
- **Recommendations** for testing for gonorrhoea.
- **Rationale** for the recommendations.
- **References.**

Key points

1. **Both identification of individuals with gonorrhoea, and testing to establish infection status, are important components of good sexual health.**

2. **Identifying cases of gonorrhoea, administering effective antibiotic treatment and notifying partners will interrupt transmission and prevent spread of antimicrobial resistance.**

3. **The prevalence of gonorrhoea is very low in the general population, but significantly higher in certain defined subpopulations.**

4. **Sequelae (such as upper genital tract infection) caused by *N. gonorrhoeae* are uncommon, but serious. Gonorrhoea is known to facilitate the transmission of HIV.**

5. **All current NAAT platforms will detect *Neisseria gonorrhoeae,* in addition to *Chlamydia trachomatis,* and will be used by many laboratories. Attention must be given to their correct use and their limitations. No test is 100% sensitive or specific and patient consent is required when using them in opportunistic screening settings.**

6. **Rectal and pharyngeal specimens contain higher levels (than genital sites) of closely related *Neisseria* sp, which have the capacity to cause false positive results when NAAT platforms are used.**

Recommendations

1. **There is no evidence base to support widespread unselected testing for gonorrhoea in the community.**

2. **Laboratories undertaking dual testing should be CPA-accredited and provide timely turnaround of results to the clinician.**

3. **Laboratories must ensure that they use recommended algorithms when testing for gonorrhoea.**

4. **The prevalence of gonorrhoea in most areas is low. Therefore, the testing algorithm should give a positive predictive value of >90%. This will usually require a supplementary test with a different nucleic acid target.**

5. **Dual NAATs can be used with a range of genital samples taken invasively and non-invasively. Urine from women is not the optimal sample for detection of *N. gonorrhoeae*.**

6. **NAATs have a superior sensitivity to culture for the detection of *N. gonorrhoeae* in extra-genital specimens. All GC-positive NAATs from extra-genital specimens must be confirmed by a supplementary test with a different target. Care should be taken to use a NAAT which exhibits little cross-reactivity, to reduce misdiagnosis.**

7. **Care must be taken in both clinic and laboratory settings to avoid contamination with extraneous DNA or rRNA, which could cause false positive results.**

8. **Care pathways must be in place to ensure prompt and effective treatment of gonorrhoea and contact tracing in all settings. In non-GUM settings, referral into specialist STI clinics is recommended for appropriate treatment and partner notification, and to complete a full STI screen, including HIV testing.**

9. **Culture is necessary in patients with signs and symptoms compatible with gonorrhoea and/or with a confirmed NAAT result, so that susceptibility testing can be performed and resistant strains identified.**

Rationale

Gonorrhoea is primarily an uncomplicated infection of the lower genital tract and is believed to be symptomatic in most men (90-95%) and asymptomatic in approximately 50% of women. If gonorrhoea goes undetected, or is inadequately treated, it can lead to complicated infection of the upper genital tract. This presents as prostatitis or epididymitis in men and salpingitis or pelvic inflammatory disease in women and is more common in women than men, due to the asymptomatic nature of the primary infection. Complicated gonococcal infection is uncommon in the UK. The total number reported in 2008 was 348 cases, of which 248 were from women, compared with 3,834 cases of complicated chlamydial infection, of which 2,828 were from women (2). It is possible that this is under-reported, as many of these infections will present to emergency departments, rather than sexual health clinics.

Complicated gonococcal and chlamydial infections both have the serious sequelae of infertility and ectopic pregnancy. Gonorrhoea is known to facilitate the acquisition and transmission of HIV. As gonorrhoea prevalence is high in men who have sex with men (MSM), who are also at high risk of acquiring HIV, early detection and treatment is of paramount importance.

Aims of testing:

The key objectives when testing for any sexually transmitted infection are to:

- Promote good sexual health.
- Guide individual patient management.
- Ensure effective treatment.
- Break the transmission chain.
- Prevent serious sequelae.

Screening for gonorrhoea

There is no evidence base to support widespread unselected screening for gonorrhoea, and evidence for selective community screening in UK settings is sparse. Data for all STIs is limited outside GUM clinic returns and prevalence studies are rare. Gonorrhoea diagnoses and subsequent complications are uncommon, compared with chlamydia. Immediate benefits to health from diagnosis of gonorrhoea, and subsequent reduction of risk of HIV onward transmission or acquisition, may be seen as supportive of an intervention, but the cost and adverse effects of screening also need to be considered.

The prevalence of gonorrhoea infection varies widely between and within communities and patient populations. Inner-city residents, GUM attendees, military personnel, prisoners and MSM have a higher prevalence of infection than

the general population (2, 3). Localised interventions targeted at these high-risk core groups is likely to be more cost-effective and beneficial than unselected community screening.

Distribution of gonorrhoea

The prevalence of gonorrhoea across England and Wales is variable among individuals attending GUM clinics and there is limited information regarding the prevalence among individuals attending non-GUM settings (4-6).

Laboratory standards

Laboratories must be appropriately accredited by a nationally approved accreditation scheme, such as Clinical Pathology Accreditation (UK) Ltd (http://www.cpa-uk.co.uk/), now part of the United Kingdom Accreditation Service (UKAS). They must also be seen to comply with the international standards for medical laboratory accreditation, ISO 15189.

In addition, the laboratory should show active participation in an External Quality Assurance (EQA) programme.

Detection of *N. gonorrhoeae*

Genital specimens

The choice of approach and method used for detection of *N. gonorrhoeae* should be decided by considering the prevalence of gonorrhoea in the local population.

In the population being tested, any testing algorithm should give a positive predictive value (PPV) of >90%. In low-prevalence populations it will be necessary to use a supplementary/confirmatory test to achieve an acceptable PPV (7).

The specimen type and sampling site used should be validated for the test used. Some commercial kits are not approved for use on all specimen types but, if validation data is available and validation files (8) are completed, this complies with CPA accreditation.

The methodology used should comply with the standard method for use of GC NAATs (1). Isolation of *N. gonorrhoeae* from a patient with a positive molecular test should be obtained (where possible), so that sensitivity testing can be performed to ensure that appropriate treatment has been given.

Urines are not considered a suitable sample for culturing for *N.* gonorrhoeae and are not recommended (9). However, urines are used widely for screening for *C. trachomatis* and so may be tested additionally for *N. gonorrhoeae*. NAATs can detect *N. gonorrhoeae* in urine in both men and women but, in

women, the sensitivity varies between commercial kits and is lower than if an endocervical or self-taken vulvovaginal swab is used

Extra-genital specimens

Culture for *N. gonorrhoeae* is now known to be inferior to use of NAATs (10, 11).

NAATs are the method of choice for extra-genital sites in men who have sex with men (MSM) and other high-risk individuals (11). However, rectal and pharyngeal specimens contain higher levels of closely related *Neisseria* sp. and care should be taken to use a NAAT which exhibits little cross-reactivity (12).

It is essential that a positive result using NAATs with either a rectal or pharyngeal specimen is always confirmed using a supplementary test with a different target, to prevent high numbers of false positives (1).

Use in low-prevalence groups should be undertaken with extreme caution.

Validation data is not available for specimens taken from the conjunctiva.

Handling of the specimen

Nucleic acid amplification tests are extremely sensitive and will detect very small amounts of DNA or rRNA. Detection does not necessarily indicate that the organism is viable.

Care should be taken to regularly clean (or decontaminate) both clinic and laboratory areas where positive specimens have been collected or processed.

Clinics should be aware that it is possible for DNA or rRNA to be transferred to inanimate objects during specimen collection, either by the clinician or the patient, which could then be transferred to another patient's specimen.

Laboratories must have decontamination protocols in place to prevent cross-contamination between samples during processing.

Turnaround times

The turnaround time for a test includes the time taken for the specimen to reach the laboratory, performing (and confirming where appropriate) and reporting the test result, and delivering the result report to the clinician.

The turnaround time in the laboratory, from receiving the sample to issuing a report,should be:

- Primary test: two working days.
- Confirmed positive: three to five working days.

If delay is envisaged, an interim report should be issued.

The overall turnaround time, from taking the sample from the patient, to the clinician receiving the results, should be no more than seven working days.

Care pathways

Before a GC NAAT service is offered, a care pathway, which includes notifying the patient of the result, appropriate treatment and partner notification, needs to be in place. It is recommended practice that a patient should be managed (that is, from the specimen being taken to the patient receiving treatment) within 14 working days (13).

Antimicrobial resistance

The national surveillance programme in England and Wales, GRASP, (Gonococcal Resistance to Antimicrobials Programme) has identified continual high levels of resistance to ciprofloxacin, previous first-line treatment, and emergence of decreased susceptibility to cefixime and ceftriaxone, the third generation cephalosporins (14) currently recommended for therapy (15). It is, therefore, recommended that antimicrobial susceptibility testing is necessary, both for patient management and surveillance purposes, and is essential to guide appropriate therapy to interrupt transmission of resistant infection. Susceptibility testing for either purpose will require a viable organism and it is essential to retain culture facilities and expertise to enable testing.

References

1. Health Protection Agency (2010). *Detection of Neisseria gonorrhoeae using Molecular methods*. National Standard Method QSOP 62 Issue 1 (http://www.hpa-standardmethods.org.uk/documents/qsop/pdf/qsop62.pdf)

2. Health Protection Agency. STI annual data tables. London. http://www.hpa.org.uk/web/HPAweb&HPAwebStandard/HPAweb_C/1203348026613 (accessed 09-02-2010).

3. Delpech V, Martin IM, Hughes G, Nichols T, James L, Ison CA. Epidemiology and clinical presentation of gonorrhoea in England & Wales: Findings from the Gonococcal Resistance to Antimicrobials Surveillance Programme 2001-2006. Sex Transm Infect. 2009;85:317-21.

4. Stanley B, Todd A. Testing for *Neisseria gonorrhoeae* by nucleic acid amplification testing of chlamydia samples using Roche Cobas Amplicor in

a rural area in the north of England does not find more gonorrhoea in primary care. *Sex. Transm Infect* 2005;**81**:518

5. Lavelle SJ, Jones KE, Mallinson H, Webb AM. Finding, confirming, and managing gonorrhoea in a population screened for chlamydia using the Gen-Probe Aptima Combo2 assay. *Sex Transm Infect* 2006;**82**:221-224

6. Gopal Rao G, Bacon L, Evans J, Dejahang Y, Michalczyk P, Donaldson N and on behalf of Lewisham Chlamydia and Gonoccoccus Screening Programme. Prevalence of *Neisseria gonorrhoeae* infection in young subjects attending community clinics in South London. *Sex. Transm. Inf* 2008; 84:117-121

7. Whiley DM, Garland SM, Harnett G et al. Exploring 'best practice'for nucleic acid detection of *Neisseria gonorrhoeae*. Sexual health 2008;5:17-23

8. Health Protection Agency (2008). *Commercial and in-house diagnostic tests: evaluations and validations*. National Standard Method QSOP 23 Issue 4.1. http://www.hpa-standardmethods.org.uk/pdf_sops.asp.

9. Cook RL, Hutchinson SL, Otergaard L, Braithwaite RS, Ness RB. Systematic review: noninvasive testing for *Chlamydia trachomatis* and *Neisseria gonorrhoeae*. *Ann Intern Med* 2005;142:914-25

10. Whiley DM, Tapsall JW, Sloots TP. Nucliec acid amplification testing for *Neisseria gonorrhoeae*: an ongoing challenge. J Mol Diagn 2006;8:3-15

11. Alexander S. The challenges of detecting gonorrhoea and Chlamydia in rectal and pharyngeal sites: could we, should we, be doing more? Sex Transm Infect. 2009:85:159-160

12. Palmer HM, Mallinson H, Wood RL, Herring AJ. Evaluation of the specificities of five DNA amplification methods for the detection of *Neisseria gonorrhoeae*. *J Clin Microbiol* 2003; 41:835-7.

13. Standards for the management of sexually transmitted infections (STIs). Published by Medical Foundation for AIDS & Sexual Health (MEDFASH) ISBN 978-1-905545-42-1 January 2010 http://www.medfash.org.uk/publications/documents/Recommended_standards_for_sexual_health_services.pdf (accessed 10/2/10)

14. GRASP Steering Group. The Gonococcal Resistance to Antimicrobials Surveillance Programme (GRASP), Year 2008 collection. London, Health Protection Agency 2009. http://www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1245914960426 (accessed 10/2/10)

15. Bignell C. National guideline on the diagnosis and treatment of gonorrhoea in adults 2005. www.bashh.org/guidelines (accessed 3/2/10)

Health Protection Agency
Central Office
7th Floor
Holborn Gate
330 High Holborn
London WC1V 7PP
www.hpa.org.uk

For information or queries relating to this document please contact:
catherine.ison@hpa.org.uk
February 2010
© Health Protection Agency

This publication is also available in large print

Corporate member of
Plain English Campaign
Committed to clearer communication.
339

Work Smart Session - MRCP Part 1

Time taken: 26 mins 25 secs

Question: 20 of 100

Which of the following is correct concerning oseltamivir?

(Please select 1 option)

○	It is a direct viral cytotoxic agent
○	It is administered via an inhaler
○	It is a haemaglutinase inhibitor
○	It is effective if administered within 72 hours of symptoms of flu
◉	It is of value in prophylaxis against influenza ✓ Correct

Oseltamivir (Tamiflu), like its predecessor zanamivir (Relenza) functions as an antiviral through inhibition of the enzyme neuraminidase inhibitor, thus slowing viral replication down rather than directly killing the virus particle.

This slowing down of replication is important in permitting time for the body's own immune system to deal with the virus.

Unlike inhaled zanamivir, oseltamivir is administered orally.

However, viral replication is rapid and to be effective, the drug must be given as early as possible after the development of symptoms of flu and preferably within 48 hours.

There is evidence to support its use as a prophylactic agent against influenza and it is also generally free from serious side effects.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 26 mins 25 secs

Question: 21 of 100

An 82-year-old female is reviewed after the staff of the nursing home in which she resides expressed concern regarding a vaginal discharge.

She has been in the nursing home for the last year and has profound Alzheimer's dementia.

Culture of the discharge reveals *Neisseria gonorrhoeae*.

Which is the most appropriate course of action for this patient?

(Please select 1 option)

○	Contact the police
○	Contact tracing of sexual partners
○	Informal enquiry to the nursing home
○	Seek advice from the MDU
○	Treat the patient and discharge back to the nursing home

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Shop

(Please select 1 option)

○	Contact the police
○	Contact tracing of sexual partners
○	Informal enquiry to the nursing home
◉	Seek advice from the MDU ✓ Correct
○	Treat the patient and discharge back to the nursing home

These ethical questions can be quite tough to answer with accuracy.

This question specifically relates to elder abuse, in this case potential elder sexual abuse. The scenario is one that is often played out in the press, in which a care worker sexually abuses elderly patients in his or her care.

However, you are given very little information here and what you would do is undoubtedly treat the patient and establish how she contracted gonorrhoea.

The question states that she has a profound dementia, suggesting that abuse has occurred rather than consensual sex. Nonetheless, you need to establish the facts. You have a personal duty of care to the patient and next of kin to do this before contacting the police.

It is likely that the police will need to be called but first it would be worth talking things through and obtaining advice from the MDU. The advice may entail investigating the set-up at the nursing home, talking with the next of kin, (and social services if a social worker has been involved) and finely detailing any injuries that may be present on examination.

Only then should the decision to contact the police be made.

Next question | Tag Question | Remove question

http://my.onexamination.com/Assessment/Questions.aspx

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 27 mins 11 secs

Question: 22 of 100

A 35-year-old man is seen six months after a cadaveric renal allograft. He receives azathioprine and prednisolone. He has felt generally unwell for the past week with a pyrexia of 38.6°C, anorexia and a cough productive of thick green sputum.

Chest x ray reveals a left lower lobe nodule of approximately 5 cm diameter with central cavitation. Analysis of the sputum reveals long, crooked, branching and beaded Gram-positive filaments.

Which of the following antimicrobials is the most appropriate initial therapy for this patient?

(Please select 1 option)

- Ceftazidime
- Co-amoxiclav
- Co-trimoxazole
- Erythromycin
- Rifampicin and isoniazid

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

A 35-year-old man is seen six months after a cadaveric renal allograft. He receives azathioprine and prednisolone. He has felt generally unwell for the past week with a pyrexia of 38.6°C, anorexia and a cough productive of thick green sputum.

Chest x ray reveals a left lower lobe nodule of approximately 5 cm diameter with central cavitation. Analysis of the sputum reveals long, crooked, branching and beaded Gram-positive filaments.

Which of the following antimicrobials is the most appropriate initial therapy for this patient?

(Please select 1 option)

○	Ceftazidime
○	Co-amoxiclav
○	Co-trimoxazole ← This is the correct answer
○	Erythromycin
◉	Rifampicin and isoniazid ✕ Incorrect answer selected

The likely diagnosis is nocardiosis.

Nocardia are aerobic, Gram-positive branching filamentous bacteria which often appear beaded on staining. Nocardiosis can be diagnosed rapidly by examination of sputum or pus with the Gram stain and a modified acid-fast stain.

Pneumonia is typically found in the immunocompromised, as in this case and may be a single lesion or extensive pneumonic consolidation.

The drug of choice is trimethoprim-sulfamethoxazole.

Next question | Remove Tag | Remove question

http://my.onexamination.com/Assessment/Questions.aspx

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 29 mins 19 secs

Question: 23 of 100

The drug of choice for the treatment of *Chlamydia trachomatis* infection during pregnancy is:

(Please select 1 option)

- Metronidazole
- Cephazolin
- Amoxicillin
- Tetracycline
- Clindamycin

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 29 mins 59 secs

Question: 23 of 100

The drug of choice for the treatment of *Chlamydia trachomatis* infection during pregnancy is:

(Please select 1 option)

- Metronidazole
- Cephazolin
- Amoxicillin ✓ Correct
- Tetracycline
- Clindamycin

Chlamydia infection in the non-pregnant state is usually treated with a tetracycline, or with erythromycin. More recently, however, amoxicillin has been found to be as effective as the latter.

During pregnancy, tetracycline therapy is contraindicated because of its incorporation into fetal bones and teeth.

Thus, of the options listed, amoxicillin is the drug of choice.

Next question

Tag Question
Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 29 mins 59 secs

Question: 24 of 100

A 17-year-old girl presents with three day history of vaginal discharge.

What is the most likely causative organism?

(Please select 1 option)

○	Bacterial vaginosis
○	*Candida albicans*
○	*Chlamydia trachomatis*
○	*Neisseria gonorrhoeae*
○	*Trichomonas vaginalis*

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 31 mins 6 secs

Question: 24 of 100

A 17-year-old girl presents with three day history of vaginal discharge.

What is the most likely causative organism?

(Please select 1 option)

◉	Bacterial vaginosis ✕ Incorrect answer selected
○	*Candida albicans* ← This is the correct answer
○	*Chlamydia trachomatis*
○	*Neisseria gonorrhoeae*
○	*Trichomonas vaginalis*

There is very little information given in this young girl's case, save for the three day history of vaginal discharge.

There is no information given with regard to pruritus, sexual exposure or whether the discharge is malodorous.

Without this information it is rather pot luck, but the most likely organism would be *Candida* as a cause of a vaginal discharge with few other symptoms.

Next question | Remove Tag | Remove question

Show tools

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 31 mins 6 secs

Question: 25 of 100

An otherwise asymptomatic 22-year-old HIV positive male presents to the infectious diseases clinic.

Investigations revealed:

Viral load	250,000 copies/ml	
CD4 count	200 x 10^6/ml	(500-1600)

What is the most appropriate treatment strategy for this patient?

(Please select 1 option)

- Start anti-retroviral therapy
- Start anti-retrovirals together with prophylactic antibiotic therapy
- Start anti-retrovirals when count is 100
- Start anti-retrovirals when count is 150
- Start prophylactic antibiotic therapy

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Investigations revealed:

Viral load	250,000 copies/ml	
CD4 count	200 x 10^6/ml	(500-1600)

What is the most appropriate treatment strategy for this patient?

(Please select 1 option)

○	Start anti-retroviral therapy ← This is the correct answer
◉	Start anti-retrovirals together with prophylactic antibiotic therapy ✕ Incorrect answer selected
○	Start anti-retrovirals when count is 100
○	Start anti-retrovirals when count is 150
○	Start prophylactic antibiotic therapy

Both CD4 cell counts and plasma HIV RNA levels are independent predictors of clinical outcome.

The most appropriate treatment strategy for this young man would be the introduction of anti-retroviral therapy.

Generally, anti-retroviral therapy would be initiated in asymptomatic patients with a CD4 count between 200 and 350.

An HIV RNA level greater than 30,000 copies/ml merits the introduction of anti-retroviral therapy irrespective of CD4 count.

Further reading:
AIDS and HIV AIDSinfo

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 32 mins 52 secs

Question: 26 of 100

Twenty one people are on a Nile boat cruise and present one week into their cruise with diarrhoea.

What is the most likely causative organism?

(Please select 1 option)

○	*Campylobacter*
○	*Cryptosporidium parvum*
○	*Entamoeba histolytica*
○	*Giardia lamblia*
○	*Shigella* species

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 33 mins 29 secs

Question: 26 of 100

Twenty one people are on a Nile boat cruise and present one week into their cruise with diarrhoea.

What is the most likely causative organism?

(Please select 1 option)

○	*Campylobacter*
○	*Cryptosporidium parvum*
◉	*Entamoeba histolytica* ✕ Incorrect answer selected
○	*Giardia lamblia*
○	*Shigella* species ← This is the correct answer

The most likely organism from this history is *Shigella* which accounts for approximately 15% of all traveller's diarrhoea.

Next question

Remove Tag

Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 33 mins 29 secs

Question: 27 of 100

Which of the following statements regarding Japanese encephalitis is most true?

(Please select 1 option)

- Is endemic in East Africa
- It is a DNA virus
- It is only recognised in travellers who have spent prolonged periods in endemic areas
- Previous exposure to a flavivirus predisposes to increased risk of death on infection with Japanese encephalitis
- Transplacental transmission occurs

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 34 mins 6 secs

Question: 27 of 100

Which of the following statements regarding Japanese encephalitis is most true?

(Please select 1 option)

○	Is endemic in East Africa
○	It is a DNA virus
○	It is only recognised in travellers who have spent prolonged periods in endemic areas
○	Previous exposure to a flavivirus predisposes to increased risk of death on infection with Japanese encephalitis
◉	Transplacental transmission occurs ✓ Correct

Japanese encephalitis is an RNA virus which is endemic in India, East Asia, Malaysia and the Phillipines.

Previous infection by a pathogen which is a member of the *Flavivirus* family seems to protect against serious disease or death when infection occurs with another member of the *Flavivirus* family. For instance previous exposure to dengue lowers the risk of death when infected by Japanese encephalitis.

Infection with Japanese encephalitis has been reported in travellers who have spent only short periods in endemic areas and transplacental transmission can occur.

An immunisation is available for travellers.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 34 mins 6 secs

Question: 28 of 100

A patient is planning to travel through the southern states of America, but is worried about West Nile virus.

Which of the following statements regarding West Nile virus is correct?

(Please select 1 option)

○	Infection is non-fatal
○	Is a member of the arborvirus family
○	May be associated with poliomyelitis-like paralysis
○	Transplacental transmission does not occur
○	Treatment with interferon is effective in West Nile virus encephalitis

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

A patient is planning to travel through the southern states of America, but is worried about West Nile virus.

Which of the following statements regarding West Nile virus is correct?

(Please select 1 option)

○	Infection is non-fatal
○	Is a member of the arborvirus family
◉	May be associated with poliomyelitis-like paralysis ✓ Correct
○	Transplacental transmission does not occur
○	Treatment with interferon is effective in West Nile virus encephalitis

Neurological manifestations of West Nile virus include

- A poliomyelitis-like paralysis
- Seizures
- A parkinsonian movement disorder.

West Nile virus is a *Flavivirus* of the Japanese encephalitis family and transplacental transmission has been reported.

In 2003 there were 276 deaths attributed to West Nile virus. Interestingly, West Nile Virus is endemic in the avian population. The deaths of large numbers of birds in an area may thus herald an imminent epidemic of West Nile virus.

Next question | Tag Question | Remove question

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 34 mins 50 secs

Question: 29 of 100

A 15-year-old female is a close contact of a student who has developed meningitis C. The last contact she had with her friend was two days ago when her friend developed headache.

She has not received any previous vaccination for meningitis.

What is the most appropriate action for this girl?

(Please select 1 option)

○	No treatment is required and the girl can be reassured
○	She should receive the meningococcal A and C vaccination only
○	She should receive the meningococcal A and C vaccination plus rifampicin
○	She should receive meningococcal immunoglobulin only
○	Treat with rifampicin only

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Question: 29 of 100

A 15-year-old female is a close contact of a student who has developed meningitis C. The last contact she had with her friend was two days ago when her friend developed headache.

She has not received any previous vaccination for meningitis.

What is the most appropriate action for this girl?

(Please select 1 option)

○	No treatment is required and the girl can be reassured
○	She should receive the meningococcal A and C vaccination only
◉	She should receive the meningococcal A and C vaccination plus rifampicin ✓ Correct
○	She should receive meningococcal immunoglobulin only
○	Treat with rifampicin only

This girl runs a reasonably high risk of developing meningitis and should receive meningitis C vaccination together with rifampicin.

Antibiotics used for chemoprophylaxis are rifampicin, minocycline, spiramycin, ciprofloxacin and ceftriaxone. More here Guidelines and Advice - Meningococcal

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Question: 2 of 100

Which of the following statements is true about immunological reactions?

(Please select 1 option)

○	Angio-neurotic oedema is the most severe form of type I reaction
◉	Deficiencies in the terminal components of complement increase the risk of meningococcal disease ✓ Correct
○	Graves' disease is caused by a type IV reaction
○	Serum sickness is caused by a type II reaction
○	Urticaria usually responds to cimetidine

Serum sickness is due to circulating antibody-antigen complexes (type III).

Graves' disease is due to stimulating antibody (type V).

The most severe variety of type I reaction is anaphylaxis, with angio-oedema an intermediate reaction associated with wheeze and swelling of the lips and severe urticaria. These reactions are mediated by histamine 1 receptor stimulation.

Congenital C1 inhibitor deficiency is also caused by hereditary angio-oedema. Deficiencies in C1r, s, and 2-4 result in vasculitides; while deficiencies in C2, 3 and 5-8 are associated with an increased risk of septicaemia.

Copyright © 2002 Dr Colin Melville

Next question

Tag Que

Work Smart Session - MRCP Part 1

Time taken: 3 mins 53 secs

Question: 3 of 100

Which of the following is true of BCG vaccination?

(Please select 1 option)

- **A** Is a killed polysaccharide antigen vaccine
- **B** Is contraindicated in neonates
- **C** Is presently routinely offered in the UK at age 16 years
- **D** Provides protection against leprosy
- **E** Should be given to all children who have a strongly positive tuberculin test

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 39 mins 57 secs

Question: 30 of 100

A 16-year-old boy presented with fever, headache and neck stiffness for 24 hours. He had an identical illness requiring admission to hospital for one year previously.

Cerebrospinal fluid analysis shows white cells of 400/ml with a 90% neutrophilia and gram stain revealed scanty gram-negative diplococci.

Which component of the immune system is likely to be defective?

(Please select 1 option)

○	B lymphocytes
○	Complement pathway
○	Immunoglobulin
○	Neutrophils
○	T lymphocytes

Submit answer | Skip question | Tag Question | Remove question

Question: 30 of 100

A 16-year-old boy presented with fever, headache and neck stiffness for 24 hours. He had an identical illness requiring admission to hospital for one year previously.

Cerebrospinal fluid analysis shows white cells of 400/ml with a 90% neutrophilia and gram stain revealed scanty gram -negative diplococci.

Which component of the immune system is likely to be defective?

(Please select 1 option)

○	B lymphocytes
◉	Complement pathway ✓ Correct
○	Immunoglobulin
○	Neutrophils
○	T lymphocytes

This young man has a recurrent meningococcal meningitis, and deficiencies of complement C5-9 predispose to *Neisseria* infections(complement deficiencies).

One must recognise that the diplococci seen on microscopy are those of *Neisseria meningitides*.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 40 mins 43 secs

Question: 31 of 100

A 45-year-old man presented with a three day history of headache and increasing confusion.

On examination he was febrile with marked neck stiffness.

Investigations revealed:

Cerebrospinal fluid analysis (normal ranges are shown in brackets):

White cell count	600/ml (<5)
White cell differential	>90% Neutrophils
Gram stain	Gram-negative diplococci

Which one of the following antibiotics, given intravenously, is the most appropriate treatment?

(Please select 1 option)

- Ampicillin
- Benzylpenicillin
- Cefuroxime
- Ciprofloxacin
- Gentamicin

○	Benzylpenicillin ← This is the correct answer
◉	Cefuroxime ✕ Incorrect answer selected
○	Ciprofloxacin
○	Gentamicin

This is clearly a case of meningococcal meningitis. The commonest causes of bacterial meningitis in adults are:

- *Neisseria meningitidis* (Gram negative diplococci)
- *Streptococcus pneumoniae* (Gram positive diplococci).

Treatment of bacterial meningitis

On the basis of Gram stain results:

- Gram stain unavailable or no stainable organisms: Cefotaxime ± ampicillin
- Gram-positive cocci: Cefotaxime + vancomycin
- Gram-positive bacilli: Ampicillin + gentamicin
- Gram-negative cocci: Benzyl penicillin (Penicillin G)
- Gram-negative bacilli: Cefotaxime + gentamicin

On the basis of CSF culture:

- *Streptococcus pneumoniae*
  - If penicillin MIC <0.06 µgrams/mL: Benzyl penicillin (Penicillin G) or cefotaxime
  - If penicillin MIC >0.1 µgrams/ml (that is, penicillin-resistant pneumococcus): Cefotaxime (+ vancomycin if susceptibility to broad-spectrum cephalosporins reduced)
- *Neisseria meningitidis*: Benzyl penicillin (Penicillin G)
- *Haemophilus influenzae*: Cefotaxime
- *Listeria monocytogenes*: Ampicillin + gentamicin
- Group B streptococcus: Benzyl penicillin (Penicillin G).

A 52-year-old man presented to the Emergency Unit with a two day history of increasing breathlessness, productive cough and fever. He was previously fit and well with no past history of note. He was not a cigarette smoker.

On examination he was febrile, temperature was 38.5°C, pulse rate 100/ minute and regular, blood pressure 120/80 mmHg and respiratory rate of 25 breaths/ minute.

Investigations:

Hb	15.0 g/dl	(13.0-18.0)
WBC	18.5 x 10^9/l	(4-11)
Platelets	350 x 10^9/l	(150-400)
Serum sodium	137 mmol/l	(137-144)
Serum potassium	4.5 mmol/l	(3.5-4.9)
Serum urea	5.1 mmol/l	(2.5-7.5)
Serum creatinine	110 µmol/l	(60-110)
PaO_2 (Arterial blood, on air)	9.0 kPa	(11.3-12.6)

Chest x ray showed right middle lobe consolidation

What is the most appropriate choice of antibiotics?

(Please select 1 option)

- ○ Amoxicillin
- ○ Amoxicillin plus erythromycin
- ○ Ceftriaxone
- ○ Ciprofloxacin
- ○ Co-amoxiclav

○	Amoxicillin ← This is the correct answer
◉	Amoxicillin plus erythromycin ✕ Incorrect answer selected
○	Ceftriaxone
○	Ciprofloxacin
○	Co-amoxiclav

While in practice it is perfectly acceptable to give such a patient both amoxicillin and clarithromycin, the question tests deeper knowledge of the British Thoracic Society guidlelines on the management of community-acquired pneumonia.

Given this patient's symptoms, signs and results, he falls in to the good prognosis category (see BTS guidelines). Adverse prognostic features include:

- Age >50 years
- Co-existing disease
- Confusion (MMS <8)
- Respiratory rate >30
- Systolic blood pressure <90 and/or diastolic <60
- Raised serum urea (>7 mmol/l)
- Hypoxia (PaO_2 < 8 kPa)
- Bilateral/multilobar consolidation on chest x ray.

Essentially, he appears relatively well and could be managed at home.

According to BTS guidelines, such patients could be treated with antibiotic monotherapy so amoxicillin alone would suffice.

Further reading:
Guidelines for the Management of Community Acquired Pneumonia in Adults The British Thoracic Society

Next question | Remove Tag | Remove question

Work Smart Session - MRCP Part 1

Time taken: 43 mins 59 secs

Question: 33 of 100

Which of the following is least true regarding IgA nephropathy?

(Please select 1 option)

- Commonly follows a sore throat
- Is the most common glomerulonephritis in the world
- Light chains may be found in the urine
- May be associated with a rash and arthritis
- Predominantly affects young men

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 44 mins 49 secs

Question: 33 of 100

Which of the following is least true regarding IgA nephropathy?

(Please select 1 option)

○	Commonly follows a sore throat
○	Is the most common glomerulonephritis in the world
◉	Light chains may be found in the urine ✓ Correct
○	May be associated with a rash and arthritis
○	Predominantly affects young men

IgA nephropathy (Berger's disease) is the most common glomerulonephritis worldwide and characteristically affects young males, presenting with frank haematuria after an episode of pharyngitis.

However it may also present with proteinuria, microscopic haematuria, renal failure or hypertension.

It is probably part of a spectrum of disease with Henoch-Schonlein purpura, which presents with arthritis, rash, abdominal pain and nephritis. In both there are mesangial IgA deposits in the kidney.

Next question

Tag Question
Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 44 mins 49 secs

Question: 34 of 100

A 47-year-old woman presents with high fever, rigors and myalgia.

Nasal aspirate is positive for influenza virions.

Which of the following is true of her B-cell response?

(Please select 1 option)

- Affinity maturation takes place in the blood stream
- Deficiency of either CD40 or CD40L still allows an IgG response
- Her B-cells express immunoglobulin on their surface
- Memory cells are not formed as repeated infections with influenza often occur
- The antibody response to the virus does not require T-cell help

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

(Please select 1 option)

○	Affinity maturation takes place in the blood stream
○	Deficiency of either CD40 or CD40L still allows an IgG response
◉	Her B-cells express immunoglobulin on their surface ✓ Correct
○	Memory cells are not formed as repeated infections with influenza often occur
○	The antibody response to the virus does not require T-cell help

B-cells usually require T-cell help for full activation.

B-cells activated in the primary immune response initially produce IgM. With continuing T-cell help B-cells then undergo heavy chain class switching and enter germinal centres in secondary lymphoid organs. The germinal centres are the sites of immunoglobulin affinity maturation and memory B-cell formation.

Various factors including the nature of T-cell help, antigen exposure site and cytokine profile, determine the isotype of heavy chain produced.

CD40 and CD40L are required for co-stimulation by T-cells. Deficiency of either CD40 or CD40L impairs class switching.

Certain antigens can activate B-cells in the absence of T-cell help - thymus independent antigen. T-cell independent B-cell responses are mainly to carbohydrate antigen, for example, pneumococcal polysaccharide. These antigens are not processed and presented in association with MHC molecules, and therefore cannot activate T-helper cells.

Most TI antigens have highly repetitive epitopes (for example, LPS/endotoxin), which are able to cross link B-cell surface immunoglobulin and activate these cells.

Some T-cell independent antigens can cause proliferation of B-cells regardless of their specificity - polyclonal B-cell activation. B cell responses to T-independent antigens consist mainly of IgM antibodies of low affinity without the production of memory cells.

The influenza virus will activate T- and B-cells, and result in memory cell production.

Genetic mutation in the virus is responsible for immune evasion and repeated infections.

Work Smart Session - MRCP Part 1

Time taken: 46 mins 3 secs

Question: 35 of 100

A 30-year-old male presents with acute, profuse, watery diarrhoea with some blood after returning from a holiday in Tanzania. He had been taking oral rehydration salts.

Which one of the following is the most appropriate treatment?

(Please select 1 option)

- Ciprofloxacin
- Loperamide
- Metronidazole
- Prednisolone
- Vancomycin

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 47 mins 27 secs

Question: 35 of 100

A 30-year-old male presents with acute, profuse, watery diarrhoea with some blood after returning from a holiday in Tanzania. He had been taking oral rehydration salts.

Which one of the following is the most appropriate treatment?

(Please select 1 option)

◉	Ciprofloxacin ✓ Correct
○	Loperamide
○	Metronidazole
○	Prednisolone
○	Vancomycin

The most likely cause of such traveller's diarrhoea is *Escherichia coli* and hence ciprofloxacin is recommended for first line antibiotic therapy (when needed) before stool culture results are available.

Metronidazole would be suitable for *Giardia* infection but its course is usually more insidious.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 47 mins 27 secs

Question: 36 of 100

A 55-year-old female who had a long history of alcohol abuse presents with diarrhoea and back pain one month after having a pacemaker inserted.

On examination she had a fever of 39°C and her abdomen was soft and non-tender.

What is the most likely diagnosis?

(Please select 1 option)

○	Diverticulitis
○	Ischaemic colitis
○	Pancreatitis
○	Pseudomembranous colitis
○	Staphylococcal discitis

Submit answer | Skip question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 48 mins 15 secs

Question: 36 of 100

A 55-year-old female who had a long history of alcohol abuse presents with diarrhoea and back pain one month after having a pacemaker inserted.

On examination she had a fever of 39°C and her abdomen was soft and non-tender.

What is the most likely diagnosis?

(Please select 1 option)

○	Diverticulitis
○	Ischaemic colitis
○	Pancreatitis
○	Pseudomembranous colitis
◉	Staphylococcal discitis ✓ Correct

All patients with alcohol dependence have an increased risk of pancreatitis, but this is less likely without any abdominal signs.

Ischaemic colitis classically presents with bloody diarrhoea.

The prophylactic antibiotics given four weeks previously for her pacemaker insertion would not really have predisposed her to pseudomembranous colitis.

Staphylococci are skin organisms most commonly introduced during pacemaker insertion and such a discitis would present with back pain.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 48 mins 15 secs

Question: 37 of 100

An 80-year-old man with a five year history of diet controlled type 2 diabetes mellitus presents with a one month history of cough and weight loss. He was a non-smoker and had difficulty expectorating.

Investigation revealed a HbA1c of 7% (3.8-6.4) but his chest x ray showed a cavitating left apical shadow.

Which of the following investigations would be most useful in establishing the cause of this lesion?

(Please select 1 option)

- Bronchoscopy
- CT scan of the chest
- Gastric aspirate for acid-fast bacilli
- Percutaneous lung biopsy
- Sputum for acid-fast bacilli

Submit answer | Skip question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

◉	Bronchoscopy ✓ Correct
○	CT scan of the chest
○	Gastric aspirate for acid-fast bacilli
○	Percutaneous lung biopsy
○	Sputum for acid-fast bacilli

The differential diagnosis of cavitating lung lesions is shown below.

The most likely diagnosis in this non-smoking man is post primary tuberculosis as a result of reactivation of quiescent disease. He has several risk factors including increasing age and diabetes.

The patient is unable to produce sputum therefore undertaking a bronchoscopy with bronchial washings for microscopy staining and culture is the investigation of choice. Gastric lavage for AFB is unpleasant for the patient has a lower yield than bronchoscopy and is therefore rarely undertaken now.

Causes of cavitating masses on CXR:

(a) Lung abscess

(b) Tuberculosis

(c) Fungal infection (for example, histoplasmosis, cocccidioidomycosis)

(d) Malignancy

(e) Wegener's granulomatosis commonly

(f) Rheumatoid arthritis (multiple)

(g) Infarction.

Work Smart Session - MRCP Part 1

Time taken: 49 mins 38 secs

Question: 38 of 100

A 55-year-old Caucasian man presented to hospital with fever, intermittent rigors, and worsening fatigue. He had returned from a business trip to West Africa six months previously.

What is the most likely diagnosis?

(Please select 1 option)

- Brucellosis
- Leishmaniasis
- *Plasmodium falciparum* malaria
- *Plasmodium ovale* malaria
- Typhoid fever

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

What is the most likely diagnosis?

(Please select 1 option)

○	Brucellosis
○	Leishmaniasis
◉	*Plasmodium falciparum* malaria ✕ Incorrect answer selected
○	*Plasmodium ovale* malaria ← This is the correct answer
○	Typhoid fever

The Duffy blood group on the red blood cells acts as a receptor for *P. vivax*. West Africans lack the Duffy blood group and therefore *P. ovale* replaces *P. vivax* in this region.

Both *P. vivax* and *P. ovale* have a liver hypnozoite stage which can cause repeated relapses.

P. falciparum typically presents within the first three months of return.

Visceral leishmaniasis is not endemic in West Africa.

Brucellosis is a zoonosis transmitted through contaminated and untreated milk and by direct contact with infected animals. The incubation period of brucellosis is usually one to three weeks, but sometimes may be several months. It may have either a sudden or insidious onset and is accompanied by continued, intermittent, or irregular fever.

Typhoid fever presents within one to three weeks from return from an endemic area.

Next question

Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 50 mins 15 secs

Question: 39 of 100

A 29-year-old man is diagnosed with pulmonary tuberculosis.

A blood sample is sent to determine his acetylator status prior to starting therapy. This showed that he was a fast acetylator. He was subsequently started on antituberculous therapy that included isoniazid.

Which of the following statements is correct?

(Please select 1 option)

- There is an increased risk of convulsions
- There is an increased risk of drug resistance
- There is an increased risk of hepatitis
- There is an increased risk of megaloblastic anaemia
- There is an increased risk of peripheral neuropathy

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Question: 39 of 100

A 29-year-old man is diagnosed with pulmonary tuberculosis.

A blood sample is sent to determine his acetylator status prior to starting therapy. This showed that he was a fast acetylator. He was subsequently started on antituberculous therapy that included isoniazid.

Which of the following statements is correct?

(Please select 1 option)

○	There is an increased risk of convulsions
○	There is an increased risk of drug resistance
○	There is an increased risk of hepatitis ← This is the correct answer
○	There is an increased risk of megaloblastic anaemia
◉	There is an increased risk of peripheral neuropathy ✕ Incorrect answer selected

Isoniazid is metabolised primarily by acetylation and dehydrazination.

The rate of acetylation is genetically determined. Approximately 50% of Blacks and Caucasians are "slow acetylators" and the rest are "rapid acetylators"; the majority of Eskimos and Orientals are "rapid acetylators".

Fast acetylation leads to higher blood levels of the toxic metabolite acetylisoniazid and thus to an increase in toxic reactions - hepatitis which is 250 times more common than in slow acetylators.

Fast acetylators on the other hand require higher doses but there increased tubercle resistance is not a problem.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Question: 3 of 100

Which of the following is true of BCG vaccination?

(Please select 1 option)

○	**A** Is a killed polysaccharide antigen vaccine
○	**B** Is contraindicated in neonates
○	**C** Is presently routinely offered in the UK at age 16 years
◉	**D** Provides protection against leprosy ✓ Correct
○	**E** Should be given to all children who have a strongly positive tuberculin test

A The BCG vaccine is an attenuated strain; it provides approximately 70% protection.

B BCG vaccine may given to newborns at high risk of exposure.

C BCG is given at comprehensive school entry (age 11-13).

D It has also found a use in stimulating the immune system for the treatment of some cancers.

E It should not be given to these children. A low reactivity Heaf test (grade 0-1) should be documented before administration.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 4 mins 23 secs

Question: 4 of 100

Deficiency of which of the following components of the complement system predisposes to infection with *Neisseria meningitidis*?

(Please select 1 option)

○	C1q
◉	C1r
○	C1s
○	C3
○	C4

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 51 mins 8 secs

Question: 40 of 100

A 48-year-old man with a known history of chronic alcohol abuse presented with a three-day history of fevers, night sweats and a cough productive of purulent sputum.

There was no past history of respiratory disease.

On examination he was febrile (39.1°C). Percussion note was dull over the right apex and there was bronchial breathing in this area on auscultation.

The chest x-ray showed right upper lobar consolidation.

Other investigations revealed:

WBC	23 $x10^9$/L (4-11 $x10^9$)
Neutrophils	18.3 $x10^9$/L (1.5-7 $X10^9$)

What is the most likely diagnosis?

(Please select 1 option)

- Aspiration pneumonia
- Klebsiella pneumonia
- Legionnella pneumonia
- Mycoplasma pneumonia
- Primary tuberculosis

Submit answer | Skip question | Remove question

- Shop

The chest x-ray showed right upper lobar consolidation.

Other investigations revealed:

WBC	23 $x10^9$/L (4-11 $x10^9$)
Neutrophils	18.3 $x10^9$/L (1.5-7 $X10^9$)

What is the most likely diagnosis?

(Please select 1 option)

- ○ Aspiration pneumonia
- ◉ Klebsiella pneumonia ✓ Correct
- ○ Legionnella pneumonia
- ○ Mycoplasma pneumonia
- ○ Primary tuberculosis

Community-acquired Klebsiella pneumonia is a disease of debilitated middle-aged and older men with alcoholism. Mortality rates are as high as 50% regardless of treatment.

Klebsiella pneumonia characteristically affects one of the upper lobes of the lung, although infection of the lower lobes is not uncommon. There is an increased tendency toward abscess formation.

Aspiration pneumonia typically affects in right lower lobe in persons with impaired swallowing.

Legionnaires' disease is associated with contaminated air conditioning and water delivery systems.

Mycoplasma pneumoniae infections have an insidious onset with malaise, myalgia, sore throat and headache. Cough is characteristically dry.

Chest x-ray (CXR) changes are usually patchy and involve the lower or middle lobes.

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 52 mins 8 secs

Question: 41 of 100

A 17-year-old man presented to casualty complaining of difficulty breathing. He had been brought to hospital by ambulance, having collapsed shortly after being stung on the hand by a bee.

On examination, his blood pressure was 80/40 mmHg, and facial swelling was noted.

Which one of the following investigations is most likely to confirm the nature of the reaction?

(Please select 1 option)

- Haemolytic complement (CH50) level
- Plasma tryptase activity
- Serum complement C3 level
- Serum total IgE level
- Serum venom-specific IgE level

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

On examination, his blood pressure was 80/40 mmHg, and facial swelling was noted.

Which one of the following investigations is most likely to confirm the nature of the reaction?

(Please select 1 option)

○	Haemolytic complement (CH50) level
○	Plasma tryptase activity ← This is the correct answer
○	Serum complement C3 level
◉	Serum total IgE level ✗ Incorrect answer selected
○	Serum venom-specific IgE level

Type I hypersensitivity, also known as immediate or anaphylactic hypersensitivity, usually takes 15 - 30 minutes from the time of exposure to the antigen. The reaction may cause a range of symptoms from minor inconvenience to death.

The reaction involves preferential production of IgE in response to certain antigens which in turn initiates a sequence of events leading to the release of various pharmacologically active substances that are responsible for the clinical features.

Diagnostic tests include skin tests, measurement of total IgE and specific IgE antibodies against the suspected allergens. However, this question asks which of the following tests would provide confirmatory information and that would be tryptase.

Tryptase is a neutral protease stored in mast cell secretory granules that is secreted by human mast cells. Levels in normal blood are undetectable (< 1 ng/ml). Elevated serum levels demonstrate that mast cell activation with mediator release has occurred whether triggered by IgE-mediated anaphylaxis or non-IgE-mediated anaphylactoid reactions. The greater the severity of anaphylaxis, the more likely that serum -tryptase levels will be elevated.

Next question

Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

A 22-year-old man presented to the casualty department one week after returning from a six month visit to Pakistan.

He complained of fever, rigors and headache.

On examination he was febrile (38°C) with a blood pressure of 115/65 mmHg, and a pulse of 100/minute. His abdomen was tender in the right upper quadrant.

Investigations showed:

Hb	11.0 g/dL (13.0-18.0)
WBC	15.5 $x10^9$/L (4-11 $x10^9$)
Neutrophils	13.5 $xl0^9$/L (1.5-7 $x10^9$)
Platelets	350 $x10^9$/L (150-400 $x10^9$)
Blood film	No malaria parasites seen
Alk Phos	450 U/L (45-105)
AST	50 U/L (1-31)
CRP	88 mg/L (<10)
Stool culture	Negative
Chest x-ray:	Small right pleural effusion noted

Which of the following investigations would be of most diagnostic value?

(Please select 1 option)

- Hepatitis E serology
- Sigmoidoscopy
- Stool microscopy for ova, cysts and parasites
- Typhoid serology
- Ultrasound scan of the abdomen

(Please select 1 option)

○	Hepatitis E serology
○	Sigmoidoscopy
○	Stool microscopy for ova, cysts and parasites
○	Typhoid serology
◉	Ultrasound scan of the abdomen ✓ Correct

The presentation is not consistent with hepatitis E infection.

Typhoid serology is unreliable.

The differential diagnosis is mainly pyogenic or amoebic liver abscess.

Pyogenic abscesses present with:

- swinging pyrexia

- neutrophilia and

- high inflammatory markers.

Right-sided pleural effusions are common and blood cultures are often positive.

The presentation of amoebic liver abscess (ALA) is very similar. Most patients do not have bowel symptoms at any time and amoebic cysts are found in stool in less than 50% of proven cases of ALA.

Serology is the mainstay of diagnosis.

Ultrasound scan would confirm most moderate-sized to large liver abscesses and could guide a diagnostic aspiration.

Small lesions are best demonstrated by computerised tomography (CT) or magnetic resonance imaging (MRI).

Work Smart Session - MRCP Part 1

Time taken: 56 mins

Question: 43 of 100

A 15-year-old girl presents to casualty with mild gastrointestinal upset. She had recently returned from holiday where she had been swimming in the hotel pool.

What is the most likely causative organism?

(Please select 1 option)

- *Campylobacter jejuni*
- *Cryptosporidium parvum*
- *Salmonella enteridis*
- *Shigella flexneri*
- *Staphylococcus aureus*

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 57 mins 34 secs

Question: 43 of 100

A 15-year-old girl presents to casualty with mild gastrointestinal upset. She had recently returned from holiday where she had been swimming in the hotel pool.

What is the most likely causative organism?

(Please select 1 option)

○	*Campylobacter jejuni*
◉	*Cryptosporidium parvum* ✓ Correct
○	*Salmonella enteridis*
○	*Shigella flexneri*
○	*Staphylococcus aureus*

Human cryptosporidiosis causes self-limited diarrhoeal illness in healthy individuals, mostly children; and severe prolonged diarrhoea in patients with AIDS.

Transmission is via human-to-human fecal-oral contamination.

Animals are the major reservoir and outbreaks have been associated with water supplies and public swimming pools.

Next question

Tag Question
Remove question

© 2011 BMJ Publishing Group Ltd. All rights reserved. Terms and conditions Privacy policy

Work Smart Session - MRCP Part 1

Time taken: 57 mins 34 secs

Question: 44 of 100

Which of the following is a cause of isolated B-cell immune deficiency?

(Please select 1 option)

- Infection with measles
- Multiple myeloma
- Treatment with azathioprine
- Treatment with corticosteroids
- Treatment with cyclophosphamide

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 5 mins 22 secs

Question: 44 of 100

Which of the following is a cause of isolated B-cell immune deficiency?

(Please select 1 option)

○	Infection with measles
◉	Multiple myeloma ✓ Correct
○	Treatment with azathioprine
○	Treatment with corticosteroids
○	Treatment with cyclophosphamide

Excessive production of myeloma paraprotein is associated with progressive reduction in normal immunoglobulin levels and impairment of immune function.

Azathioprine, cyclophosphamide, corticosteroids and measles infection all cause reversible impairment of cell mediated immunity.

Next question

Tag Question
Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 5 mins 22 secs

Question: 45 of 100

Which one of the following measures would be most effective in reducing transmission of E coli O157:H7 during an outbreak of diarrhoea caused by this organism?

(Please select 1 option)

- Drinking only boiled water
- Ensuring that meat products are thoroughly cooked
- Giving antibiotics to individuals who are positive for *Escherichia coli* on stool culture
- Hand washing before preparing food
- Isolation of individuals with diarrhoea

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 5 mins 57 secs

Question: 45 of 100

Which one of the following measures would be most effective in reducing transmission of E coli O157:H7 during an outbreak of diarrhoea caused by this organism?

(Please select 1 option)

- Drinking only boiled water
- Ensuring that meat products are thoroughly cooked ← This is the correct answer
- Giving antibiotics to individuals who are positive for *Escherichia coli* on stool culture
- Hand washing before preparing food ✕ Incorrect answer selected
- Isolation of individuals with diarrhoea

Cattle are a major reservoir of *Escherichia coli* O157:H7 and contaminated meat is the most commonly implicated source of outbreaks.

Raw meat should be separated from cooked and ready-to-eat food. Hands should be washed after handling raw meat.

Antibiotics are not routinely indicated and patients should be educated on personal hygiene.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 5 mins 57 secs

Question: 46 of 100

Which of the following statements regarding disseminated intravascular coagulation (DIC) is most correct?

(Please select 1 option)

- DIC is associated with an elevated D-dimer
- DIC is associated with rising fibrinogen levels
- DIC is associated with a rising platelet count
- Normal clotting parameters effectively exclude a diagnosis of DIC
- Removal of the underlying cause of the DIC will lead to resolution of the manifestations of DIC

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 6 mins 33 secs

Question: 46 of 100

Which of the following statements regarding disseminated intravascular coagulation (DIC) is most correct?

(Please select 1 option)

◉	DIC is associated with an elevated D-dimer ✓ Correct
○	DIC is associated with rising fibrinogen levels
○	DIC is associated with a rising platelet count
○	Normal clotting parameters effectively exclude a diagnosis of DIC
○	Removal of the underlying cause of the DIC will lead to resolution of the manifestations of DIC

DIC is caused by the enhanced and abnormally sustained generation of thrombin, and is associated with elevated products of fibrin breakdown, one of these being D-dimer.

Treatment of the underlying cause , for example, sepsis, does not always lead to resolution of the condition, and recombinant human activated protein C has been shown to be effective in reducing mortality from DIC in patients with sepsis.

DIC is associated with a falling platelet count and decreased fibrinogen, but the clotting factors may be normal, especially when one considers that the acute phase response may shorten the activated partial thromboplastin time (APTT) and increase fibrinogen.

For an excellent review see BMJ 2003;327:974-7.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 6 mins 33 secs

Question: 47 of 100

A 28-year-old shop worker is referred with a three month history of recurrent episodes of disorientation and confusion.

Her boyfriend has found her wandering around the house on several occasions, apparently with no idea of where she is or how she got there. Her mood has been very low, with frequent emotional outbursts, and she has considered leaving her job because of problems with working the computer and managing customer's queries. Her boyfriend feels her condition is significantly worsening.

Physical examination is normal, apart from recurrent, asymetrical, jerks in all four limbs.

Which of the following investigations is likely to be most useful in reaching a diagnosis?

(Please select 1 option)

- Chest x ray
- CT head
- EEG
- Liver function tests
- Visual evoked potentials

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Shop

Which of the following investigations is likely to be most useful in reaching a diagnosis?

(Please select 1 option)

○	Chest x ray
◉	CT head ✕ Incorrect answer selected
○	EEG ← This is the correct answer
○	Liver function tests
○	Visual evoked potentials

This kind of rapid cognitive decline in a young person with myoclonus is strongly suggestive of Creutzfeldt-Jakob disease (CJD). This may be new variant (in which the electroencephalogram [EEG] may be abnormal though is often normal) or sporadic in which case characteristic EEG abnormalities may be expected.

The EEG in sporadic CJD may show significant abnormalities involving deep brain areas such as the thalami. Initially the changes are diffuse, and non-specific, developing into stereotyped high voltage components on a slow background. High voltage sharp waves may be synchronous with myoclonic jerks.

Tonsillar biopsy for 14-3-3 protein marker has a diagnostic sensitivity of around 80% for prion proteins.

Other investigations to exclude other causes of rapid cognitive decline, would include magnetic resonance imaging (MRI) and lumbar puncture.

Computed tomography (CT) may show non-specific changes with atrophy out of keeping with the patient's age.

Diagnosis is confirmed with biopsy.

Next question

Remove Tag | Remove question

Question: 48 of 100

You are called to the Emergency Department to assess a 21-year-old student who has presented with bloody diarrhoea.

The diarrhoea started two weeks previously and was associated with increasing nausea and malaise and mild swelling of the lower limbs. She was having difficulty passing urine. She had eaten steak from the local butcher at a friend's barbeque the day before developing diarrhoea.

On examination she was pale with evidence of petechiae over her legs. Her face appeared puffy. Blood pressure was 160/95 mmHg. She was apyrexial but had a tachycardia and crackles on inspiration at both lung bases. There was an old appendicectomy scar in the right iliac fossa.

Investigations showed:

Haemoglobin	8.5 g/dl	(11.5-16.5)
White cell count	13.2 x 10^9/l	(4-11)
Neutrophils	9.5 x 10^9/l	(1.5-7)
Platelets	35 x 10^9/l	(150-400)
PT	12 s	(11.5-15.5)
APTT	34 s	(30-40)
Fibrinogen	4 g/l	(1.8-5.4)
Serum sodium	139 mmol/l	(137-144)
Serum potassium	6.1 mmol/l	(3.5-4.9)
Serum urea	40 mmol/l	(2.5-7.5)
Serum creatinine	411 µmol/l	(60-110)
Serum albumin	27 g/l	(37-49)
Dipstick urine	Blood ++ Protein +	

What is the single most important next investigation to determine the diagnosis?

(Please select 1 option)

White cell count	13.2 x 10^9/l	(4-11)
Neutrophils	9.5 x 10^9/l	(1.5-7)
Platelets	35 x 10^9/l	(150-400)
PT	12 s	(11.5-15.5)
APTT	34 s	(30-40)
Fibrinogen	4 g/l	(1.8-5.4)
Serum sodium	139 mmol/l	(137-144)
Serum potassium	6.1 mmol/l	(3.5-4.9)
Serum urea	40 mmol/l	(2.5-7.5)
Serum creatinine	411 µmol/l	(60-110)
Serum albumin	27 g/l	(37-49)
Dipstick urine	Blood ++ Protein +	

What is the single most important next investigation to determine the diagnosis?

(Please select 1 option)

- ASO titres
- Renal tract ultrasound
- Stool culture
- Transthoracic echocardiogram
- Urine microscopy

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

(Please select 1 option)

○	ASO titres
○	Renal tract ultrasound
◉	Stool culture ✓ Correct
○	Transthoracic echocardiogram
○	Urine microscopy

This patient has haemolytic uraemic syndrome (HUS).

It typically presents with a triad of

- Acute renal failure (ARF)
- Microangiopathic haemolytic anaemia
- Thrombocytopaenia with normal clotting.

HUS is a complication of infection with verocytotoxin producing *Escherichia coli* usually of the serotype 0157:H7.

Toxins produced in the intestine enter the blood and bind to endothelial cells in target organs. Endothelial cell damage leads to platelet and fibrin deposition with resultant fragmentation of circulating red blood cells and microvascular occlusion.

The syndrome has also been reported after infections with coxsackie, echovirus and *Shigella*.

HUS is characterised by the sudden onset of haemolytic anaemia with fragmentation of red blood cells, thrombocytopaenia and acute renal failure after a prodromal illness of acute gastroenteritis often with bloody diarrhoea.

Clinical signs include increasing pallor, haematuria, oliguria and purpura. Jaundice is occasionally seen. Hypertension may be present.

Typical results show an anaemia, thrombocytopaenia, and often a neutrophilia. Blood film shows fragmented erythrocytes.

Urea and electrolytes are typical of acute renal failure. There is normal coagulation and fibrinogen.

Neurological complications include

Neurological complications include

- Stroke, seizure and coma occur in 25% of patients
- Rarely pancreatitis
- Pleural and pericardial effusions.

Approximately 5% of patients will develop end stage renal failure.

Long term renal sequelae range from proteinuria to chronic renal failure.

Therapy is supportive with

- correction of anaemia
- correction of uraemia by early dialysis
- strict fluid balance
- treatment of hypertension.

Major differential diagnosis is

1. Sepsis with DIC - presents with abnormalities of clotting parameters.
2. TTP - thrombotic thrombocytopaenic purpura presents with microangiopathic haemolytic anaemia, thrombocytopaenic purpura, neurologic abnormalities, fever, and renal disease.

Renal abnormalities tend to be more severe in HUS.

Although once considered variants of a single syndrome, recent evidence suggests that the pathogenesis of TTP and HUS is different. Patients with TTP lack a plasma protease that is responsible for the breakdown of von Willebrand factor (vWF) multimers and these accumulate in the plasma. The activity of this protease is normal in patients with HUS.

Until the test for vWF protease activity becomes available, differentiation between HUS and TTP is based on the presence of central nervous system involvement in TTP and the more severe renal involvement in HUS.

In HUS 90% of patients are children and a history of prodromal diarrhoeal illness is more common.

The therapy of choice for TTP is plasma exchange with fresh frozen plasma.

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 12 mins 12 secs

Question: 49 of 100

A 28-year-old man had been treated for pulmonary tuberculosis with rifampicin, isoniazid, pyrazinamide and ethambutol for four weeks.

Pre-treatment liver function tests (LFTs) were normal but his most recent investigations revealed:

Serum total bilirubin	98 micromol/l (0-18)
Serum alanine aminotransferase	620u/l (5-45)
Serum aspartate aminotransferase	450 u/l (5-45)
Serum alkaline phosphatase	720 u/l (40-110)

Which one of the following is the most appropriate next step?

(Please select 1 option)

- Stop all treatment
- Stop ethambutol
- Stop isoniazid
- Stop pyrazinamide
- Stop rifampicin

Avira
Update was finished successfully.
Your product is already up-to-date.
You currently have optimum protection.
Do not show this message again.
OK

(Please select 1 option)

◉	Stop all treatment ✓ Correct
○	Stop ethambutol
○	Stop isoniazid
○	Stop pyrazinamide
○	Stop rifampicin

All tuberculosis patients should have pre-treatment LFT, should be supervised by a chest physician and should be informed of possible side-effects of treatment.

If there is no pre-existing liver disease, LFTs are only repeated (and treatment stopped) if fever, malaise, vomiting , jaundice or unexplained deterioration occurs during treatment.

Regular LFTs should be performed in patients with previously known chronic liver disease. If AST/ALT levels rise by five times normal/ bilirubin level rises, then rifampicin/isoniazid/pyrazinamide should be stopped.

If the patient is not unwell and/or has non-infectious TB, no treatment until LFT returns to normal.

If clinically unwell or sputum smear is positive within rwo weeks of starting treatment, consider streptomycin and ethambutol until LFT returns to normal.

Once LFT is back to normal, challenge dosages can be reintroduced sequentially in order of isoniazid, rifampicin and pyrazinamide with daily monitoring of patient's condition and LFT.

If there is a further reaction the offending drug should be excluded and a suitable alternative regimen used.

meningitidis?

(Please select 1 option)

○	C1q
◉	C1r ✕ Incorrect answer selected
○	C1s
○	C3 ← This is the correct answer
○	C4

The complement system often gives rise to questions in the MRCP examination. It would be wise to make a cursory review of this topic.

C3 is the point at which the classical, alternative and lectin complement pathways converge.

C1qrs, C2 and C4 are strongly associated with systemic lupus erythematosus (SLE).

Patients with C3 deficiency, be it absolute, relative, genetically determined (autosomal dominant or recessive) or due to properdin deficiency, are predisposed to recurrent infection with encapsulated proteins, particularly *N. meningitidis*.

C5 deficiency is associated with Leiner disease, a syndrome of recurrent diarrhoea, wasting and generalised seborrhoeic dermatitis presenting in infants.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 5 mins 2 secs

Question: 5 of 100

A young girl returns from a trip to India with a protracted history of watery diarrhoea.

Giardiasis is suspected but three stool samples are negative.

What is the best investigation to confirm *Giardia* as a diagnosis?

(Please select 1 option)

○	CT abdomen
○	Rectal biopsy
○	Serum IgM *Giardia* antibodies
○	Small intestine biopsy
○	Stool microscopy

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 14 mins 20 secs

Question: 50 of 100

A 28-year-old man who had had tuberculosis of the mediastinal lymph nodes diagnosed two weeks previously and who had been started on chemotherapy with rifampicin, isoniazid and pyrazinamide was admitted because of the increasing dyspnoea and stridor.

Chest x ray showed compression of both main bronchi by carinal lymph node enlargement.

What is the next step in management?

(Please select 1 option)

- Mediastinoscopy and biopsy
- Refer for stent insertion/tracheostomy
- Refer for urgent CT scan of the mediastinum
- Start prednisolone
- The addition of ethambutol

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Question: 50 of 100

A 28-year-old man who had had tuberculosis of the mediastinal lymph nodes diagnosed two weeks previously and who had been started on chemotherapy with rifampicin, isoniazid and pyrazinamide was admitted because of the increasing dyspnoea and stridor.

Chest x ray showed compression of both main bronchi by carinal lymph node enlargement.

What is the next step in management?

(Please select 1 option)

○	Mediastinoscopy and biopsy
○	Refer for stent insertion/tracheostomy
○	Refer for urgent CT scan of the mediastinum
◉	Start prednisolone ✓ Correct
○	The addition of ethambutol

The treatment of TB mediastinal lymphadenitis is the same as pulmonary TB.

The nodes may enlarge during or after treatment as a result of hypersensitivity.

Corticosteroids are effective in reducing the enlargement and hence will help the stridor and breathlessness.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 15 mins 21 secs

Question: 51 of 100

A 26-year-old man with a history of alcohol and drug abuse was admitted with a 14 day history of fever, cough and fatigue.

He was emaciated. His temperature was 39.4C. Cervical and axillary lymphadenopathy were present. Chest x ray revealed bilateral areas of pulmonary shadowing.

Which of the following is the most likely diagnosis?

(Please select 1 option)

- Alcoholic cardiomyopathy
- Pneumococcal pneumonia
- Pneumocystis pneumonia
- Pulmonary tuberculosis
- Tricuspid endocarditis

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

He was emaciated. His temperature was 39.4C. Cervical and axillary lymphadenopathy were present. Chest x ray revealed bilateral areas of pulmonary shadowing.

Which of the following is the most likely diagnosis?

(Please select 1 option)

○	Alcoholic cardiomyopathy
○	Pneumococcal pneumonia
◉	Pneumocystis pneumonia ✓ Correct
○	Pulmonary tuberculosis
○	Tricuspid endocarditis

Pneumocystis carinii is the most common opportunistic infection in AIDS.

This patient is at risk of HIV with the history of drug abuse. Persistent generalised lymphadenopathy may develop in HIV before the patient fulfils the criteria of AIDS.

As the disease progresses, there is atrophy of the lymph nodes.

Less likely is pulmonary tuberculosis which can also cause any abnormality on chest x ray and involve peripheral lymph nodes.

The others are unlikely to cause lymphadenopathy.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 18 mins 7 secs

Question: 52 of 100

A 30-year-old intravenous drug abuser develops acute aortic regurgitation due to infective endocarditis.

Which of the following is NOT typical of acute aortic regurgitation?

(Please select 1 option)

○	Decrescendo diastolic murmur
○	Hypotension
○	Mitral valve pre-closure
○	Normal cardiac output
○	Peripheral vasodilatation

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

A 30-year-old intravenous drug abuser develops acute aortic regurgitation due to infective endocarditis.

Which of the following is NOT typical of acute aortic regurgitation?

(Please select 1 option)

○	Decrescendo diastolic murmur
○	Hypotension
○	Mitral valve pre-closure
◉	Normal cardiac output ✕ Incorrect answer selected
○	Peripheral vasodilatation ← This is the correct answer

Findings that would be typical include:

- Large pulse volume
- Increased pulse pressure
- A decrescendo murmur
- A low diastolic blood pressure.

Vasoconstriction not dilatation is typically found.

Further reading:
Aortic Regurgitation eMedicine

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd. All rights reserved. Terms and conditions Privacy policy

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 19 mins 16 secs

Question: 53 of 100

A 56-year-old man from Thailand presented with abdominal pain and a mass in the right upper quadrant. He reported that he had been diagnosed with viral hepatitis several years previously.

Investigations showed:

Serum alpha-fetoprotein	13,500 IU/L	(< 10)

What is the most likely underlying viral infection?

(Please select 1 option)

- Hepatitis A virus
- Hepatitis B virus
- Hepatitis C virus
- Hepatitis D virus
- Hepatitis E virus

Submit answer | Skip question | Tag Question | Remove question

A 56-year-old man from Thailand presented with abdominal pain and a mass in the right upper quadrant. He reported that he had been diagnosed with viral hepatitis several years previously.

Investigations showed:

Serum alpha-fetoprotein	13,500 IU/L	(< 10)

What is the most likely underlying viral infection?

(Please select 1 option)

- ○ Hepatitis A virus
- ◉ Hepatitis B virus ✓ Correct
- ○ Hepatitis C virus
- ○ Hepatitis D virus
- ○ Hepatitis E virus

Very difficult! The patient has chronic viral hepatitis and presents with a hepatoma.

The underlying cause must be either hepatitis B virus (HBV) or hepatitis C virus (HCV).

There is a higher prevalence of HBV in the Far East and since his country of origin is the only other detail that gives a clue to the cause of his hepatitis, the most likely viral agent is HBV.

Next question

Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 28 mins 23 secs

Question: 54 of 100

A 35-year-old man presented with cellulitis of his right leg. On examination he was mildly confused and febrile (40.1°C) with a pulse was 120/minute and BP 80/55 mmHg.

He was treated with intravenous benzylpenicillin and flucloxacillin. Group A streptococcus was isolated from two sets of blood cultures. There was no significant clinical improvement after 24 hours.

What antibiotic should be added?

(Please select 1 option)

- Ciprofloxacin
- Clindamycin
- Gentamicin
- Rifampicin
- Vancomycin

Submit answer | Skip question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Question: 54 of 100

A 35-year-old man presented with cellulitis of his right leg. On examination he was mildly confused and febrile (40.1°C) with a pulse was 120/minute and BP 80/55 mmHg.

He was treated with intravenous benzylpenicillin and flucloxacillin. Group A streptococcus was isolated from two sets of blood cultures. There was no significant clinical improvement after 24 hours.

What antibiotic should be added?

(Please select 1 option)

○	Ciprofloxacin
○	Clindamycin ← This is the correct answer
○	Gentamicin
○	Rifampicin
◉	Vancomycin ✕ Incorrect answer selected

The patient has a severe cellulitis with features of streptococcal toxic shock syndrome (TSS). Streptococcal TSS is mediated via streptococcal exotoxins.

Although clindamycin is a bacteriostatic antibiotic, it acts by switching off protein synthesis within bacteria; this in turn will lead to decreased exotoxin expression, thereby removing the mediators of TSS.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Question: 55 of 100

A 22-year-old female student attended the casualty department complaining of fever and rigors for two days.

She had returned from a sabbatical in Africa six weeks previously.

She was febrile (39.9°C) and a mild petechial rash was also noted.

Laboratory investigations showed:

Hb	10.1 g/dL (11.5-16.5)
WBC	3.0 $x10^9$/L (4-11 $x10^9$)
Platelets	115 $x10^9$/L (150-400 $x10^9$)
Prothrombin time	Normal

What is the most likely diagnosis?

(Please select 1 option)

- Acute HIV infection (seroconversion illness)
- Cytomegalovirus (CMV) infection
- Dengue fever
- *Plasmodium falciparum* malaria
- Typhoid fever

Submit answer | Skip question | Tag Question | Remove question

(Please select 1 option)

○	Acute HIV infection (seroconversion illness) ← This is the correct answer
○	Cytomegalovirus (CMV) infection
◉	Dengue fever ✕ Incorrect answer selected
○	*Plasmodium falciparum* malaria
○	Typhoid fever

A difficult question that partly hinges on the incubation times of these illnesses.

The incubation time is too long for dengue, typhoid and falciparum malaria.

The presentation is not typical of CMV.

Acute human immunodeficiency virus (HIV) HIV presents two weeks to three months after exposure to the virus; the illness typically consists of:

- fever

- arthritis

- rash

- lymphadenopathy.

The presentation given here is not characteristic of acute HIV, but is the most reasonable of the options listed.

Next question | Tag Question | Remove question

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 32 mins 13 secs

Question: 56 of 100

A 70-year-old man presented to his GP with a two day history of increasing confusion. He also complained of a headache.

He was febrile on examination; nuchal rigidity was noted. A lumbar puncture was performed and CSF microscopy revealed:

WBC 800 cells/mL (< 5) 90% neutrophils. A few Gram positive diplococci were also noted.

What is the cause of his meningitis?

(Please select 1 option)

- *Cryptococcus neoformans*
- *Haemophilus influenzae*
- *Listeria monocytogenes*
- *Neisseria meningitidis*
- *Streptococcus pneumoniae*

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

WBC 800 cells/mL (< 5) 90% neutrophils. A few Gram positive diplococci were also noted.

What is the cause of his meningitis?

(Please select 1 option)

○	*Cryptococcus neoformans*
○	*Haemophilus influenzae*
○	*Listeria monocytogenes*
○	*Neisseria meningitidis*
◉	*Streptococcus pneumoniae* ✓ Correct

A question on Gram staining properties of organisms causing meningitis.

Pneumococcal meningitis is commoner in older patients.

Neisseria meningitidis is a Gram negative diplococcus whilst *Haemophilus influenzae* is a Gram negative bacillus.

Listeria monocytogenes is a cause of neonatal meningitis, and is a small Gram positive bacillus that is carried in the intestine and vagina and may be transmitted to the neonate during the birth process.

Cryptococcus neoformans is a fungus and yeast cells may be seen on microscopic examination of the cerebrospinal fluid (CSF).

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Question: 57 of 100

A 35-year-old man returned from a two week holiday complaining of pain in the loins and painful swollen knees. On examination he was afebrile and had significant bilateral knee effusions. Mild penile erythema was also noted.

Laboratory investigations showed:

Hb	15.6 g/dl	(13.0-18.0)
WBC	16.2 x 10^9/l	(4-11)
Neutrophils	14.1 x 10^9/l	(1.5-7)
ESR	65 mm/hr	(0-15 mm/1^{st} hr)
Rheumatoid factor	10 U/l	
Urinalysis	No cells, casts or bacteria seen	

What is the most likely diagnosis?

(Please select 1 option)

- Arthritis due to *Neisseria gonorrhoeae* infection
- *Lymphogranuloma venereum*
- Reactive arthritis
- Reiter's syndrome
- Rheumatoid arthritis

- Shop

Neutrophils	14.1 x 10^9/l	(1.5-7)
ESR	65 mm/hr	(0-15 mm/1^{st} hr)
Rheumatoid factor	10 U/l	
Urinalysis	No cells, casts or bacteria seen	

What is the most likely diagnosis?

(Please select 1 option)

◉	Arthritis due to *Neisseria gonorrhoeae* infection ✓ Correct
○	*Lymphogranuloma venereum*
○	Reactive arthritis
○	Reiter's syndrome
○	Rheumatoid arthritis

The history is relatively acute with the arthritis and urethritis plus there is a neutrophilia.

The diagnostic possibilities include Reiter's or a Gonococcal arthritis. However, in this scenario, the acuteness of the illness on return from a holiday with no evidence of a preceding illness such as diarrhoea, and involvement of the larger joints, i.e. knees with effusions - suggests gonorrhoea.

Guidelines:
British Association for Sexual Health and HIV

Next question | Tag Question | Remove question

Question: 58 of 100

A 50-year-old man presented to hospital feeling generally unwell for three days.

He had returned from a business trip to Thailand six weeks previously and had taken mefloquine as prophylaxis against malaria.

On examination he was afebrile, temperature 36.5°C, pulse was 100/minute and regular, his BP was 85/60 mm Hg.

Investigations showed:

Hb	14.2 g/dL (13.0-18.0)
WBC	19.0 $x10^9$/L (4-11 $x10^9$)
Neutrophils	18.0 $x10^9$/L (1.5-7.0 $x10^9$)
AST	72 U/L (1-31)
Alkaline phosphatase	255 U/L (45-105)

What is the most likely diagnosis?

(Please select 1 option)

○	Acute HIV infection (seroconversion illness)
○	Dengue fever
○	Gram-negative bacteraemia ← This is the correct answer
◉	Hepatitis B ✕ Incorrect answer selected
○	Mefloquine-induced hepatitis

Neutrophils	18.0 x10^9/L (1.5-7.0 x10^9)
AST	72 U/L (1-31)
Alkaline phosphatase	255 U/L (45-105)

What is the most likely diagnosis?

(Please select 1 option)

- ○ Acute HIV infection (seroconversion illness)
- ○ Dengue fever
- ○ Gram-negative bacteraemia ← This is the correct answer
- ◉ Hepatitis B ✕ Incorrect answer selected
- ○ Mefloquine-induced hepatitis

A difficult question.

The neutrophilia essentially excludes most viral causes.

The presentation is not typical of acute human immunodeficiency virus (HIV) (fever, pharyngitis, rash & lymphadenopathy).

Mefloquine can cause abnormal liver function tests (LFTs), but is not common.

Even though the patient is afebrile, the likeliest diagnosis is therefore Gram-negative bacteraemia.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 37 mins 27 secs

Question: 59 of 100

A 68-year-old man has been very ill for months following the onset of chronic liver disease with hepatitis C infection.

He experiences a sudden loss of consciousness and then exhibits hemiplegia on the right. A cerebral angiogram reveals lack of perfusion in the left middle cerebral artery distribution.

What is the most likely cardiac lesion to be associated with this finding?

(Please select 1 option)

- Acute rheumatic fever
- Left atrial myxoma
- Libman-Sacks endocarditis
- Non-bacterial thrombotic endocarditis
- Paradoxical thromboembolus

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 39 mins 27 secs

Question: 59 of 100

A 68-year-old man has been very ill for months following the onset of chronic liver disease with hepatitis C infection.

He experiences a sudden loss of consciousness and then exhibits hemiplegia on the right. A cerebral angiogram reveals lack of perfusion in the left middle cerebral artery distribution.

What is the most likely cardiac lesion to be associated with this finding?

(Please select 1 option)

○	Acute rheumatic fever
○	Left atrial myxoma
○	Libman-Sacks endocarditis
◉	Non-bacterial thrombotic endocarditis ✓ Correct
○	Paradoxical thromboembolus

Marantic endocarditis has platelet-fibrin thrombi that are prone to embolising.

This form of non-infective endocarditis can be seen in persons who are very debilitated or who have a hypercoagulable state.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

A young girl returns from a trip to India with a protracted history of watery diarrhoea.

Giardiasis is suspected but three stool samples are negative.

What is the best investigation to confirm *Giardia* as a diagnosis?

(Please select 1 option)

○	CT abdomen
○	Rectal biopsy
○	Serum IgM *Giardia* antibodies
◉	Small intestine biopsy ✓ Correct
○	Stool microscopy

Giardia may be difficult to diagnose from stool samples alone. Concentration techniques and optimising sample preparation may improve stool sample yield.

However, parasitic antigen detection in stool is at least as sensitive and specific as good microscopic examination of stool, and maybe easier to perform.

In this case detection of *Giardia* may be achieved by sampling of duodenal fluid, or small bowel biopsy.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 5 mins 39 secs

Question: 6 of 100

A 82-year-old lady is admitted from her nursing home with headache, photophobia and neck stiffness.

Her temperature is 39.0°C, pulse rate 115 beats/min. There is no skin rash or focal neurological signs and her Glasgow coma scale is 15/15.

A CT scan shows no contraindication to lumbar puncture. CSF is obtained and Gram stain shows Gram-negative coccobacilli, subsequent culture confirms a *Haemophilus influenzae* meningitis.

What chemoprophylaxis should be offered to the nurses at her home?

(Please select 1 option)

○	Azithromycin
○	Ceftriaxone
○	Ciprofloxacin
○	No chemoprophylaxis required
○	Rifampicin

Submit answer | Skip question | Tag Question | Remove question

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 39 mins 27 secs

Question: 60 of 100

Which of the following statements is true of psittacosis (ornithosis)?

(Please select 1 option)

○	Infection responds rapidly to penicillin therapy
○	It does spread from person to person
○	It is more of a risk to children than to adults who are exposed to birds
○	It is only a risk from contact with psittacines (parrots), not other birds
○	It usually causes many polymorphs to be present in the sputum

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 41 mins

Question: 60 of 100

Which of the following statements is true of psittacosis (ornithosis)?

(Please select 1 option)

○	Infection responds rapidly to penicillin therapy
◉	It does spread from person to person ✓ Correct
○	It is more of a risk to children than to adults who are exposed to birds
○	It is only a risk from contact with psittacines (parrots), not other birds
○	It usually causes many polymorphs to be present in the sputum

Chlamydia psittaci is endemic in birds including psittacine birds, canaries, finches, pigeons and poultry.

Pet owners, vets and zoo keepers are most at risk. It is rare in children.

Person to person transmission occurs especially in a hospital environment.

Sputum Gram stain reveals a few leucocytes and no predominant bacteria. There are few signs and few laboratory/x ray findings.

Positive serology is with complement-fixing antibodies.

It is treated with tetracycline.

Next question

Tag

2006 UK National Guideline for the Management of Genital Tract Infection with *Chlamydia trachomatis*

Introduction and Methodology

Scope and Purpose

The main objective is to reduce the number of sexually transmitted infections (STIs) and the complications that can arise in people either presenting with signs and symptoms of an STI, or undergoing investigation for possible infection.

Specifically:
This guideline offers recommendations on the diagnostic tests, treatment regimens and health promotion principles needed for the effective management of C.*trachomatis*. It covers management of the initial presentation, as well as how to prevent transmission and future infection.

It is aimed primarily at people aged 16 years or older (see specific guidelines for those under 16) presenting to health care professionals, working in departments offering level 3 care in STI management (see national strategy) within the United Kingdom. However, the principles of the recommendations should be adopted across all levels (levels 1 and 2 may need to develop, where appropriate, local care pathways).

Stakeholder Involvement

This guideline has been produced by medical specialists from relevant disciplines with input from patients attending UK GUM clinics. Successive drafts have been reviewed by GUM patients, GUM physicians, nurses, health advisers and key professional organisations.

Rigour of Development

An extensive literature reviewed was carried out using Medline searches for the years 1970 to 2001 using keywords “Chlamydia trachomatis” in association

with "polymerase chain reaction" or "PCR" or "ligase chain reaction" or "lcr" or "lcx" and "immunoenzyme techniques" or "enzyme-linked immunosorbent assay". "Chlamydia trachomatis" combined with the following key words "detection", "diagnosis", "treatment". The Cochrane library: "Chlamydia trachomatis". This literature search was updated in 2005 and included nucleic acid amplification technique, Aptima, Probetec and SDA.

What's New?

NAATs to be used for medico-legal cases

EIAs to be replaced by NAATs

Update on performances of NAATs

Offer epidemiological treatment to contacts of *C.trachomatis* as per index case.

Azithromycin 1 gm stat in pregnancy recommended by WHO; unlicensed in UK (2006). BNF recommend use only if no other alternative available.

Recommendation for partner notification rates: 0.43 contacts per case in cities, 0.64 contacts per case elsewhere.

Aetiology

C.trachomatis is the most common curable sexually transmitted infection in Britain. Approximately 5-10% of sexually active women under 24 and men between 20-24 may be currently infected (1-4). Risk factors for infection includes age under 25yrs, new sexual partner or more than one sexual partner in the past year, a new sexual partner being more important than number of partners (4), and lack of consistent use of condoms (5-9). *C.trachomatis* is frequently asymptomatic in both men and women and ongoing transmission in the community is sustained by this un-recognised infection.

The natural history of *C.trachomatis* infections is poorly understood. Infection is primarily through penetrative sexual intercourse, however infection can be

detected at the conjunctiva and nasopharynx without concomitant genital tract infection (10;11).

If untreated, infection may persist or resolve spontaneously (12-17). Two thirds of sexual partners of chlamydia-positive individuals

are also chlamydia-positive (18-21).

In response to the evidence of high and increasing rates of infection, the Government has introduced a national chlamydial screening programme (NCSP) (22;23).

Clinical features

Symptoms and Signs

Women

- Asymptomatic in approximately 70%
- Post coital or intermenstrual bleeding
- Lower abdominal pain
- Purulent vaginal discharge
- Mucopurulent cervicitis and/or contact bleeding
- Dysuria

Men

- Asymptomatic in over 50% in a community setting (3)
- Urethral discharge
- Dysuria

The severity of these two symptoms is variable and may be so mild as to be unnoticed by the patient.

Rectal infections

Usually asymptomatic, but may cause anal discharge and anorectal discomfort

(proctitis) (24).

Pharyngeal infections

These are asymptomatic and are uncommon (24;25).

Complications

In the absence of treatment, 10-40% of infected women will develop pelvic inflammatory disease (PID) with a significant proportion of these cases being asymptomatic or having mild, atypical symptoms (26;27). PID can result in tubal factor infertility, ectopic pregnancy and chronic pelvic pain (26;28). The risk of developing PID increases with each recurrence of *C.trachomatis* infection, as does the risk of reproductive sequelae (29;30). Other complications include Fitz-Hugh-Curtis syndrome (perihepatitis), transmission to neonate (neonatal conjunctivitis, pneumonia), epididymo-orchitis, adult conjunctivitis and sexually acquired reactive arthritis /Reiter's syndrome (commoner in men). It is estimated that complications cost at least £100 million annually in the United Kingdom (22). The majority of health economic valuations demonstrate that chlamydia screening is cost effective (28;31;32).

Diagnosis

Nucleic Acid Amplification Technique

- Although the technology for diagnosing C.*trachomatis* continues to be a rapidly developing field, the standard of care for all cases, including medico legal cases, is a nucleic acid amplification technique (NAAT).
- NAATs are more sensitive and specific than enzyme immunoassays (EIAs) and the Department of Health has recently advised that the use of sub-optimal EIAs is no longer appropriate and has provided funding to support laboratories moving from EIAs to NAATs (33). However no test is 100% sensitive or specific (34).
- Reactive tests should confirmed in the laboratory either using the same NAAT platform but if possible a second platform is to be preferred

(34;35). This improves specificity by countering processing errors but at the expense, which is usually judged acceptable, of a small reduction in sensitivity caused by specimens with a low organism load being missed at re-test (34). Thus therapy should be offered to all patients with unconfirmed reactive NAAT results but the significance of this result must be discussed with them (36). The laboratory report should request an additional specimen for further testing when reporting an unconfirmed reactive test, but this may be not be possible (34;35).

- An inhibitory control should be used for each specimen (34;35) as substances may be present in biological fluids which can inhibit NAATs. Failure to use an inhibitory control with each specimen will lead to false negative results (37-39). The Gen-Probe Aptima system includes a nucleic acid extraction stage which removes the majority of inhibitors and thus the manufacturers state that no inhibitory control is needed (39).
- In general NAATs are 90-95% sensitive with the majority of studies indicating that as either the number of sites sampled increases, or the number of different NAAT used increases, the greater the detection of C.*trachomatis* in any given population.

Sites to be sampled

Women

- A cervical swab (Grade of recommendation B) or vulvo vaginal swab (Grade of recommendation C) are specimens of choice. To collect cervical specimens, a speculum examination is performed and as the sample must contain cervical columnar cells (40;41), swabs should be inserted inside the cervical os and firmly rotated against the endocervix. Inadequate specimens reduce the sensitivity of NAATs.
- The vulvo-vaginal swab has a sensitivity of 90-95% (47-50) and can be either taken by the patient or health care worker (43). Studies indicate that sensitivities similar to a cervical swab are obtainable. Currently,

only the APTIMA system (Gen-Probe Inc., San Diego, CA) has FDA approval for this specimen type.

- If a speculum examination is not possible then urine (Grade of recommendation B) samples can be utilized.
- Variable sensitivities (65-100%) have been reported using the first catch urine (FCU) specimen (42-46). When processed by inexperienced staff it may perform with sensitivity <90% (43). Patients should hold their urine for at least 1 hour (36) (maybe 2 hours with some kits, check manufacturer's instructions) before providing a FCU specimen.

Men

- First voided urine sample is reported to be as good as a urethral swab (44;51-54). Urine samples are easy to collect, do not cause discomfort and thus are preferable to urethral swabs. Urethral swabs should be inserted 2-4cm inside the urethra and rotated once before removal (Grade of recommendation C).
- Patients should hold their urine at least 1 hour before being tested (36), (maybe 2 hours with some kits, check manufacturer's instructions).

Rectal, Pharyngeal and Conjunctival specimens, men and women

- Currently none of the NAATs have FDA approval for these sites. Only Culture or DFA are recommended (Grade of recommendation A). However, in the absence of Culture or DFA tests, NAATs may be used (Grade of recommendation C).

  Rectal swabs should be obtained via proctoscopy.

- Due to the emergence of rectal Lymphogranuloma venereum infection in men who have sex with men(55), the current (2006) recommended method of detecting rectal LGV infection is to perform a rectal NAAT which, if positive, is sent to the Health Protection Authority for confirmation.

Medico Legal Cases

For medico legal cases a NAAT should be taken from all the sites where penetration has occurred. This guideline recommends NAAT rather than culture due to the low sensitivity (60-80%) of culture and its lack of availability in many centres (Grade of recommendation D).

- A reactive NAAT result must be confirmed using a different NAAT (36). Ideally, two swabs should be taken from each site, one for testing and one for confirmation if the initial test is positive. This avoids potential compatibility problems when retesting specimens using a different platform (34). There is evidence that the Becton Dickinson ProbeTec ET strand displacement amplification (SDA) assay has a lower analytical sensitivity than Roche Cobas Amplicor PCR(56) for some serotypes, which means that SDA may not be suitable for the confirmation of PCR results. There are also data to suggest that Gen-Probe APTIMA system has a higher sensitivity than the other two assays discussed (57). Although, this system does have its own confirmatory assay with matching sensitivity it uses the same methodology, on the same specimen, thus theoretically some causes of false positives may not be eliminated.(36)

Cell culture

- Sensitivity 60-80%
- 100% specificity
- Expertise essential
- Expensive – and only limited availability nationally
- Can be used on all specimen types
- Routine use is not recommended due to high cost and low sensitivity.

Enzyme immunoassays (EIAs)

- The sensitivity of the majority of EIAs is probably only 40-70% and their use is not recommended. This guideline recommends laboratories to

move to the use of NAATs utilizing Department of Health dedicated funding (30).

- Should be not used on non-invasive specimens in women, nor on rectal or throat specimens in women or men.

Direct fluorescent antibody (DFA)

- Routine use is not recommended.
- Labour intensive, and although a >80% sensitivity is achievable, this requires skilled personnel using a cut off of 2 elementary bodies.
- Unsuitable for large numbers of specimens (>30/day).
- Will accommodate all specimen types including rectal and pharyngeal

Management

General Advice

Ideally, treatment should be effective (microbiological cure rate >95%), easy to take (not more than twice daily), with a low side effect profile, and cause minimal interference with daily lifestyle (Grade of recommendation C). Uncomplicated genital tract infection with *C.trachomatis* is not an indication for removal of an IUS or IUD.

Patients should be advised to avoid sexual intercourse (including oral sex) until they and their partner(s) have completed treatment (or wait 7 days if treated with Azithromycin). Advice regarding appropriate action if using hormonal contraceptives is also required.

Patients should be given detailed explanation of their condition with particular emphasis on the long–term implications for their and their partner(s). This should be reinforced by giving them clear, accurate written information.

Further Investigation

All patients diagnosed with *C.trachomatis* should be encouraged to have screening for other STIs, including an HIV test and, where indicated hepatitis B

screening and vaccination (Grade of recommendation C). If the patient is within the window period for HIV and syphilis, these should be repeated at an appropriate time interval. All contacts of *C.trachomatis* should be offered the same screening tests.

Treatment of genital, rectal and pharyngeal uncomplicated infection (see appropriate guidelines for treatment of complications) and epidemiological treatment

Recommended regimens: **(Grade of recommendation A)**

- Doxycycline 100mg bd for 7 days (contraindicated in pregnancy)

or

- Azithromycin 1gm orally in a single dose

Alternative regimens*:* **(Grade of recommendation A)**

For use if either of the above treatments are contraindicated.

- Erythromycin 500mg bd for 10-14 days

or

- Ofloxacin 200mg bd or 400mg once a day for 7 days

Studies of anti-microbial efficacy

Azithromycin and Doxycycline

Doxycycline and azithromycin are the most rigorously investigated. Comparative studies with follow-up periods from 2-5 weeks have demonstrated similar efficacy, with >95% being chlamydia-negative on re-testing with a NAAT or culture (58). However there is now good evidence that when patients, treated with azithromycin 1gm or doxycycline 100mgs bd 7 days, are followed up for longer, >10% will be chlamydia-positive on retesting (59-62). In the chlamydia re-infection study, there was no difference in the re-infection rates between women who received doxycycline (n=88) and those who received azithromycin (n=325) (HR 0.8, 95% CI:0.4-1.4) even after adjusting for all covariates (personal communication D Scott LaMontagne) (63).

Resistance to tetracycline and macrolides has been detected in vivo but appears to be rare (64). It has not been documented to be significant in vitro.

Other anti-microbials

The information from published studies on efficacy of other anti-microbials is considerably less than that available for azithromycin and doxycycline. It should not be assumed that these are more efficacious than either doxycycline or azithromycin.

***Ofloxacin* (Grade of recommendation B)**

- It is unknown whether 200mg twice a day is superior to 400mg once a day (65).
- Ofloxacin has similar efficacy to doxycycline and a better side-effect profile but is considerably more expensive, so is not recommended as first-line treatment.
- Resistance to ofloxacin has been demonstrated in vivo and in vitro, but appears to be rare (64).
- No long term follow up (>6 weeks) data.

***Erythromycin* (Grade of recommendation A)**

- Erythromycin is less efficacious than either azithromycin or doxycycline.
- When taken four times a day, 20-25% may experience side-effects sufficient to cause the patient to discontinue treatment (66).
- There are only limited data on erythromycin 500mg twice a day, with efficacy reported at between 73%-95%. A 10-14 day course appears to be more efficacious than a 1 week course of 500mg twice a day, with a cure rate >95% (59;67)
- Resistance to erythromycin has been demonstrated in vivo and appears to be rare. It has not been documented to be significant in vivo.

***Other tetracyclines* (Grade of recommendation A)**

- "Deteclo" (registered trademark) is probably as efficacious as Doxycycline (68). However, photosensitivity occurs more frequently and there is insufficient data on efficacy if compliance is poor.
- Oxytetracycline 500mgs bd 10 days has also been shown to be effective (59).

Pregnancy and breast feeding

Recommended regimens; (Grade of recommendation A)

- Erythromycin 500mg four times a day for 7 days

or

- Erythromycin 500 mg twice a day for 14 days

or

- Amoxicillin 500 mg three times a day for 7 days

or

- Azithromycin 1 gm stat (see caution below from BNF)

Due to higher positive chlamydia tests after treatment in pregnancy, attributed to either less efficacious treatment regime, non compliance or re-infection, it is recommended that pregnant woman must have a test of cure 5 weeks after completing therapy, 6 weeks later if given azithromycin.

- Doxycycline and ofloxacin are contraindicated in pregnancy
- Azithromycin; is probably less than 95% effective (69-71). The safety of azithromycin in pregnancy and lactating mothers has not yet been fully assessed, although available data indicate that it is safe (71). WHO Guidelines recommend 1gm stat to treat *C.trachomatis* in pregnancy, the BNF recommends its use in pregnancy and lactation only if no alternative is available.
- Erythromycin has a significant side effect profile and is less than 95% effective. There are no trials of erythromycin 500mg twice a day for 14

days, which would be better tolerated than four times a day although the follow-up data from the Portsmouth pilot study suggests it is efficacious (59).

- Amoxycillin had a similar cure rate to erythromycin in a meta-analysis and had a much better side effect profile (71). However, penicillin *in vitro* has been shown to induce latency and re-emergence of infection at a later date is a theoretical concern of some experts.

Compliance with therapy

In general compliance with therapy is improved if there is a positive therapeutic relationship between the patient and the doctor (72) and /or nurse.

This can probably be improved if the following are applied (Grade of recommendation C):

Discuss with patient and provide clear written information on:

- What *C.trachomatis* is and how it is transmitted
    - It is primarily sexually transmitted
    - If asymptomatic there is evidence that it could have persisted for months or years
- The diagnosis of *C.trachomatis*, particularly:
    - It is often asymptomatic in both men and women
    - Whilst tests are accurate, no test is absolutely so
- The complications of untreated *C.trachomatis*
- Side effects and importance of complying fully with treatment and what to do if a dose is missed.
- Advice regarding antibiotics and hormonal contraception.
- The importance of their sexual partner(s) being evaluated and treated.

- Advised to abstain from sexual intercourse until they and their partner(s) have completed therapy (and waited 7 days if treated with azithromycin).
- Advice on safer sexual practices, including advice on correct,

  consistent condom use.

Reducing the risk of individuals retesting chlamydia-positive following treatment.

Background

- Partner notification by practice nurses who receive brief training and ongoing support from a health adviser has been shown to be at least as successful as that achieved by referral to a genitourinary medicine clinic for individuals with chlamydia diagnosed in the community (73).
- NAATs may remain positive up to five weeks post treatment. This does not necessarily mean active infection as it may represent the presence of nucleic acid from non-viable organisms.
- Re-testing *C. trachomatis*-positive can result from either sub-optimal antimicrobial therapy (see above) or re-infection. Re-infection may result either from having sexual intercourse with an untreated, sub-optimally treated or a new partner who is *C. trachomatis* positive.
- Latency and antimicrobial resistance are areas currently being researched (74).

Recommendations

- Advise (and document that advice given) no genital, oral or anal sex, even with a condom, until both index patient and their partner(s) have completed treatment or if the partner(s) choose testing only until the partner(s) have a negative test.
- Abstain as above from sexual activity, for one week after azithromycin 1gm stat.

Management of sexual partners

- All patients identified with *C. trachomatis* should have partner notification discussed at time of treatment by a trained health care professional.
- The method of partner notification agreed for each partner/contact identified should be documented, as should partner notification outcomes.
- All sexual partners should be offered, and encouraged to take up a full STI screen, including HIV test and if indicated hepatitis B screening +/- vaccination.
- Epidemiological treatment for *C.trachomatis* should be offered. If declined, patients must be advised to abstain from sex until they have received a negative result. If found to be positive, any other potentially exposed partner(s) needs screening and the offer of epidemiological treatment.

Look back period

Only limited evaluation has taken place of the incubation period following exposure to the development of symptoms. In the United Kingdom a cut-off of 4 weeks is used to identify those sexual partner(s) potentially at risk if the index patient is symptomatic. If the index case is asymptomatic, an arbitrary cut off of 6 months, or until the last previous sexual partner (whichever is the longer time period), is used. Common sense needs to be used in assessing which sex partner(s) may have been at risk in these situations.

Those at risk should be informed and invited to attend for evaluation and epidemiological treatment even if tests are negative. This may be patient or provider-led.

Follow up

Follow up by phone may be both more efficacious and cost effective than by re-attendance.

This is an important part of the management of chlamydial infection and it has a number of objectives including:

- Following up partner notification
- Reinforcing health education
- Ensuring compliance with treatment and abstinence from sexual intercourse until partner(s) have completed antibiotics (if treated with azithromycin waiting seven days).
- There is evidence to suggest that follow-up by phone may be more efficacious than asking the patient to re-attend. It is therefore likely that the former method is more cost effective (75).
- Re-treat non-compliant and/or re-exposed individuals.

Test of Cure

A test of cure is not routinely recommended but should be performed in pregnancy or if non-compliance or re-exposure is suspected. It should be deferred for 5 weeks (6 weeks if azithromycin given) after treatment is completed.

Qualifying statement

The recommendations in this guideline may not be appropriate for use in all clinical situations. Decisions to follow these recommendations must be based on the professional judgement of the clinician and consideration of individual patient circumstances and available resources. All possible care has been undertaken to ensure the publication of the correct dosage of medication and route of administration. However, it remains the responsibility of the prescribing physician to ensure the accuracy and appropriateness of the medication they prescribe.

Auditable Outcome Measures

- Compliance with clinical standards of care.
- Partner notification recommendation: In 2004, a systematic review of UK GUM clinics' work showed that a mean of 0.43 contacts per case of chlamydia were screened in large city clinics and 0.64 contacts per case of chlamydia were screened in other clinics (76).

Acknowledgements

We wish to thank the following for their valuable contributions to this guideline: Dr Caroline Carder, Dr Alan Herring, Scott LaMontagne, NCSP, Dr Nicola Low ClaSS, Dr Jan Welch and members of the Bacterial Special Interest Group of BASHH.

Author(s) and centres

Patrick J Horner, Department of Genitourinary Medicine, The Milne Centre, Bristol Royal Infirmary, Bristol and Fiona Boag, Consultant Physician, Department of GUM, Chelsea & Westminster Hospital, London on behalf of the Clinical Effectiveness Group: Chairman Keith Radcliffe; Imtyaz Ahmed-Jushuf; David Daniels; Mark FitzGerald; Neil Lazaro; Gillian McCarthy; Guy Rooney.

Editorial Independence

This guideline was commissioned and edited by the CEG of the BASHH, without external funding being sought or obtained.

Conflicts of interest: P. Horner - none.
F. Boag – none.

Version updated July 2006. Duration of currency to July2008

Updates 2002 clinical effectiveness guidelines for the management of genital tract infection with Chlamydia trachomatis.

References

(1) Fenton KA, Korovessis C, Johnson AM, McCadden A, McManus S, Wellings K et al. Sexual behaviour in Britain: reported sexually transmitted infections and prevalent genital *Chlamydia trachomatis* infection. Lancet 2001 December 1;358(9296):1851-4.

(2) LaMontagne DS, Fenton KA, Randall S, Anderson S, Carter P, on behalf of the National Chlamydia Screening Steering Group. Establishing the National Chlamydia Screening Programme in England: results from the first full year of screening. Sex Transm Infect 2004 October 1;80(5):335-41.

(3) McKay L, Clery H, Carrick-Anderson K, Hollis S, Scott G. Genital *Chlamydia trachomatis* infection in a subgroup of young men in the UK. Lancet 2003 May 24;361(9371):1792.

(4) Macleod J, Salisbury C, Low N, McCarthy A, Sterne JA, Holloway A et al. Coverage and uptake of systematic postal screening for genital *Chlamydia trachomatis* and prevalence of infection in the United Kingdom general population: cross sectional study. BMJ 2005 April 23;330(7497):940.

(5) Paz-Bailey G, Koumans EH, Sternberg M, Pierce A, Papp J, Unger ER et al. The effect of correct and consistent condom use on chlamydial and gonococcal infection among urban adolescents. Archives of Pediatrics & Adolescent Medicine 2005 June;159(6):536-42.

(6) Warner L, Macaluso M, Austin HD, Kleinbaum DK, Artz L, Fleenor ME et al. Application of the case-crossover design to reduce unmeasured confounding in studies of condom effectiveness. Am J Epidemiol 2005 April 15;161(8):765-73.

(7) Brabin L, Fairbrother E, Mandal D, Roberts SA, Higgins SP, Chandiok S et al. Biological and hormonal markers of chlamydia, human papillomavirus, and bacterial vaginosis among adolescents attending genitourinary medicine clinics. Sex Transm Infect 2005 April;81(2):128-32.

(8) Miranda AE, Szwarcwald CL, Peres RL, Page-Shafer K. Prevalence and risk behaviors for chlamydial infection in a population-based study of female adolescents in Brazil. Sexually Transmitted Diseases 2004 September;31(9):542-6.

(9) Warner L, Newman DR, Austin HD, Kamb ML, Douglas JM, Jr., Malotte CK et al. Condom effectiveness for reducing transmission of gonorrhea and chlamydia: the importance of assessing partner infection status.[see comment]. Am J Epidemiol 2004 February 1;159(3):242-51.

(10) Postema EJ, Remeijer L, van der Meijden WI. Epidemiology of genital chlamydial infections in patients with chlamydial conjunctivitis; a retrospective study. Genitourinary Medicine 1996 June;72(3):203-5.

(11) Stenberg K, Mardh PA. Treatment of concomitant eye and genital chlamydial infection with erythromycin and roxithromycin. Acta Ophthalmologica 1993 June;71(3):332-5.

(12) Joyner JL, Douglas JM, Jr., Foster M, Judson FN. Persistence of *Chlamydia trachomatis* infection detected by polymerase chain reaction in untreated patients. Sexually Transmitted Diseases 2002 April;29(4):196-200.

(13) Morre SA, van den Brule AJ, Rozendaal L, Boeke AJ, Voorhorst FJ, de Blok S et al. The natural course of asymptomatic *Chlamydia trachomatis* infections: 45% clearance and no development of clinical PID after one-year follow-up. International Journal of STD & AIDS 2002 December;13 Suppl 2:12-8.

(14) Parks KS, Dixon PB, Richey CM, Hook EW, III. Spontaneous clearance of Chlamydia trachomatis infection in untreated patients. Sexually Transmitted Diseases 1997 April;24(4):229-35.

(15) Golden MR, Schillinger JA, Markowitz L, St Louis ME. Duration of untreated genital infections with *Chlamydia trachomatis*: a review of the literature. [Review] [84 refs]. Sexually Transmitted Diseases 2000 July;27(6):329-37.

(16) van den Brule AJ, Munk C, Winther JF, Kjaer SK, Jorgensen HO, Meijer CJ et al. Prevalence and persistence of asymptomatic *Chlamydia trachomatis* infections in urine specimens from Danish male military recruits. International Journal of STD & AIDS 2002 December;13 Suppl 2:19-22.

(17) Molano M, Meijer CJ, Weiderpass E, Arslan A, Posso H, Franceschi S et al. The natural course of *Chlamydia trachomatis* infection in asymptomatic Colombian women: a 5-year follow-up study. Journal of Infectious Diseases 2005 March 15;191(6):907-16.

(18) Clad A, Prillwitz J, Hintz KC, Mendel R, Flecken U, Schulte-Monting J et al. Discordant prevalence of *Chlamydia trachomatis* in asymptomatic couples screened using urine ligase chain reaction. European Journal of Clinical Microbiology & Infectious Diseases 2001 May;20(5):324-8.

(19) Lin JS, Donegan SP, Heeren TC, Greenberg M, Flaherty EE, Haivanis R et al. Transmission of *Chlamydia trachomatis* and *Neisseria gonorrhoeae* among men with urethritis and their female sex partners. Journal of Infectious Diseases 1998 December;178(6):1707-12.

(20) Quinn TC, Welsh L, Lentz A, Crotchfelt K, Zenilman J, Newhall J et al. Diagnosis by AMPLICOR PCR of *Chlamydia trachomatis* infection in

urine samples from women and men attending sexually transmitted disease clinics. J Clin Microbiol 1996 June;34(6):1401-6.

(21) Khan AM. The Prevalence of Chlamydia, Gonorrhea, and Trichomonas in Sexual Partnerships: Implications for Partner Notification and Treatment. Sexually Transmitted Diseases 2005 April;32(4):260-4.

(22) Department of Health. National Chlamydia Screening Programme in England: Programme overview. Department of Health 2004;(2nd)Available from: URL: http://www.dh.gov.uk/assetRoot/04/09/26/48/04092648.pdf

(23) Hamlyn C. Roll out of the national chlamydia screening programme (NCSP). Department of Health 2005;Available from: URL: http://www.dh.gov.uk/assetRoot/04/11/42/07/04114207.pdf

(24) Jones RB, Rabinovitch RA, Katz BP, Batteiger BE, Quinn TS, Terho P et al. *Chlamydia trachomatis* in the pharynx and rectum of heterosexual patients at risk for genital infection. Ann Intern Med 1985 June;102(6):757-62.

(25) Winter AJ, Gilleran G, Eastick K, Ross JD. Comparison of a ligase chain reaction-based assay and cell culture for detection of pharyngeal carriage of *Chlamydia trachomatis*. J Clin Microbiol 2000 September;38(9):3502-4.

(26) Paavonen J, Eggert-Kruse W. *Chlamydia trachomatis*: impact on human reproduction. Hum Reprod Update 1999 September 1;5(5):433-47.

(27) Simms I, Stephenson JM. Pelvic inflammatory disease epidemiology: what do we know and what do we need to know? Sex Transm Infect 2000 April 1;76(2):80-7.

(28) Hu D, Hook EW, III, Goldie SJ. Screening for *Chlamydia trachomatis* in Women 15 to 29 Years of Age: A Cost-Effectiveness Analysis. Ann Intern Med 2004 October 5;141(7):501-13.

(29) Hillis SD, Joesoef R, Marchbanks PA, Wasserheit JN, Cates W, Jr., Westrom L. Delayed care of pelvic inflammatory disease as a risk factor for impaired fertility. American Journal of Obstetrics & Gynecology 1993 May;168(5):1503-9.

(30) Westrom LV. Sexually transmitted diseases and infertility. [Review] [30 refs]. Sexually Transmitted Diseases 1994 March;21(2 Suppl):S32-S37.

(31) Honey E, Augood C, Templeton A, Russell I, Paavonen J, Mardh PA et al. Cost effectiveness of screening for *Chlamydia trachomatis*: a review of published studies. Sex Transm Infect 2002 December 1;78(6):406-12.

(32) van Valkengoed I, Morre SA, van den Brule AJ, Meijer CJ, Bouter LM, Boeke AJ. Overestimation of complication rates in evaluations of

Chlamydia trachomatis screening programmes--implications for cost-effectiveness analyses. International Journal of Epidemiology 2004 April;33(2):416-25.

(33) Department of Health. *Sexual health and HIV strategy: Chlamydia Screening* . London: DoH; 2003.

(34) Skidmore S, Herring A, Horner P, Mallinson H, on behalf of the HPA Chlamydia Diagnosis Forum. Testing specimens for *Chlamydia trachomatis*. Sex Transm Infect 2006;submitted 2005.

(35) Health Protection Agency. *Chlamydia Infection* - Testing by Nucleic Acid Amplification Tests (NAATs) - minimum testing algorithm. National Standard Method VSOP 37 Issue 1 2004;Available from: URL: http://www.hpa-standardmethods.org.uk/documents/vsop/pdf/vsop37.pdf

(36) Johnson RE, Newhall WJ, Papp JR, Knapp JS, Black CM, Gift TL et al. Screening tests to detect *Chlamydia trachomatis* and *Neisseria gonorrhoeae* infections--2002. Morbidity & Mortality Weekly Report 2002 October 18;Recommendations & Reports. 51(RR-15):1-38.

(37) Horner P, Skidmore S, Herring A, Sell J, Paul I, Caul EO et al. Enhanced Enzyme Immunoassay with Negative-Gray-Zone Testing Compared to a Single Nucleic Acid Amplification Technique for Community-Based Chlamydial Screening of Men. Journal of Clinical Microbiology , In press. 2005.

(38) Mahony J, Chong S, Jang D, Luinstra K, Faught M, Dalby D et al. Urine specimens from pregnant and nonpregnant women inhibitory to amplification of *Chlamydia trachomatis* nucleic acid by PCR, ligase chain reaction, and transcription-mediated amplification: identification of urinary substances associated with inhibition and removal of inhibitory activity. J Clin Microbiol 1998 November;36(11):3122-6.

(39) Chong S, Jang D, Song X, Mahony J, Petrich A, Barriga P et al. Specimen processing and concentration of *Chlamydia trachomatis* added can influence false-negative rates in the LCx assay but not in the APTIMA Combo 2 assay when testing for inhibitors. J Clin Microbiol 2003 February;41(2):778-82.

(40) Loeffelholz MJ, Jirsa SJ, Teske RK, Woods JN. Effect of endocervical specimen adequacy on ligase chain reaction detection of *Chlamydia trachomatis*. J Clin Microbiol 2001 November;39(11):3838-41.

(41) Welsh LE, Quinn TC, Gaydos CA. Influence of endocervical specimen adequacy on PCR and direct fluorescent-antibody staining for detection of *Chlamydia trachomatis* infections. J Clin Microbiol 1997 December;35(12):3078-81.

(42) McCartney RA, Walker J, Scoular A. Detection of *Chlamydia trachomatis* in genitourinary medicine clinic attendees: comparison of strand displacement amplification and the ligase chain reaction. British Journal of Biomedical Science 2001;58(4):235-8.

(43) Schachter J, McCormack WM, Chernesky MA, Martin DH, Van Der PB, Rice PA et al. Vaginal swabs are appropriate specimens for diagnosis of genital tract infection with *Chlamydia trachomatis*. J Clin Microbiol 2003 August;41(8):3784-9.

(44) Van Der Pol B., Ferrero DV, Buck-Barrington L, Hook E, III, Lenderman C, Quinn T et al. Multicenter evaluation of the BDProbeTec ET System for detection of *Chlamydia trachomatis* and *Neisseria gonorrhoeae* in urine specimens, female endocervical swabs, and male urethral swabs. J Clin Microbiol 2001 March;39(3):1008-16.

(45) Jensen IP, Thorsen P, Moller BR. Sensitivity of ligase chain reaction assay of urine from pregnant women for *Chlamydia trachomatis*. Lancet 1997 February 1;349(9048):329-30.

(46) Moncada J, Schachter J, Hook EW, III, Ferrero D, Gaydos C, Quinn TC et al. The effect of urine testing in evaluations of the sensitivity of the Gen-Probe Aptima Combo 2 assay on endocervical swabs for *Chlamydia trachomatis* and *Neisseria gonorrhoeae*: the infected patient standard reduces sensitivity of single site evaluation. Sexually Transmitted Diseases 2004 May;31(5):273-7.

(47) Carder C, Robinson AJ, Broughton C, Stephenson JM, Ridgway GL. Evaluation of self-taken samples for the presence of genital *Chlamydia trachomatis* infection in women using the ligase chain reaction assay. International Journal of STD & AIDS 1999 December;10(12):776-9.

(48) Macmillan S, McKenzie H, Flett G, Templeton A. Feasibility of patient-collected vulval swabs for the diagnosis of *Chlamydia trachomatis* in a family planning clinic: a pilot study. British Journal of Family Planning 2000 October;26(4):202-6.

(49) Wiesenfeld HC, Heine RP, Rideout A, Macio I, DiBiasi F, Sweet RL. The vaginal introitus: a novel site for *Chlamydia trachomatis* testing in women. American Journal of Obstetrics & Gynecology 1996 May;174(5):1542-6.

(50) Gaydos CA, Quinn TC, Willis D, Weissfeld A, Hook EW, Martin DH et al. Performance of the APTIMA Combo 2 assay for detection of *Chlamydia trachomatis* and *Neisseria gonorrhoeae* in female urine and endocervical swab specimens. J Clin Microbiol 2003 January;41(1):304-9.

(51) Chernesky MA, Martin DH, Hook EW, Willis D, Jordan J, Wang S et al. Ability of new APTIMA CT and APTIMA GC assays to detect *Chlamydia*

trachomatis and *Neisseria gonorrhoeae* in male urine and urethral swabs. J Clin Microbiol 2005 January;43(1):127-31.

(52) Crotchfelt KA, Welsh LE, DeBonville D, Rosenstraus M, Quinn TC. Detection of *Neisseria gonorrhoeae* and *Chlamydia trachomatis* in genitourinary specimens from men and women by a coamplification PCR assay. J Clin Microbiol 1997 June;35(6):1536-40.

(53) Young H, Moyes A, Horn K, Scott GR, Patrizio C, Sutherland S. PCR testing of genital and urine specimens compared with culture for the diagnosis of chlamydial infection in men and women. International Journal of STD & AIDS 1998 November;9(11):661-5.

(54) Sugunendran H, Birley HD, Mallinson H, Abbott M, Tong CY. Comparison of urine, first and second endourethral swabs for PCR based detection of genital *Chlamydia trachomatis* infection in male patients. Sex Transm Infect 2001 December;77(6):423-6.

(55) French P, Ison CA, Macdonald N. Lymphogranuloma venereum in the United Kingdom. Sex Transm Infect 2005 April 1;81(2):97-8.

(56) Chalker VJ, Vaughan H, Patel P, Rossouw A, Seyedzadeh H, Gerrard K et al. External Quality Assessment for Detection of Chlamydia trachomatis. J Clin Microbiol 2005 March 1;43(3):1341-7.

(57) Schachter J, Hook EW, Martin DH, Willis D, Fine P, Fuller D et al. Confirming Positive Results of Nucleic Acid Amplification Tests (NAATs) for *Chlamydia trachomatis*: All NAATs Are Not Created Equal. J Clin Microbiol 2005 March 1;43(3):1372-3.

(58) Lau CY, Qureshi AK. Azithromycin versus doxycycline for genital chlamydial infections: a meta-analysis of randomized clinical trials. Sexually Transmitted Diseases 2002 September;29(9):497-502.

(59) Tobin JM, Harindra V, Mani R. Which treatment for genital tract Chlamydia trachomatis infection? International Journal of STD & AIDS 2004 November;15(11):737-9.

(60) Lee VF, Tobin JM, Harindra V. Re-infection of *Chlamydia trachomatis* in patients presenting to the genitourinary medicine clinic in Portsmouth: the chlamydia screening pilot study - three years on. International Journal of STD & AIDS 2004 November;15(11):744-6.

(61) Fortenberry JD, Brizendine EJ, Katz BP, Wools KK, Blythe MJ, Orr DP. Subsequent sexually transmitted infections among adolescent women with genital infection due to Chlamydia trachomatis, Neisseria gonorrhoeae, or Trichomonas vaginalis. Sexually Transmitted Diseases 1999 January;26(1):26-32.

(62) Golden MR, Whittington WL, Handsfield HH, Hughes JP, Stamm WE, Hogben M et al. Effect of expedited treatment of sex partners on

recurrent or persistent gonorrhea or chlamydial infection.[see comment]. New England Journal of Medicine 2005 February 17;352(7):676-85.

(63) La Montagne, D. S., Baster K, Emmet L, Randall, S., McClean, L., Meredith, P. and et al. For the Chlamydia Recall Study Advisory Group. The chlamydia recall study: investigating the incidence and re-infection rates of genital chlamydial infection among 16-24 year old women attending general practice, family planning and genitourinary medicine clinics, March 2002-August 2004, final report part 1. London: Health Protection Agency Centre for Infections; 2004 December.

(64) Somani J, Bhullar VB, Workowski KA, Farshy CE, Black CM. Multiple drug-resistant *Chlamydia trachomatis* associated with clinical treatment failure. Journal of Infectious Diseases 2000 April;181(4):1421-7.

(65) Kitchen VS, Donegan C, Ward H, Thomas B, Harris JR, Taylor-Robinson D. Comparison of ofloxacin with doxycycline in the treatment of non-gonococcal urethritis and cervical chlamydial infection. Journal of Antimicrobial Chemotherapy 1990 November;26 Suppl D:99-105.

(66) Linnemann CC, Jr., Heaton CL, Ritchey M. Treatment of *Chlamydia trachomatis* infections: comparison of 1- and 2-g doses of erythromycin daily for seven days. Sexually Transmitted Diseases 1987 April;14(2):102-6.

(67) Ross JD, Crean A, McMillan A. Efficacy of anti-chlamydial therapy with oxytetracycline and erythromycin. International Journal of STD & AIDS 1996 August;7(5):373-4.

(68) Munday PE, Thomas BJ, Gilroy CB, Gilchrist C, Taylor-Robinson D. Infrequent detection of *Chlamydia trachomatis* in a longitudinal study of women with treated cervical infection. Genitourinary Medicine 1995 February;71(1):24-6.

(69) Jacobson GF, Autry AM, Kirby RS, Liverman EM, Motley RU. A randomized controlled trial comparing amoxicillin and azithromycin for the treatment of *Chlamydia trachomatis* in pregnancy. American Journal of Obstetrics & Gynecology 2001 June;184(7):1352-4.

(70) Kacmar J, Cheh E, Montagno A, Peipert JF. A randomized trial of azithromycin versus amoxicillin for the treatment of *Chlamydia trachomatis* in pregnancy. Infectious Diseases in Obstetrics & Gynecology 2001;9(4):197-202.

(71) Brocklehurst P, Rooney G. Interventions for treating genital chlamydia trachomatis infection in pregnancy. Cochrane Database of Systematic Reviews 2000;(2):CD000054.

(72) Sanson-Fisher R, Bowman J, Armstrong S. Factors affecting nonadherence with antibiotics. Diagnostic Microbiology & Infectious Disease 1992 May;15(4 Suppl):103S-9S.

(73) Low N, Roberts T, Huengsberg M, Sanford E, McCarthy A, Pye K et al. Partner notification for chlamydia in primary care: randomised controlled trial and economic evaluation. BMJ 2006;332:14-8.

(74) Hogan RJ, Mathews SA, Mukhopadhyay S, Summersgill JT, Timms P. Chlamydial Persistence: beyond the Biphasic Paradigm. Infect Immun 2004 April 1;72(4):1843-55.

(75) Apoola A, Boothby M, Radcliffe K. Is telephone follow-up as good as traditional clinic follow-up in achieving the proposed national outcome standards for chlamydia management? International Journal of STD & AIDS 2004 June;15(6):376-9.

(76) Low N, Welch J, Radcliffe K. Developing national outcome standards for the management of gonorrhoea and genital chlamydia in genitourinary medicine clinics. Sex Transm Infect 2004 June 1;80(3):223-9.

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 41 mins

Question: 61 of 100

Which of the following statements is true of infections with *Mycobacterium tuberculosis?*

(Please select 1 option)

○	A positive tuberculin test indicates active disease
○	In pregnant women treatment should not be given until after delivery
○	Lymph node positive disease requires longer treatment than pulmonary disease
○	Non-sputum producing patients are non-infectious
○	Pyrazinamide has high activity against active extracellular organisms

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

	A positive tuberculin test indicates active disease
	In pregnant women treatment should not be given until after delivery
◉	Lymph node positive disease requires longer treatment than pulmonary disease ✕ Incorrect answer selected
	Non-sputum producing patients are non-infectious ← This is the correct answer
	Pyrazinamide has high activity against active extracellular organisms

Only untreated smear-positive pulmonary TB is likely to be infectious.

Active disease may be indicated by grade III/IV response to tuberculin. 80% of individuals with history of BCG vaccination have grade I/II response.

All forms of pulmonary TB may be treated equally except tuberculous pleural effusion which may require drainage (with large effusions causing breathlessness) and adjunct corticosteroids to delay reaccumulation.

Length of treatment for other forms are

- Bone TB nine months
- Meningitis one year
- Drug resistance two years.

Streptomycin has high activity against extracellular organisms whilst pyrazinamide has high activity against intracellular organisms.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

National Guideline For The Management Of Bacterial Vaginosis (2006)
Clinical Effectiveness Group
British Association for Sexual Health and HIV

Introduction and Methodology

Scope and Purpose

The main objective is to assist practitioners in managing women diagnosed with bacterial vaginosis.

This guideline offers recommendations on the diagnostic tests, treatment regimens and health promotion principles needed for the effective management of bacterial vaginosis including the management of the initial presentation, as well as recurrence.

It is aimed primarily at people aged 16 years or older (see specific guidelines for those under 16) presenting to health care professionals, working in departments offering level 3 care in STI management (see national strategy[(2)]) within the United Kingdom. However, the principles of the recommendations should be adopted across all levels (levels 1 and 2 may need to develop, where appropriate, local care pathways).

Stakeholder Involvement

This guideline has been produced by medical specialists from relevant disciplines. Successive drafts have been reviewed by the clinical effectiveness group of BASHH.

Rigour of Development

An extensive literature reviewed was carried out using Medline for the years 1970 to 2005 using the keyword "bacterial vaginosis". The Cochrane library was searched using "bacterial vaginosis". Previous guidelines were sought, and the 1998 and 2002 USA guidelines reviewed.

Where available systematic reviews were used. Additionally,randomised clinical trials and review articles were referenced. Only English language papers were used. The previous 2001 guidelines were used as a basis. Where feedback from

clinicians indicated areas of controversy these were reviewed, and areas in which new RCTs had been published were reviewed. Expert opinion was sought for difficult areas such as the management of bacterial vaginosis in pregnancy.

Aetiology

Bacterial vaginosis (BV) is the commonest cause of abnormal discharge in women of childbearing age. The reported prevalence has varied from 5% in a group of asymptomatic college students to as high as 50% of women in rural Uganda. A prevalence of 12% was found in pregnant women attending an ante-natal clinic in the United Kingdom(1), and of 30% in women undergoing termination of pregnancy(2).

BV is characterised by an overgrowth of predominantly anaerobic organisms (*Gardnerella vaginalis*, *Prevotella species*, *Mycoplasma hominis*, *Mobiluncus species*) in the vagina, leading to replacement of lactobacilli and an increase in pH from less than 4.5 to as high as 7.0.

Spontaneous onset and remission of BV can occur. Whilst BV is not regarded as a sexually transmitted disease, the prevalence is generally higher amongst sexually active than non-sexually active women(3). It is more common in black women than white, those with an intrauterine contraceptive device, and those who smoke.

Clinical features

Symptoms

Offensive fishy smelling vaginal discharge
Not associated with soreness, itching, or irritation
Many women (approximately 50%) are asymptomatic

Signs

Thin, white, homogeneous discharge, coating the walls of the vagina and vestibule.

Complications

The prevalence of BV is high in women with pelvic inflammatory disease (PID), and in one prospective study BV was predictive of subsequent PID associated with gonorrhoea or chlamydia (4)(level of evidence 11a).There are no prospective studies investigating whether treating asymptomatic women for BV reduces their risk of developing PID subsequently.

BV is common in some populations of women undergoing elective termination of pregnancy (TOP), and is associated with post-TOP endometritis and PID (level of evidence Ib)(5). In pregnancy BV is

associated with late miscarriage, preterm birth, preterm premature rupture of membranes, and postpartum endometritis (Ib) (6-10).
BV has been associated with an increased incidence of vaginal cuff cellulitis and abscess formation following transvaginal hysterectomy (III)(11), but it is unclear whether this is a problem in UK practice where many units administer perioperative antibiotics. There are no studies investigating the possible role of BV in the onset of PID following insertion of an intrauterine contraceptive device (IUCD). In one study BV was associated with NGU in male partners(12).

Diagnosis

Two approaches are available

• Amsel criteria(13).At least three of the four criteria are present for the diagnosis to be confirmed.
(1) Thin, white, homogeneous discharge
(2) Clue cells on microscopy of wet mount
(3) pH of vaginal fluid >4.5
(4) Release of a fishy odour on adding alkali (10% KOH).

• A Gram stained vaginal smear, evaluated with the Hay/Ison criteria(14) or the Nugent criteria(15).

The Hay/Ison criteria are defined as follows:
grade 1 (Normal): Lactobacillus morphotypes predominate
grade 2 (Intermediate): Mixed flora with some Lactobacilli present, but Gardnerella or Mobiluncus morphotypes also present
grade 3 (BV): Predominantly Gardnerella and/or Mobiluncus morphotypes. Few or absent Lactobacilli(1).

The Nugent score is derived from estimating the relative proportions of bacterial morphotypes to give a score between 0 and 10. A score of <4 is normal, 4-6 is intermediate, and >6 is BV(15).

The Bacterial Special Interest group of BASHH recommend using the Hay/Ison criteria in Genitourinary medicine clinics. (grade of recommendation C).

• Isolation of Gardnerella vaginalis cannot be used to diagnose BV because it can be cultured from the vagina of more than 50% normal women (IIa). In research studies a high concentration of Gardnerella vaginalis is associated with the presence of BV (IIa)(16).

Management

General advice

Patients should be advised to avoid vaginal douching, use of shower gel, and use of antiseptic agents or shampoo in the bath (grade of recommendation C).

Treatment

Treatment is indicated for:

- Symptomatic women (A)
- Women undergoing some surgical procedures (A)

- Women who do not volunteer symptoms may elect to take treatment if offered. They may report a beneficial change in their discharge following treatment.

Recommended regimens
Metronidazole 400-500 mg twice daily for 5-7 days (A)
or
Metronidazole 2 g single dose (A).

Alternative regimens

Intravaginal metronidazole gel (0.75%) once daily for 5 days (A)
or
Intravaginal clindamycin cream (2%) once daily for 7 days (A)
or
Clindamycin 300 mg twice daily for 7 days (A).
Or
Tinidazole 2G single dose (A).

Rationale
All these treatments have been shown to achieve cure rates of 70-80% after 4 weeks in controlled trials using placebo or comparison with oral metronidazole(6;7;17-20). Oral metronidazole treatment is established, usually well tolerated, and inexpensive (Ia). Dosage and duration used in trials have varied from 400 mg twice daily for 5 days to 500 mg twice daily for 7 days. The 2 g immediate dose may be slightly less effective at 4 week follow up (Ib). Intravaginal metronidazole gel and clindamycin cream have similar efficacy (Ib), but the latter is more expensive. Theoretically, metronidazole has an advantage because it is less active against lactobacilli than clindamycin. Conversely, clindamycin is more active than metronidazole against most of the

bacteria associated with BV. Oral clindamycin has only been evaluated in one study with short term follow up, and in pregnant women (Ib, IIa). It is more expensive than metronidazole. Tinidazole has similar activity to metronidazole but is also more expensive.

Caution

- With metronidazole treatment alcohol should be avoided because of the possibility of a disulfiram-like action. There are no data on the risks from consuming alcohol with intravaginal metronidazole gel, but it is not recommended at present.

- Clindamycin cream can weaken condoms, which should not be used during such treatment. Pseudomembranous colitis has been reported with both oral clindamycin and clindamycin cream(21).

Allergy

Allergy to metronidazole is uncommon. Use 2% clindamycin cream for metronidazole allergic women.

Pregnancy and breast feeding

Meta-analyses have concluded that there is no evidence of teratogenicity from the use of metronidazole in women during the first trimester of pregnancy (Ia) (22-24).
The results of clinical trials investigating the value of screening for and treating BV in pregnancy have been conflicting. It is therefore difficult to make firm recommendations. A detailed discussion of trials in pregnancy is in the appendix. In conclusion:

- Symptomatic pregnant women should be treated in the usual way (B).

- There is insufficient evidence to recommend routine treatment of asymptomatic pregnant women who attend a G-U clinic and are found to have BV.

- Metronidazole enters breast milk and may affect its taste. The manufacturers recommend avoiding high doses if breast feeding. Small

amounts of clindamycin enter breast milk. It is prudent therefore to use an intravaginal treatment for lactating women (C).

Termination of pregnancy (TOP)

Three studies have investigated whether antibiotics can reduce the rate of infectious morbidity in women with BV, following termination of pregnancy. A Scandinavian study of 231 women demonstrated a reduction in post-TOP infection by treating BV with oral metronidazole before termination(5) (Ib). Another demonstrated a reduction in infective complications following the use of clindamycin cream(35) (Ib). A UK study of 273 women again found a reduction in post-operative upper genital tract infection from 16% to 8.5%, but did not quite reach statistical significance(36). There are no data on the effectiveness of treatment administered at the time of TOP.

- These studies support screening for and treating BV with either metronidazole or clindamycin cream, to reduce the incidence of subsequent endometritis and PID (Ia).

Sexual partners

- No reduction in relapse rate was reported from two studies in which male partners of women with BV were treated with metronidazole, one study of tinidazole, and one of clindamycin(18;37) (Ib). Routine screening and treatment of male partners are therefore not indicated.

- Two studies reported a high incidence of BV in female partners of lesbian women with BV(38;39) (II). No study has investigated the value of treating partners of lesbian women simultaneously.

Follow up

A test of cure is not required if symptoms resolve.

Recurrent bacterial vaginosis

There are few published studies evaluating the optimal approach to women with frequent recurrences of BV. Possible approaches are as follows:

- Suppressive therapy. Metronidazole gel 0.75%. twice weekly for 4 to 6 months to decrease symptoms, after an initial treatment daily for 10 days, is being evaluated.
- Metronidazole orally 400 mg bd for 3 days at the start and end of menstruation, combined with fluconazole 150 mg as a single dose if there is a history of candidiasis also (III).
- A recent observational study reported that acigel used at the time of menstruation and following unprotected sexual intercourse was associated with a reduction in relapse rate following a course of metronidazole(40)(III).
- Small studies of live yoghurt or Lactobacillus acidophilus have not demonstrated benefit (IIa)13.
- Other treatments being studied at present include the use of combinations of antibiotics with probiotic therapy and hydrogen peroxide.

Qualifying statement

The recommendations in this guideline may not be appropriate for use in all clinical situations. Decisions to follow these recommendations must be based on the professional judgement of the clinician and consideration of individual patient circumstances and available resources.

All possible care has been undertaken to ensure the publication of the correct dosage of medication and route of administration. However, it remains the responsibility of the prescribing physician to ensure the accuracy and appropriateness of the medication they prescribe.

Auditable outcome measures

- Diagnosis of BV in clinical practice. Compare routine diagnosis with stored vaginal smears examined by Gram stain.
- Screening and treatment of women undergoing termination of pregnancy. This should also include screening for *Chlamydia trachomatis* (see guideline for chlamydia).

Acknowledgements

I wish to thank Dr. Francis Keane, Dr. Janet Wilson and Prof. Cathy Ison for their valuable contributions to this guideline.

Author and centre

Phillip Hay, St George's, University of London

Membership of the CEG

Dr Keith Radcliffe (Chair), Whittall Street Clinic, Birmingham (BASHH); Dr Imtyaz Ahmed-Jusuf, Nottingham City Hospital (BASHH); Dr David Daniels, West Middlesex Hospital (Chair, NAG); Dr Mark FitzGerald, Taunton & Somerset (BASHH); Dr Neil Lazaro (RCGP); Dr Guy Rooney, Swindon & Oxford (RCP) ,Dr Gill McCarthy,Kingston Hospital(BASHH)

Editorial Independence

This guideline was commissioned and edited by the CEG of the BASHH, without external funding being sought or obtained. The author has declared potential conflicts of interest.

Appendix

Treatment of BV in pregnancy

In summary, three randomised controlled trials have shown a reduction in the incidence of preterm birth following screening for and treatment of BV with metronidazole in women with a history of prior idiopathic preterm birth or second trimester loss. However, this was based on a subgroup analysis in two studies(16;25), and all three studies used different treatments: metronidazole 500mg twice daily for 7 days(26); metronidazole 400 mg twice daily for 2 days repeated after 4 weeks if indicated(16); a combination of metronidazole 250 mg and erythromycin 333 mg both three times daily for 7 days(25).
The largest multi-centre RCT randomised 1953 asymptomatic unselected women with BV to receive two Grams metronidazole or placebo, taken under supervision in the clinic, repeated at home two days later(27). The course was repeated four weeks later. There was no difference in gestational age at delivery between the two groups, or in the sub-group of women with a prior preterm birth. Possible limitations of this study include the relatively late gestational age at which treatment was administered (mostly 20-24 weeks gestation), the short course of metronidazole administered, and the high number of women screened positive for BV who were not randomised. A UK based study in which women with a high level of fetal fibronectin at 24 – 28 weeks gestation were treated with oral metronidazole 400 mg tds for 7 days, was terminated early with the conclusion that the treatment increased the rate of preterm delivery(28). Only 5 women in the placebo group and 8 in the treatment group had BV: BV only resolved in one subject after treatment was administered. There was a non-significant trend for metronidazole treatment to be associated with early preterm birth: 11/53 (21%) women who received metronidazole delivered before 30 weeks gestation of women receiving metronidazole compared to 5/46 (11%) of those receiving placebo (risk ratio 1.9, 95% CI 0.72–5.09, P = 0.18). There were significantly more preterm

deliveries (before 37 weeks) in women treated with metronidazole 33/53 (62%) than placebo 18/46 (39%) (risk ratio 1.6, 95% CI 1.05–2.4, p= 0.022). The authors have been quoted as stating that metronidazole should not be prescribed to pregnant women because it appeared to increase the risk of preterm birth in those with a history of prior preterm birth. Given that this was a selected group with positive fetal fibronectin, treated relatively late in pregnancy (> 24 weeks gestation), and that < 10% had BV this study does not provide sufficient data to say that metronidazole should not be used to treat BV in pregnancy. Moreover, the larger Carey study did not show an increase in preterm birth associated with metronidazole use at a similar gestational age(27).

One further study from the USA has shown a benefit from treatment with oral clindamycin 300 mg bd for 7 days(29). However, a cohort design was used rather than randomisation, which limits the value of the study for making treatment recommendations (IIa). More recently, a UK RCT found that treating asymptomatic women with BV or intermediate flora detected on Gram stain produced a five-fold reduction in late miscarriage and two and a half-fold reduction in spontaneous preterm birth(30). Treatment was clindamycin 300 mg twice daily at a median gestation of 15.8 weeks.
The use of clindamycin cream to treat BV in the second trimester of pregnancy has not produced a reduction in preterm birth in two small studies (Ib)(8;31). Again a UK study reported a sixty percent reduction in spontaneous preterm birth using clindamycin cream 100 mg daily for three days, followed by a seven day course if BV persisted 4 weeks later{Lamont, Duncan, et al. 2003 1163 /id}. In a large Austrian RCT of antenatal screening for BV, candida and Trichomonas, Kiss and colleagues reported that screening and treatment for infections between 15 and 20 weeks gestation in 4429 women produced a preterm birth rate of 3% compared to 5.3% in the control group(32). Of the 177 women treated for BV with 2% clindamycin vaginal cream, 59 (29%) required retreatment with oral clindamycin for persistent BV after 28 weeks gestation. Numerically the majority of the benefit appeared to be in women treated for candidal infection. In the intervention group 6/175 women treated for BV had a spontaneous preterm birth compared to 10/176 in the control group (OR 0.59, 95% CI 0.17 – 1.54, p > 0.05).

Reference List

1. Hay PE, Lamont RF, Taylor-Robinson D, Morgan DJ, Ison C, Pearson J. Abnormal bacterial colonisation of the genital tract and subsequent preterm delivery and late miscarriage. Br Med J 1994;308(6924):295-8.

2. Blackwell AL, Thomas PD, Wareham K, Emery SJ. Health gains from

screening for infection of the lower genital tract in women attending for termination of pregnancy. Lancet 1993;342(8865):206-10.

3. Yen S, Shafer MA, Moncada J, Campbell CJ, Flinn SD, Boyer CB. Bacterial vaginosis in sexually experienced and non-sexually experienced young women entering the military. Obstet Gynecol 2003;102(5 Pt 1):927-33.

4. Ness RB, Hillier SL, Kip KE, Soper DE, Stamm CA, McGregor JA et al. Bacterial Vaginosis and Risk of Pelvic Inflammatory Disease. Obstet Gynecol Surv 2005;60:99-100.

5. Larsson PG, Platz-Christensen JJ, Thejls H, Forsum U, Pahlson C. Incidence of pelvic inflammatory disease after first-trimester legal abortion in women with bacterial vaginosis after treatment with metronidazole: a double-blind, randomized study. Am J Obstet Gynecol 1992;166(1 Pt 1):100-3.

6. Hay PE. Therapy of bacterial vaginosis. J Antimicrob Chemother 1998;41(1):6-9.

7. 1998 guidelines for treatment of sexually transmitted diseases. Centers for Disease Control and Prevention. MMWR Morb Mortal Wkly Rep 1998;47(RR-1):1-111.

8. McGregor JA, French JI, Jones W, Milligan K, McKinney PJ, Patterson E et al. Bacterial vaginosis is associated with prematurity and vaginal fluid mucinase and sialidase: results of a controlled trial of topical clindamycin cream. Am J Obstet Gynecol 1994;170(4):1048-59.

9. Watts DH, Krohn MA, Hillier SL, Eschenbach DA. Bacterial vaginosis as a risk factor for post-cesarean endometritis. Obstet Gynecol 1990;75(1):52-8.

10. Goldenberg RL, Hauth JC, Andrews WW. Intrauterine infection and preterm delivery. N Engl J Med 2000;342(20):1500-7.

11. Soper DE. Bacterial vaginosis and postoperative infections. Am J Obstet Gynecol 1993;169(2:Pt 2):467-9.

12. Keane FE, Thomas BJ, Whitaker L, Renton A, Taylor-Robinson D. An association between non-gonococcal urethritis and bacterial vaginosis and the implications for patients and their sexual partners. Genitourin Med 1997;73(5):373-7.

13. Amsel R, Totten PA, Spiegel CA, Chen KC, Eschenbach D, Holmes KK. Nonspecific vaginitis. Diagnostic criteria and microbial and epidemiologic associations. Am J Med 1983; 74(1):14-22.

14. Ison CA, Hay PE. Validation of a simplified grading of Gram stained vaginal smears for use in genitourinary medicine clinics. Sex Transm.Infect. 2002;78(6):413-5.

15. Nugent RP, Krohn MA, Hillier SL. Reliability of diagnosing bacterial vaginosis is improved by a standardized method of gram stain interpretation. J Clin Microbiol 1991;29(2):297-301.

16. McDonald HM, O'Loughlin JA, Vigneswaran R, Jolley PT, Harvey JA, Bof A et al. Impact of metronidazole therapy on preterm birth in women with bacterial vaginosis flora (Gardnerella vaginalis): a randomised, placebo controlled trial [see comments]. Br J Obstet Gynaecol 1997;104(12):1391-7.

17. Anonymous. Management of bacterial vaginosis. DTB 1998;36(5):33-5.

18. Larsson PG. Treatment of bacterial vaginosis. Int J STD AIDS 1992;3(4):239-47.

19. Lugo-Miro VI, Green M, Mazur L. Comparison of different metronidazole therapeutic regimens for bacterial vaginosis. A meta-analysis. JAMA 1992;268(1):92-5.

20. Hillier SL, Lipinski C, Briselden AM, Eschenbach DA. Efficacy of intravaginal 0.75% metronidazole gel for the treatment of bacterial vaginosis. Obstet Gynecol 1993;81(6):963-7.

21. Trexler MF, Fraser TG, Jones MP. Fulminant pseudomembranous colitis caused by clindamycin phosphate vaginal cream. Am.J Gastroenterol.1997.Nov. 1992:2112-3.

22. Burtin P, Taddio A, Ariburnu O, Einarson TR, Koren G. Safety of metronidazole in pregnancy: a meta-analysis. Am J Obstet Gynecol 1995;172:525-9.

23. Caro-Paton T, Carvajal A, Martin dD, I, Martin-Arias LH, Alvarez RA, Rodriguez PE. Is metronidazole teratogenic? A meta-analysis . Br J Clin Pharmacol 1997;44:179-82.

24. Czeizel AE, Rockenbauer M. A population based case-control teratologic study of oral metronidazole treatment during pregnancy. Br J Obstet Gynaecol 1998;105:322-7.

25. Hauth JC, Goldenberg RL, Andrews WW, DuBard MB, Copper RL. Reduced incidence of preterm delivery with metronidazole and erythromycin in women with bacterial vaginosis. N Engl J Med 1995;333(26):1732-6.

26. Morales WJ, Schorr S, Albritton J. Effect of metronidazole in patients with preterm birth in preceding pregnancy and bacterial vaginosis: a placebo-controlled, double-blind study. Am J Obstet Gynecol 1994;171(2):345-7.

27. Carey JC, Klebanoff MA, Hauth JC, Hillier SL, Thom EA, Ernest JM et al. Metronidazole to prevent preterm delivery in pregnant women with asymptomatic bacterial vaginosis. N Engl J Med 2000;342(8):534-40.

28. Shennan A, Crawshaw S, Briley A, Hawken J, Seed P, Jones G et al. A randomised controlled trial of metronidazole for the prevention of preterm birth in women positive for cervicovaginal fetal fibronectin: the PREMET Study. BJOG 2006;113 :65-74.

29. McGregor JA, French JI, Parker R, Draper D, Patterson E, Jones W et al. Prevention of premature birth by screening and treatment for common genital tract infections: results of a prospective controlled evaluation. Am J Obstet Gynecol 1995;173(1):157-67.

30. Ugwumadu A, Manyonda I, Reid F, Hay P. Effect of early oral clindamycin on late miscarriage and preterm delivery in asymptomatic women with abnormal vaginal flora and bacterial vaginosis: a randomised controlled trial. Lancet 2003;361(9362):983-8.

31. Joesoef MR, Hillier SL, Wiknjosastro G, Sumampouw H, Linnan M, Norojono W et al. Intravaginal clindamycin treatment for bacterial vaginosis: effects on preterm delivery and low birth weight. Am J Obstet Gynecol 1995;173(5):1527-31.

32. Kiss H, Petricevic L, Husslein P. Prospective randomised controlled trial of an infection screening programme to reduce the rate of preterm delivery. Br Med J 2004; 7462:371-6.

33. Okun N, Gronau KA, Hannah ME. Antibiotics for bacterial vaginosis or Trichomonas vaginalis in pregnancy: a systematic review. Obstet Gynecol 2005;105:857-68.

34. Varma R, Gupta JK. Antibiotic treatment of bacterial vaginosis in pregnancy: Multiple meta-analyses and dilemmas in interpretation. Eur J Obstet Gynecol Reprod Biol 2006;124:10-4.

35. Larsson PG, Platz-Christensen JJ, Dalaker K, Eriksson K, Fahraeus L, Irminger K et al. Treatment with 2% clindamycin vaginal cream prior to first trimester surgical abortion to reduce signs of postoperative infection: a prospective, double-blinded, placebo-controlled, multicenter study . Acta Obstet Gynecol Scand 2000;79(5):390-6.

36. Crowley T, Low N, Turner A, Harvey I, Bidgood K, Horner P. Antibiotic prophylaxis to prevent post-abortal upper genital tract infection in women with bacterial vaginosis: randomised controlled trial. BJOG 2001;108:396-402.

37. Colli E, Landoni M, Parazzini F. Treatment of male partners and recurrence of bacterial vaginosis: a randomised trial. Genitourin Med 1997;73(4):267-70.

38. Berger BJ, Kolton S, Zenilman JM, Cummings MC, Feldman J, McCormack WM. Bacterial vaginosis in lesbians: a sexually transmitted disease. Clin Infect Dis 1995;21(6):1402-5.

39. Marrazzo JM, Koutsky LA, Eschenbach DA, Agnew K, Stine K, Hillier SL. Characterization of vaginal flora and bacterial vaginosis in women who have sex with women. J Infect Dis 2002;185(9):1307-13.

40. Wilson JD, Shann SM, Brady SK, Mammen-Tobin AG, Evans AL, Lee RA. Recurrent bacterial vaginosis: the use of maintenance acidic vaginal gel following treatment. Int J STD AIDS 2005;16:736-8.

Declaration of Personal Interests

Name of guideline:

1. Do you, your partner (if applicable) or any member of your immediate family have any commercial interest such as personal shares etc. with any companies that are, or could be, involved in the above named guideline?

No

2. Do you, your partner (if applicable) or any member of your immediate family receive sponsorship or paid consultancy work within commercial organisations that are, or could be, involved in the above named guideline?

No

3. Does your department or unit receive financial support from commercial organisations that are, or could be, involved in the above named guideline?

No

4. Are you a consultant to or a member of any national body, charity or pressure group whose work is related to the above named guideline?

No

5. Do you receive significant editorial fees for commissioned articles for publication (in any format) or are you paid editorial work for any publication related to the above named guideline?

No

6. Do you or your department hold a patent (existing or pending) related to the above named guideline?

No

Name: Dr. Phillip Hay title: Consultant in G-U Medicine

Role in guideline development: author

Signature: date: 14 March 2006

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 42 mins 28 secs

Question: 62 of 100

Which of the following is true of spontaneous bacterial peritonitis (SBP)?

(Please select 1 option)

○	A survival rate of over 50% is expected at one year
○	Gentamicin is the treatment of choice
○	Is characteristically caused by aerobic bacteria.
○	Is diagnosed by culture of ascitic fluid.
○	Is due to intestinal perforation

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 43 mins 14 secs

Question: 62 of 100

Which of the following is true of spontaneous bacterial peritonitis (SBP)?

(Please select 1 option)

○	A survival rate of over 50% is expected at one year
○	Gentamicin is the treatment of choice
◉	Is characteristically caused by aerobic bacteria. ✓ Correct
○	Is diagnosed by culture of ascitic fluid.
○	Is due to intestinal perforation

SBP is a frequent complication of the ascites of cirrhosis. It is diagnosed by ascitic fluid examination which reveals a PMN count of >250/ml.

SBP has poor prognostic significance with a one year survival after a diagnosis of between 30-50%.

It is, as the name suggests, a spontaneous event that is not a consequence of intestinal perforation. It is speculated that the infective organism may leak into the ascitic fluid via the blood or from intestinal overgrowth.

Organisms should be cultured by directly collecting into blood culture bottles.

It is typically caused by aerobic Gram-negative bacteria. Hence cefotaxime is regarded as the drug of choice for treatment.

Next question | Tag Question | Remove question

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 43 mins 14 secs

Question: 63 of 100

Which of the following is correct regarding herpes simplex encephalitis?

(Please select 1 option)

○	Is associated with a polymorphonuclear pleocytosis in the CSF
○	Produces a diffuse, evenly distributed inflammation of cerebral tissues
○	Produces a typical EEG pattern with lateralised periodic discharges at 2 Hz
○	Should be treated with acyclovir as soon as the diagnosis is confirmed by urgent CSF viral antibody titres
○	Shows a peak incidence in the autumn

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 44 mins 28 secs

Question: 63 of 100

Which of the following is correct regarding herpes simplex encephalitis?

(Please select 1 option)

○	Is associated with a polymorphonuclear pleocytosis in the CSF
○	Produces a diffuse, evenly distributed inflammation of cerebral tissues
◉	Produces a typical EEG pattern with lateralised periodic discharges at 2 Hz ✓ Correct
○	Should be treated with acyclovir as soon as the diagnosis is confirmed by urgent CSF viral antibody titres
○	Shows a peak incidence in the autumn

This EEG pattern is seen but is not diagnostic.

Winter is the peak incidence.

A lymphocytosis is characteristic in the cerebrospinal fluid (CSF).

Temporal lobe location is typical not diffuse.

Immediate treatment is required on clinical suspicion - do not wait!

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 44 mins 28 secs

Question: 64 of 100

Which of the following is correct regarding infection with *Salmonella typhi*?

(Please select 1 option)

- A. Children are particularly likely to become carriers
- B. Most carriers are female
- C. Faecal culture is almost always positive during the first week of illness
- D. Relapse does not occur if antibiotics are taken for two weeks
- E. Vaccinated individuals who develop the disease will have a mild illness

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 45 mins 21 secs

Question: 64 of 100

Which of the following is correct regarding infection with *Salmonella typhi*?

(Please select 1 option)

○	A. Children are particularly likely to become carriers
◉	B. Most carriers are female ✓ Correct
○	C. Faecal culture is almost always positive during the first week of illness
○	D. Relapse does not occur if antibiotics are taken for two weeks
○	E. Vaccinated individuals who develop the disease will have a mild illness

Children are rarely chronic carriers of the organism although for some unknown reason females are more commonly long-term carriers than males (remember Typhoid Mary).

C. Only 50% of cases.

E. Higher threshold but same disease.

Next question | Tag Question | Remove question

Show tools

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 45 mins 21 secs

Question: 65 of 100

A 38-year-old female presents with red target lesions confined to the hands and is diagnosed with erythema multiforme.

Which of the following could be the cause?

(Please select 1 option)

○	Cytomegalovirus infection
○	Group B streptococci
○	Langerhan's cells histiocytosis
○	Penicillin V
○	*Ureaplasma urealyticum*

Submit answer | Skip question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

http://my.onexamination.com/Assessment/Que
Questions Set : REF4323
Shop

Langerhan's cells histiocytosis

Penicillin V ✓ Correct

Ureaplasma urealyticum

Potential causes of erythema multiforme include:

1. Infections

- Viruses: herpes simplex 1 and 2, hepatitis B, Epstein-Barr virus (EBV), enteroviruses
- Small agents: *Mycoplasma pneumoniae*
- Bacteria: Group A Streptococcus, eosina
- Other: *Mycobacterium tuberculosis*, histoplasma, coccidioides.

2. Neoplasia

- Leukaemia
- Lymphoma.

3. Antibiotics

- Penicillins, sulphonamides, isoniazid, tetracycline.

4. Anticonvulsants

- Phenytoin, phenobarbitone, carbamazepine.

5. Other

- Aspirin
- Radiation therapy
- Etoposide
- NSAIDs
- Sunlight
- Pregnancy.

Question: 66 of 100

A 54-year old woman was admitted with acute breathlessness.

On examination she had a temperature of 37°C, a respiratory rate of 32 breaths per minute, a pulse of 120 beats per minute, a blood pressure of 100/60 mmHg, and a peak expiratory flow rate of 250 litres per minute.

Auscultation of the heart and chest was normal.

The chest x ray was normal and blood gases on air showed:

pH	7.35	(7.36-7.44)
$Pa0_2$	6.0kPa	(11.3-12.6)
$PaC0_2$	3.9 kPa	(4.7-6.0)
Serum bicarbonate	20 mmol/l	(20-28)

She was started on high flow oxygen.

What is the most important next treatment?

(Please select 1 option)

- ○ Aminophylline intravenously
- ○ Amoxicillin intravenously
- ○ Intravenous fluids
- ○ Low molecular weight heparin (LMWH)
- ○ Nebulised salbutamol

Submit answer | Skip question | Tag Question | Remove question

Serum bicarbonate	20 mmol/l	(20-28)

She was started on high flow oxygen.

What is the most important next treatment?

(Please select 1 option)

○	Aminophylline intravenously
○	Amoxicillin intravenously
○	Intravenous fluids
◉	Low molecular weight heparin (LMWH) ✓ Correct
○	Nebulised salbutamol

This patient has features of a type 1 respiratory failure with mixed acid-base disturbances.

The differential diagnosis here lies between pulmonary embolism (PE) and acute severe asthma.

On the basis of the reasonable peak expiry flow rate (PEFR) of 250, the tachycardia and hypotension, PE seems the more likely explanation and LMWH would be the treatment of choice.

Intravenous (IV) fluids are potentially harmful since the cause of the shock is an obstructed right ventricle. Fluids may dilate the ventricle further and reduce cardiac output.

There is a role for fluids in those patients with rapidly falling blood pressure but this should preferably be done (if there is time) with central pressure monitoring.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 49 mins 49 secs

Question: 67 of 100

A 19-year-old male student attends the Emergency Department complaining of an urethral discharge one week after having casual unprotected sex.

Gram stain shows numerous neutrophils, some of which contain gram-negative intracellular diplococci. The patient is treated with Ceftriaxone, 250 mg as an intramuscular injection. Five days later, the patient re-attends with persisting discharge.

Which of the following is the most likely cause of this discharge?

(Please select 1 option)

- *Chlamydia trachomatis*
- Penicillin-resistant *Neisseria gonorrhoeae*
- Re-infection with *Neisseria gonorrhoeae*
- *Ureaplasma urealyticum*
- Urethral stricture

Submit answer | Skip question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 51 mins 10 secs

Question: 67 of 100

A 19-year-old male student attends the Emergency Department complaining of an urethral discharge one week after having casual unprotected sex.

Gram stain shows numerous neutrophils, some of which contain gram-negative intracellular diplococci. The patient is treated with Ceftriaxone, 250 mg as an intramuscular injection. Five days later, the patient re-attends with persisting discharge.

Which of the following is the most likely cause of this discharge?

(Please select 1 option)

○	*Chlamydia trachomatis* ← This is the correct answer
○	Penicillin-resistant *Neisseria gonorrhoeae*
◉	Re-infection with *Neisseria gonorrhoeae* ✕ Incorrect answer selected
○	*Ureaplasma urealyticum*
○	Urethral stricture

This patient has been adequately treated for gonorrhoea and a persistent discharge would be unusual unless, as is often the case, there is a co-infection.

The patient is likely to have a non-specific urethritis due to *Chlamydia trachomatis*, requiring treatment with either doxycycline or erythromycin for 7-14 days.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 51 mins 10 secs

Question: 68 of 100

A 41-year-old African man has a history of multiple episodes of sudden onset of severe abdominal pain and back pain lasting for hours. Each time this happens, his peripheral blood smear demonstrates numerous sickled erythrocytes.

A haemoglobin electrophoresis shows 94% Hgb S, 5% Hgb F, and 1% Hgb A2.

He now has increasing pain in his right groin radiating to the anterior aspect of the thigh and to the knee. His temperature was 38°C and examination of his hip revealed pain on internal rotation. A radiograph reveals irregular bony destruction of the femoral head.

The most likely organism to be responsible for these findings is?

(Please select 1 option)

- *Candida albicans*
- *Clostridium perfringens*
- Group B *Streptococcus*
- *Salmonella* species
- *Yersinia pestis*

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Question: 68 of 100

A 41-year-old African man has a history of multiple episodes of sudden onset of severe abdominal pain and back pain lasting for hours. Each time this happens, his peripheral blood smear demonstrates numerous sickled erythrocytes.

A haemoglobin electrophoresis shows 94% Hgb S, 5% Hgb F, and 1% Hgb A2.

He now has increasing pain in his right groin radiating to the anterior aspect of the thigh and to the knee. His temperature was 38°C and examination of his hip revealed pain on internal rotation. A radiograph reveals irregular bony destruction of the femoral head.

The most likely organism to be responsible for these findings is?

(Please select 1 option)

○	*Candida albicans*
○	*Clostridium perfringens*
○	Group B *Streptococcus*
◉	*Salmonella* species ✓ Correct
○	*Yersinia pestis*

Salmonella osteomyelitis is seen in patients with sickle cell anemia. Other organisms that are frequent causes for osteomyelitis with sickle cell anemia include *Staphylococcus aureus* and Gram negatives such as *Klebsiella*.

Why *Salmonella* species predominate in patients with sickle cell disease instead of *Staphylococcus aureus* is a matter of debate. Etiology of Osteomyelitis Complicating Sickle Cell Disease. Pediatrics 1998;101;296-297

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 52 mins 16 secs

Question: 69 of 100

You are considering starting a patient on griseofulvin.

Which of the following statements concerning its pharmacology is true?

(Please select 1 option)

○	It is active against *Candida albicans*
○	It is active against aspergillus
○	It should not be used in renal failure
○	It used for a maximum of two weeks
○	It is associated with drug-induced Stevens-Johnson syndrome

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 52 mins 55 secs

Question: 69 of 100

You are considering starting a patient on griseofulvin.

Which of the following statements concerning its pharmacology is true?

(Please select 1 option)

○	It is active against *Candida albicans*
○	It is active against aspergillus
○	It should not be used in renal failure
○	It used for a maximum of two weeks
◉	It is associated with drug-induced Stevens-Johnson syndrome ✓ Correct

For griseofulvin and Stevens-Johnson syndrome read Am J Emerg Med 1984;2:129-135. Many other drugs are implicated in causing Stevens-Johnson syndrome.

Griseofulvin is not active against *Candida albicans*. It is active against trichophytons (tinea) and other dermatophytes.

It is metabolised in the liver (note also, it is an enzyme inducer). Only 0.1-0.2% is excreted in urine.

Treatment with griseofulvin is often needed for a long period, sometimes years, depending on the rate of nail growth.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Question: 6 of 100

A 82-year-old lady is admitted from her nursing home with headache, photophobia and neck stiffness.

Her temperature is 39.0°C, pulse rate 115 beats/min. There is no skin rash or focal neurological signs and her Glasgow coma scale is 15/15.

A CT scan shows no contraindication to lumbar puncture. CSF is obtained and Gram stain shows Gram-negative coccobacilli, subsequent culture confirms a *Haemophilus influenzae* meningitis.

What chemoprophylaxis should be offered to the nurses at her home?

(Please select 1 option)

○	Azithromycin
○	Ceftriaxone
○	Ciprofloxacin
◉	No chemoprophylaxis required ✕ Incorrect answer selected
○	Rifampicin ← This is the correct answer

Close contacts of *Haemophilus influenzae* meningitis should receive rifampicin; children under two years should be vaccinated.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 8 mins 39 secs

Question: 7 of 100

An 35-year-old man presented with high fever, headache and mild jaundice on returning from a holiday in Spain. The group of 20 had travelled together visiting forestry on the hills with fishing trips in mountain streams.

Which of the following organisms is most likely to be responsible for their illness?

(Please select 1 option)

○	*Borrelia burgdorferi*
○	*Legionella pneumophila*
○	*Leptospira icterohaemorrhagica*
○	*Mycoplasma pneumoniae*
○	*Pneumococcus*

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 52 mins 55 secs

Question: 70 of 100

You are an occupational health physician and have been asked by an anxious employee about contraindications to pertussis immunisation.

Which of the following is a contraindication?

(Please select 1 option)

○	Eczema
○	Cow's milk protein intolerance.
○	Fever to 39.5°C following the first dose.
○	Hydrocephalus
○	Redness of >2.5cm at the injection site after the first dose.

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Which of the following is a contraindication?

(Please select 1 option)

○	Eczema
○	Cow's milk protein intolerance.
◉	Fever to 39.5°C following the first dose. ✓ Correct
○	Hydrocephalus
○	Redness of >2.5cm at the injection site after the first dose.

True contraindications to pertussis immunisation include:

- Acute illness - until recovered
- Previous reaction to pertussis:
  - Local: an extensive area of redness and swelling which becomes indurated, involving most of the anterolateral surface of the thigh or a major part of the circumference of the upper arm
  - General: fever equal to or more than 39.5°C within 48 hours of vaccine, anaphylaxis, bronchospasm, laryngeal oedema, generalised collapse, prolonged hyporesponsiveness, prolonged inconsolable or high-pitched screaming of more than four hours, convulsions or encephalopathy occurring within 72 hours.

A personal family history of allergy is not a contraindication, nor are stable neurological conditions such as cerebral palsy or spina bifida.

In patients who have had a previous reaction, immunisations should be completed with DT vaccine, and acellular vaccine considered.

Copyright © 2002 Dr Colin Melville

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd. All rights reserved. Terms and conditions Privacy policy

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 53 mins 41 secs

Question: 71 of 100

Regarding diphtheria which of the following statements is correct?

(Please select 1 option)

- About 50 cases per year are seen in the UK.
- It is characterised by an inflammatory exudate forming a greyish membrane on the buccal mucosa.
- It is predominantly spread from cutaneous lesions.
- It produces a toxin which affects the myocardium, nervous and adrenal tissues.
- 3 doses of toxoid provides 75% protection.

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Question: 71 of 100

Regarding diphtheria which of the following statements is correct?

(Please select 1 option)

○	About 50 cases per year are seen in the UK.
○	It is characterised by an inflammatory exudate forming a greyish membrane on the buccal mucosa.
○	It is predominantly spread from cutaneous lesions.
◉	It produces a toxin which affects the myocardium, nervous and adrenal tissues. ✓ Correct
○	3 doses of toxoid provides 75% protection.

Diphtheria is spread by droplets, through contact with soiled articles (fomites), and, in areas of poor hygiene, from cutaneous spread.

The inflammatory exudate forms a greyish membrane on the tonsils and respiratory tract which may cause respiratory obstruction.

Incubation is between two and five days, and patients may be infectious for four weeks.

The toxin affects the myocardium, nervous and adrenal tissues.

The immunisation has been tremendously successful, and most cases seen in the United Kingdom are imported from the Indian subcontinent or Africa.

Recently, there has been a worrying epidemic of diphtheria in Russia and the newly independent states of the former Soviet Union. In 1995, 52,000 cases and 1,700 deaths were reported.

Copyright © 2002 Dr Colin Melville

Next question

Tag Question | Remove question

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 55 mins 1 secs

Question: 72 of 100

Which of the following forms of encephalitis is caused by a neuroimmunological response?

(Please select 1 option)

○	Cytomegalovirus
○	Enteral viruses
○	Herpes simplex
○	HIV infection
○	Measles

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Question: 72 of 100

Which of the following forms of encephalitis is caused by a neuroimmunological response?

(Please select 1 option)

○	Cytomegalovirus
○	Enteral viruses
○	Herpes simplex
○	HIV infection
◉	Measles ✓ Correct

Encephalitis may be caused by:

- Direct invasion by a neurotoxic virus (encephalitis)
- Post-infectious encephalopathy: delayed brain swelling because of an immunological response to the antigen
- Slow virus infection, for example, human immunodeficiency virus [HIV] or subacute sclerosing panencephalitis [SSPE].

Direct infection is most commonly caused by enteral viruses, herpes simplex virus (HSV) 1 and 2, varicella, cytomegalovirus (CMV), and Epstein-Barr virus (EBV).

It is also occasionally caused by respiratory viruses, human herpes virus 6 (HHV6), rubella or mumps.

A post-infectious illness may also be caused by measles or varicella zoster (cerebellar ataxia).

Copyright © 2002 Dr Colin Melville

Next question | Tag Question | Remove question

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 55 mins 36 secs

Question: 73 of 100

A young teenager presents with fever and headache. He has received oral amoxicillin for three days.

Which of the following cerebrospinal fluid (CSF) findings would virtually exclude a partially treated bacterial meningitis?

(Please select 1 option)

- A CSF glucose of 45% of blood glucose
- A negative CSF culture
- A negative gram stain
- A negative Kernig's Sign
- A white cell count of 3

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 56 mins 38 secs

Question: 73 of 100

A young teenager presents with fever and headache. He has received oral amoxicillin for three days.

Which of the following cerebrospinal fluid (CSF) findings would virtually exclude a partially treated bacterial meningitis?

(Please select 1 option)

- (●) A CSF glucose of 45% of blood glucose ✗ Incorrect answer selected
- ( ) A negative CSF culture
- ( ) A negative gram stain
- ( ) A negative Kernig's Sign
- ( ) A white cell count of 3 ← This is the correct answer

The assessment of children with suspected bacterial meningitis who have already received antibiotic therapy from their GP is a common diagnostic problem.

Partial treatment may reduce the incidence of positive CSF gram stains to < than 60%, and it also reduces the ability to grow the bacteria, particularly meningococcus.

CSF glucose, protein, neutrophils and bacterial antigen testing or polymerase chain reaction (PCR) should be completely unaffected. A normal white cell count would make the diagnosis very unlikely.

Copyright © 2002 Dr Colin Melville

Next question | Remove Tag | Remove question

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 56 mins 38 secs

Question: 74 of 100

A 14-year-old boy presents with fever.

Which of the following might contribute to a diagnosis of rheumatic fever?

(Please select 1 option)

○	A CRP of 10
○	A prolonged PR interval on ECG
○	Finding target lesions on the hands
○	Finding tender nodules in the fingertips
○	Positive Romberg's sign

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

○	A CRP of 10
◉	A prolonged PR interval on ECG ✓ Correct
○	Finding target lesions on the hands
○	Finding tender nodules in the fingertips
○	Positive Romberg's sign

The modified Jones criteria include:

- Finding of preceding streptococcal infection (recent scarlet fever, raised ASOT or other streptococcal antibodies)
- Positive throat swab for Group A *Strep*.

Plus:

(a) Major Criteria:

- Carditis
- Polyarthritis
- Chorea
- Subcutaneous nodules
- Erythema marginatum.

(b) Minor Criteria:

- Fever
- Arthralgia
- Previous history of rheumatic fever
- Elevated acute phase reactions

- Polyarthritis
- Chorea
- Subcutaneous nodules
- Erythema marginatum.

(b) Minor Criteria:

- Fever
- Arthralgia
- Previous history of rheumatic fever
- Elevated acute phase reactions
- Prolonged PR interval.

Erythema marginatum involves red circular lesions which gradually enlarge with central clearing.

Sydenham's chorea consists of choreoathetoid movements with increased clumsiness, for example, deteriorating handwriting. This is often associated with emotional lability.

Target lesions suggest erythema multiforme.

A C-reactive protein (CRP) of 10 is not elevated much beyond the normal range.

Erythema marginatum initially manifests as non-specific pink macules seen over the trunk, with later blanching in the middle of the lesions and sometimes fusing of the borders resulting in a serpiginous (serpent-like) looking lesion. The rash is worsened with heat, but is characteristically evanescent. It does not itch, and can be mistaken for the rash of Lyme disease.

Sub-cutaneous nodules are pea-sized, firm and non-tender. There is no associated inflammation and they are characteristically seen on the extensor surfaces of joints such as knees and elbows and also over the spine.

© 2002 Dr Colin Melville

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 57 mins 12 secs

Question: 75 of 100

Which is true regarding eczema herpeticum?

(Please select 1 option)

- Is invariably fatal if untreated
- Is more severe in reactivation disease
- Is typically associated with a high fever for over a week
- Only a single crop of vesicles usually appear
- Usually has an indolent onset

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 58 mins 23 secs

Question: 75 of 100

Which is true regarding eczema herpeticum?

(Please select 1 option)

○	Is invariably fatal if untreated
○	Is more severe in reactivation disease
◉	Is typically associated with a high fever for over a week ✓ Correct
○	Only a single crop of vesicles usually appear
○	Usually has an indolent onset

Eczema herpeticum is the result of primary infection of eczematous skin with *Herpes simplex* virus (HSV). The severity varies from mild to fatal.

There is usually an abrupt onset with crops appearing over seven to nine days. These may become coalesced. Typically, the child has a high fever for seven days, and recurrent attacks can occur.

Death can result from physiological disturbances (loss of fluid electrolytes and protein through the skin) or dissemination of the virus to brain and other organs or from secondary bacterial sepsis.

© 2002 Dr Colin Melville

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Brucellosis is characterised by neutrophil leucocytosis

Brucellosis is a recognised cause of spondylitis ✓ Correct

Serological evidence of toxoplasmosis is rare in adults

Toxoplasmosis causes vasculitic anterior uveitis

Toxoplasmosis causes visceral larva migrans

Brucellosis is a zoonosis, spreading from infected animals particularly cattle. There are four species: melitensis, abortus, suis, and canis.

Pasteurisation of milk has dramatically decreased the incidence in the UK.

Brucella are Gram-negative bacilli which are fastidious. There is usually a history of exposure, and the symptoms are rather non-specific with fever, malaise, arthralgia and depression. 35% have hepatosplenomegaly.

Leukopaenia is common, and 75% have a positive blood culture (90% of bone marrow cultures will be positive).

Toxoplasma is most frequent in farming communities where contact occurs with cats, and patients eat raw meat. Clinical manifestations include:

- Focal choroidoretinitis
- Granulomatous uveitis
- Optic atrophy
- Retinal detachment
- Cataract
- Posterior uveitis
- Glaucoma.

Copyright © 2002 Dr Colin Melville

Brucellosis is characterised by neutrophil leucocytosis

Brucellosis is a recognised cause of spondylitis ✓ Correct

Serological evidence of toxoplasmosis is rare in adults

Toxoplasmosis causes vasculitic anterior uveitis

Toxoplasmosis causes visceral larva migrans

Brucellosis is a zoonosis, spreading from infected animals particularly cattle. There are four species: melitensis, abortus, suis, and canis.

Pasteurisation of milk has dramatically decreased the incidence in the UK.

Brucella are Gram-negative bacilli which are fastidious. There is usually a history of exposure, and the symptoms are rather non-specific with fever, malaise, arthralgia and depression. 35% have hepatosplenomegaly.

Leukopaenia is common, and 75% have a positive blood culture (90% of bone marrow cultures will be positive).

Toxoplasma is most frequent in farming communities where contact occurs with cats, and patients eat raw meat. Clinical manifestations include:

- Focal choroidoretinitis
- Granulomatous uveitis
- Optic atrophy
- Retinal detachment
- Cataract
- Posterior uveitis
- Glaucoma.

Copyright © 2002 Dr Colin Melville

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 1 secs

Question: 77 of 100

Which of the following is true of tetanus?

(Please select 1 option)

- **A** Failure to culture *Clostridium tetani* from the wound would make the diagnosis doubtful
- **B** Infection confers lifelong immunity
- **C** There is a characteristic EEG
- **D** Clostridium-specific intravenous immunoglobulin is of no benefit once spasm has started
- **E** Cephalic tetanus causes severe dysphagia

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 1 mins 14 secs

Question: 77 of 100

Which of the following is true of tetanus?

(Please select 1 option)

○	**A** Failure to culture *Clostridium tetani* from the wound would make the diagnosis doubtful
○	**B** Infection confers lifelong immunity
○	**C** There is a characteristic EEG
◉	**D** Clostridium-specific intravenous immunoglobulin is of no benefit once spasm has started ✕ Incorrect answer selected
○	**E** Cephalic tetanus causes severe dysphagia ← This is the correct answer

A Absence of a wound does not exclude tetanus.

B Patients need to be actively immunised after recovery.

C The toxin tetanospasmin does not cross the blood brain barrier, it diffuses through the blood to bind to receptors containing gangliosides on the neuronal membranes of presynaptic nerve terminals in muscles. The toxin does reach the brain by axonal transport.

D It is ineffective once the toxin is attached to nervous tissue but may prevent progression.

E Cephalic means involving the cranial nerves usually from a wound on the head and neck. It may be confused with rabies but hydrophobia never occurs. (OTM, 3e, 7.11.20)

Next question | Tag Question | Remove question

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 1 mins 14 secs

Question: 78 of 100

A 25-year-old male homosexual is admitted with dyspnoea and weight loss of two months duration.

He is diagnosed with *Pneumocystis pneumoniae* due to AIDS.

Which of the following concerning *Pneumocystis* pneumonia is true?

(Please select 1 option)

- A. May have an extra pulmonary presentation
- B. It is always associated with x ray changes
- C. It is caused by a bacterium
- D. Elevated serum antibodies to *P. carinii* are helpful diagnostically
- E. It is best treated with intravenous pentamidine

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 3 mins 11 secs

Question: 78 of 100

A 25-year-old male homosexual is admitted with dyspnoea and weight loss of two months duration.

He is diagnosed with *Pneumocystis pneumoniae* due to AIDS.

Which of the following concerning *Pneumocystis* pneumonia is true?

(Please select 1 option)

◉	A. May have an extra pulmonary presentation ✓ Correct
○	B. It is always associated with x ray changes
○	C. It is caused by a bacterium
○	D. Elevated serum antibodies to *P. carinii* are helpful diagnostically
○	E. It is best treated with intravenous pentamidine

A. Any HIV associated condition.

B. Five to 15% have normal CXR (always is always false ... but not always!).

C. A fungus.

D. There is polyclonal B-cell activation in AIDS.

E. intravenous cotrimoxazole.

Next question | Tag Question | Remove question

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 3 mins 11 secs

Question: 79 of 100

Which of the following is true of the the T cell response to antigen?

(Please select 1 option)

○	a. A process of affinity maturation of the T cell receptor occurs.
○	b. Intact antigen is presented in association with self MHC molecules.
○	c. Co-operation with other cell types is required for T cell recognition of antigen.
○	d. Gamma/delta + T cells respond to antigen presented in association with MHC class II molecules.
○	e. Interactions of the TcR with an appropriate Ag/MHC complex activates a resting T cell.

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Question: 79 of 100

Which of the following is true of the the T cell response to antigen?

(Please select 1 option)

○	a. A process of affinity maturation of the T cell receptor occurs.
○	b. Intact antigen is presented in association with self MHC molecules.
○	c. Co-operation with other cell types is required for T cell recognition of antigen. ← This is the correct answer
○	d. Gamma/delta + T cells respond to antigen presented in association with MHC class II molecules.
◉	e. Interactions of the TcR with an appropriate Ag/MHC complex activates a resting T cell. ✕ Incorrect answer selected

a. Affinity maturation in an ongoing immune response is a feature of the antibody response. There is no evidence that a similar process occurs in the T cell response.

b. Major histocompatability complex (MHC) molecules present short antigen-derived peptides, not the intact antigen.

c. T cells recognise antigen only when presented by (self) MHC molecules on an antigen presenting cell.

d. MHC class II molecules present antigen to CD4+, alpha/beta+ T cells. It is still not clear how gamma/delta+ T cells recognise antigen, however most gamma/delta+ T cells do not appear to be restricted by (self) MHC molecules.

e. Additional 'costimulatory' signals are required to activate a resting T cell. Interaction of the T cell reactor (TcR) of a resting T cell with an appropriate Ag/MHC complex in the absence of costimulatory signals may lead to the induction of anergy.

(c) Dr Alan Cann

Next question | Tag Question | Remove question

- Scores
- Community
- Help
- Shop

Which of the following organisms is most likely to be responsible for their illness?

(Please select 1 option)

○	*Borrelia burgdorferi*
○	*Legionella pneumophila*
◉	*Leptospira icterohaemorrhagica* ✓ Correct
○	*Mycoplasma pneumoniae*
○	*Pneumococcus*

Leptospirosis, or Weil's disease, is transmitted to man by animals, including rodents (rat urine and faeces), skunks, foxes, cattle, dogs.

The disease is characterised by

- Jaundice
- Fever
- Oliguria
- Headache
- Myalgia
- Haemorrhagic tendencies with purpura or petechiae
- Enlargement of liver and spleen.

Next question | Tag Question | Remove question

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 9 mins 40 secs

Question: 8 of 100

A 20-year-old man presented to hospital two days after returning from visiting his family in Bangladesh.

Within a day of his return to the United Kingdom he suddenly developed profuse watery diarrhoea. He says there had been an outbreak of diarrhoea in his family's village in the week before his return.

Stool culture revealed a growth of *Vibrio cholerae*.

Which one of the following blood types is associated with the greatest susceptibilty to severe cholera?

(Please select 1 option)

- Blood Group A
- Blood Group AB
- Blood Group B
- Blood Group O
- Rhesus -ve

Submit answer | Skip question | Remove Tag | Remove question

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 5 mins 1 secs

Question: 80 of 100

Which of the following is a feature of vancomycin-resistant enterococci?

(Please select 1 option)

- a. Cause resistant infective diarrhoea
- b. Produce an enzyme that inactivates vancomycin
- c. May be found in healthy community volunteers not recently hospitalised
- d. High dose ampicillin is the treatment of choice
- e. Are commonly vancomycin-dependent

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

○	a. Cause resistant infective diarrhoea
○	b. Produce an enzyme that inactivates vancomycin
◉	c. May be found in healthy community volunteers not recently hospitalised ✓ Correct
○	d. High dose ampicillin is the treatment of choice
○	e. Are commonly vancomycin-dependent

a. When they cause clinical problems they are usually urinary tract infections (UTI), bacteraemia, wound infections, neonatal infections, endocarditis etcetera.

b. They alter peptidoglycan precursors used to build cell walls. Vancomycin binds to D-ala-D-ala but the resistant enterococci have D-ala-D-lac or D-ala terminating precursors. They aquire genes that produce enzymes to change the precursors.

c. 2% in the United Kingdom general practice, 28% in Belgium. Community reservoir in meat, poultry and perhaps cheese.

d. Only if the MIC (minimum inhibitory concentration) of ampicillin is not too high. Anecdotal evidence exists for its use in *E. faecalis* endocarditis. (20g / day).

e. Some strains only. An explanation for this curious process is that there is an inability to produce cell walls because the vancomycin-sensitive precursor genes have been turned off and the resistant ones only appear in the presence of vancomycin.

(Source: Am J Med 1997;102:284-293)

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 6 mins 1 secs

Question: 81 of 100

Which of the following is true of cutaneous anthrax?

(Please select 1 option)

○	Causes a black eschar which overlies pus
○	Is very likely to occur in subjects exposed to anthrax spores
◉	Lesions are associated with marked oedema
○	Lesions are usually painful and tender
○	Mortality is approximately 20% despite antibiotic therapy

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Which of the following is true of cutaneous anthrax?

(Please select 1 option)

○	Causes a black eschar which overlies pus
○	Is very likely to occur in subjects exposed to anthrax spores
◉	Lesions are associated with marked oedema ✓ Correct
○	Lesions are usually painful and tender
○	Mortality is approximately 20% despite antibiotic therapy

Anthrax is caused by *Bacillus anthracis* a Gram-positive rod.

Cutaneous anthrax is caused by direct contact of the bacteria into an open wound (usually touching an infected animal). Cutaneous anthrax is associated with a black eschar without pus, tends to be painless and to have widespread oedema.

Without antibiotics mortality is of the order of 20%, but with antibiotics, mortality is low, which contrasts with pulmonary anthrax.

Further reading:
Cutaneous Anthrax Management Algorithm American Academy of Dermatology

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 6 mins 30 secs

Question: 82 of 100

Which of the following concerning *Corynebacterium diphtheriae* is correct?

(Please select 1 option)

○	Causes skin infection
○	Infection is often complicated by myocardial fibrosis after recovery from severe infection
○	Is most unlikely to cause infection in an individual with a positive Schick test
○	Mitis strain is generally more virulent than the intermedius strain
○	Toxin is better absorbed through the nasal than the pharyngeal mucosa

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Scores
- Community
- Help
- Shop

○	Causes skin infection ← This is the correct answer
○	Infection is often complicated by myocardial fibrosis after recovery from severe infection
○	Is most unlikely to cause infection in an individual with a positive Schick test
◉	Mitis strain is generally more virulent than the intermedius strain ✕ Incorrect answer selected
○	Toxin is better absorbed through the nasal than the pharyngeal mucosa

Corynebacterium diphtheriae is a gram positive, non-spore forming, pleomorphic bacteria that is also a facultative anaerobe.

Corynebacterium diphtheriae causes diphtheria.

Typically diphtheria attacks the respiratory system, but may also affect the skin, conjunctiva and external genitalia.

Signs and symptoms include sore throat, fever, and swelling of lymph nodes in the neck and general malaise.

As the disease progresses diphtheria toxin is secreted. This destroys the membrane surface of the affected areas and replaces them with a greyish tough leathery "pseudomembrane" made of dead tissue, leukocytes and bacteria.

Toxin could also affect the heart, nerves and other organs in the body causing heart failure, nerve damage or suffocation.

Toxin can be neutralised by the immune serum produced by the host cells.

Diphtheria is transmitted from person to person. Human beings are the main reservoir.

Next question | Tag Question | Remove question

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 10 mins 45 secs

Question: 83 of 100

Which of the following is true concerning whooping cough (pertussis)?

(Please select 1 option)

○	Is a greater threat to children during the second six months of life, after maternal antibody has declined, than during the first six months
○	Is associated with convulsions less frequently than is the case with other febrile conditions
○	Is characteristically associated with a polymorph leucocytosis
○	May lead to hemiplegia
○	Rapidly resolves with antibiotic treatment

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Which of the following is true concerning whooping cough (pertussis)?

(Please select 1 option)

◉	Is a greater threat to children during the second six months of life, after maternal antibody has declined, than during the first six months ✗ Incorrect answer selected
○	Is associated with convulsions less frequently than is the case with other febrile conditions
○	Is characteristically associated with a polymorph leucocytosis
○	May lead to hemiplegia ← This is the correct answer
○	Rapidly resolves with antibiotic treatment

Whooping cough (pertussis) is caused by the bacterium *Bordetella pertussis*.

B. pertussis is a very small gram-negative aerobic coccobacillus that appears singly or in pairs.

Infection is characterised by paroxysms of coughing.

Lymphocytosis is typically found.

Hemiplegia is a recognised effect of severe whooping cough.

The pertussis vaccine is estimated to be 63% to 94% effective in the diphtheria-pertussis-tetanus (DPT) shot.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 13 mins 46 secs

Question: 84 of 100

Twenty of thirty patients in an adult ward develop colicky abdominal pain and diarrhoea without vomiting between 21:00 and 01:00 hrs.

Meat stew was served for lunch at noon.

Which of the following is the likely diagnosis?

(Please select 1 option)

○	*Bacillus Cereus*
○	*Clostridium perfringens*
○	Enterotoxigenic *E.Coli*
○	Enterovirus
○	*Staphylococcus Aureus*

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Which of the following is the likely diagnosis?

(Please select 1 option)

○	*Bacillus Cereus*
◉	*Clostridium perfringens* ✓ Correct
○	Enterotoxigenic *E.Coli*
○	Enterovirus
○	*Staphylococcus Aureus*

This food poisoning with no vomiting and an incubation period between between 9-13 hours is typical of *Clostridium perfringens*.

The history is too long for a typical *Staph. aureus* infection (vomiting a typical feature, incubation period 1-6 hours) and rather short of enterovirus (24 hours).

The predominant symptom of *B.cereus* (incubation period 1-5 hours) is marked vomting with diarrhoea occasionally seen.

Escherichia coli infection has an incubation period of 12-24 hours and is also associated with marked vomiting.

Supportive treatment is all that is generally required with symptoms resolving after 24 hours.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

javascript:__doPostBack('ctl00$LoginStatus1$ctl00','')

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 15 mins 24 secs

Question: 85 of 100

Which one of the following statements concerning T-lymphocytes is correct?

(Please select 1 option)

○	Are infected by Epstein-Barr virus in infectious mononucleosis
○	Are the primary host response in bacterial infection
○	Compose the majority of lymphocytes in plasma
○	Produce IgG
○	T cell lymphoma has a better prognosis than B cell lymphoma

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Which one of the following statements concerning T-lymphocytes is correct?

(Please select 1 option)

○	Are infected by Epstein-Barr virus in infectious mononucleosis
○	Are the primary host response in bacterial infection
◉	Compose the majority of lymphocytes in plasma ✓ Correct
○	Produce IgG
○	T cell lymphoma has a better prognosis than B cell lymphoma

The primary host response to bacterial infections is dependent on mononuclear phagocytes and neutrophils.

T-lymphocytes are involved in cell-mediated acquired immune responses, whereas B-lymphocytes are involved in humoral immunity and produce immunoglobulins.

T lymphocytes compose the majority of circulating lymphocytes in plasma.

Epstein-Barr virus infects B-lymphocytes and squamous epithelial cells of the oropharynx. The virus can transform B cells and epithelial cells to produce Burkitt's lymphoma, a subset of Hodgkin's lymphoma, nasopharyngeal carcinoma and oral hairy leukoplakia.

T cell lymphoma makes up about 10-20% of non-Hodgkin's lymphomas and has a worse prognosis than B cell lymphoma.

Next question | Tag Question | Remove question

http://my.onexamination.com/Assessment/Questions.aspx?id=680195&ws=true

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 16 mins 14 secs

Question: 86 of 100

A 19-year-old man returned to the UK two weeks after working in a refugee camp in sub-Saharan Africa.

On examination he was febrile, dyspnoeic and widespread inspiratory crackles were present. He had an extensive maculo-papular rash, conjunctivitis, generalised stomatitis and some bluish-grey spots on the buccal mucosa.

What is the most likely diagnosis?

(Please select 1 option)

- ○ Epidemic typhus
- ○ Epstein-Barr virus infection
- ○ Leptospirosis
- ○ Measles
- ○ Parvovirus infection

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Questions
- Scores
- Community
- Help
- Shop

A 19-year-old man returned to the UK two weeks after working in a refugee camp in sub-Saharan Africa.

On examination he was febrile, dyspnoeic and widespread inspiratory crackles were present. He had an extensive maculo-papular rash, conjunctivitis, generalised stomatitis and some bluish-grey spots on the buccal mucosa.

What is the most likely diagnosis?

(Please select 1 option)

○	Epidemic typhus
○	Epstein-Barr virus infection
○	Leptospirosis
◉	Measles ✓ Correct
○	Parvovirus infection

Although seldom seen in countries in which a vaccine is available, measles is a major health problem in refugee camps in Africa.

The clinical picture described is characteristic.

The major complications of measles involve the respiratory tract and central nervous system.

Pneumonia may be caused by the virus itself or through bacterial superinfection.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

A 30-year-old man developed a febrile illness three days after returning from a holiday in Thailand. He was admitted complaining of severe myalgia.

On examination he was febrile (39ºC) with a diffuse macular rash on the trunk. There was no lymphadenopathy.

Investigations revealed:

Haemoglobin	15.1 g/dL (13.0-18.0)
White cell count	7.5 $x10^9$/L (4-11 $x10^9$)
Platelet count	105 $x10^9$/L (150-400 $x10^9$)
Serum total bilirubin	18 µmol/L (1-22)
Serum alanine aminotransferase	120 U/L (5-35)

What is the most likely diagnosis?

(Please select 1 option)

- ○ Acute HIV infection (seroconversion illness)
- ○ Dengue fever
- ○ Hepatitis E
- ○ Secondary syphilis
- ○ Typhoid

What is the most likely diagnosis?

(Please select 1 option)

○	Acute HIV infection (seroconversion illness)
◉	Dengue fever ✓ Correct
○	Hepatitis E
○	Secondary syphilis
○	Typhoid

The symptoms are most consistent with dengue fever.

While acute retroviral syndrome (acute HIV) is associated with a widespread macular rash, it is also usually associated with pharyngitis and generalised lymphadenopathy.

Hepatitis E presents in a similar manner to hepatitis A, that is, as an acute febrile illness with jaundice.

The history is too acute for secondary syphilis, which is not typically associated with myalgia.

Typhoid fever is usually a diarhoeal illness associated with subtle 'rose spots' on the abdomen.

Dengue fever is caused by an arthropod-borne *Flavivirus*. The disease has an incubation period of approximately seven days, followed by headaches and retro-orbital pain. Symptoms evolve rapidly and severe musculoskeletal pain is a prominent feature, with a maculopapular rash.

Next question

Tag Question

Remove question

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 19 mins 58 secs

Question: 88 of 100

Four members of a football team develop diarrhoea due to *Salmonella enteritidis*.

Eating which food was the most likely source of the infection?

(Please select 1 option)

- Chicken at a fast food outlet 20 hours earlier
- Fried rice at a takeaway 4 hours earlier
- Raw eggs in milk 6 hours earlier
- Raw oysters at a hotel 24 hours earlier
- Soft cheeses 48 hours earlier

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 20 mins 45 secs

Question: 88 of 100

Four members of a football team develop diarrhoea due to *Salmonella enteritidis*.

Eating which food was the most likely source of the infection?

(Please select 1 option)

◉	Chicken at a fast food outlet 20 hours earlier ✓ Correct
○	Fried rice at a takeaway 4 hours earlier
○	Raw eggs in milk 6 hours earlier
○	Raw oysters at a hotel 24 hours earlier
○	Soft cheeses 48 hours earlier

The incubation time for *Salmonella enteritidis* is 12-48 hours and the likely sources are poultry and eggs.

Raw oysters are associated with infections such as the Norwalk agent.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 20 mins 45 secs

Question: 89 of 100

A 27-year-old man presents with fever, urethritis and arthralgia. He is found to have a swollen ankle with a pustular rash on the dorsal aspect of his foot.

What is the most likely diagnosis?

(Please select 1 option)

- Gonococcal sepsis
- Lyme disease
- Reiter's syndrome
- Staphylococcal arthritis
- Tuberculous arthritis

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

A 27-year-old man presents with fever, urethritis and arthralgia. He is found to have a swollen ankle with a pustular rash on the dorsal aspect of his foot.

What is the most likely diagnosis?

(Please select 1 option)

◉	Gonococcal sepsis ✓ Correct
○	Lyme disease
○	Reiter's syndrome
○	Staphylococcal arthritis
○	Tuberculous arthritis

The most likely cause for this acute presentation is gonococcal septicaemia - with a pustular rash on the dorsum of his foot, fever, urethritis and oligoarthritis.

Reiter's is associated with an acute infection - urethritis/diarrhoea and later the development of an arthritis.

Further reading:
National Guideline on the Diagnosis and Treatment of Gonorrhoea in Adults 2005 (pdf) British Association for Sexual Health and HIV

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 10 mins 39 secs

Question: 8 of 100

A 20-year-old man presented to hospital two days after returning from visiting his family in Bangladesh.

Within a day of his return to the United Kingdom he suddenly developed profuse watery diarrhoea. He says there had been an outbreak of diarrhoea in his family's village in the week before his return.

Stool culture revealed a growth of *Vibrio cholerae*.

Which one of the following blood types is associated with the greatest susceptibilty to severe cholera?

(Please select 1 option)

○	Blood Group A
○	Blood Group AB
○	Blood Group B
◉	Blood Group O ✓ Correct
○	Rhesus -ve

"Individuals with blood group O are more susceptible than other individuals to severe cholera, although the mechanism underlying this association is unknown." Infect Immun. 2005 Nov; 73(11): 7422-7.

Next question | Remove Tag | Remove question

A 24-year-old female student presented with fever and rigors for two days, fatigue, headache especially retro-orbital and diarrhoea. In particular she complained of a weakness of the left side of her face and drooping of the lip.

She had recently returned from a sabbatical in Uganda four weeks previously.

She was febrile (39.9°C), had a mild left facial nerve palsy, lymphadenopathy in her axillae and groin and she had an erythematous, maculopapular rash.

Laboratory investigations showed:

Haemoglobin	12.0 g/dl (11.5-16.5)
WBC	3.0 $x10^9$/l (4-11 $x10^9$)
Platelets	150 $x10^9$/l (150-400 $x10^9$)
Blood film	Lymphopaenia, some atypical lymphocytes seen

Which of the following is the most likely diagnosis?

(Please select 1 option)

- ○ Acute HIV infection (seroconversion illness)
- ○ Dengue fever
- ○ Infectious mononucleosis
- ○ Typhoid fever
- ○ Viral hepatitis

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 21 mins 25 secs

Question: 90 of 100

A 75-year-old man has a history of chronic lymphocytic leukaemia. He has had treatment with several courses of chemotherapy and has now been admitted to hospital with pneumonia. His past medical history revealed that he had suffered several previous upper respiratory tract infections over the previous six months.

Which of the following components of his immune system is likely to be deficient?

(Please select 1 option)

- Complement
- Immunoglobulin G
- Macrophages
- Mast cells
- T lymphocytes

Submit answer | Skip question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 23 mins 25 secs

Question: 90 of 100

A 75-year-old man has a history of chronic lymphocytic leukaemia. He has had treatment with several courses of chemotherapy and has now been admitted to hospital with pneumonia. His past medical history revealed that he had suffered several previous upper respiratory tract infections over the previous six months.

Which of the following components of his immune system is likely to be deficient?

(Please select 1 option)

○	Complement
◉	Immunoglobulin G ✓ Correct
○	Macrophages
○	Mast cells
○	T lymphocytes

Chronic lymphocytic leukaemia (CLL) is commonly complicated by panhypogammaglobulinaemia.

Although intravenous immunoglobulin prevents recurrent infections it does not prolong survival.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 23 mins 25 secs

Question: 91 of 100

A 40-year-old man presented with pityriasis versicolor.

What is the most appropriate treatment?

(Please select 1 option)

○	Methotrexate
○	Oral terbinafine
○	Phototherapy with ultraviolet light (UVB)
○	Psoralen with ultraviolet light (PUVA) therapy
○	Topical selenium sulphide

Submit answer | Skip question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 23 mins 48 secs

Question: 91 of 100

A 40-year-old man presented with pityriasis versicolor.

What is the most appropriate treatment?

(Please select 1 option)

○	Methotrexate
○	Oral terbinafine
○	Phototherapy with ultraviolet light (UVB)
◉	Psoralen with ultraviolet light (PUVA) therapy ✕ Incorrect answer selected
○	Topical selenium sulphide ← This is the correct answer

Pityriasis versicolor (also called tinea versicolor) is a skin lesion caused by a fungus called *Malassezia furfur*.

The treatment is topical selenium sulphide. Oral itraconazole is also effective.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Show tools

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 23 mins 48 secs

Question: 92 of 100

A 40-year-old single man returned from holiday in Europe with mild bloody diarrhoea which had lasted for two weeks.

He had lost 2.5 kg in weight, had occasional lower abdominal cramping discomfort and a painful swelling of his left knee.

What is the most likely diagnosis?

(Please select 1 option)

○	Amoebiasis
○	*Campylobacter* infection
◉	Crohn's disease
○	Gonococcal septicaemia
○	Ulcerative colitis

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

A 40-year-old single man returned from holiday in Europe with mild bloody diarrhoea which had lasted for two weeks.

He had lost 2.5 kg in weight, had occasional lower abdominal cramping discomfort and a painful swelling of his left knee.

What is the most likely diagnosis?

(Please select 1 option)

○	Amoebiasis
○	*Campylobacter* infection ← This is the correct answer
◉	Crohn's disease ✕ Incorrect answer selected
○	Gonococcal septicaemia
○	Ulcerative colitis

Campylobacter infection is one of the commonest causes of inflammatory diarrhoea. Abdominal pain is often a prominent feature of the illness frequently localising to the right iliac fossa. Diarrhoea may be mild or very severe often with passage of blood. Symptoms may last a week or longer.

Reactive arthritis and Reiter's syndrome can develop following infection with a number of enteric pathogens including *Shigella*, *Salmonella*, *Campylobacter* and *Yersinia*.

Further reading:
Campylobacter World Health Organization

Next question

Remove Tag | Remove question

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 24 mins 36 secs

Question: 93 of 100

Which of the following infections is least likely to cause myocarditis?

(Please select 1 option)

○	Chagas disease
○	Coxsackie virus
○	Diphtheria
○	Syphilis
○	Toxoplasmosis

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 25 mins 7 secs

Question: 93 of 100

Which of the following infections is least likely to cause myocarditis?

(Please select 1 option)

○	Chagas disease
○	Coxsackie virus
○	Diphtheria
◉	Syphilis ✓ Correct
○	Toxoplasmosis

Quaternary syphilis involves the cardiovascular system, commonly in the form of ascending aortic aneurysm and aortic regurgitation.

Diphtheria, coxsackie virus, Chagas disease and toxoplasmosis are all associated with myocarditis.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 25 mins 7 secs

Question: 94 of 100

A 63-year-old female presents with a one day history of confusion with headaches.

On examination she is confused, with a Glasgow Coma Scale of 13 and a temperature of 39.5°C.

She has nuchal rigidity and photophobia.

CSF examination reveals a glucose of 0.5 mmol/l (3.3-4.4), a white cell count of 2500 per mm and Gram-positive cocci in pairs.

Which of the following is correct?

(Please select 1 option)

- A characteristic rash would be expected
- Nerve deafness would be a common complication in this case
- Rifampicin should be given to close contacts
- The most likely infective organism is *Staphylococcus aureus*
- The organism is likely to be penicillin resistant

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

She has nuchal rigidity and photophobia.

CSF examination reveals a glucose of 0.5 mmol/l (3.3-4.4), a white cell count of 2500 per mm and Gram-positive cocci in pairs.

Which of the following is correct?

(Please select 1 option)

○	A characteristic rash would be expected
◉	Nerve deafness would be a common complication in this case ✓ Correct
○	Rifampicin should be given to close contacts
○	The most likely infective organism is *Staphylococcus aureus*
○	The organism is likely to be penicillin resistant

This patient has pneumococcal meningitis, caused by the Gram-positive coccus *Strep. pneumoniae*.

This is the second commonest cause of bacterial meningitis (commonest in the elderly) and is associated with the highest mortality (20%) and highest morbidity, such as deafness which may occur in 50%.

Contacts do not require treatment and there is no rash associated with pneumococcal meningitis.

Meningococcus is Gram-negative.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 26 mins 40 secs

Question: 95 of 100

The antibiotic combination quinupristin and dalfopristin are:

(Please select 1 option)

○	Administered orally.
○	Effective against multi-resistant Staph. aureus
○	Effective against resistant mycobacterium TB.
○	Indicated in subjects with chronic renal impairment.
○	Particularly effective in the treatment of pseudomonas infection in cystic fibrosis.

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 27 mins 12 secs

Question: 95 of 100

The antibiotic combination quinupristin and dalfopristin are:

(Please select 1 option)

○	Administered orally.
◉	Effective against multi-resistant Staph. aureus ✓ Correct
○	Effective against resistant mycobacterium TB.
○	Indicated in subjects with chronic renal impairment.
○	Particularly effective in the treatment of pseudomonas infection in cystic fibrosis.

Quinupristin and dalfopristin are a synergistic combination of a streptogramin A and B respectively.

They are effective against gram positive aerobes and are particularly useful against resistant *Strep. pneumoniae* and *Staph. aureus*.

They can be administered only via a central line.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 27 mins 12 secs

Question: 96 of 100

Chronic liver disease is not a complication of:

(Please select 1 option)

○	Alpha1 antitrypsin deficiency
○	Cystic fibrosis
○	Haemochromatosis
○	Haemosiderosis
○	Hepatitis C

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Chronic liver disease is not a complication of:

(Please select 1 option)

○	Alpha1 antitrypsin deficiency
◉	Cystic fibrosis ✗ Incorrect answer selected
○	Haemochromatosis
○	Haemosiderosis ← This is the correct answer
○	Hepatitis C

50% of hepatitis C infections lead to chronic liver disease (treat with interferon-a).

Liver disease from chronic cholestasis occurs in cystic fibrosis.

Alpha1 antitrypsin deficiency causes both cirrhosis and emphysema.

Haemochromatosisis is autosomal recessive and is characterised by excessive iron deposition in various organs causing organ failure (diabetes, heart failure, chronic liver disease, hypogonadism, skin pigmentation and arthritis).

Haemosiderosis usually arises due to parenteral iron overload, for example, in patients with aplastic anaemia after multiple transfusions. It is not commonly associated with cirrhosis.

If cirrhosis does develop as a result of massive iron overload the condition is known as secondary haemochromatosis.

Next question | Remove Tag | Remove question

http://my.onexamination.com/Assessment/Questions.aspx

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 27 mins 48 secs

Question: 97 of 100

A 20-year-old Caucasian student returns from Ghana with a spiking temperature and nocturnal sweats. She has 0.5% of red blood cells infected with *Plasmodium falciparum*.

Select one of the following answers relating to quinine therapy in this case.

(Please select 1 option)

○	Glucose levels should be monitored in those being treated with quinine
○	Pregnancy is a contraindication for quinine
○	Quinine is contraindicated in those taking mefloquine prophylactically
○	Quinine must always be given parenterally initially
○	The dose of quinine should be reduced in liver impairment

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

A 20-year-old Caucasian student returns from Ghana with a spiking temperature and nocturnal sweats. She has 0.5% of red blood cells infected with *Plasmodium falciparum*.

Select one of the following answers relating to quinine therapy in this case.

(Please select 1 option)

◉	Glucose levels should be monitored in those being treated with quinine ✓ Correct
○	Pregnancy is a contraindication for quinine
○	Quinine is contraindicated in those taking mefloquine prophylactically
○	Quinine must always be given parenterally initially
○	The dose of quinine should be reduced in liver impairment

Severe malaria is indicated by more than 1% of RBC infected.

Hypoglycaemia is an important side-effect of quinine therapy and should be monitored in those having intravenous quinine.

Intravenous infusion of quinine is reserved for severe or cerebral malaria (most deaths from *M. falciparum* occur in first 96 hours of starting treatment).

The initial dose should **not** be reduced in those severely ill with renal/hepatic impairment.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 28 mins 33 secs

Question: 98 of 100

Which of the following is true regarding varicella zoster infection?

(Please select 1 option)

○	Associated pneumonitis is equally common in smokers and non-smokers
○	Causes congenital limb deformity
○	Causes urinary incontinence
○	Gamma Interferon is an effective treatment.
○	Produces latent infection within the anterior horn cells

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Which of the following is true regarding varicella zoster infection?

(Please select 1 option)

○	Associated pneumonitis is equally common in smokers and non-smokers
◉	Causes congenital limb deformity ✓ Correct
○	Causes urinary incontinence
○	Gamma Interferon is an effective treatment.
○	Produces latent infection within the anterior horn cells

Varicella zoster infection causes herpes zoster and chicken pox.

Herpes zoster is due to reactivation of the virus lying dormant in the cells of dorsal root ganglion.

Autonomic involvement can cause urinary retention.

Pregnancy increases risk of pneumontis.

Chicken pox in the first and second trimester can produce a syndrome of skin scarring, hypoplastic limbs, eye and central nervous system impairments.

Pneumonitis is uncommon in children with incidence of 0.3% in immunocompetent adults. The risk is higher in smokers.

Antiviral treatment includes acyclovir and vidabarine.

Next question

Tag Question | Remove question

Work Smart Session - MRCP Part 1

Time taken: 2 hrs 29 mins 54 secs

Question: 99 of 100

Which of the following is true of *Giardia lamblia* infection?

(Please select 1 option)

○	Causes steatorrhoea
○	Diagnosed by stool culture
○	Is eradicated by mebendazole
○	Is often symptomatic
○	Is usually spread by contaminated meats

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Question: 99 of 100

Which of the following is true of *Giardia lamblia* infection?

(Please select 1 option)

◉	Causes steatorrhoea ✓ Correct
○	Diagnosed by stool culture
○	Is eradicated by mebendazole
○	Is often symptomatic
○	Is usually spread by contaminated meats

It is usually acquired by the faeco-oral route.

Many individuals excreting cysts are asymptomatic and are thus carriers. Others have diarrhoea, steatorrhoea, abdominal pain and nausea.

It is diagnosed by stool microscopy - if negative, parasite found in duodenal aspirates or biopsy. Testing of serum antibodies against *G. lamblia* trophozoites is not useful in diagnosing current infection.

Eradicate with metronidazole (or quinacrine, tinidazole, ornidazole, furazolidone, paromomycin). Mebendazole is used in treating hookworm infections, for example, ascaris, whipworm and threadworm.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

◉	Acute HIV infection (seroconversion illness) ✓ Correct
○	Dengue fever
○	Infectious mononucleosis
○	Typhoid fever
○	Viral hepatitis

Acute human immunodeficiency virus (HIV) seroconversion illness should be suspected where there has been a risk of exposure.

The symptoms and signs are often vague but the clinical presentation here is consistent. The median time from exposure to presentation is 25 days.

More than three quarters of patients who become infected with HIV develop symptoms consistent with primary HIV infection.

Symptoms typically appear a few days to a few weeks after exposure to HIV, and generally include several of the following:

- Fever
- Rash, often erythematous maculopapular
- Fatigue
- Pharyngitis
- Generalised lymphadenopathy
- Urticaria
- Myalgia/arthralgia
- Anorexia
- Mucocutaneous ulceration
- Headache, retro-orbital pain
- Neurologic symptoms, e.g.
    - aseptic meningitis
    - radiculitis
    - myelitis.

DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents
Financial Disclosures – December 2010

Below is a list of financial disclosures of Panel members' relationships with antiretroviral-related pharmaceutical or diagnostic entities for January 2010–December 2010.

Name	Panel Status*	Company	Relationship
Jean R. Anderson	M	Tibotec	• Advisory Board
John G. Bartlett	C	None	N/A†
John T. Brooks	M	None	N/A
Victoria Ann Cargill	M	None	N/A
Laura W. Cheever	M	None	N/A
Lei Chou	M	Bristol-Myers Squibb Genentech/Roche Merck Tibotec	• Travel Support • Travel Support • Travel Support • Travel Support
Eric Daar	M	Abbott Bristol-Myers Squibb Gilead GlaxoSmithKline Merck Pfizer ViiV	• Research Support • Consultant • Advisory Board • Consultant, Research Support • Consultant, Research Support • Consultant, Research Support • Consultant, Research Support
Paul Dalton	M	None	N/A
Steven G. Deeks	M	Bristol-Myers Squibb Gilead Hoffmann-La Roche Merck Tobira	• Research Support • Research Support • Advisory Board, Travel Support • Research Support, Travel Support • Advisory Board
Carlos del Rio	M	Merck Sanofi Pasteur Schering-Plough	• Honoraria, Research Support • Research Support • Research Support
Robert T. Dodge	M	Abbott Boehringer Ingelheim Gilead ViiV	• Advisory Board, Speakers' Bureau, Consultant • Advisory Board, Speakers' Bureau, Consultant • Advisory Board, Speakers' Bureau, Consultant • Advisory Board, Speakers' Bureau, Consultant
Courtney V. Fletcher	M	Bristol-Myers Squibb Merck	• Advisory Board • Advisory Board
Gerald H. Friedland	M	Bristol-Myers Squibb Merck	• Research Support • Research Support
Joel E. Gallant	M	Bristol-Myers Squibb Gilead GlaxoSmithKline Merck Sangamo Biosciences Tibotec	• Advisory Board • Advisory Board, DSMB‡ Member, Research Support • Advisory Board, Research Support • Advisory Board • DSMB Member • Advisory Board
Christopher M. Gordon	M	None	N/A
Roy M. Gulick	M	Bristol-Myers Squibb Gilead GlaxoSmithKline/ViiV MedImmune Merck Pfizer ViroStatics	• Consultant • Consultant • Consultant • Consultant • Research Support • Research Support • Consultant

Name	Panel Status*	Company	Relationship
W. Keith Henry	M	Gilead GlaxoSmithKline/ViiV Pfizer Tibotec	• Advisory Board, Research Support, Speakers' Bureau, Honoraria, Consultant • Advisory Board, Research Support, Speakers' Bureau, Honoraria, Consultant • Research Support • Research Support
Martin S. Hirsch	M	Merck TaiMed	• Consultant • DSMB Member
Michael D. Hughes	M	Boehringer Ingelheim Medicines Dev., Ltd. Pfizer Tibotec Virionyx Corp. Ltd.	• DSMB Member • DSMB Member • DSMB Member • DSMB Member • DSMB Member
Jonathan E. Kaplan	M	None	N/A
Bill G. Kapogiannis	M	None	N/A
Daniel R. Kuritzkes	M	Abbott Avexa Boehringer Ingelheim Gilead GlaxoSmithKline Human Genome Sciences Merck Oncolys Roche Schering-Plough Tobira ViroStatics VIRxSYS	• Advisory Board • Advisory Board • Advisory Board • Advisory Board, Research Support • Advisory Board • DSMB Member • Advisory Board, Research Support • Advisory Board • Advisory Board • Advisory Board, Research Support • Advisory Board • Advisory Board • Advisory Board
H. Clifford Lane	C	None	N/A
Henry Masur	M	None	N/A
Lynne Mofenson	M	None	N/A
Jeffrey Murray	M	None	N/A
Heidi M. Nass	M	None	N/A
James Neaton	M	Merck	• DSMB Member, Consultant; Science Advisor
Alice K. Pau	ES	None	N/A
Richard W. Price	M	Abbott Merck	• Honoraria • Research Support
Michael Saag	M	Ardea Biosciences Avexa Boehringer Ingelheim Bristol-Myers Squibb Gilead GlaxoSmithKline Merck Monogram Biosciences Pain Therapeutics Pfizer Tibotec Vertex ViiV	• Advisory Board, Research Support • Advisory Board, Research Support • Advisory Board, Research Support • Advisory Board, Research Support • Advisory Board, Research Support • Advisory Board, Research Support • Advisory Board, Research support • Research Support • Consultant • Advisory Board, Research Support,Consultant • Advisory Board, Research Support • Advisory Board, Research Support • Advisory Board, Consultant

Name	Panel Status*	Company	Relationship
Paul E. Sax	M	Abbott Bristol-Myers Squibb Gilead GlaxoSmithKline/ViiV Merck Serono Tibotec	• Consultant • Advisory Board • Advisory Board, Research Support • Consultant, Research Support • Advisory Board, Research Support • Advisory Board • Advisory Board, Research Support
Kimberly Struble	M	None	N/A
Mark Sulkowski	M	Abbott Biolex Boehringer Ingelheim Bristol-Myers Squibb Gilead GlaxoSmithKline Merck Pfizer Roche Teva Tibotec Vertex	• Advisory Board, Research Support • Consultant • Advisory Board, Research Support • Advisory Board, Research Support • Advisory Board, Research Support • Advisory Board • Advisory Board, Research Support • Study Steering Committee • Advisory Board, Research Support • Consultant • Advisory Board, Research Support • Advisory Board, Research Support
Jeffrey Taylor	M	BioNor Immuno Boehringer Ingelheim	• Advisory Board, Travel Support • Advisory Board
Zelalem Temesgen	M	Gilead Merck Pfizer Tibotec ViiV	• Advisory Board, Educational Program Support • Advisory Board • Research Support • Educational Program Support • Advisory Board
Nelson R. Vergel	M	Boehringer Ingelheim	• Speakers' Bureau
Paul Volberding	M	Bristol-Myers Squibb Gilead Merck TaiMed	• Scientific Advisory Board • Advisory Board, DSMB Member • DSMB Member • DSMB Member
David Alain Wohl	M	Abbott Argos GlaxoSmithKline Merck Tibotec	• Advisory Board • DSMB Member • Research Support • Research Support • Advisory Board

* C = Co-Chair, ES = Executive Secretary, M = Member
† N/A = Not applicable
‡ DSMB = Data Safety Monitoring Board

Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents

January 10, 2011

"Boxed" Recommendations

Many recommendations included in the January 10, 2011, edition of the DHHS ***Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*** are presented in "boxes" at the beginning of sections or subsections of the Guidelines. This document is a compilation of all "boxed" recommendations included in the Guidelines. The "boxed" recommendations are presented by section, or section and subsection, as they appear in the Guidelines.

Laboratory Testing for Initial Assessment and Monitoring While on Antiretroviral Therapy

(Updated January 10, 2011)

DRUG-RESISTANCE TESTING (Updated January 10, 2011)

Panel's Recommendations:

- ***HIV drug-resistance testing is recommended for persons with HIV infection when they enter into care regardless of whether antiretroviral therapy (ART) will be initiated immediately or deferred (AIII). If therapy is deferred, repeat testing at the time of ART initiation should be considered (CIII).***
- ***Genotypic testing is recommended as the preferred resistance testing to guide therapy in antiretroviral (ARV)-naïve patients (AIII).***
- ***Standard genotypic drug-resistance testing in ARV-naïve persons involves testing for mutations in the reverse transcriptase (RT) and protease (PR) genes. If transmitted integrase strand transfer inhibitor (INSTI) resistance is a concern, providers may wish to supplement standard genotypic resistance testing with genotypic testing for resistance to this class of drug (CIII).***
- ***HIV drug-resistance testing should be performed to assist in the selection of active drugs when changing ARV regimens in persons with virologic failure and HIV RNA levels >1,000 copies/mL (AI). In persons with HIV RNA levels >500 but <1,000 copies/mL, testing may be unsuccessful but should still be considered (BII).***
- ***Drug-resistance testing should also be performed when managing suboptimal viral load reduction (AII).***
- ***In persons failing INSTI-based regimens, genotypic testing for INSTI resistance should be considered to determine whether to include a drug from this class in subsequent regimens (BIII).***
- ***Drug-resistance testing in the setting of virologic failure should be performed while the person is taking prescribed ARV drugs or, if not possible, within 4 weeks after discontinuing therapy (AII).***
- ***Genotypic testing is recommended as the preferred resistance testing to guide therapy in patients with suboptimal virologic responses or virologic failure while on first or second regimens (AIII).***
- ***Addition of phenotypic to genotypic testing is generally preferred for persons with known or suspected complex drug-resistance mutation patterns, particularly to protease inhibitors (PIs) (BIII).***
- ***Genotypic resistance testing is recommended for all pregnant women prior to initiation of therapy (AIII) and for those entering pregnancy with detectable HIV RNA levels while on therapy (AI).***

Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = data from randomized controlled trials; II = data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = expert opinion

HLA-B*5701 SCREENING (Updated December 1, 2007)

Panel's Recommendations:

- ***The Panel recommends screening for HLA-B*5701 before starting patients on an abacavir (ABC)-containing regimen to reduce the risk of hypersensitivity reaction (HSR) (AI).***
- ***HLA-B*5701-positive patients should not be prescribed ABC (AI).***
- ***The positive status should be recorded as an ABC allergy in the patient's medical record (AII).***
- ***When HLA-B*5701 screening is not readily available, it remains reasonable to initiate ABC with appropriate clinical counseling and monitoring for any signs of HSR (CIII).***

Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = data from randomized controlled trials; II = data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = expert opinion

CORECEPTOR TROPISM ASSAYS (Updated January 10, 2011)

Panel's Recommendations:

- ***Coreceptor tropism assay should be performed whenever the use of a CCR5 inhibitor is being considered (AI).***
- ***Coreceptor tropism testing might also be considered for patients who exhibit virologic failure on a CCR5 inhibitor (CIII).***

Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = data from randomized controlled trials; II = data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = expert opinion

Initiating Antiretroviral Therapy in Treatment-Naïve Patients (Updated January 10, 2011)

Panel's Recommendations:

- ***Antiretroviral therapy (ART) should be initiated in all patients with a history of an AIDS-defining illness or with a CD4 count <350 cells/mm^3 (AI).***
- ***ART is also recommended for patients with CD4 counts between 350 and 500 cells/mm^3 (A/B*-II).***
- ***ART should be initiated, regardless of CD4 count, in patients with the following conditions: HIV-associated nephropathy (HIVAN) (AII) and hepatitis B virus (HBV) coinfection when treatment of HBV is indicated (AIII).***
- ***A combination antiretroviral (ARV) drug regimen is also recommended for pregnant women who do not meet criteria for treatment with the goal to prevent perinatal transmission (AI).***
- ***For patients with CD4 counts >500 cells/mm^3, Panel members are evenly divided: 50% favor starting ART at this stage of HIV disease (B); 50% view initiating therapy at this stage as optional (C) (B/C-III).***
- ***Patients initiating ART should be willing and able to commit to lifelong treatment and should understand the benefits and risks of therapy and the importance of adherence (AIII). Patients may choose to postpone therapy, and providers, on a case-by-case basis, may elect to defer therapy based on clinical and/or psychosocial factors.***

Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = data from randomized controlled trials; II = data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = expert opinion

* ***Panel members are divided on the strength of this recommendation: 55% voted for strong recommendation (A) and 45% voted for moderate recommendation (B).***

What to Start: Initial Combination Regimens for the Antiretroviral-Naïve Patient (Updated January 10, 2011)

Panel's Recommendations:

- ***The Panel recommends the following as preferred regimens for antiretroviral (ARV)-naïve patients:***
  - ***efavirenz/tenofovir/emtricitabine (EFV/TDF/FTC) (AI)***
  - ***ritonavir-boosted atazanavir + tenofovir/emtricitabine (ATV/r + TDF/FTC) (AI)***
  - ***ritonavir-boosted darunavir + tenofovir/emtricitabine (DRV/r + TDF/FTC) (AI)***
  - ***raltegravir + tenofovir/emtricitabine (RAL + TDF/FTC) (AI)***
- ***A list of Panel-recommended alternative and acceptable regimens can be found in Table 5a and Table 5b.***
- ***Selection of a regimen should be individualized based on virologic efficacy, toxicity, pill burden, dosing frequency, drug-drug interaction potential, resistance-testing results, and comorbid conditions.***
- ***Based on individual patient characteristics and needs, in some instances, an alternative regimen may actually be a preferred regimen for a patient.***

Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = data from randomized controlled trials; II = data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = expert opinion

Management of the Treatment-Experienced Patient

VIROLOGIC AND IMMUNOLOGIC FAILURE (Updated January 10, 2011)

Panel's Recommendations:

- ***Assessing and managing an antiretroviral (ARV)-experienced patient experiencing failure of antiretroviral therapy (ART) is complex. Expert advice is critical and should be sought.***
- ***Evaluation of virologic failure should include an assessment of the severity of the patient's HIV disease, ART history, use of concomitant medications with consideration of adverse drug interactions with ARV agents, HIV RNA and CD4 T-cell count trends over time, and prior drug-resistance testing results.***
- ***Drug-resistance testing should be obtained while the patient is taking the failing ARV regimen or within 4 weeks of treatment discontinuation (AII).***
- ***The goal of treatment for ARV-experienced patients with drug resistance who are experiencing virologic failure is to re-establish virologic suppression (e.g., HIV RNA <48 copies/mL) (AI).***
- ***To design a new regimen, the patient's treatment history and past and current resistance test results should be used to identify at least two (preferably three) fully active agents to combine with an optimized background ARV regimen (AI). A fully active agent is one that is likely to have ARV activity on the basis of the patient's treatment history, drug-resistance testing, and/or a novel mechanism of action.***
- ***In general, adding a single, fully active ARV in a new regimen is not recommended because of the risk of rapid development of resistance (BII).***
- ***In patients with a high likelihood of clinical progression (e.g., CD4 count <100 cells/mm^3) and limited drug options, adding a single drug may reduce the risk of immediate clinical progression, because even transient decreases in HIV RNA and/or transient increases in CD4 cell counts have been associated with clinical benefits (CI).***
- ***For some highly ART-experienced patients, maximal virologic suppression is not possible. In this case, ART should be continued (AI) with regimens designed to minimize toxicity, preserve CD4 cell counts, and avoid clinical progression.***
- ***Discontinuing or briefly interrupting therapy in a patient with viremia may lead to a rapid increase in HIV RNA and a decrease in CD4 cell count and increases the risk of clinical progression. Therefore, this strategy is not recommended (AI).***
- ***In the setting of virologic suppression, there is no consensus on how to define or treat immunologic failure.***

Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = data from randomized controlled trials; II = data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = expert opinion

EXPOSURE-RESPONSE RELATIONSHIP AND THERAPEUTIC DRUG MONITORING (TDM) FOR ANTIRETROVIRAL AGENTS (Updated January 10, 2011)

Panel's Recommendations:

- ***Therapeutic drug monitoring (TDM) for antiretroviral (ARV) agents is not recommended for routine use in the management of the HIV-infected adult (CIII).***
- ***TDM may be considered in selected clinical scenarios, as discussed in the text below.***

Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = data from randomized controlled trials; II = data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = expert opinion

Considerations for Antiretroviral Use in Special Patient Populations

ACUTE HIV INFECTION (Updated January 10, 2011)

Panel's Recommendations:

- ***It is unknown if treatment of acute HIV infection results in long-term virologic, immunologic, or clinical benefit; treatment should be considered optional at this time (CIII).***
- ***Therapy should also be considered optional for patients with HIV seroconversion in the previous 6 months (CIII).***
- ***All pregnant women with acute or recent HIV infection should start a combination antiretroviral (ARV) regimen as soon as possible to prevent mother-to-child transmission (MTCT) of HIV (AI).***
- ***If the clinician and patient elect to treat acute HIV infection, treatment should be implemented with the goal of suppressing plasma HIV RNA to below detectable levels (AIII).***
- ***For patients with acute HIV infection in whom therapy is initiated, testing for plasma HIV RNA levels and CD4 count and toxicity monitoring should be performed as described for patients with established, chronic HIV infection (AII).***
- ***If the decision is made to initiate therapy in a person with acute HIV infection, genotypic resistance testing at baseline will be helpful in guiding the selection of an ARV regimen that can provide the optimal virologic response; this strategy is therefore recommended (AIII). If therapy is deferred, genotypic resistance testing should still be performed because the result may be useful in optimizing the virologic response when therapy is ultimately initiated (AIII).***
- ***Because clinically significant resistance to protease inhibitors (PIs) is less common than resistance to non-nucleoside reverse transcriptase inhibitors (NNRTIs) in antiretroviral therapy (ART)-naïve persons who harbor drug-resistant virus, a ritonavir (RTV)-boosted PI-based regimen should be used if therapy is initiated before drug-resistance test results are available (AIII).***

Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = data from randomized controlled trials; II = data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = expert opinion

HIV-INFECTED WOMEN (Updated January 10, 2011)

Panel's Recommendations:

- ***The indications for initiation of antiretroviral therapy (ART) and the goals of treatment are the same for HIV-infected women as for other HIV-infected adults and adolescents (AI).***
- ***Women taking antiretroviral (ARV) drugs that have significant pharmacokinetic interactions with oral contraceptives should use an additional or alternative contraceptive method for prevention of unintended pregnancy (AIII).***
- ***In pregnant women, an additional goal of therapy is prevention of mother-to-child transmission (PMTCT), with a goal of maximal viral suppression to reduce the risk of transmission of HIV to the fetus and newborn (AI).***
- ***Genotypic resistance testing is recommended for all HIV-infected persons, including pregnant women, prior to initiation of ART (AIII) and for women entering pregnancy with detectable HIV RNA levels while on therapy (AI).***
- ***When selecting an ARV combination regimen for a pregnant woman, clinicians should consider the known safety, efficacy, and pharmacokinetic data of each agent during pregnancy (AIII).***
- ***Efavirenz (EFV) should be avoided in a pregnant woman during the first trimester or in a woman who desires to become pregnant or who does not or cannot use effective and consistent contraception (AIII).***
- ***Clinicians should consult the most current Health and Human Services (HHS) Perinatal Guidelines when designing a regimen for a pregnant woman (AIII).***

Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = data from randomized controlled trials; II = data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = expert opinion

Considerations for Antiretroviral Use in Patients with Coinfections

HEPATITIS B (HBV)/HIV COINFECTION (January 10, 2011)

Panel's Recommendations:

- ***Prior to intiation of antiretroviral therapy (ART), all patients who test positive for hepatitis B surface antigen (HBsAg) should be tested for hepatitis B virus (HBV) DNA using a quantitative assay to determine the level of HBV replication (AIII).***
- ***Because emtricitabine (FTC), lamivudine (3TC), and tenofovir (TDF) have activity against both HIV and HBV, if HBV or HIV treatment is needed, ART should be initiated with the combination of TDF + FTC or TDF + 3TC as the nucleoside reverse transcriptase inhibitor (NRTI) backbone of a fully suppressive antiretroviral (ARV) regimen (AI).***
- ***If HBV treatment is needed and TDF cannot safely be used, the alternative recommended HBV therapy is entecavir in addition to a fully suppressive ARV regimen (BI). Other HBV treatment regimens include peginterferon alfa monotherapy or adefovir in combination with 3TC or FTC or telbivudine in addition to a fully suppressive ARV regimen (BII).***
- ***Entecavir has activity against HIV; its use for HBV treatment without ART in patients with dual infection may result in the selection of the M184V mutation that confers HIV resistance to 3TC and FTC. Therefore, entecavir must be used in addition to a fully suppressive ARV regimen when used in HIV/HBV-coinfected patients (AII).***
- ***Discontinuation of agents with anti-HBV activity may cause serious hepatocellular damage resulting from reactivation of HBV; patients should be advised against self-discontinuation and carefully monitored during interruptions in HBV treatment (AII).***
- ***If ART needs to be modified due to HIV virologic failure and the patient has adequate HBV suppression, the ARV drugs active against HBV should be continued for HBV treatment in combination with other suitable ARV agents to achieve HIV suppression (AIII).***

Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = data from randomized controlled trials; II = data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = expert opinion

MYCOBACTERIUM TUBERCULOSIS DISEASE WITH HIV COINFECTION

(Updated January 10, 2011)

Panel's Recommendations:

- ***The treatment of active tuberculosis (TB) disease in patients with HIV infection should follow the same principles for persons without HIV infection (AI).***
- ***All HIV-infected patients with diagnosed active TB should be started on TB treatment immediately (AI).***
- ***All HIV-infected patients with diagnosed active TB should be treated with antiretroviral therapy (ART) (AI).***
- ***For patients with CD4 count <200 cells/mm^3, ART should be initiated within 2–4 weeks of starting TB treatment (AI).***
- ***For patients with CD4 count 200–500 cells/mm^3, the Panel recommends initiation of ART within 2–4 weeks, or at least by 8 weeks after commencement of TB therapy (AIII).***
- ***For patients with CD4 count >500 cells/mm^3, most Panel members also recommend starting ART within 8 weeks of TB therapy (BIII).***
- ***Despite pharmacokinetic drug interactions, a rifamycin should be included in regimens for patients receiving ART, with dosage adjustment if necessary (AII).***
- ***If a protease inhibitor (PI)-based regimen is used, rifabutin is the preferred rifamycin in HIV-infected patients with active TB disease due to its lower risk of substantial interactions with PIs (AII). Coadministration of rifampin and PIs (with or without ritonavir [RTV] boosting) is <u>not</u> recommended (AII).***
- ***Immune reconstitution inflammatory syndrome (IRIS) may occur after initiation of ART. Both ART and TB treatment should be continued while managing IRIS (AIII).***
- ***Treatment support, including directly observed therapy (DOT) of TB treatment, is strongly recommended for HIV-infected patients with active TB disease (AII).***

Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = data from randomized controlled trials; II = data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = expert opinion

Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents

January 10, 2011

Tables

This document includes all tables found in the January 10, 2011, edition of the DHHS ***Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents***. The tables are presented in the order they appear in the Guidelines. Refer to the appropriate sections of the Guidelines for references noted within the tables.

Table 1. Outline of the Guidelines Development Process (Updated November 3, 2008)

Topic	Comment
Goal of the guidelines	Provide guidance to HIV care practitioners on the optimal use of ARV agents for the treatment of HIV infection in adults and adolescents in the United States.
Panel members	The Panel is composed of more than 30 voting members who have expertise in HIV care and research. The U.S. government representatives include at least 1 representative from each of the following DHHS agencies: Centers for Disease Control and Prevention (CDC), FDA, Health Resource Services Administration (HRSA), and National Institutes of Health (NIH). These members are appointed by their respective agencies. Approximately 2/3 of the Panel members are nongovernmental scientific members. There are 4–5 community members with knowledge in HIV treatment and care. Members who do not represent U.S. government agencies are selected after an open announcement to call for nominations. Each member serves on the Panel for a 4-year term, with an option to be reappointed for an additional term. A list of the current members can be found on **Page vii** of this document.
Financial disclosure	All members of the Panel submit a written financial disclosure annually reporting any association with manufacturers of ARV drugs or diagnostics used for management of HIV infections. A list of the latest disclosures is available on the AIDS*info* Web site (**http://aidsinfo.nih.gov/contentfiles/AA_Roster.pdf**).
Users of the guidelines	HIV treatment providers
Developer	Panel on Antiretroviral Guidelines for Adults and Adolescents—a working group of the OARAC
Funding source	Office of AIDS Research, NIH
Evidence collection	The recommendations in the guidelines are generally based on studies published in peer-reviewed journals. On some occasions, particularly when new information may affect patient safety, unpublished data presented at major conferences or prepared by the FDA and/or manufacturers as warnings to the public may be used as evidence to revise the guidelines.
Recommendation grading	As described in **Table 2**
Method of synthesizing data	Each section of the guidelines is assigned to a working group of Panel members with expertise in the area of interest. The members of the working group synthesize the available data and propose recommendations to the Panel. All proposals are discussed at monthly teleconferences and then voted on by the Panel before being endorsed as official recommendations.
Other guidelines	These guidelines focus on treatment for HIV-infected adults and adolescents. Separate guidelines outline the use of ART for other populations, such as pregnant women and children. These guidelines are also available on the AIDS*info* Web site (**http://www.aidsinfo.nih.gov**). There is a brief discussion of the management of women of reproductive age and pregnant women in this document. For a more detailed and up-to-date discussion on this group of women and other special populations, the Panel defers to the designated expertise offered by panels that have developed those guidelines.
Update plan	The Panel meets monthly by teleconference to review data that may warrant modification of the guidelines. Updates may be prompted by new drug approvals (or new indications, dosing formulations, or frequency), new significant safety or efficacy data, or other information that may have a significant impact on the clinical care of patients. For cases in which significant new data become available that may affect patient safety, a warning announcement with the Panel's recommendations may be made on the AIDS*info* Web site until appropriate changes can be made in the guidelines document. Updated guidelines are available on the AIDS*info* Web site (**http://www.aidsinfo.nih.gov**).
Public comments	After release of an update on the AIDS*info* Web site, the public is given a 2-week period to submit comments to the Panel. These comments are reviewed, and a determination is made as to whether revisions are indicated. The public may also submit comments to the Panel at any time at **contactus@aidsinfo.nih.gov**.

Table 2. Rating Scheme for Recommendations (Updated November 3, 2008)

Strength of Recommendation	Quality of Evidence for Recommendation
A: Strong recommendation for the statement **B:** Moderate recommendation for the statement **C:** Optional recommendation for the statement	**I:** One or more randomized trials with clinical outcomes and/or validated laboratory endpoints **II:** One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes **III:** Expert opinion

Table 3. Laboratory Monitoring Schedule for Patients Prior to and After Initiation of Antiretroviral Therapy (Updated January 10, 2011)

	Entry into care	Follow-up before ART	ART initiation or modification[1]	2–8 weeks post-ART initiation or modification	Every 3–6 months	Every 6 months	Every 12 months	Treatment failure	Clinically indicated
CD4 count	√	every 3–6 months	√		√	In clinically stable patients with suppressed viral load, CD4 count can be monitored every 6–12 months (see text)		√	√
Viral load	√	every 3–6 months	√	√[2]	√[3]			√	√
Resistance testing	√		√[4]					√	√
HLA-B*5701 testing			√ if considering ABC						
Tropism testing			√ if considering a CCR5 antagonist					√ if considering a CCR5 antagonist or for failure of CCR5 antagonist-based regimen	√
Hepatitis B serology[5]	√		√ may repeat if HBsAg (-) and HBsAb (-) at baseline						√
Basic chemistry[6]	√	every 6–12 months	√	√	√				√
ALT, AST, T. bilirubin	√	every 6–12 months	√	√	√				√
CBC with differential	√	every 3–6 months	√	√ if on ZDV	√				√
Fasting lipid profile	√	if normal, annually	√	√ consider 4–8 weeks after starting new ART		√ if abnormal at last measurement	√ if normal at last measurement		√
Fasting glucose	√	if normal, annually	√		√ if abnormal at last measurement	√ if normal at last measurement			√
Urinalysis[7]	√		√			√ if on TDF[8]	√		√
Pregnancy test			√ if starting EFV						√

[1]ARV modification may be done for treatment failure, adverse effects, or simplification.
[2]If HIV RNA is detectable at 2–8 weeks, repeat every 4–8 weeks until suppression to <200 copies/mL, then every 3–6 months.
[3]For adherent patients with suppressed viral load and stable clinical and immunologic status for >2–3 years, some experts may extend the interval for HIV RNA monitoring to every 6 months.
[4]For ART-naïve patients, if resistance testing was performed at entry into care, repeat testing is optional; for patients with viral suppression who are switching therapy for toxicity or convenience, resistance testing will not be possible and therefore is not necessary.
[5]If HBsAg is positive at baseline or prior to initiation of ART, TDF + (FTC or 3TC) should be used as part of ARV regimen to treat both HBV and HIV infections. If HBsAg and HBsAb are negative at baseline, hepatitis B vaccine series should be administered.
[6] Serum Na, K, HCO_3, Cl, BUN, creatinine, glucose (preferably fasting); some experts suggest monitoring phosphorus while on TDF; determination of renal function should include estimation of creatinine clearance using Cockcroft-Gault equation or estimation of glomerular filtration rate based on MDRD equation.
[7]For patients with renal disease, consult "Guidelines for the Management of Chronic Kidney Disease in HIV-Infected Patients: Recommendations of the HIV Medicine Association of the Infectious Diseases Society of America" *[1]*.
[8] More frequent monitoring may be indicated for patients with increased risk of renal insufficiency, such as patients with diabetes, hypertension, etc.

Acronyms: 3TC = lamivudine, ABC = abacavir, ALT = alanine aminotransferase, ART = antiretroviral therapy, AST = aspartate aminotranserase, CBC = complete blood count, EFV = efavirenz, FTC = emtricitabine, HBsAb = hepatitis B surface antibody, HBsAg = hepatitis B surface antigen, HBV = hepatitis B virus, MDRD = modification of diet in renal disease (equation), TDF = tenofovir, ZDV = zidovudine

Table 4. Recommendations for Using Drug-Resistance Assays (Updated January 10, 2011)

Clinical Setting/Recommendation	Rationale
Drug-resistance assay recommended	
In acute HIV infection: Drug-resistance testing is recommended regardless of whether ART is initiated immediately or deferred **(AIII)**. A genotypic assay is generally preferred **(AIII)**.	If ART is to be initiated immediately, drug-resistance testing will determine whether drug-resistant virus was transmitted. Test results will help in the design of initial regimens or to modify or change regimens if results are obtained subsequent to treatment initiation. Genotypic testing is preferable to phenotypic testing because of lower cost, faster turnaround time, and greater sensitivity for detecting mixtures of wild-type and resistant virus.
If ART is deferred, repeat resistance testing should be considered at the time therapy is initiated **(CIII)**. A genotypic assay is generally preferred **(AIII)**.	If ART is deferred, testing should still be performed because of the greater likelihood that transmitted resistance-associated mutations will be detected earlier in the course of HIV infection. Results of resistance testing may be important when treatment is initiated. Repeat testing at the time ART is initiated should be considered because the patient may have acquired a drug-resistant virus (i.e., superinfection).
In ART-naïve patients with chronic HIV infection: Drug-resistance testing is recommended at the time of entry into HIV care, regardless of whether therapy is initiated immediately or deferred **(AIII)**. A genotypic assay is generally preferred **(AIII)**.	Transmitted HIV with baseline resistance to at least one drug is seen in 6%–16% of patients, and suboptimal virologic responses may be seen in patients with baseline resistant mutations. Some drug-resistance mutations can remain detectable for years in untreated chronically infected patients.
If therapy is deferred, repeat resistance testing should be considered prior to the initiation of ART **(CIII)**. A genotypic assay is generally preferred **(AIII)**.	Repeat testing prior to initiation of ART should be considered because the patient may have acquired a drug-resistant virus (i.e., a superinfection). Genotypic testing is preferable to phenotypic testing because of lower cost, faster turnaround time, and greater sensitivity for detecting mixtures of wild-type and resistant virus.
If an INSTI is considered for an ART-naïve patient and transmitted INSTI resistance is a concern, providers may wish to supplement standard resistance testing with a specific INSTI genotypic resistance assay **(CIII)**.	Standard genotypic drug-resistance assays test only for mutations in the RT and PR genes.

Clinical Setting/Recommendation	Rationale
In patients with virologic failure: Drug-resistance testing is recommended in persons on combination ART with HIV RNA levels >1,000 copies/mL **(AI)**. In persons with HIV RNA levels >500 but <1,000 copies/mL, testing may be unsuccessful but should still be considered **(BII)**.	Testing can help determine the role of resistance in drug failure and maximize the clinician's ability to select active drugs for the new regimen. Drug-resistance testing should be performed while the patient is taking prescribed ARV drugs or, if not possible, within 4 weeks after discontinuing therapy.
A standard genotypic resistance assay is generally preferred for those experiencing virologic failure on their first or second regimens **(AIII)**.	Genotypic testing is preferable to phenotypic testing because of lower cost, faster turnaround time, and greater sensitivity for detecting mixtures of wild-type and resistant virus.
In patients failing INSTI-based regimens, genotypic testing for INSTI resistance should be considered to determine whether to include drugs from this class in subsequent regimens **(BIII)**.	Standard genotypic drug-resistance assays test only for mutations in the RT and PR genes.
Addition of phenotypic assay to genotypic assay is generally preferred for those with known or suspected complex drug-resistance patterns, particularly to PIs **(BIII)**.	Phenotypic testing can provide useful additional information for those with complex drug-resistance mutation patterns, particularly to PIs.
In patients with suboptimal suppression of viral load: Drug-resistance testing is recommended for persons with suboptimal suppression of viral load after initiation of ART **(AII)**.	Testing can help determine the role of resistance and thus assist the clinician in identifying the number of active drugs available for a new regimen.
In HIV-infected pregnant women: Genotypic resistance testing is recommended for all pregnant women prior to initiation of ART **(AIII)** and for those entering pregnancy with detectable HIV RNA levels while on therapy **(AI)**.	The goal of ART in HIV-infected pregnant women is to achieve maximal viral suppression for treatment of maternal HIV infection and for prevention of perinatal transmission of HIV. Genotypic resistance testing will assist the clinician in selecting the optimal regimen for the patient.
Drug-resistance assay not usually recommended	
After therapy discontinued: Drug-resistance testing is not usually recommended after discontinuation (>4 weeks) of ARV drugs **(BIII)**.	Drug-resistance mutations might become minor species in the absence of selective drug pressure, and available assays might not detect minor drug-resistant species. If testing is performed in this setting, the detection of drug resistance may be of value; however, the absence of resistance does not rule out the presence of minor drug-resistant species.
In patients with low HIV RNA levels: Drug-resistance testing is not usually recommended in persons with a plasma viral load <500 copies/mL **(AIII)**.	Resistance assays cannot be consistently performed given low HIV RNA levels.

Table 5a. Preferred and Alternative Antiretroviral Regimens for Antiretroviral Therapy-Naïve Patients (Updated January 10, 2011)

Selection of a regimen should be individualized based on virologic efficacy, toxicity, pill burden, dosing frequency, drug-drug interaction potential, resistance testing results, and comorbid conditions. Refer to **Table 6** for a list of advantages and disadvantages and **Appendix B, Tables 1–6** for dosing information for individual ARV agents listed below. The regimens in each category are listed in alphabetical order.

Preferred Regimens (Regimens with optimal and durable efficacy, favorable tolerability and toxicity profile, and ease of use) **The preferred regimens for nonpregnant patients are arranged by order of FDA approval of components other than nucleosides, thus, by duration of clinical experience.**	
NNRTI-Based Regimen • EFV/TDF/FTC[1] **(AI)** **PI-Based Regimens** *(in alphabetical order)* • ATV/r + TDF/FTC[1] **(AI)** • DRV/r (once daily) + TDF/FTC[1] **(AI)** **INSTI-Based Regimen** • RAL + TDF/FTC[1] **(AI)** **Preferred Regimen[2] for Pregnant Women** • LPV/r (twice daily) + ZDV/3TC[1] **(AI)**	**Comments** **EFV** should not be used during the first trimester of pregnancy or in women trying to conceive or not using effective and consistent contraception. **ATV/r** should not be used in patients who require >20 mg omeprazole equivalent per day. Refer to **Table 15a** for dosing recommendations regarding interactions between ATV/r and acid-lowering agents.
Alternative Regimens (Regimens that are effective and tolerable but have potential disadvantages compared with preferred regimens. An alternative regimen may be the preferred regimen for some patients.)	
NNRTI-Based Regimens *(in alphabetical order)* • EFV + (ABC or ZDV)/3TC[1] **(BI)** • NVP + ZDV/3TC[1] **(BI)** **PI-Based Regimens** *(in alphabetical order)* • ATV/r + (ABC or ZDV)/3TC[1] **(BI)** • FPV/r (once or twice daily) + either [(ABC or ZDV)/3TC[1]] or TDF/FTC[1] **(BI)** • LPV/r (once or twice daily) + either [(ABC or ZDV)/3TC[1]] or TDF/FTC[1] **(BI)**	**Comments** **NVP** • NVP should not be used in patients with moderate to severe hepatic impairment (Child-Pugh B or C)[3] • NVP should not be used in women with pre-ARV CD4 count >250 cells/mm^3 or men with pre-ARV CD4 count >400 cells/mm^3. **ABC** • ABC should not be used in patients who test positive for HLA-B*5701. • Use ABC with caution in patients with high risk of cardiovascular disease or with pretreatment HIV RNA >100,000 copies/mL. (See text.) **Once-daily LPV/r** is not recommended in pregnant women.

[1]3TC may substitute for FTC or vice versa.
[2]For more detailed recommendations on ARV use in an HIV-infected pregnant woman, refer to the ***Perinatal Guidelines*** available at **http://aidsinfo.nih.gov/guidelines**.
[3]Refer to **Appendix B, Table 7** for the criteria for Child-Pugh classification.

The following combinations in the recommended list above are available as fixed-dose combination formulations: ABC/3TC, EFV/TDF/FTC, LPV/r, TDF/FTC, and ZDV/3TC.

Acronyms: 3TC = lamivudine, ABC = abacavir, ATV = atazanavir, ATV/r = atazanavir/ritonavir, DRV = darunavir, DRV/r = darunavir/ritonavir, EFV = efavirenz, FPV = fosamprenavir, FPV/r = fosamprenavir/ritonavir, FTC = emtricitabine, INSTI = integrase strand transfer inhibitor, LPV = lopinavir, LPV/r = lopinavir/ritonavir, NNRTI = non-nucleoside reverse transcriptase inhibitor, NRTI = nucleos(t)ide reverse transcriptase inhibitor, NVP = nevirapine, PI = protease inhibitor, RAL = raltegravir, TDF = tenofovir, ZDV = zidovudine

Table 5b. Acceptable Antiretroviral Regimens for Treatment-Naïve Patients
(Updated January 10, 2011)

Acceptable Regimens (CI) (Regimens that may be selected for some patients but are less satisfactory than preferred or alternative regimens) **and Regimens that may be Acceptable but more definitive data are needed (CIII)**	
NNRTI-Based Regimen • EFV + ddI + (3TC or FTC) **(CI)** **PI-Based Regimens** • ATV + (ABC or ZDV)/3TC[1] **(CI)** • DRV/r + (ABC or ZDV)/3TC[1] **(CIII)** **INSTI-Based Regimen** • RAL + (ABC or ZDV)/3TC[1] **(CIII)** **CCR5 Antagonist-Based Regimens** • MVC + ZDV/3TC[1] **(CI)** • MVC + TDF/FTC[1] or ABC/3TC[1] **(CIII)**	**Comments** **EFV + ddI + (FTC or 3TC)** has only been studied in small clinical trials. **ATV/r** is generally preferred over ATV. Unboosted ATV may be used when RTV boosting is not possible. **MVC** Tropism testing should be performed before initiation of therapy; only patients found to have only CCR5-tropic virus are candidates for MVC.
Regimens that may be acceptable but should be used with caution (Regimens that have demonstrated virologic efficacy in some studies but have safety, resistance, or efficacy concerns. See comments below.)	
NNRTI-Based Regimens • NVP + ABC/3TC[1] **(CIII)** • NVP + TDF/FTC[1] **(CIII)** **PI-Based Regimens** • FPV + [(ABC or ZDV)/3TC[1] or TDF/FTC[1]] **(CIII)** • SQV/r + TDF/FTC[1] **(CI)** • SQV/r + (ABC or ZDV)/3TC[1] **(CIII)**	**Comments** Use **NVP** and **ABC** together with caution because both can cause HSRs within first few weeks after initiation of therapy. Early virologic failure with high rates of resistance has been reported in some patients receiving **NVP + TDF + (3TC or FTC)**. Larger clinical trials are currently in progress. **FPV/r** is generally preferred over unboosted FPV. Virologic failure with unboosted FPV-based regimen may select mutations that confer cross resistance to DRV. **SQV/r** • SQV/r was associated with PR and QT prolongation in a healthy volunteer study. • Baseline ECG is recommended before initiation of SQV/r. • SQV/r is not recommended in patients with any of the following: 1. pretreatment QT interval >450 msec 2. refractory hypokalemia or hypomagnesemia 3. concomitant therapy with other drugs that prolong QT interval 4. complete AV block without implanted pacemaker 5. risk of complete AV block

[1]3TC maybe substituted with FTC or vice versa.

Acronyms: 3TC = lamivudine, ABC = abacavir, ATV = atazanavir, ATV/r = atazanavir/ritonavir, AV = atrioventricular, ddI = didanosine, DRV = darunavir, DRV/r = darunavir/ritonavir, ECG = electrocardiogram, EFV = efavirenz, FPV = fosamprenavir, FPV/r = fosamprenavir/ritonavir, FTC = emtricitabine, HSR = hypersensitivity reaction, INSTI = integrase strand transfer inhibitor, msec = millisecond, MVC = maraviroc, NNRTI = non-nucleoside reverse transcriptase inhibitor, NVP = nevirapine, PI = protease inhibitor, RAL = raltegravir, RTV = ritonavir, SQV = saquinavir, SQV/r = saquinavir/ritonavir, TDF = tenofovir, ZDV = zidovudine

Table 6. Advantages and Disadvantages of Antiretroviral Components Recommended as Initial Antiretroviral Therapy (Updated January 10, 2011)

ARV Class	ARV Agent(s)	Advantages	Disadvantages
NNRTI (in alphabetical order)		**NNRTI Class Advantages:** • Long half-lives	**NNRTI Class Disadvantages:** • Low genetic barrier to resistance (single mutation confers resistance for EFV, NVP, and DLV); greater risk of resistance at the time of failure or treatment interruption • Potential for cross resistance • Skin rash • Potential for CYP450 drug interactions (See Tables 14, 15b, and 16b.) • Transmitted resistance to NNRTIs more common than resistance to PIs
	EFV	• Virologic responses equivalent or superior to all comparators to date • Lowest pill burden; once-daily dosing • Fixed-dose combination with TDF/FTC	• Neuropsychiatric side effects • Teratogenic in nonhuman primates, and several cases of neural tube defect reported in infants of women with first-trimester exposure. EFV is contraindicated in first trimester of pregnancy; avoid use in women with pregnancy potential. • Dyslipidemia
	NVP	• No food effect • Fewer lipid effects than EFV	• Higher incidence of rash than with other NNRTIs, including rare but serious hypersensitivity reactions (Stevens-Johnson syndrome or toxic epidermal necrolysis) • Higher incidence of hepatotoxicity than with other NNRTIs, including serious and even fatal cases of hepatic necrosis • Contraindicated in patients with moderate or severe (Child-Pugh B or C) hepatic impairment • Some data suggest that ART-naïve patients with high pre-NVP CD4 counts (>250 cells/mm^3 for females, >400 cells/mm^3 for males) are at higher risk of symptomatic hepatic events. NVP is not recommended in these patients unless benefit clearly outweighs risk. • Early virologic failure of NVP + TDF + (FTC or 3TC) in small clinical trials • Fewer clinical trial data than for EFV
PI (in alphabetical order)		**PI Class Advantages:** • Higher genetic barrier to resistance • PI resistance uncommon with failure (boosted PIs)	**PI Class Disadvantages:** • Metabolic complications (e.g., dyslipidemia, insulin resistance, hepatotoxicity) • Gastrointestinal adverse effects • CYP3A4 inhibitors and substrates: potential for drug interactions (more pronounced with RTV-based regimens) (See Tables 14 and 15a.)
	ATV	• Fewer adverse effects on lipids than other PI • Once-daily dosing • Low pill burden (two pills per day) • Good GI tolerability • Signature mutation (I50L) not associated with broad PI cross resistance	• Indirect hyperbilirubinemia sometimes leading to jaundice or scleral icterus • PR interval prolongation: generally inconsequential unless combined with another drug with similar effect • Cannot be coadministered with TDF, EFV, or NVP (See ATV/r.) • Nephrolithiasis • Skin rash • Food requirement • Absorption depends on food and low gastric pH (See Table 15a for detailed information regarding interactions with H2 antagonists, antacids, and PPIs.)
	ATV/r	• RTV boosting: higher trough ATV concentration and greater antiviral effect • Once-daily dosing • Low pill burden (two pills per day)	• More adverse effects on lipids than unboosted ATV • More hyperbilirubinemia and jaundice than unboosted ATV • Food requirement • Absorption depends on food and low gastric pH (See Table 15a for interactions with H_2 antagonists, antacids, and PPIs.) • RTV boosting required with TDF and EFV. With EFV, use ATV 400 mg and RTV 100 mg once daily (PI-naïve patients only). • Should not be coadministered with NVP

ARV Class	ARV Agent(s)	Advantages	Disadvantages
	DRV/r	• Once-daily dosing	• Skin rash • Food requirement
	FPV	• No food effect	• Skin rash • Potential for PI resistance with failure, including emergence of mutations that can cause DRV cross resistance
	FPV/r	• Twice-daily dosing resulted in efficacy comparable to LPV/r • RTV boosting: higher trough APV concentration and greater antiviral effect • Once-daily dosing possible with RTV 100 mg or 200 mg daily • No food effect	• Skin rash • Hyperlipidemia • Once-daily dosing results in lower APV concentrations than twice-daily dosing • For FPV 1,400 mg + RTV 200 mg: requires 200 mg of RTV and no coformulation • Fewer data on FPV 1,400 mg + RTV 100 mg dose than on DRV/r and ATV/r
	LPV/r	• Coformulated • No food requirement • Recommended PI in pregnant women (twice daily only) • Greater CD4 count increase than with EFV-based regimens	•Requires 200 mg per day of RTV •Lower drug exposure in pregnant women—may need dose increase in third trimester • Once-daily dosing not recommended in pregnant women • Once-daily dosing: lower trough concentration than twice-daily dosing • Possible higher risk of MI associated with cumulative use of LPV/r • PR and QT interval prolongation have been reported. Use with caution in patients at risk of cardiac conduction abnormalities or receiving other drugs with similar effect.
	SQV/r	• Efficacy similar to LPV/r with less hyperlipidemia	• Highest pill burden among available PI regimens (6 pills per day) • Requires 200 mg of RTV • Food requirement • PR and/or QT interval prolongations in a healthy volunteer study • Pretreatment ECG recommended • SQV/r is not recommended for patients with any of the following conditions: (1) congenital or acquired QT prolongation; (2) pretreatment ECG >450 msec; (3) on concomitant therapy with other drugs that prolong QT interval; (4) complete AV block without implanted pacemakers; (5) risk of complete AV block.
INSTI	**RAL**	• Virologic response noninferior to EFV • Fewer drug-related adverse events and lipid changes than EFV • No food effect • Fewer drug-drug interactions than PI- or NNRTI-based regimens	•Less long-term experience in ART-naïve patients than with boosted PI- or NNRTI-based regimens •Twice-daily dosing •Lower genetic barrier to resistance than with boosted PI-based regimens •No data with NRTIs other than TDF/FTC in ART-naïve patients
CCR5 Antagonist	**MVC**	• Virologic response noninferior to EFV in post-hoc analysis of MERIT study (See text.) • Fewer adverse effects than EFV	• Requires viral tropism testing prior to initiation of therapy with additional cost and possible delay in initiation of therapy •More MVC-treated than EFV-treated patients discontinued therapy due to lack of efficacy in MERIT study •Less long-term experience in ART-naïve patients than with boosted PI- or NNRTI-based regimens •Limited experience with 2-NRTI other than ZDV/3TC •Twice-daily dosing •CYP 3A4 substrate, dosing depends on presence or absence of concomitant CYP3A4 inducer(s) or inhibitor(s)
Dual NRTIs		**Dual-NRTI Class Advantage:** Established backbone of combination ART	**Dual-NRTI Class Disadvantage:** Rare but serious cases of lactic acidosis with hepatic steatosis reported with d4T, ddI, and ZDV

Dual-NRTI pairs (in alphabetical order)	**ABC/3TC**	• Virologic response noninferior to ZDV/3TC • Better CD4 count response than with ZDV/3TC • Once-daily dosing • Coformulation • No food effect • No cumulative TAM-mediated resistance	• Potential for ABC HSR in patients with HLA-B*5701 • Potential for increased cardiovascular events, especially in patients with cardiovascular risk factors • Inferior virologic responses when compared with TDF/FTC in patients with baseline HIV RNA >100,000 copies/mL in ACTG 5202 study; however, this was not seen in the HEAT study.
	ddI + (3TC or FTC)	• Once-daily dosing • No cumulative TAM-mediated resistance	• Peripheral neuropathy, pancreatitis • Reports of noncirrhotic portal hypertension • Food effect; must be taken on an empty stomach • Requires dosing separation from some PIs • Increase in toxicities when used with ribavirin, TDF, d4T, or hydroxyurea • Preliminary data showed inferior virologic responses of ATV/ddI/FTC when compared with EFV/ZDV/3TC or EFV/TDF/FTC. Combination of ATV/ddI/FTC should be avoided.
	TDF/FTC or TDF + 3TC	• Better virologic responses than with ZDV/3TC • Better virologic responses than with ABC/3TC in patients with baseline HIV RNA >100,000 copies/mL in ACTG 5202 study; however, this was not seen in the HEAT study. • Active against HBV; recommended dual-NRTI for HBV/HIV coinfection • Once-daily dosing • No food effect • Coformulated (TDF/FTC) and (EFV/TDF/FTC) • No cumulative TAM-mediated resistance	• Potential for renal impairment, including rare reports of Fanconi syndrome and acute renal insufficiency • Early virologic failure of NVP + TDF + (FTC or 3TC) in small clinical trials • Potential for decrease in bone mineral density
	ZDV/3TC	• Coformulated (ZDV/3TC and ZDV/3TC/ABC) • No food effect (although better tolerated with food) • Preferred 2 NRTI in pregnant women	• Bone marrow suppression, especially anemia and neutropenia • GI intolerance, headache • Mitochondrial toxicity, including lipoatrophy, lactic acidosis, hepatic steatosis • Inferior to TDF/FTC in combination with EFV • Diminished CD4 T-cell responses compared with ABC/3TC

Acronyms: 3TC = lamivudine, ABC = abacavir, ART = antiretroviral therapy, ARV = antiretroviral, ATV = atazanavir, ATV/r = atazanavir/ritonavir, AV = atrioventricular, CYP = cytochrome P, ddI = didanosine, DLV = delavirdine, DRV/r = darunavir/ritonavir, ECG = electrocardiogram, EFV = efavirenz, FPV = fosamprenavir, FPV/r = fosamprenavir/ ritonavir, FTC = emtricitabine, GI = gastrointestinal, HBV = hepatitis B virus, HSR = hypersensitivity reaction, INSTI = integrase strand transfer inhibitor, LPV/r = lopinavir/ritonavir, MI = myocardial infarction, msec = milliseconds, MVC = maraviroc, NNRTI = non-nucleoside reverse transcriptase inhibitor, NRTI = nucleoside reverse transcriptase inhibitor, NVP = nevirapine, PI = protease inhibitor, PPI = proton pump inhibitor, SQV/r = saquinavir/ritonavir, TAM = thymidine analogue mutation, TDF = tenofovir, ZDV = zidovudine

Table 7. Antiretroviral Components Not Recommended as Initial Therapy
(Updated December 1, 2009)

ARV Drugs or Components (in alphabetical order)	**Reasons for NOT recommending as initial therapy**
ABC/3TC/ZDV (coformulated) as triple-NRTI combination regimen **(BI)**	• Inferior virologic efficacy
ABC + 3TC + ZDV + TDF as quadruple-NRTI combination **(BI)**	• Inferior virologic efficacy
ABC + ddI **(BIII)**	• Insufficient data in ART-naïve patients
ABC + TDF **(BIII)**	• Insufficient data in ART-naïve patients
DRV (unboosted)	• Use without RTV has not been studied
DLV **(BII)**	• Inferior virologic efficacy • Inconvenient (three times daily) dosing
ddI + TDF **(BII)**	• High rate of early virologic failure • Rapid selection of resistance mutations • Potential for immunologic nonresponse/CD4 T-cell decline • Increased ddI drug exposure and toxicities
T-20 **(BIII)**	• No clinical trial experience in ART-naïve patients • Requires twice-daily subcutaneous injections
ETR **(BIII)**	• Insufficient data in ART-naïve patients
IDV (unboosted) **(BIII)**	• Inconvenient dosing (three times daily with meal restrictions) • Fluid requirement
IDV (RTV-boosted) **(BIII)**	• High incidence of nephrolithiasis
NFV **(BI)**	• Inferior virologic efficacy • High incidence of diarrhea
RTV as sole PI **(BIII)**	• High pill burden • Gastrointestinal intolerance
SQV (unboosted) **(BI)**	• Inferior virologic efficacy
d4T + 3TC **(BI)**	• Significant toxicities including lipoatrophy; peripheral neuropathy; and hyperlactatemia, including symptomatic and life-threatening lactic acidosis, hepatic steatosis, and pancreatitis
TPV (ritonavir-boosted) **(BI)**	• Inferior virologic efficacy

Acronyms: 3TC = lamivudine, ABC = abacavir, ARV = antiretroviral, d4T = stavudine, ddI = didanosine, DLV = delavirdine, DRV = darunavir, ETR = etravirine; IDV = indinavir, IDV/r = ritonavir-boosted indinavir, NFV = nelfinavir, NRTI = nucleoside reverse transcriptase inhibitor, RTV = ritonavir, SQV = sacquinavir, T-20 = enfuvirtide, TDF = tenofovir, TPV = tipranavir, ZDV = zidovudine

Table 8. Antiretroviral Regimens or Components That Should Not Be Offered At Any Time
(Updated January 10, 2011)

	Rationale	Exception
Antiretroviral Regimens Not Recommended		
Monotherapy with NRTI (AII)	• Rapid development of resistance • Inferior ARV activity when compared with combination of three or more ARV agents	• No exception
Dual-NRTI regimens (AI)	• Rapid development of resistance • Inferior ARV activity when compared with combination of three or more ARV agents	• No exception
Triple-NRTI regimens (AI) except for ABC/ZDV/3TC (BI) or possibly TDF + ZDV/3TC (BII)	• High rate of early virologic nonresponse seen when triple-NRTI combinations, including ABC/TDF/3TC and TDF/ddI/3TC, were used as initial regimen in ART-naïve patients. • Other triple-NRTI regimens have not been evaluated.	• ABC/ZDV/3TC (BI) and possibly TDF + ZDV/3TC (BII) in patients in whom other combinations are not desirable
Antiretroviral Components Not Recommended as Part of an Antiretroviral Regimen		
ATV + IDV (AIII)	• Potential additive hyperbilirubinemia	• No exception
ddI + d4T (AII)	• High incidence of toxicities: peripheral neuropathy, pancreatitis, and hyperlactatemia • Reports of serious, even fatal, cases of lactic acidosis with hepatic steatosis with or without pancreatitis in pregnant women	• When no other ARV options are available and potential benefits outweigh the risks (BIII)
ddI + TDF (AII)	• Increased ddI concentrations and serious ddI-associated toxicities • Potential for immunologic nonresponse and/or CD4 cell count decline • High rate of early virologic failure • Rapid selection of resistance mutations at failure	• Clinicians caring for patients who are clinically stable on regimens containing TDF + ddI should consider altering the NRTIs to avoid this combination.
2-NNRTI combination (AI)	• When EFV combined with NVP, higher incidence of clinical adverse events seen when compared with either EFV- or NVP-based regimen. • Both EFV and NVP may induce metabolism and may lead to reductions in ETR exposure; thus, they should not be used in combination with ETR.	• No exception
EFV in first trimester of pregnancy or in women with significant childbearing potential (AIII)	• Teratogenic in nonhuman primates	• When no other ARV options are available and potential benefits outweigh the risks (BIII)
FTC + 3TC (AIII)	• Similar resistance profiles • No potential benefit	• No exception
ETR + unboosted PI (AII)	• ETR may induce metabolism of these PIs; appropriate doses not yet established	• No exception
ETR + RTV-boosted ATV or FPV (AII)	• ETR may alter the concentrations of these PIs; appropriate doses not yet established	• No exception
ETR + RTV-boosted TPV (AII)	• ETR concentration may be significantly reduced by RTV-boosted TPV	• No exception
NVP in ARV-naïve women with CD4 count >250 cells/mm^3 or men with CD4 count >400 cells/mm^3 (BI)	• High incidence of symptomatic hepatotoxicity	• If no other ARV option available; if used, patient should be closely monitored
d4T + ZDV (AII)	• Antagonistic effect on HIV-1	• No exception
Unboosted DRV, SQV, or TPV (AII)	• Inadequate bioavailability	• No exception

Acronyms:
3TC = lamivudine, ABC = abacavir, ATV = atazanavir, d4T = stavudine, ddI = didanosine, DRV = darunavir, EFV = efavirenz, ETR = etravirine, FPV = fosamprenavir, FTC = emitricitabine, IDV = indinavir, NVP = nevirapine, RTV = ritonavir, SQV = saquinavir, TDF = tenofovir, TPV = tipranavir, ZDV = zidovudine

Table 9a. Trough Concentrations of Antiretroviral Drugs for Patients Who Have Drug-Susceptible Virus (Updated January 10, 2011)

Drug	Concentration (ng/mL)
Suggested minimum target trough concentrations in patients with HIV-1 susceptible to the ARV drugs *[2-9]*	
Fosamprenavir (FPV)	400 (measured as amprenavir concentration)
Atazanavir (ATV)	150
Indinavir (IDV)	100
Lopinavir (LPV)	1,000
Nelfinavir[1] (NFV)	800
Saquinavir (SQV)	100–250
Efavirenz (EFV)	1,000
Nevirapine (NVP)	3,000

[1]Measurable active (M8) metabolite

Table 9b. Trough Concentrations of Antiretroviral Drugs for Treatment-Experienced Patients with Virologic Failure (Updated January 10, 2011)

Drug	Concentration (ng/mL)
Suggested minimum target trough concentrations for ART-experienced patients who have resistant HIV-1 strains	
Maraviroc (MVC)	>50
Tipranavir (TPV)	20,500
Median (Range) Trough Concentrations from Clinical Trials *[12-14]*	
Darunavir (DRV) (600 mg twice daily)	3,300 (1,255–7,368)
Etravirine (ETR)	275 (81–2,980)
Raltegravir (RAL)	72 (29–118)

Table 10. Identifying, Diagnosing, and Managing Acute HIV-1 Infection (Updated January 10, 2011)

- **Suspecting acute HIV infection:** Signs or symptoms of acute HIV infection with recent (within 2–6 weeks) high risk of exposure to HIV*
  - Signs/symptoms/laboratory findings may include but are not limited to one or more of the following: fever, lymphadenopathy, skin rash, myalgia/arthralgia, headache, diarrhea, oral ulcers, leucopenia, thrombocytopenia, transaminase elevation.
  - High-risk exposures include sexual contact with a person infected with HIV or at risk of HIV, sharing of injection drug use paraphernalia, or contact of potentially infectious blood with mucous membranes or breaks in skin.*

- **Differential diagnosis:** Epstein-Barr virus (EBV)- and non-EBV (e.g., cytomegalovirus [CMV])-related infectious mononucleosis syndromes, influenza, viral hepatitis, streptococcal infection, syphilis

- **Evaluation/diagnosis of acute/primary HIV infection**
  - HIV antibody enzyme immunoassay (EIA) (rapid test if available)
    - Reactive EIA must be followed by Western blot.
    - Negative EIA or reactive EIA with negative or indeterminate Western blot should be followed by a virologic test.†
  - Positive virologic test† in this setting is consistent with acute HIV infection.
  - When acute HIV infection is diagnosed by a positive virologic test (such as HIV RNA or p24 antigen) that was preceded by a negative HIV antibody test, a confirmatory HIV antibody test should be performed over the next 3 months to confirm seroconversion.

- **Considerations for antiretroviral therapy:**
  - All pregnant women with acute or recent HIV infection should start on a combination ARV regimen as soon as possible because of the high risk of MTCT of HIV **(AI)**.
  - Treatment of acute and early HIV infection in nonpregnant persons is considered optional **(CIII)**.
  - Potentially unique benefits associated with ART during acute and early infection exist, although they remain unproven.
  - The risks of ART during acute and early infection are consistent with those for initiating ART in chronically infected asymptomatic patients with high CD4 counts.
  - If therapy is initiated, the goal should be for maintenance of maximal viral suppression.
  - Enrollment in a clinical trial should be considered.

* In some settings, behaviors conducive to acquisition of HIV infection might not be ascertained or might not be perceived as "high risk" by the health care provider or the patient or both. Thus, symptoms and signs consistent with acute retroviral syndrome should motivate consideration of this diagnosis even in the absence of reported high-risk behaviors.

† p24 antigen or HIV RNA assay. The p24 antigen is less sensitive but more specific than HIV RNA tests; HIV RNA tests are generally preferred. HIV RNA tests include quantitative branched DNA (bDNA), reverse transcriptase-polymerase chain reaction (RT-PCR), or qualitative transcription-mediated amplification (APTIMA, GenProbe).

Table 11. Drug Interactions between Antiretroviral Agents and Drugs Used to Treat Opioid Addiction (January 10, 2011)

Concomitant Drug	Antiretroviral Class/Drug	Pharmacokinetic Interactions Recommendations/Clinical Comments
Buprenorphine	EFV	buprenorphine AUC ↓ 50%; norbuprenorphine* AUC ↓ 71% No withdrawal symptoms reported. No dosage adjustment recommended; however, monitor for withdrawal symptoms.
	ATV	buprenorphine AUC ↑ 93%; norbuprenorphine AUC ↑ 76%; ↓ ATV levels possible Do not coadminister buprenorphine with unboosted ATV.
	ATV/r	buprenorphine AUC ↑ 66%; norbuprenorphine AUC ↑ 105% Monitor for sedation. Buprenorphine dose reduction may be necessary.
	DRV/r	buprenorphine: no significant effect, norbuprenorphine AUC ↑ 46% and C_{min} ↑ 71% No dose adjustment necessary.
	TPV/r	buprenorphine: no significant effect; norbuprenorphine AUC, C_{max}, and C_{min} ↓ 80%; TPV C_{min} ↓ 19%–40% Consider monitoring TPV level.
	3TC, ddI, TDF, ZDV, NVP, LPV/r, NFV	No significant effect No dosage adjustment necessary.
	ABC, d4T, FTC, ETR, FPV +/- RTV, IDV +/- RTV, SQV/r, RAL, MVC, T20	No data

Concomitant Drug	Antiretroviral Class/Drug	Pharmacokinetic Interactions Recommendations/Clinical Comments
Methadone	ABC	methadone clearance ↑ 22% No dosage adjustment necessary.
	d4T	d4T AUC ↓ 23% and C_{max} ↓ 44% No dosage adjustment necessary.
	ZDV	ZDV AUC ↑ 29%–43% Monitor for ZDV-related adverse effects.
	EFV	methadone AUC ↓ 52% Opioid withdrawal common; increased methadone dose often necessary.
	NVP	methadone AUC ↓ 41% NVP: no significant effect Opioid withdrawal common; increased methadone dose often necessary.
	ATV/r, DRV/r, FPV/r, IDV/r, LPV/r, SQV/r, TPV/r	With ATV/r, DRV/r, FPV/r: R-methadone† AUC ↓ 16%–18%; With LPV/r: methadone AUC ↓ 26%–53%; With SQV/r 1,000/100mg BID: R-methadone AUC ↓ 19%; With TPV/r: R-methadone AUC ↓ 48% Opioid withdrawal unlikely but may occur. No adjustment in methadone usually required; however, monitor for opioid withdrawal and increase methadone dose as clinically indicated.
	FPV	No data with FPV (unboosted) With APV: R-methadone C_{min} ↓ 21%, AUC no significant change Monitor and titrate methadone as clinically indicated. The interaction with FPV is presumed to be similar.
	NFV	methadone AUC ↓ 40% Opioid withdrawal rarely occurs. Monitor and titrate dose as clinically indicated. May require increased methadone dose.
	ddI (EC capsule), 3TC, TDF, ETR, RTV, ATV, IDV, RAL	No significant effect No dosage adjustment necessary.
	FTC, MVC, T20	No data

* Norbuprenorphine is an active metabolite of buprenorphine.
† R-methadone is the active form of methadone.

Acronyms: 3TC = lamivudine, d4T = stavudine, T20 = enfuvirtide, ABC = abacavir, APV = amprenavir, ATV = atazanavir, ATV/r = atazanavir/ritonavair, ddI = didanosine, DRV/r = darunavir/ritonavir, EFV = efavirenz, ETR = etravirine, FPV = fosamprenavir, FPV/r = fosamprenavir/ritonavir, FTC = emtricitabine, IDV = indinavir, IDV/r = indinavir/ritonavir, LPV/r = lopinavir/ritonavir, MVC = maraviroc, NFV = nelfinavir, NVP = nevirapine, RAL = raltegravir, RTV = ritonavir, SQV/r = sacquinavir/ritonavir, TDF = tenofovir, TPV = tipranavir, TPV/r = tipranavir/ritonavir, ZDV = zidovudine

Table 12. Strategies to Improve Adherence to Antiretroviral Therapy

Strategies	Examples
Use a multidisciplinary team approach Provide an accessible, trusting health care team	• Nurses, social workers, pharmacists, and medication managers
Establish a trusting relationship with the patient	
Establish readiness to start ART	
Identify potential barriers to adherence prior to starting ART	• Psychosocial issues • Active substance abuse or at high risk of relapse • Low literacy level • Busy daily schedule and/or travel away from home • Lack of disclosure of HIV diagnosis • Skepticism about ART • Lack of prescription drug coverage
Provide resources for the patient	• Referrals for mental health and/or substance abuse treatment • Resources to obtain prescription drug coverage • Pillboxes
Involve the patient in antiretroviral (ARV) regimen selection	• For each option, review potential side effects, dosing frequency, pill burden, storage requirements, food requirements, and consequences of nonadherence
Assess adherence at every clinic visit	• Use a simple checklist the patient can complete in the waiting room • Have other members of the health care team also assess adherance • Ask the patient open-ended questions (e.g., *In the last 3 days, please tell me how you took your medicines.*)
Identify the type of nonadherence	• Failure to fill the prescription(s) • Failure to take the right dose(s) at the right time(s) • Nonadherence to food requirements
Identify reasons for nonadherence	• Adverse effects from medications • Complexity of regimen (pill burden, dosing frequency, etc.) • Difficulty swallowing large pills • Forgetfulness • Failure to understand dosing instructions • Inadequate understanding of drug resistance and its relationship to adherence • Pill fatigue • Other potential barriers (see list above)
Assess and simplify regimen, if possible	

Table 13. Antiretroviral Therapy-Associated Common and/or Severe Adverse Effects (January 10, 2011)

(See Appendix B for additional information listed by drug.)

Adverse Effects	NRTIs	NNRTIs	PIs	INSTI	EI
Bleeding events			**All PIs:** ↑ spontaneous bleeding, hematuria in hemophilia **TPV:** Reports of intracranial hemorrhage. Risks include CNS lesions; trauma; surgery; hypertension; alcohol abuse; coagulopathy, anti-coagulant, or anti-platelet agents including vitamin E		
Bone marrow suppression	**ZDV:** Anemia, neutropenia				
Cardiovascular disease (CVD)	**ABC** and **ddI:** Associated with myocardial infarction (MI) in some but not all cohort studies. Risk greatest among those with traditional CVD risk factors.		**PIs:** Associated with MI and stroke in some cohort studies. Risk greatest among those with traditional CVD risk factors. Limited data on newer PIs (ATV, DRV, TPV). **SQV/r**, **ATV/r,** and **LPV/r:** PR interval prolongation. Risks include structural heart disease, conduction system abnormalities, cardiomyopathy, ischemic heart disease, and coadministration with drugs that prolong PR interval. **SQV/r:** QT interval prolongation in a healthy volunteer study. Risks include underlying heart conditions, pre-existing prolonged QT or arrhythmia, or use with other QT-prolonging drugs. ECG prior to SQV initiation is recommended and should be considered during therapy.		
Central nervous system (CNS) effects	**d4T:** Associated with rapidly progressive ascending neuromuscular weakness resembling Guillain-Barré syndrome (rare)	**EFV:** Somnolence, insomnia, abnormal dreams, dizziness, impaired concentration, depression, psychosis, suicidal ideation. Most symptoms subside or diminish after 2–4 weeks. Bedtime dosing may reduce symptoms. Risks include history of psychiatric illness, concomitant use of agents with neuropsychiatric effects, and ↑ plasma EFV concentrations due to genetic factors or absorption (i.e., with food).			
Diabetes mellitus (DM)/Insulin resistance/	**ZDV, d4T,** and **ddI**		• Reported for some **PIs (IDV, LPV/r**), but not all PIs studied • **ATV** +/- **RTV** not found to alter insulin sensitivity		
Dyslipidemia	**d4T > ZDV > ABC:** •↑ LDL and TG	**EFV** •↑TG •↑LDL •↑HDL	↑LDL, ↑TG, ↑HDL: **all RTV-boosted PIs** ↑TG: **LPV/r** = **FPV/r** and **LPV/r** > **DRV/r** and **ATV/r**		
Gastrointestinal (GI)	Nausea and vomiting: **ddI** and **ZDV** > other **NRTIs** Pancreatitis: **ddI**		GI intolerance (diarrhea, nausea, vomiting) Diarrhea: common with **NFV**. **LPV/r** > **DRV/r** and **ATV/r**		

Adverse Effects	NRTIs	NNRTIs	PIs	INSTI	EI
Hepatic effects	Reported for most **NRTIs** **ddI:** prolonged exposure linked to noncirrhotic portal hypertension, some cases with esophageal varicees Steatosis: most commonly seen with **ZDV**, **d4T**, or **ddI** Flares: hepatitis B virus (HBV)-coinfected patients may develop severe hepatic flare when **TDF**, **3TC**, and **FTC** are withdrawn or when HBV resistance develops.	**NVP > other NNRTIs** **NVP:** • Severe hepatic toxicity with **NVP** is often associated with skin rash or symptoms of hypersensitivity. • For ARV-naïve patients, risk is greater for women with pre-**NVP** CD4 count >250 cells/mm^3 and men with pre-**NVP** CD4 count >400 cells/mm^3. Risk is higher for women. • 2-week dose escalation of **NVP** reduces risk of rash and possibly hepatotoxicity if related to hypersensitivity. • Given high risk in those with competent immune systems, **NVP** should never be used for post-exposure prophylaxis in HIV-uninfected individuals. • **NVP** is contraindicated in patients with Child-Pugh classification B or C.	**All PIs:** Drug-induced hepatitis and hepatic decompensation (and rare cases of fatalities) have been reported with all PIs to varying degrees. **TPV/r** has a higher frequency of hepatic events than other PIs. **IDV, ATV**: jaundice due to indirect hyperbilirubinemia **TPV/r:** Contraindicated in patients with moderate to severe hepatic insufficiency (Child-Pugh classification B or C)		
Hypersensitivity reaction (HSR) (excluding rash alone or Stevens Johnson syndrome[SJS])	**ABC**: • HLA-B*5701 screening prior to initiation of **ABC**. Should not be started if HLA-B*5701 is positive. • Symptoms of HSR include (in descending frequency): fever, skin rash, malaise, nausea, headache, myalgia, chills, diarrhea, vomiting, abdominal pain, dyspnea, arthralgia, respiratory symptoms • Worsen with continuation of **ABC** • Median onset 9 days; ~ 90% of reactions within first 6 weeks • Onset of rechallenge reactions is within hours of rechallenge dose	**NVP**: • Hypersensitivity syndrome of hepatic toxicity and rash that may be accompanied by fever, general malaise, fatigue, myalgias, arthralgias, blisters, oral lesions, conjunctivitis, facial edema, eosinophilia, granulocytopenia, lymphadenopathy, or renal dysfunction. • For ARV-naïve patients, risk is greater for women with pre-**NVP** CD4 count >250 cells/mm^3 and men with pre-**NVP** CD4 count >400 cells/mm^3. Risk is higher for women. • 2-week dose escalation of **NVP** reduces risk.			
Lactic acidosis	**NRTIs,** especially **d4T, ZDV,** and **ddI** • Insidious onset with GI prodrome, weight loss, and fatigue. May be rapidly progressive, with tachycardia, tachypnea, jaundice, muscular weakness, mental status changes, respiratory distress, pancreatitis, and organ failure. • Mortality up to 50% in some case series, especially in patients with serum lactate >10 mmol/L • Increased risk: female sex, obesity Laboratory findings: • ↑ lactate (often >5 mmol/L), anion gap, AST, ALT, PT, bilirubin • ↑ amylase and lipase in patients with pancreatitis • ↓ arterial pH, serum bicarbonate, serum albumin				

Adverse Effects	NRTIs	NNRTIs	PIs	INSTI	EI
Lipodystrophy	Lipoatrophy: **Thymidine analogs (d4T > ZDV).** May be more likely when combined with **EFV** vs. **boosted PI**.	Lipohypertophy: Trunk fat increase observed with **EFV**-, **PI**-, and **RAL**-containing regimens; however, causal relationship has not been established.			
Myopathy/elevated CPK	**ZDV:** myopathy			**RAL:** ↑ CPK. muscle weakness and rhabdomyolysis	
Nephrotoxicity/ urolithiasis	**TDF:** ↑ serum creatinine, proteinuria, hypophosphatemia, urinary phosphate wasting, glycosuria, hypokalemia, non-anion gap metabolic acidosis Concurrent use of **PI** may increase risk.		**IDV**: ↑ serum creatinine, pyuria; hydronephrosis or renal atrophy **IDV, ATV**: Stone, crystal formation; adequate hydration may reduce risk.		
Osteopenia/ osteoporosis	**TDF:** Associated with greater loss of bone mineral density (BMD) compared with **ZDV, d4T,** and **ABC.**	Decreases in BMD observed in studies of regimens containing different **NRTIs** combined with either **NNRTIs** or **PIs**.			
Peripheral neuropathy	Peripheral neuropathy (pain and/or paresthesias, lower extremities > upper extremities): **d4T > ddI** and **ddC** (can be irreversible) **d4T:** Associated with rapidly progressive ascending neuromuscular weakness resembling Guillain-Barré syndrome (rare)				
Rash		**All NNRTIs**	**ATV, DRV, FPV**		**MVC**
Stevens-Johnson syndrome (SJS)/ toxic epidermal necrosis (TEN)	**ddI, ZDV:** Reported cases	**NVP > DLV, EFV, ETR** For **NVP** risks include: •Female sex •Black, Asian, Hispanic race/ethnicity	**FPV, DRV, IDV, LPV/r, ATV:** Reported cases		

Acronyms:
Drug Classes: EI = entry inhibitor; INSTI = integrase strand transfer inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PIs = protease inhibitor
Antiretroviral Drugs: 3TC = lamivudine; ABC = abacavir; ATV = atazanavir; ATV/r = atazanavir + ritonavir; d4T = stavudine; ddC = zalcitabine; ddI = didanosine; DLV = delaviridine; DRV = darunavir; DRV/r = darunavir + ritonavir; EFV = efavirenz; ETR = etravirine; FPV = fosamprenavir; FPV/r = fosamprenavir + ritonavir; FTC = emtricitabine; IDV = indinavir; LPV/r = lopinavir + ritonavir; MVC = maraviroc; NFV = nelfinavir; NVP = nevirapine; RAL = raltegravir; RTV = ritonavir; SQV/r = saquinavir + ritonavir; TDF = tenofovir; TPV = tipranavir; ZDV = zidovudine
Other: ALT = alanine aminotransferase; ARV = antiretroviral; AST = aspartate aminotransferase; BMD = bone mineral density; CNS = central nervous system; CPK = creatine phosphokinase; CVD = cardiovascular disease; DM = diabetes mellitus; ECG = electrocardiogram; GI = gastrointestinal; HBV = hepatitis B virus; HDL = high-density lipoprotein; HSR = hypersensitivity reaction; LDL = low-density lipoprotein; MI = myocardial infarction; PT = prothrombin time; SJS = Stevens-Johnson syndrome; TEN = toxic epidermal necrosis; TG = triglyceride

Table 14. Drugs That Should Not Be Used With PI, NNRTI, or CCR5 Antagonist
(Updated January 10, 2011)

This table lists only drugs that should not be coadministered at any dose and regardless of RTV boosting. See **Tables 15 and 16** for more detailed pharmacokinetic interaction data and dosage adjustments.

Drug Categories										
Antiretroviral Agents[1, 2]	**Cardiac Agents**	**Lipid-lowering Agents**	**Antimyco-bacterials**	**Gastro-intestinal Drugs**	**Neuro-leptics**	**Psycho-tropics**	**Ergot Derivatives (vasoconstrictors)**	**Herbs**	**Antiretroviral Agents**	**Others**
ATV +/− RTV	none	lovastatin pitavastatin simvastatin	rifampin rifapentine[3]	cisapride[5]	pimozide	midazolam[6] triazolam	dihydroergotamine ergonovine ergotamine methylergonovine	St. John's wort	ETR NVP	alfuzosin irinotecan salmeterol sildenafil for PAH
DRV/r	none	lovastatin pitavastatin simvastatin	rifampin rifapentine[3]	cisapride[5]	pimozide	midazolam[6] triazolam	dihydroergotamine ergonovine ergotamine methylergonovine	St. John's wort	none	alfuzosin salmeterol sildenafil for PAH
FPV +/− RTV	flecainide propafenone	lovastatin pitavastatin simvastatin	rifampin rifapentine[3]	cisapride[5]	pimozide	midazolam[6] triazolam	dihydroergotamine ergonovine ergotamine methylergonovine	St. John's wort	ETR	alfuzosin salmeterol sildenafil for PAH
LPV/r	none	lovastatin pitavastatin simvastatin	rifampin[4] rifapentine[3]	cisapride[5]	pimozide	midazolam[6] triazolam	dihydroergotamine ergonovine ergotamine methylergonovine	St. John's wort	none	alfuzosin salmeterol sildenafil for PAH
RTV	amiodarone flecainide propafenone quinidine	lovastatin pitavastatin simvastatin	rifapentine[3]	cisapride[5]	pimozide	midazolam[6] triazolam	dihydroergotamine ergonovine ergotamine methylergonovine	St. John's wort	none	alfuzosin sildenafil for PAH
SQV/r	amiodarone dofetilide flecainide lidocaine propafenone quinidine	lovastatin pitavastatin simvastatin	rifampin[4] rifapentine	cisapride[5]	pimozide	midazolam[6] triazolam trazodone	dihydroergotamine ergonovine ergotamine methylergonovine	St. John's wort garlic supplements	none	alfuzosin salmeterol sildenafil for PAH
TPV/r	amiodarone flecainide propafenone quinidine	lovastatin pitavastatin simvastatin	rifampin rifapentine[3]	cisapride[5]	pimozide	midazolam[6] triazolam	dihydroergotamine ergonovine ergotamine methylergonovine	St. John's wort	ETR	alfuzosin salmeterol sildenafil for PAH
EFV	none	none	rifapentine[3]	cisapride[5]	pimozide	midazolam[6] triazolam	dihydroergotamine ergonovine ergotamine methylergonovine	St. John's wort	other NNRTIs	none
ETR	none	none	rifampin rifapentine[3]	none	none	none	none	St John's wort	unboosted PIs ATV/r, FPV/r, or TPV/r other NNRTIs	carbamazepine phenobarbital phenytoin clopidogrel
NVP	none	none	rifapentine[3]	none	none	none	none	St. John's wort	ATV +/− RTV other NNRTIs	ketoconazole
MVC	none	none	rifapentine[3]	none	none	none	none	St. John's wort	none	none

1 DLV, IDV, and NFV are not included in this table. Refer to the FDA package insert for information regarding DLV-, IDV-, and NFV-related drug interactions.
2 Certain listed drugs are contraindicated based on theoretical considerations. Thus, drugs with narrow therapeutic indices and suspected metabolic involvement with CYP450 3A, 2D6, or unknown pathways are included in this table. Actual interactions may or may not occur in patients.
3 HIV-infected patients treated with rifapentine have a higher rate of TB relapse than those treated with other rifamycin-based regimens; an alternative agent is recommended.
4 A high rate of Grade 4 serum transaminase elevation was seen when a higher dose of RTV was added to LPV/r or SQV or when double-dose LPV/r was used with rifampin to compensate for rifampin's induction effect, so these dosing strategies should not be used.
5 The manufacturer of cisapride has a limited-access protocol for patients who meet specific clinical eligibility criteria.
6 Use of oral midazolam is contraindicated. Parenteral midazolam can be used with caution as a single dose and can be given in a monitored situation for procedural sedation.

Suggested alternatives to:
Lovastatin, simvastatin: Pravastatin and fluvastatin have the least potential for drug-drug interactions (except for pravastatin with DRV/r, see **Table 15a**). Use atorvastatin and rosuvastatin with caution; start with the lowest possible dose and titrate based on tolerance and lipid-lowering efficacy.
Rifampin: Rifabutin (with dosage adjustment – see **Tables 15a and 15b**)
Midazolam, triazolam: temazepam, lorazepam, oxazepam

Acronyms: ATV +/- RTV = atazanavir +/- ritonavir, DLV = delavirdine, DRV/r = darunavir/ritonavir, EFV = efavirenz, ETV = etravirine, FDA = Food and Drug Administration, FPV +/- RTV = fosamprenavir +/- ritonavir, HIV = human immunodeficiency virus, IDV = indinavir, LPV/r = lopinavir/ritonavir, MVC = maraviroc, NFV = nelfinavir, NNRTI = non-nucleoside reverse transcriptase inhibitor, NVP = nevirapine, PAH = pulmonary arterial hypertension, PI = protease inhibitor, RTV = ritonavir, SQV/r = saquinavir/ritonavir, TPV/r = tipranavir/ritonavir

Table 15a. Drug Interactions between PIs* and Other Drugs (Updated January 10, 2011)

*NFV and IDV are not included in this table. Please refer to the FDA package insert for information regarding NFV and IDV drug interactions.

This table provides information relating to pharmacokinetic interactions between PIs and non-ARV drugs. When information is available, interactions with boosted and unboosted PIs are listed separately. For interactions among ARV agents and for dosing recommendations, refer to **Table 16a**.

Concomitant Drug	PI	Effect on PI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Acid Reducers			
Antacids	ATV +/– RTV	↓ ATV expected when given simultaneously	Give ATV at least 2 hours before or 1 hour after antacids or buffered medications.
	FPV	APV AUC ↓ 18%; no significant change in APV C_{min}	Give FPV simultaneously with or at least 2 hours before or 1 hour after antacids.
	TPV/r	TPV AUC ↓ 27%	Give TPV at least 2 hours before or 1 hour after antacids.
H_2 receptor antagonists	**RTV-boosted PIs**		
	ATV/r	↓ ATV	H_2 receptor antagonist dose should not exceed a dose equivalent to famotidine 40 mg BID in ART-naïve patients or 20 mg BID in ART-experienced patients. Give ATV 300 mg + RTV 100 mg simultaneously with and/or ≥10 hours after the H_2 receptor antagonist. If using TDF and H_2 receptor antagonist in ART-experienced patients, use ATV 400 mg + RTV 100 mg.
	DRV/r, LPV/r	No significant effect	
	PIs without RTV		
	ATV	↓ ATV	H_2 receptor antagonist single dose should not exceed a dose equivalent of famotidine 20 mg or total daily dose equivalent of famotidine 20 mg BID in ART-naïve patients. Give ATV at least 2 hours before and at least 10 hours after the H_2 receptor antagonist.
	FPV	APV AUC ↓ 30%; no significant change in APV C_{min}	Give FPV at least 2 hours before H_2 receptor antagonist if concomitant use is necessary. Consider boosting with RTV.
Proton pump inhibitors (PPIs)	ATV	↓ ATV	**PPIs are not recommended in patients receiving unboosted ATV.** In these patients, consider alternative acid-reducing agents, RTV boosting, or alternative PIs.
	ATV/r	↓ ATV	PPIs should not exceed a dose equivalent to omeprazole 20 mg daily in PI-naïve patients. PPIs should be administered at least 12 hours prior to ATV/r. **PPIs are not recommended in PI-experienced patients**.
	DRV/r, TPV/r	↓ omeprazole PI: no significant effect	May need to increase omeprazole dose with TPV/r.
	FPV +/– RTV, LPV/r	No significant effect	
	SQV/r	SQV AUC ↑ 82%	Monitor for SQV toxicities.
Anticoagulants			
Warfarin	ATV +/- RTV, DRV/r, FPV +/- RTV, LPV/r, SQV/r, TPV/r	↑ or ↓ warfarin possible DRV/r ↓ S-warfarin AUC 21%	Monitor INR closely when stopping or starting PI and adjust warfarin dose accordingly.

Table 15a. Drug Interactions between PIs and Other Drugs

Concomitant Drug	PI	Effect on PI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Anticonvulsants			
Carbamazepine	**RTV-boosted PIs**		
	ATV/r, FPV/r, LPV/r, SQV/r, TPV/r	↑ carbamazepine possible TPV/r ↑ carbamazepine AUC 26% May ↓ PI levels substantially	Consider alternative anticonvulsant or monitor levels of both drugs and assess virologic response. **Do not coadminister with LPV/r once daily.**
	DRV/r	carbamazepine AUC ↑ 45% DRV: no significant change	Monitor anticonvulsant level and adjust dose accordingly.
	PIs without RTV		
	ATV, FPV	May ↓ PI levels substantially	Monitor anticonvulsant level and virologic response. Consider alternative anticonvulsant; RTV boosting for ATV and FPV; and/or monitoring PI level.
Lamotrigine	LPV/r	lamotrigine AUC ↓ 50% LPV: no significant change	Titrate lamotrigine dose to effect. A similar interaction is possible with other RTV-boosted PIs.
Phenobarbital	All PIs	May ↓ PI levels substantially	Consider alternative anticonvulsant or monitor levels of both drugs and assess virologic response. **Do not coadminister with LPV/r once daily.**
Phenytoin	**RTV-boosted PIs**		
	ATV/r, DRV/r, SQV/r, TPV/r	↓ phenytoin possible ↓ PI possible	Consider alternative anticonvulsant or monitor levels of both drugs and assess virologic response.
	FPV/r	phenytoin AUC ↓ 22% APV AUC ↑ 20%	Monitor phenytoin level and adjust dose accordingly. No change in FPV/r dose recommended.
	LPV/r	phenytoin AUC ↓ 31% LPV/r AUC ↓ 33%	Consider alternative anticonvulsant or monitor levels of both drugs and assess virologic response. **Do not coadminister with LPV/r once daily.**
	PIs without RTV		
	ATV, FPV	May ↓ PI levels substantially	Consider alternative anticonvulsant; RTV boosting for ATV and FPV; and/or monitoring PI level. Monitor anticonvulsant level and virologic response.
Valproic acid (VPA)	LPV/r	↓VPA possible LPV AUC ↑ 75%	Monitor VPA levels and response. Monitor for LPV-related toxicities.
Antidepressants			
Bupropion	LPV/r	bupropion AUC ↓ 57%	Titrate bupropion dose based on clinical response.
	TPV/r	bupropion AUC ↓ 46%	
Paroxetine	DRV/r	paroxetine AUC ↓ 39%	Titrate paroxetine dose based on clinical response.
	FPV/r	paroxetine AUC ↓ 58%	
Sertraline	DRV/r	sertraline AUC ↓ 49%	Titrate sertraline dose based on clinical response.
Trazodone	ATV +/- RTV, DRV/r, FPV +/- RTV, LPV/r, TPV/r	RTV 200 mg BID (for 2 days) ↑ trazodone AUC 240%	Use lowest dose of trazodone and monitor for CNS and cardiovascular adverse effects.
	SQV/r	↑ trazodone expected	**Contraindicated. Do not coadminister.**
Tricyclic antidepressants (TCAs) (amitriptyline, desipramine, imipramine, nortriptyline)	All RTV-boosted PIs	↑ TCA expected	Use lowest possible TCA dose and titrate based on clinical assessment and/or drug levels.

Concomitant Drug	PI	Effect on PI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antifungals			
Fluconazole	**RTV-boosted PIs**		
	ATV/r	No significant effect	
	SQV/r	No data with RTV boosting SQV (1,200 mg TID) AUC ↑ 50%	
	TPV/r	TPV AUC ↑ 50%	Fluconazole >200 mg daily is not recommended. If high-dose fluconazole is indicated, consider alternative PI or another class of ARV drug.
Itraconazole	**RTV-boosted PIs**		
	ATV/r, DRV/r, FPV/r, TPV/r	↑ itraconazole possible ↑ PI possible	Consider monitoring itraconazole level to guide dosage adjustments. High doses (>200 mg/day) are not recommended unless dosing is guided by drug levels.
	LPV/r	↑ itraconazole	Consider not exceeding 200 mg itraconazole daily or monitor itraconazole level.
	SQV/r	Bidirectional interaction has been observed	Dose not established, but decreased itraconazole dosage may be warranted. Consider monitoring itraconazole level.
	PIs without RTV		
	ATV, FPV	↑ itraconazole possible ↑ PI possible	Consider monitoring itraconazole level to guide dosage adjustments.
Posaconazole	ATV/r	ATV AUC ↑ 146%	Monitor for adverse effects of ATV.
	ATV	ATV AUC ↑ 268%	Monitor for adverse effects of ATV.
Voriconazole	**RTV-boosted PIs**		
	ATV/r, DRV/r, FPV/r, LPV/r, SQV/r, TPV/r	RTV 400 mg BID ↓ voriconazole AUC 82% RTV 100 mg BID ↓ voriconazole AUC 39%	**Do not coadminister** voriconazole and RTV unless benefit outweighs risk. If administered, consider monitoring voriconazole level.
	PIs without RTV		
	ATV, FPV	↑ voriconazole possible ↑ PI possible	Monitor for toxicities.
Anti-mycobacterials			
Clarithromycin	ATV +/− RTV	clarithromycin AUC ↑ 94%	May cause QTc prolongation. Reduce clarithromycin dose by 50%. Consider alternative therapy.
	DRV/r, FPV/r, LPV/r, SQV/r, TPV/r	DRV/r ↑ clarithromycin AUC 57% FPV/r ↑ clarithromycin possible LPV/r ↑ clarithromycin expected RTV 500 mg BID ↑ clarithromycin 77% SQV unboosted ↑ clarithromycin 45% TPV/r ↑ clarithromycin 19% and ↓ active metabolite 97% clarithromycin ↑ unboosted SQV 177% clarithromycin ↑ TPV 66%	Monitor for clarithromycin-related toxicities. Reduce clarithromycin dose by 50% in patients with CrCl 30–60 mL/min. Reduce clarithromycin dose by 75% in patients with CrCl <30 mL/min.
	FPV	APV AUC ↑ 18%	No dose adjustment

Concomitant Drug	PI	Effect on PI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Rifabutin	**RTV-boosted PIs**		
	ATV +/– RTV	rifabutin (150 mg once daily) AUC ↑ 110% and metabolite AUC ↑ 2,101% compared with rifabutin 300 mg daily alone	Rifabutin 150 mg every other day or three times a week. Some experts recommend rifabutin 150 mg daily or 300 mg three times a week. Monitor for antimycobacterial activity. Therapeutic drug monitoring for rifabutin is recommended. Rifabutin 150 mg three times a week in combination with LPV/r has resulted in inadequate rifabutin levels and has led to acquired rifamycin resistance in patients with HIV-associated TB. Pharmacokinetic data reported in this table are results from healthy volunteer studies.
	DRV/r	rifabutin (150 mg every other day) and metabolite AUC ↑ 55% compared with rifabutin 300 mg once daily alone	
	FPV/r	rifabutin (150 mg every other day) and metabolite AUC ↑ 64% compared with rifabutin 300 mg once daily alone	
	LPV/r	rifabutin (150 mg once daily) and metabolite AUC ↑ 473% compared with rifabutin 300 mg daily alone	
	SQV/r	↑ rifabutin with unboosted SQV	
	TPV/r	rifabutin (150 mg x 1 dose) and metabolite AUC ↑ 333%	
	PIs without RTV		
	FPV	↑ rifabutin AUC expected	Rifabutin 150 mg daily or 300 mg three times a week
Rifampin	All PIs	↓ PI >75% approximately	**Do not coadminister rifampin and PIs.** Additional RTV does not overcome this interaction and increases hepatotoxicity.
Benzodiazepines			
Alprazolam **Diazepam**	All PIs	↑ benzodiazepine possible RTV 200 mg BID for two days ↑ alprazolam half-life 222% and AUC 248%	Consider alternative benzodiazepines such as lorazepam, oxazepam, or temazepam.
Lorazepam **Oxazepam** **Temazepam**	All PIs	No data	Metabolism of these benzodiazepines via non-CYP450 pathways decreases interaction potential compared with other benzodiazepines.
Midazolam	All PIs	↑ midazolam expected SQV/r ↑ midazolam (oral) AUC 1,144% and C_{max} 327%	**Do not coadminister oral midazolam and PIs.** Parenteral midazolam can be used with caution as a single dose and can be given in a monitored situation for procedural sedation.
Triazolam	All PIs	↑ triazolam expected RTV 200 mg BID ↑ triazolam half-life 1,200% and AUC 2,000%	**Do not coadminister triazolam and PIs.**
Cardiac Medications			
Bosentan	All PIs	LPV/r ↑ bosentan 48-fold (Day 4) and 5-fold (Day 10) ↓ ATV expected	**Do not coadminister bosentan and ATV without RTV.** In patients on a PI (other than unboosted ATV) >10 days: start bosentan at 62.5 mg once daily or every other day. In patients on bosentan who require a PI (other than unboosted ATV): stop bosentan ≥36 hours prior to PI initiation and restart 10 days after PI initiation at 62.5 mg once daily or every other day.

Concomitant Drug	PI	Effect on PI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Digoxin	RTV, SQV/r	RTV 200 mg BID ↑ digoxin AUC 29% and half-life 43% SQV/r ↑ digoxin AUC 49%	Use with caution. Monitor digoxin levels. Digoxin dose may need to be decreased.
Dihydropyridine calcium channel blockers (CCBs)	All PIs	↑ dihydropyridine possible	Use with caution. Titrate CCB dose and monitor closely. ECG monitoring is recommended when used with ATV.
Diltiazem	ATV +/– RTV	diltiazem AUC ↑ 125%	Decrease diltiazem dose by 50%. ECG monitoring is recommended.
	DRV/r, FPV +/– RTV, LPV/r, SQV/r, TPV/r	↑ diltiazem possible	Use with caution. Adjust diltiazem according to clinical response and toxicities.
Corticosteroids			
Dexamethasone	All PIs	↓ PI levels possible	Use systemic dexamethasone with caution or consider alternative corticosteroid for long-term use.
Fluticasone (inhaled or intranasal)	All RTV-boosted PIs	RTV 100 mg BID ↑ fluticasone AUC 350-fold and ↑ C_{max} 25-fold	Coadministration can result in adrenal insufficiency, including Cushing's syndrome. **Do not coadminister unless potential benefit outweighs risk of systemic corticosteroid adverse effects.**
Prednisone	LPV/r	↑ prednisolone AUC 31%	No dosage adjustment necessary.
Herbal Products			
St. John's wort	All PIs	↓ PI expected	**Do not coadminister.**
Hormonal Contraceptives			
Hormonal contraceptives	**RTV-boosted PIs**		
	ATV/r	↓ ethinyl estradiol ↑ norgestimate	Oral contraceptive should contain at least 35 mcg of ethinyl estradiol. Oral contraceptives containing progestins other than norethindrone or norgestimate have not been studied.
	DRV/r	ethinyl estradiol AUC ↓ 44% norethindrone AUC ↓ 14%	Use alternative or additional method.
	FPV/r	ethinyl estradiol AUC ↓ 37% norethindrone AUC ↓ 34%	Use alternative or additional method.
	LPV/r	ethinyl estradiol AUC↓ 42% norethindrone AUC ↓ 17%	Use alternative or additional method.
	SQV/r	↓ ethinyl estradiol	Use alternative or additional method.
	TPV/r	ethinyl estradiol AUC ↓ 48% norethindrone: no significant change	Use alternative or additional method.
	PIs without RTV		
	ATV	ethinyl estradiol AUC ↑ 48% norethindrone AUC ↑ 110%	Oral contraceptive should contain no more than 30 mcg of ethinyl estradiol or use alternate method. Oral contraceptives containing less than 25 mcg of ethinyl estradiol or progestins other than norethindrone or norgestimate have not been studied.
	FPV	With APV: ↑ ethinyl estradiol and ↑ norethindrone; ↓ APV 20%	Use alternative method.

Concomitant Drug	PI	Effect on PI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
HMG-CoA Reductase Inhibitors			
Atorvastatin	All PIs	DRV/r + atorvastatin 10 mg similar to atorvastatin 40 mg alone; FPV +/– RTV ↑ atorvastatin AUC 130%–153%; LPV/r ↑ atorvastatin AUC 488%; SQV/r ↑ atorvastatin AUC 79%; TPV/r ↑ atorvastatin AUC 836%	Use lowest possible starting dose with careful monitoring for toxicities or consider other HMG-CoA reductase inhibitors with less potential for interaction.
Lovastatin	All PIs	Significant ↑ lovastatin expected	**Contraindicated. Do not coadminister.**
Pitavastatin	ATV	pitavastatin AUC ↑ 31%; C_{max} ↑ 60% ATV: no significant effect	No dosage adjustment needed for ATV without RTV.
	All RTV-boosted PIs	↑ pitavastatin possible	**Do not coadminister** due to possible increase in pitavastatin concentration and increased risk of rhabdomyolitis.
Pravastatin	DRV/r	pravastatin AUC ↑ 81%	Use lowest possible starting dose with careful monitoring.
	LPV/r	pravastatin AUC ↑ 33%	No dose adjustment necessary
	SQV/r	pravastatin AUC ↓ 47%–50%	No dose adjustment necessary
Rosuvastatin	ATV/r	rosuvastatin AUC ↑ 213% and C_{max} ↑ 600%	Use lowest possible starting dose with careful monitoring or consider other HMG-CoA reductase inhibitors with less potential for interaction.
	DRV/r, FPV +/- RTV, SQV/r	↑ rosuvastatin possible	
	LPV/r	rosuvastatin AUC ↑ 108% and C_{max} ↑ 366%	
	TPV/r	rosuvastatin AUC ↑ 26% and C_{max} ↑ 123%	
Simvastatin	All PIs	Significant ↑ simvastatin level; SQV/r 400 mg/400 mg BID ↑ simvastatin AUC 3,059%	**Contraindicated. Do not coadminister**.
Narcotics/Treatment for Opioid Dependence			
Buprenorphine	ATV	buprenorphine AUC ↑ 93% norbuprenorphine AUC ↑ 76% ↓ ATV possible	**Do not coadminister buprenorphine with unboosted ATV.** Norbuprenorphine is an active metabolite of buprenorphine.
	ATV/r	buprenorphine AUC ↑ 66% norbuprenorphine AUC ↑ 105%	Monitor for sedation. Buprenorphine dose reduction may be necessary. Norbuprenorphine is an active metabolite of buprenorphine.
	DRV/r	buprenorphine: no significant effect norbuprenorphine AUC ↑ 46% and C_{min} ↑ 71%	No dose adjustment necessary. Clinical monitoring is recommended. Norbuprenorphine is an active metabolite of buprenorphine.
	LPV/r	No significant effect	No dose adjustment necessary
	TPV/r	buprenorphine: no significant effect norbuprenorphine AUC, C_{max}, and C_{min} ↓ 80% TPV C_{min} ↓ 19–40%	Consider monitoring TPV level. Norbuprenorphine is an active metabolite of buprenorphine.
Methadone	**RTV-boosted PIs**		
	ATV/r, DRV/r, FPV/r, LPV/r, SQV/r, TPV/r	ATV/r, DRV/r, FPV/r ↓ R-methadone AUC 16%–18%; LPV/r ↓ methadone AUC 26%–53%; SQV/r 1,000/100 mg BID ↓ R-methadone AUC 19%; TPV/r ↓ R-methadone AUC 48%	Opioid withdrawal unlikely but may occur. No adjustment in methadone usually required but monitor for opioid withdrawal and increase methadone dose as clinically indicated. (R-methadone is the active form of methadone.)

Table 15a. Drug Interactions between PIs and Other Drugs

Concomitant Drug	PI	Effect on PI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Methadone (continued)	**PIs without RTV**		
	ATV	No significant effect	No dosage adjustment necessary.
	FPV	No data with unboosted FPV APV ↓ R-methadone C_{min} 21%, AUC no significant change	Monitor and titrate methadone as clinically indicated. The interaction with FPV is presumed to be similar. (R-methadone is the active form of methadone.)
Phosphodiesterase Type 5 (PDE5) Inhibitors			
Sildenafil	All PIs	DRV/r + sildenafil 25 mg similar to sildenafil 100mg alone; RTV 500 mg BID ↑ sildenafil AUC 1,000%; SQV unboosted ↑ sildenafil AUC 210%	For treatment of erectile dysfunction Start with sildenafil 25 mg every 48 hours and monitor for adverse effects of sildenafil. For treatment of pulmonary arterial hypertension **Contraindicated**
Tadalafil	All PIs	RTV 200 mg BID ↑ tadalafil AUC 124%; TPV/r (1st dose) ↑ tadalafil AUC 133%; TPV/r steady state: no significant effect	For treatment of erectile dysfunction Start with tadalafil 5-mg dose and do not exceed a single dose of 10 mg every 72 hours. Monitor for adverse effects of tadalafil. For treatment of pulmonary arterial hypertension *In patients on a PI >7 days*: Start with tadalafil 20 mg once daily and increase to 40 mg once daily based on tolerability. *In patients on tadalafil who require a PI*: Stop tadalafil ≥24 hours prior to PI initiation, restart 7 days after PI initiation at 20 mg once daily, and increase to 40 mg once daily based on tolerability.
Vardenafil	All PIs	RTV 600 mg BID ↑ vardenafil AUC 49-fold	Start with vardenafil 2.5 mg every 72 hours and monitor for adverse effects of vardenafil.
Miscellaneous Interactions			
All PIs	Colchicine	All PIs	For treatment of gout flares Colchicine 0.6 mg x 1 dose, followed by 0.3 mg 1 hour later. Do not repeat dose for at least 3 days. *With FPV without RTV*: 1.2 mg x 1 dose and no repeat dose for at least 3 days For prophylaxis of gout flares Colchicine 0.3 mg once daily or every other day *With FPV without RTV*: colchicine 0.3 mg BID or 0.6 mg once daily or 0.3 mg once daily For treatment of familial Mediterranean fever Do not exceed colchicine 0.6 mg once daily or 0.3 mg BID. *With FPV without RTV*: Do not exceed 1.2 mg once daily or 0.6 mg BID. **Do not coadminister in patients with hepatic or renal impairment.**
	Salmeterol	↑ salmeterol possible	**Do not coadminister** because of potential increased risk of salmeterol-associated cardiovascular events, including QT prolongation, palpitations, and sinus tachycardia.
ATV/r LPV/r	Atovaquone/proguanil	ATV/r ↓ atovaquone AUC 46% and ↓ proguanil AUC 41% LPV/r ↓ atovaquone AUC 74% and ↓ proguanil AUC 38%	No dosage recommendation. Consider alternative drug for malaria prophylaxis, if possible.

Acronyms: APV = amprenavir, ARV = antiretroviral, ATV = atazanavir, ATV/r = atazanavir + ritonavir, AUC = area under the curve, BID = twice daily, CCB = calcium channel blocker, C_{max} = maximum plasma concentration, C_{min} = minimum plasma concentration, CNS = central nervous system, CrCl = creatinine clearance, CYP = cytochrome P, DRV/r = darunavir + ritonavir, ECG = electrocardiogram, FDA = Food and Drug Administration, FPV = fosamprenavir (FPV is a prodrug of APV), FPV/r = fosamprenavir + ritonavir, IDV = indinavir, IDV/r = indinavir + ritonavir, INR = international normalized ratio, LPV = lopinavir, LPV/r = lopinavir + ritonavir, NFV = nelfinavir, PDE5 = phosphodiesterase type 5, PI = protease inhibitor, PPI = proton pump inhibitor, RTV = ritonavir, SQV = saquinavir, SQV/r = saquinavir + ritonavir, TB = tuberculosis, TCA = tricyclic antidepressant, TID = three times a day, TPV = tipranavir, TPV/r = tipranavir + ritonavir, VPA = valproic acid.

Table 15b. Drug Interactions between NNRTIs* and Other Drugs (Updated January 10, 2011)

*DLV is not included in this table. Please refer to the FDA package insert for information regarding DLV drug interactions.

This table provides information relating to pharmacokinetic interactions between NNRTIs and non-ARV drugs. For interactions among ARV agents and for dosing recommendations, refer to **Table 16b**.

Concomitant Drug Class/Name	NNRTI	Effect on NNRTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Anticoagulants/Antiplatelets			
Warfarin	EFV, NVP	↑ or ↓ warfarin possible	Monitor INR and adjust warfarin dose accordingly.
	ETR	↑ warfarin possible	Monitor INR and adjust warfarin dose accordingly.
Clopidogrel	ETR	↓ activation of clopidogrel possible	ETR may prevent metabolism of clopidogrel (inactive) to its active metabolite. Avoid coadministration, if possible.
Anticonvulsants			
Carbamazepine **Phenobarbital** **Phenytoin**	EFV	carbamazepine + EFV: carbamazepine AUC ↓ 27% and EFV AUC ↓ 36% phenytoin + EFV: ↓ EFV and ↓ phenytoin possible	Monitor anticonvulsant and EFV levels or, if possible, use alternative anticonvulsant.
	ETR	↓ anticonvulsant and ETR possible	**Do not coadminister.** Consider alternative anticonvulsants.
	NVP	↓ anticonvulsant and NVP possible	Monitor anticonvulsant and NVP levels and virologic responses.
Antidepressants			
Bupropion	EFV	bupropion AUC ↓ 55%	Titrate bupropion dose based on clinical response.
Paroxetine	ETR	No significant effect	No dosage adjustment necessary.
Sertraline	EFV	sertraline AUC ↓ 39%	Titrate sertraline dose based on clinical response.
Antifungals			
Fluconazole	EFV	No significant effect	
	ETR	ETR AUC ↑ 86%	No dosage adjustment. Use with caution.
	NVP	NVP AUC ↑ 110%	Increased risk of hepatotoxicity possible with this combination Monitor NVP toxicity or use alternative antiretroviral agent.
Itraconazole	EFV	itraconazole and OH-itraconazole AUC, C_{max}, and C_{min} ↓ 35%–44%	Dose adjustments for itraconazole may be necessary. Monitor itraconazole level and antifungal response.
	ETR	↓ itraconazole possible ↑ ETR possible	Dose adjustments for itraconazole may be necessary. Monitor itraconazole level and antifungal response.
	NVP	↓ itraconazole possible ↑ NVP possible	Consider monitoring NNRTI and itraconazole levels and antifungal response.
Posaconazole	EFV	posaconazole AUC ↓ 50% ↔ EFV	Consider alternative antifungal if possible or consider monitoring posaconazole level if available.
	ETR	↑ ETR possible	No dosage adjustment necessary
Voriconazole	EFV	voriconazole AUC ↓ 77% EFV AUC ↑ 44%	**Contraindicated at standard doses**. Dose: voriconazole 400 mg BID, EFV 300 mg daily
	ETR	voriconazole AUC ↑ 14% ETR AUC ↑ 36%	No dosage adjustment; use with caution. Consider monitoring voriconazole level.
	NVP	↓ voriconazole possible ↑ NVP possible	Monitor for toxicity and antifungal response and/or voriconazole level.
Antimycobacterials			
Clarithromycin	EFV	clarithromycin AUC ↓ 39%	Monitor for efficacy or consider alternative agent, such as azithromycin, for MAC prophylaxis and treatment.
	ETR	clarithromycin AUC ↓ 39% OH-clarithromycin AUC ↑ 21% ETR AUC ↑ 42%	Consider alternative agent, such as azithromycin, for MAC prophylaxis and treatment.
	NVP	clarithromycin AUC ↓ 31% OH-clarithromycin AUC ↑ 42%	Monitor for efficacy or use alternative agent, such as azithromycin, for MAC prophylaxis and treatment.

Table 15b. Drug Interactions between NNRTIs* and Other Drugs
Page 2 of 3

Concomitant Drug Class/Name	NNRTI	Effect on NNRTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antimycobacterials (continued)			
Rifabutin	EFV	rifabutin ↓ 38%	Dose: rifabutin 450–600 mg once daily or 600 mg three times a week if EFV is not coadministered with a PI.
	ETR	rifabutin and metabolite AUC ↓ 17% ETR AUC ↓ 37%	**If ETR is used with an RTV-boosted PI, rifabutin should not be coadministered.** Dose: rifabutin 300 mg once daily **if** ETR is not coadministered with an RTV-boosted PI.
	NVP	rifabutin AUC ↑ 17% and metabolite AUC ↑ 24% NVP C_{min} ↓ 16%	No dosage adjustment necessary. Use with caution.
Rifampin	EFV	EFV AUC ↓ 26%	Maintain EFV dose at 600 mg once daily and monitor for virologic response. Some clinicians suggest EFV 800 mg dose in patients >60kg.
	ETR	Significant ↓ ETR possible	**Do not coadminister.**
	NVP	NVP ↓ 20%–58%	**Do not coadminister.**
Benzodiazepines			
Alprazolam	EFV, ETR, NVP	No data	Monitor for therapeutic efficacy of alprazolam.
Diazepam	ETR	↑ diazepam possible	Decreased dose of diazepam may be necessary.
Lorazepam	EFV	lorazepam C_{max} ↑ 16%, AUC no significant effect	No dosage adjustment necessary
Midazolam	EFV	Significant↑ midazolam expected	**Do not coadminister with oral midazolam.** Parenteral midazolam can be used with caution as a single dose and can be given in a monitored situation for procedural sedation.
Triazolam	EFV	Significant ↑ triazolam expected	**Do not coadminister.**
Cardiac Medications			
Dihydropyridine calcium channel blockers (CCBs)	EFV, NVP	↓ CCBs possible	Titrate CCB dose based on clinical response.
Diltiazem	EFV	diltiazem AUC ↓ 69%	Titrate diltiazem dose based on clinical response.
	NVP	↓ diltiazem possible	
Corticosteroids			
Dexamethasone	ETR*	↓ ETR possible	Use systemic dexamethasone with caution or consider alternative corticosteroid for long-term use.
Herbal Products			
St. John's wort	EFV, ETR, NVP	↓ NNRTI	**Do not coadminister.**
Hormonal Contraceptives			
Hormonal contraceptives	EFV	ethinyl estradiol ↔ levonorgestrel AUC ↓ 83% norelgestromin AUC ↓ 64%	Use alternative or additional methods. Norelgestromin and levonorgestrel are active metabolites of norgestimate.
	ETR	ethinyl estradiol AUC ↑ 22% norethindrone: no significant effect	No dosage adjustment necessary.
	NVP	ethinyl estradiol AUC ↓ 20% norethindrone AUC ↓ 19%	Use alternative or additional methods.
		depomedroxyprogesterone acetate: no significant change	No dosage adjustment necessary
Levonorgestrel	EFV	levonorgestrel AUC ↓ 58%	Effectiveness of emergency postcoital contraception may be diminished.
HMG-CoA Reductase Inhibitors			
Atorvastatin	EFV, ETR, NVP	atorvastatin AUC ↓ 32%–43% with EFV, ETR	Adjust atorvastatin according to lipid responses, not to exceed the maximum recommended dose.
Fluvastatin	ETR	↑ fluvastatin possible	Dose adjustments for fluvastatin may be necessary.

** Error corrected January 18, 2011*

Table 15b. Drug Interactions between NNRTIs* and Other Drugs
Page 3 of 3

Concomitant Drug Class/Name	NNRTI	Effect on NNRTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
HMG-CoA Reductase Inhibitors (continued)			
Lovastatin **Simvastatin**	EFV	simvastatin AUC ↓ 68%	Adjust simvastatin dose according to lipid responses, not to exceed the maximum recommended dose. If used with RTV-boosted PI, simvastatin and lovastatin should be avoided.
	ETR, NVP	↓ lovastatin possible ↓ simvastatin possible	Adjust lovastatin or simvastatin dose according to lipid responses, not to exceed the maximum recommended dose. If used with RTV-boosted PI, simvastatin and lovastatin should be avoided.
Pitavastatin	EFV, ETR, NVP	No data	No dosage recommendation
Pravastatin **Rosuvastatin**	EFV	pravastatin AUC ↓ 44% rosuvatatin: no data	Adjust statin dose according to lipid responses, not to exceed the maximum recommended dose.
	ETR	No significant effect expected with either pravastatin or rosuvastatin	No dosage adjustment necessary
Narcotics/Treatment for Opioid Dependence			
Buprenorphine	EFV	buprenorphine AUC ↓ 50% norbuprenorphine AUC ↓ 71%	No withdrawal symptoms reported. No dosage adjustment recommended, but monitor for withdrawal symptoms.
	NVP	No significant effect	No dosage adjustment necessary
Methadone	EFV	methadone AUC ↓ 52%	Opioid withdrawal common; increased methadone dose often necessary.
	ETR	No significant effect	No dosage adjustment necessary
	NVP	methadone AUC ↓ 41% NVP: no significant effect	Opioid withdrawal common; increased methadone dose often necessary.
Phosphodiesterase Type 5 (PDE5) Inhibitors			
Sildenafil	ETR	sildenafil AUC ↓ 57%	May need to increase sildenafil dose based on clinical effect.
Tadalafil	ETR	↓ tadalafil possible	May need to increase tadalafil dose based on clinical effect.
Vardenafil	ETR	↓ vardenafil possible	May need to increase vardenafil dose based on clinical effect.
Miscellaneous Interactions			
Atovaquone/proguanil	EFV	↓ atovaquone AUC 75% ↓ progaunil AUC 43%	No dosage recommendation. Consider alternative drug for malaria prophylaxis, if possible.

Acronyms: ARV = antiretroviral, AUC = area under the curve, CCB = calcium channel blocker, C_{max} = maximum plasma concentration, C_{min} = minimum plasma concentration, DLV = delavirdine, EFV = efavirenz, ETR = etravirine, FDA = Food and Drug Administration, INR = international normalized ratio, MAC = *Mycobacterium avium* complex, NNRTI = non-nucleoside reverse transcriptase inhibitor, NVP = nevirapine, OH-clarithromycin = active metabolite of clarithromycin, PDE5 = phosphodiesterase type 5, PI = protease inhibitor

Table 15c. Drug Interactions between NRTIs and Other Drugs (Including ARV Agents)
(Updated January 10, 2011)

Concomitant Drug Class/Name	NRTI	Effect on NRTI or Concomitant Drug Concentrations	Dosage Recommendations and Clinical Comments
Antivirals			
Ganciclovir Valganciclovir	TDF	No data	Serum concentrations of these drugs and/or TDF may be increased. Monitor for dose-related toxicities.
	ZDV	No significant pharmacokinetic effects	Potential increase in hematologic toxicities
Ribavirin	ddI	↑ intracellular ddI	**Contraindicated. Do not coadminister.** Fatal hepatic failure and other ddI-related toxicities have been reported with coadministration.
	ZDV	Ribavirin inhibits phosphorylation of ZDV.	Avoid coadministration if possible or closely monitor virologic response and hematologic toxicities.
Integrase Inhibitor			
RAL	TDF	RAL AUC ↑ 49%, C_{max} ↑ 64%	No dosage adjustment necessary
Narcotics/Treatment for Opioid Dependence			
Buprenorphine	3TC, ddI, TDF, ZDV	No significant effect	No dosage adjustment necessary
Methadone	ABC	methadone clearance ↑ 22%	No dosage adjustment necessary
	d4T	d4T AUC ↓ 23% and C_{max} ↓ 44%	No dosage adjustment necessary
	ZDV	ZDV AUC ↑ 29%–43%	Monitor for ZDV-related adverse effects.
NRTIs			
ddI	d4T	No significant PK interaction	**Avoid coadministration**. Additive toxicities of peripheral neuropathy, lactic acidosis, and pancreatitis seen with this combination.
	TDF	ddI-EC AUC and C_{max} ↑ 48%–60%	**Avoid coadministration**.
Other			
Allopurinol	ddI	ddI AUC ↑ 113% ddI AUC ↑ 312% with renal impairment	**Contraindicated. Do not coadminister.** Potential for increased ddI-associated toxicities.
PIs			
ATV	ddI	With ddI-EC + ATV (with food): ddI AUC ↓ 34%; ATV no change	Administer ATV with food 2 hours before or 1 hour after didanosine.
	TDF	ATV AUC↓ 25% and C_{min} ↓ 23%–40% (higher C_{min} with RTV than without) TDF AUC ↑ 24%–37%	Dose: ATV/r 300/100 mg daily coadministered with TDF 300 mg daily. Avoid concomitant use without RTV. If using TDF and H_2 receptor antagonist in ART-experienced patients, use ATV/r 400 mg/100 mg daily. Monitor for TDF-associated toxicity.
	ZDV	ZDV C_{min} ↓ 30%, no change in AUC	Clinical significance unknown.
DRV/r	TDF	TDF AUC↑ 22%, C_{max} ↑ 24% and C_{min} ↑ 37%	Clinical significance unknown. Monitor for TDF toxicity.
LPV/r	TDF	LPV/r AUC ↓ 15% TDF AUC ↑ 34%	Clinical significance unknown. Monitor for TDF toxicity.
TPV/r	ABC	ABC ↓ 35%–44% with TPV/r 1,250/100 mg BID	Appropriate doses for this combination have not been established.
	ddI	ddI-EC ↓ 10% and TPV C_{min} ↓34% with TPV/r 1,250/100 mg BID	Separate doses by at least 2 hours.
	ZDV	ZDV AUC ↓ 31%–43% and C_{max} ↓ 46%–51% with TPV/r 1,250/100 mg BID	Appropriate doses for this combination have not been established.

Acronyms: 3TC = lamivudine, ABC = abacavir, ARV = antiretroviral, ATV = atazanavir, AUC = area under the curve, BID = twice daily, C_{max} = maximum plasma concentration, C_{min} = minimum plasma concentration, d4T = stavudine, ddI = didanosine, DRV/r = darunavir/ritonavir, EC = enteric coated, LPV/r = lopinavir/ritonavir, NRTI = nucleoside reverse transcriptase inhibitor, PI = protease inhibitor, PK = pharmacokinetic, RAL = raltegravir, TDF = tenofovir, TPV/r = tipranavir/ritonavir, ZDV = zidovudine.

Table 15d. Drug Interactions between CCR5 Antagonist and Other Drugs (Updated January 10, 2011)

This table provides information relating to pharmacokinetic interactions between MVC and non-ARV drugs. For interactions among ARV agents and for dosing recommendations, please refer to **Table 16b**.

Concomitant Drug Class/Name	CCR5 Antagonist	Effect on CCR5 Antagonist or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Anticonvulsants			
Carbamazepine **Phenobarbital** **Phenytoin**	MVC	↓ MVC possible	If used without a strong CYP3A inhibitor, use MVC 600 mg BID or an alternative antiepileptic agent.
Antifungal			
Itraconazole	MVC	↑ MVC possible	Dose: MVC 150 mg BID
Ketoconazole	MVC	MVC AUC ↑ 400%	Dose: MVC 150 mg BID
Voriconazole	MVC	↑ MVC possible	Consider dose reduction to MVC 150 mg BID
Antimycobacterials			
Clarithromycin	MVC	↑ MVC possible	Dose: MVC 150 mg BID
Rifabutin	MVC	↓ MVC possible	If used without a strong CYP3A inducer or inhibitor, use MVC 300 mg BID. If used with a strong CYP3A inhibitor, use MVC 150 mg BID.
Rifampin	MVC	MVC AUC ↓ 64%	Coadministration is not recommended. If coadministration is necessary use MVC 600 mg BID. If coadministered with a strong CYP3A inhibitor, use MVC 300 mg BID.
Herbal Products			
St. John's wort	MVC	↓ MVC possible	Coadministration is not recommended.
Hormonal Contraceptives			
Hormonal contraceptives	MVC	No significant effect on ethinyl estradiol or levonorgestrel	Safe to use in combination
Narcotics/Treatment for Opioid Dependence			
Methadone	MVC	No data	

Acronyms: ARV = antiretroviral, AUC = area under the curve, BID = twice daily, CYP = cytochrome P, MVC = maraviroc

Table 15e. Drug Interactions between Integrase Inhibitor and Other Drugs (Updated January 10, 2011)

Concomitant Drug Class/Name	Integrase Inhibitor	Effect on Integrase Inhibitor or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Acid Reducers			
Omeprazole	RAL	RAL AUC ↑ 212%, C_{max} ↑ 315%, and C_{min} ↑ 46%	No dosage adjustment recommended
Antimycobacterials			
Rifabutin	RAL	RAL AUC ↑ 19%, C_{max} ↑ 39%, and C_{min} ↓ 20%	No dosage adjustment recommended
Rifampin	RAL	RAL AUC ↓ 40% and C_{min} ↓ 61% with RAL 400 mg Rifampin with RAL 800 mg BID compared with RAL 400 mg BID alone: RAL AUC ↑ 27% and C_{min} ↓ 53%	Dose: RAL 800 mg BID Monitor closely for virologic response.
Hormonal Contraceptives			
Hormonal contraceptives	RAL	No clinically significant effect	Safe to use in combination
Narcotics/Treatment for Opioid Dependence			
Methadone	RAL	No significant effect	No dosage adjustment necessary

Acronyms: AUC = area under the curve, BID = twice daily, C_{max} = maximum plasma concentration, C_{min} = minimum plasma concentration, RAL = raltegravir

Table 16a. Interactions Among PIs* (Updated January 10, 2011)

*NFV and IDV are not included in this table. Please refer to the FDA package insert for information regarding NFV and IDV drug interactions.

Drug Affected	ATV	FPV	LPV/r	RTV	SQV	TPV
DRV	Dose: ATV 300 mg once daily + DRV 600 mg BID + RTV 100 mg BID	No data	**Should not be coadministered because doses are not established**	Dose: (DRV 600 mg + RTV 100 mg) BID or (DRV 800 mg + RTV 100 mg) once daily	**Should not be coadministered because doses are not established**	No data
FPV	Dose: Insufficient data	•	**Should not be coadministered because doses are not established**	Dose: (FPV 1,400 mg + RTV 100 mg or 200 mg) once daily; or (FPV 700 mg + RTV 100 mg) BID	Dose: Insufficient data	**Should not be coadministered because doses are not established**
LPV/r	Dose: ATV 300 mg once daily + LPV/r 400/100 mg BID	See LPV/r + FPV cell	•	LPV is coformulated with RTV as Kaletra.	See LPV/r + SQV cell	**Should not be coadministered because doses are not established**
RTV	Dose: (ATV 300 mg + RTV 100 mg) once daily	See RTV + FPV cell	LPV is coformulated with RTV as Kaletra.	•	Dose: (SQV 1,000 mg + RTV 100 mg) BID	Dose: (TPV 500 mg + RTV 200 mg) BID
SQV	Dose: Insufficient data	Dose: Insufficient data	Dose: SQV 1,000 mg BID + LPV/r 400/100 mg BID	See SQV + RTV cell	•	**Should not be coadministered because doses are not established**

Acronyms: ATV = atazanavir, BID = twice daily, DRV = darunavir, FDA = Food and Drug Administration, FPV = fosamprenavir, IDV = indinavir, LPV/r = lopinavir/ritonavir, NFV = nelfinavir, PI = protease inhibitor, RTV = ritonavir, SQV = saquinavir, TPV = tipranavir

Table 16b. Interactions between NNRTIs*, MVC, RAL, and PIs* (Updated January 10, 2011)

*DLV, IDV, and NFV are not included in this table. Refer to the FDA package insert for information regarding DLV, IDV, and NFV drug interactions.

		EFV	ETR	NVP	MVC	RAL
ATV	**PK data**	With unboosted ATV ATV: AUC ↓ 74% EFV: no significant change With (ATV 300 mg + RTV 100 mg) once daily with food ATV concentrations similar to unboosted ATV without EFV	With unboosted ATV ETR: AUC ↑ 50%, C_{max} ↑ 47%, and C_{min} ↑ 58% ATV: AUC ↓ 17% and C_{min} ↓ 47% With (ATV 300 mg + RTV 100 mg) once daily ETR: AUC, C_{max}, and C_{min} ↑ approximately 30% ATV: AUC ↓ 14% and C_{min} ↓ 38%	With (ATV 300 mg + RTV 100 mg) once daily ATV: AUC ↓ 42% and C_{min} ↓ 72% NVP: AUC ↑ 25%	With unboosted ATV MVC: AUC ↑ 257% With (ATV 300 mg + RTV 100 mg) once daily MVC: AUC ↑ 388%	With unboosted ATV RAL: AUC ↑ 72% With (ATV 300 mg + RTV 100 mg) once daily RAL: AUC ↑ 41%
	Dose	**Do not coadminister with unboosted ATV.** In ART-naïve patients (ATV 400 mg + RTV 100 mg) once daily **Do not coadminister in ART-experienced patients.**	**Do not coadminister with ATV +/− RTV.**	**Do not coadminister with ATV +/− RTV.**	MVC 150 mg BID with ATV +/− RTV	Standard
DRV – always use with RTV	**PK data**	With (DRV 300 mg + RTV 100 mg) BID DRV: AUC ↓ 13%, C_{min} ↓ 31% EFV: AUC ↑ 21%	ETR 100 mg BID with (DRV 600 mg + RTV 100 mg) BID DRV: no significant change ETR: AUC ↓ 37%, C_{min} ↓ 49%	With (DRV 400 mg + RTV 100 mg BID) DRV: AUC ↑ 24%[†] NVP: AUC ↑ 27% and C_{min} ↑ 47%	With (DRV 600 mg + RTV 100 mg) BID MVC: AUC ↑ 305% With (DRV 600 mg + RTV 100 mg) BID + ETR MVC: AUC ↑ 210%	With (DRV 600 mg + RTV 100 mg) BID RAL: AUC ↓ 29% and C_{min} ↑ 38%
	Dose	Clinical significance unknown. Use standard doses and monitor closely. Consider monitoring levels.	Standard (ETR 200 mg BID) Despite decreased ETR, safety and efficacy established with this combination in a clinical trial	Standard	MVC 150 mg BID	Standard
EFV	**PK data**	•	↓ ETR possible	NVP: no significant change EFV: AUC ↓ 22%	MVC: AUC ↓ 45%	EFV: AUC ↓ 36%
	Dose		**Do not coadminister.**	**Do not coadminister.**	MVC: 600 mg BID	Standard
ETR	**PK data**	↓ ETR possible	•	↓ ETR possible	MVC: AUC ↓ 53%, C_{max} ↓ 60%	ETR: C_{min} ↓ 17% RAL: C_{min} ↓ 34%
	Dose	**Do not coadminister.**		**Do not coadminister**.	MVC 600 mg BID	Standard
FPV	**PK data**	With (FPV 1,400 mg + RTV 200 mg) once daily APV: C_{min} ↓ 36%	With (FPV 700 mg + RTV 100 mg) BID APV: AUC ↑ 69%, C_{min} ↑ 77%	With unboosted FPV 1,400 mg BID APV: AUC ↓ 33% NVP: AUC ↑ 29% With (FPV 1,400 mg + RTV 100 mg) BID NVP: C_{min} ↑ 19%	Unknown; ↑ MVC possible	No data
	Dose	(FPV 1,400 mg + RTV 300 mg) once daily; or (FPV 700 mg + RTV 100 mg) BID EFV standard	**Do not coadminister with FPV +/− RTV.**	(FPV 700 mg + RTV 100 mg) BID NVP standard	MVC 150 mg BID	Standard
LPV/r	**PK data**	With LPV/r tablets 500/125 mg BID[‡] + EFV 600 mg LPV levels similar to LPV/r 400/100 mg BID without EFV	With LPV/r tablets ETR: levels ↓ 30%–45% (comparable to the decrease with DRV/r) LPV: levels ↓ 13%–20%	With LPV/r capsules LPV: AUC ↓ 27% and C_{min} ↓51%	MVC: AUC ↑ 295% With LPV/r + EFV MVC: AUC ↑153%	↓ RAL ↔ LPV/r
	Dose	LPV/r tablets 500/125 mg[‡] BID; LPV/r oral solution 533/133 mg BID EFV standard	Standard	LPV/r tablets 500/125 mg[‡] BID; LPV/r oral solution 533/133 mg BID NVP standard	MVC 150 mg BID	Standard

		EFV	ETR	NVP	MVC	RAL
NVP	**PK data**	NVP: no significant change EFV: AUC ↓ 22%	↓ ETR possible	•	No significant change	No data
	Dose	**Do not coadminister.**	**Do not coadminister.**		Without PI MVC 300 mg BID With PI (except TPV/r) MVC 150 mg BID	Standard
RAL	**PK data**	RAL: AUC ↓ 36%	ETR: C_{min} ↑ 17% RAL: C_{min} ↓ 34%	No data	RAL: AUC ↓ 37% MVC: AUC ↓ 21%	•
	Dose	Standard	Standard	No data	Standard	
RTV	**PK data**	Refer to information for boosted PI	Refer to information for boosted PI	Refer to information for boosted PI	With RTV 100 mg BID MVC: AUC ↑ 161%	With RTV 100 mg BID RAL: AUC ↓ 16%
	Dose				MVC 150 mg BID	Standard
SQV - always use with RTV	**PK data**	With SQV 1,200 mg TID SQV: AUC ↓ 62% EFV: AUC ↓ 12%	With (SQV 1,000 mg + RTV 100 mg) BID SQV: AUC unchanged ETR: AUC ↓ 33%, C_{min} ↓ 29% Reduced ETR levels similar to reduction with DRV/r	With SQV 600 mg TID SQV: AUC ↓ 38% NVP: no significant change	With (SQV 1,000 mg + RTV 100 mg) BID MVC: AUC ↑ 877% With (SQV 1,000 mg + RTV 100 mg) BID + EFV MVC: AUC ↑ 400%	No data
	Dose	(SQV 1,000 mg + RTV 100 mg) BID	(SQV 1,000 mg + RTV 100 mg) BID	(SQV 1,000 mg + RTV 100mg) BID	MVC 150 mg BID	Standard
TPV – always use with RTV	**PK data**	With (TPV 500 mg + RTV 100 mg) BID TPV: AUC ↓ 31%, C_{min} ↓ 42% EFV: no significant change With (TPV 750 mg + RTV 200 mg) BID TPV: no significant change EFV: no significant change	With (TPV 500 mg + RTV 200 mg) BID ETR: AUC ↓ 76%, C_{min} ↓ 82% TPV: AUC ↑ 18%, C_{min} ↑ 24%	With (TPV 250 mg + RTV 200 mg) BID and with (TPV 750 mg + RTV 100 mg) BID NVP: no significant change TPV: no data	With (TPV 500 mg + RTV 200 mg) BID MVC: no significant change in AUC TPV: no data	With (TPV 500 mg + RTV 200 mg) BID RAL: AUC ↓ 24%
	Dose	Standard	**Do not coadminister.**	Standard	MVC 300 mg BID	Standard

† Based on between-study comparison.

‡Use a combination of two LPV/r 200 mg/50 mg tablets + one LPV/r 100 mg/25 mg tablet to make a total dose of LPV/r 500 mg/125* mg. *(* Error corrected January 18, 2011)*

Acronyms: AUC = area under the curve, ATV = atazanavir, BID = twice daily, C_{max} = maximum plasma concentration, C_{min} = minimum plasma concentration, DLV = delavirdine, DRV = darunavir, EFV = efavirenz, ETR = etravirine, FDA = Food and Drug Administration, FPV = fosamprenavir, IDV = indinavir, LPV/r = lopinavir/ritonavir, MVC = maraviroc, NFV = nelfinavir, NNRTI = non-nucleoside reverse transcriptase inhibitor, NVP = nevirapine, PI = protease inhibitor, PK = pharmacokinetic, RAL = raltegravir, RTV = ritonavir, SQV = saquinavir, TID = three times a day, TPV = tipranavir

Appendix B, Table 1. Characteristics of Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

(Updated January 10, 2011)

Generic Name (abbreviation)/ Trade Name	Formulations	Dosing Recommendations (For dosage adjustment in renal or hepatic insufficiency, see Appendix B, Table 7.)	Elimination	Serum/ Intracellular Half-lives	Adverse Events (Also see Table 13)
Abacavir (ABC)/ Ziagen **Also available as**:	Ziagen - 300-mg tablets - 20-mg/mL oral solution	Ziagen 300 mg BID or 600 mg once daily Take without regard to meals	Metabolized by alcohol dehydrogenase and glucuronyl transferase Renal excretion of metabolites 82% Dosage adjustment for ABC recommended in patients with hepatic insufficiency (See Appendix B, Table 7.)	1.5 hrs/ 12–26 hrs	• *Hypersensitivity reactions (HSR)*: Patients positive for HLA-B*5701 are at highest risk. HLA screening should be done prior to initiation of ABC. Rechallenge is not recommended. • Symptoms of HSR may include fever, rash, nausea, vomiting, diarrhea, abdominal pain, malaise, or fatigue or respiratory symptoms such as sore throat, cough, or shortness of breath. • Some cohort studies suggest increased risk of myocardial infarction (MI) with recent or current use of ABC, but this risk is not substantiated in other studies.
Trizivir ABC with ZDV+3TC	Trizivir ABC 300 mg + ZDV 300 mg + 3TC 150 mg	Trizivir 1 tablet BID			
Epzicom ABC with 3TC	Epzicom ABC 600 mg + 3TC 300 mg	Epzicom 1 tablet once daily			
Didanosine (ddI)/ Videx EC (generic available; dose same as Videx EC)	Videx EC 125-, 200-, 250-, 400-mg capsules Buffered tablets (non-EC) no longer available Videx 10-mg/mL oral solution	**Body weight ≥60kg**: 400 mg once daily* *With TDF*: 250 mg once daily **Body weight <60kg**: 250 mg once daily* *With TDF*: 200 mg once daily Take 1/2 hour before or 2 hours after a meal *Preferred dosing with oral solution is BID (total daily dose divided into 2 doses)	Renal excretion 50% Dosage adjustment in renal insufficiency recommended (See Appendix B, Table 7.)	1.5 hrs/ >20 hrs	• Pancreatitis • Peripheral neuropathy • Retinal changes, optic neuritis • Lactic acidosis with hepatic steatosis +/- pancreatitis (rare but potentially life-threatening toxicity) • Nausea, vomiting • Potential association with noncirrhotic portal hypertension, some cases presented with esophageal varices • One cohort study suggested increased risk of MI with recent or current use of ddI, but this risk is not substantiated in other studies. • Insulin resistance/diabetes mellitus
Emtricitabine (FTC)/ Emtriva **Also available as:**	Emtriva - 200-mg hard gelatin capsule - 10-mg/mL oral solution	Emtriva *Capsule*: 200 mg once daily *Oral solution*: 240 mg (24 mL) once daily Take without regard to meals	Renal excretion 86% Dosage adjustment in renal insufficiency recommended (See Appendix B, Table 7.)	10 hrs/ >20 hrs	• Minimal toxicity • Hyperpigmentation/skin discoloration • Severe acute exacerbation of hepatitis may occur in HBV-coinfected patients who discontinue FTC.
Atripla FTC with EFV+TDF	Atripla FTC 200 mg + EFV 600 mg + TDF 300 mg	Atripla 1 tablet at or before bedtime Take on an empty stomach to reduce side effects			
Truvada FTC with TDF	Truvada FTC 200 mg + TDF 300 mg	Truvada 1 tablet once daily			

Appendix B, Table 1. Characteristics of Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

Generic Name (abbreviation)/ Trade Name	Formulations	Dosing Recommendations (For dosage adjustment in renal or hepatic insufficiency, see Appendix B, Table 7.)	Elimination	Serum/ Intracellular Half-lives	Adverse Events (Also see Table 13)
Lamivudine (3TC)/ Epivir **Also available as:**	Epivir • 150-, 300-mg tablets • 10-mg/mL oral solution	Epivir 150 mg BID or 300 mg once daily Take without regard to meals	Renal excretion 70% Dosage adjustment in renal insufficiency recommended (See Appendix B, Table 7.)	5–7 hrs/ 18–22 hrs	• Minimal toxicity • Severe acute exacerbation of hepatitis may occur in HBV-coinfected patients who discontinue 3TC.
Combivir 3TC with ZDV	Combivir 3TC 150 mg + ZDV 300 mg	Combivir 1 tablet BID			
Epzicom 3TC with ABC	Epzicom 3TC 300 mg + ABC 600 mg	Epzicom 1 tablet once daily			
Trizivir 3TC with ZDV+ABC	Trizivir 3TC 150 mg + ZDV 300 mg + ABC 300 mg	Trizivir 1 tablet BID			
Stavudine (d4T)/ Zerit	Zerit • 15-, 20-, 30-, 40-mg capsules • 1-mg/mL oral solution	**Body weight ≥60 kg**: 40 mg BID **Body weight <60 kg**: 30 mg BID* Take without regard to meals *WHO recommends 30 mg BID dosing regardless of body weight.	Renal excretion 50% Dosage adjustment in renal insufficiency recommended (See Appendix B, Table 7.)	1 hr/ 7.5 hrs	• Peripheral neuropathy • Lipoatrophy • Pancreatitis • Lactic acidosis/severe hepatomegaly with hepatic steatosis (rare but potentially life-threatening toxicity) • Hyperlipidemia • Insulin resistance/diabetes mellitus • Rapidly progressive ascending neuromuscular weakness (rare)
Tenofovir Disoproxil Fumarate (TDF)/ Viread **Also available as:**	Viread 300-mg tablet	Viread 1 tablet once daily Take without regard to meals	Renal excretion Dosage adjustment in renal insufficiency recommended (See Appendix B, Table 7.)	17 hrs/ >60 hrs	• Renal insufficiency, Fanconi syndrome • Osteomalacia • Potential decrease in bone mineral density • Severe acute exacerbation of hepatitis may occur in HBV-coinfected patients who discontinue TDF. • Asthenia, headache, diarrhea, nausea, vomiting, and flatulence
Atripla TDF with EFV+FTC	Atripla TDF 300 mg + EFV 600 mg + FTC 200 mg	Atripla 1 tablet at or before bedtime Take on an empty stomach to reduce side effects			
Truvada TDF with FTC	Truvada TDF 300 mg + FTC 200 mg	Truvada 1 tablet once daily Take without regard to meals			
Zidovudine (ZDV)/ Retrovir (generic available; dose same as retrovir) **Also available as:**	Retrovir • 100-mg capsules • 300-mg tablets • 10-mg/mL intravenous solution • 10-mg/mL oral solution	Retrovir 300 mg BID or 200 mg TID Take without regard to meals	Metabolized to GAZT Renal excretion of GAZT Dosage adjustment in renal insufficiency recommended (See Appendix B, Table 7.)	1.1 hrs/ 7 hrs	• Bone marrow suppression: macrocytic anemia or neutropenia • Nausea, vomiting, headache, insomnia, asthenia • Nail pigmentation • Lactic acidosis/severe hepatomegaly with hepatic steatosis (rare but potentially life-threatening toxicity) • Hyperlipidemia • Insulin resistance/diabetes mellitus • Lipoatrophy • Myopathy
Combivir ZDV with 3TC	Combivir ZDV 300 mg + 3TC 150 mg	Combivir 1 tablet BID			
Trizivir ZDV with 3TC+ABC	Trizivir ZDV 300 mg + 3TC 150 mg + ABC 300 mg	Trizivir 1 tablet BID			

Appendix B, Table 2. Characteristics of Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) (Updated January 10, 2011)

Generic Name (abbreviation)/ Trade Name	Formulations	Dosing Recommendations (For dosage adjustment in renal or hepatic insufficiency, see Appendix B, Table 7.)	Elimination	Serum Half-life	Adverse Events (Also see Table 13)
Delavirdine (DLV)/ Rescriptor	100-, 200-mg tablets	400 mg TID (Four 100-mg tablets can be dispersed in >3 oz. of water to produce a slurry; 200-mg tablets should be taken as intact tablets.) Take without regard to meals Separate dose from antacids by 1 hour	CYP3A4 substrate and inhibitor; 51% excreted in urine (<5% unchanged) and 44% in feces	5.8 hrs	• Rash* • Increased transaminase levels • Nausea, headache
Efavirenz (EFV)/ Sustiva **Also available as**:	• 50-, 200-mg capsules • 600-mg tablets	600 mg once daily at or before bedtime Take on an empty stomach to reduce side effects	Metabolized by CYPs 2B6 and 3A4 CYP3A4 mixed inducer/ inhibitor (more an inducer than an inhibitor)	40–55 hrs	• Rash* • Neuropsychiatric symptoms† • Increased transaminase levels • Hyperlipidemia • False-positive results reported with some cannabinoid and benzodiazepine screening assays • Teratogenic in nonhuman primates and potentially teratogenic in humans
Atripla EFV with FTC + TDF	Atripla EFV 600 mg + FTC 200 mg + TDF 300 mg	Atripla 1 tablet once daily at or before bedtime			
Etravirine (ETR)/ Intelence	• 100-mg tablets • 200-mg tablets	200 mg BID Take following a meal	CYP3A4, 2C9, and 2C19 substrate 3A4 inducer; 2C9 and 2C19 inhibitor	41 +/– 20 hrs	• Rash, including Stevens-Johnson syndrome* • Hypersensitivity reactions (HSRs) have been reported, characterized by rash, constitutional findings, and sometimes organ dysfunction, including hepatic failure • Nausea
Nevirapine (NVP)/ Viramune	• 200-mg tablets • 50-mg/5-mL oral suspension	200 mg once daily for 14 days (lead-in period); thereafter, 200 mg BID Take without regard to meals Repeat lead-in period if therapy is discontinued for >7 days In patients who develop mild to moderate rash without constitutional symptoms, continue lead-in period until rash resolves but no longer than 28 days total.	CYP450 substrate, inducer of 3A4 and 2B6; 80% excreted in urine (glucuronidated metabolites, <5% unchanged); 10% in feces	25–30 hrs	• Rash, including Stevens-Johnson syndrome* • Symptomatic hepatitis, including fatal hepatic necrosis, has been reported‡

* During clinical trials, NNRTI was discontinued because of rash among 7% of NVP-treated, 4.3% of DLV-treated, 1.7% of EFV-treated, and 2% of ETR-treated patients. Rare cases of Stevens-Johnson syndrome have been reported with all NNRTIs; the highest incidence was seen with NVP.

† Adverse events can include dizziness, somnolence, insomnia, abnormal dreams, confusion, abnormal thinking, impaired concentration, amnesia, agitation, depersonalization, hallucinations, and euphoria. Approximately 50% of patients receiving EFV may experience any of these symptoms. Symptoms usually subside spontaneously after 2–4 weeks, but may necessitate discontinuation of EFV in a small percentage of patients.

‡ Symptomatic, sometimes serious, and even fatal hepatic events (accompanied by rash in approximately 50% of cases) occur at significantly higher frequency in ARV-naïve female patients with pre-NVP CD4 counts >250 cells/mm^3 or in ARV-naïve male patients with pre-NVP CD4 counts >400 cells/mm^3. NVP should not be initiated in these patients unless the benefit clearly outweighs the risk. This toxicity has not been observed when NVP is given as single doses to mothers or infants for prevention of mother-to-child transmission of HIV.

Appendix B, Table 3. Characteristics of Protease Inhibitors (PIs) (Updated January 10, 2011)

Generic Name (abbreviation)/ Trade Name	Formulations	Dosing Recommendations (For dosage adjustment in hepatic insufficiency, see Appendix B, Table 7)	Elimination	Serum Half-life	Storage	Adverse Events (Also see Table 13)
Atazanavir (ATV)/ Reyataz	100-, 150-, 200-, 300-mg capsules	ARV-naïve patients: 400 mg once daily or (ATV 300 mg + RTV 100 mg) once daily With TDF or for ARV-experienced patients: (ATV 300 mg + RTV 100 mg) once daily With EFV in ARV-naïve patients: (ATV 400 mg + RTV 100 mg) once daily (For dosing recommendations with H_2 antagonists and proton pump inhibitor (PPIs), refer to Table 16a) Take with food	CYP3A4 inhibitor and substrate Dosage adjustment in hepatic insufficiency recommended (See Appendix B, Table 7.)	7 hrs	Room temperature (up to 25ºC or 77ºF)	• Indirect hyperbilirubinemia • PR interval prolongation: First degree symptomatic atrioventricular (AV) block reported. Use with caution in patients with underlying conduction defects or on concomitant medications that can cause PR prolongation. • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in patients with hemophilia • Nephrolithiasis • Skin rash (20%) • Serum transaminase elevations • Hyperlipidemia (especially with RTV boosting)
Darunavir (DRV)/ Prezista	75-, 150-, 300-, 400-, 600-mg tablets	ARV-naïve patients or ARV-experienced patients with no DRV mutations: (DRV 800 mg + RTV 100 mg) once daily ARV-experienced patients with at least one DRV mutation: (DRV 600 mg + RTV 100 mg) BID Unboosted DRV is **not** recommended Take with food	CYP3A4 inhibitor and substrate	15 hrs (when combined with RTV)	Room temperature (up to 25ºC or 77ºF)	• Skin rash (10%): DRV has a sulfonamide moiety; Stevens-Johnson syndrome and erythrema multiforme have been reported. • Hepatotoxicity • Diarrhea, nausea • Headache • Hyperlipidemia • Serum transaminase elevation • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in patients with hemophilia
Fosamprenavir (FPV)/ Lexiva (a prodrug of amprenavir [APV])	• 700-mg tablet • 50-mg/mL oral suspension	ARV-naïve patients: • FPV 1,400 mg BID or • (FPV 1,400 mg + RTV 100–200 mg) once daily or • (FPV 700 mg + RTV 100 mg) BID PI-experienced patients (once-daily dosing **not** recommended): • (FPV 700 mg + RTV 100 mg) BID With EFV: • (FPV 700 mg + RTV 100 mg) BID or • (FPV 1,400 mg + RTV 300 mg) once daily *Tablet*: Take without regard to meals (if not boosted with RTV tablet) *Suspension*: Take without food *FPV w/RTV tablet*: Take with meals	APV is a CYP3A4 substrate, inhibitor, and inducer Dosage adjustment in hepatic insufficiency recommended (See Appendix B, Table 7.)	7.7 hrs (APV)	Room temperature (up to 25ºC or 77ºF)	• Skin rash (12%–19%) – FPV has a sulfonamide moiety • Diarrhea, nausea, vomiting • Headache • Hyperlipidemia • Serum transaminase elevation • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in patients with hemophilia • Nephrolithiasis

Appendix B, Table 3. Characteristics of Protease Inhibitors (PIs)
Page 2 of 3

Generic Name (abbreviation)/ Trade Name	Formulations	Dosing Recommendations (For dosage adjustment in hepatic insufficiency, see Appendix B, Table 7)	Elimination	Serum Half-life	Storage	Adverse Events (Also see Table 13)
Indinavir (IDV)/ Crixivan	100-, 200-, 400-mg capsules	800 mg every 8 hrs Take 1 hour before or 2 hours after meals; may take with skim milk or low-fat meal With RTV: (IDV 800 mg + RTV 100–200 mg) BID Take without regard to meals	CYP3A4 inhibitor and substrate Dosage adjustment in hepatic insufficiency recommended (See Appendix B, Table 7.)	1.5–2 hrs	Room temperature (15º–30ºC/ 59º–86ºF) Protect from moisture	• Nephrolithiasis • GI intolerance, nausea • Hepatitis • Indirect hyperbilirubinemia • Hyperlipidemia • Headache, asthenia, blurred vision, dizziness, rash, metallic taste, thrombocytopenia, alopecia, and hemolytic anemia • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in patients with hemophilia
Lopinavir + Ritonavir (LPV/r)/ Kaletra	Tablets: (LPV 200 mg + RTV 50 mg) or (LPV 100 mg + RTV 25 mg) Oral solution: Each 5 mL contains (LPV 400 mg + RTV 100 mg) Oral solution contains 42% alcohol	LPV/r 400-mg/100-mg BID or LPV/r 800-mg/200-mg once daily Once-daily dosing is not recommended for patients with ≥3 LPV-associated mutations, pregnant women, or patients receiving EFV, NVP, FPV, NFV, carbamazepine, phenytoin, or phenobarbital. With EFV or NVP (PI-naïve or PI-experienced patients): LPV/r 500-mg/125-mg tablets BID (Use a combination of two LPV/r 200-mg/50-mg tablets + one LPV/r 100-mg/25-mg tablet to make a total dose of LPV/r 500 mg/125 mg.) or LPV/r 533-mg/133-mg oral solution BID *Tablet*: Take without regard to meals *Oral solution*: Take with food	CYP3A4 inhibitor and substrate	5–6 hrs	Oral tablet is stable at room temperature. Oral solution is stable at 2°–8°C (36°–46°F) until date on label and is stable when stored at room temperature (up to 25ºC or 77ºF) for 2 months.	• GI intolerance, nausea, vomiting, diarrhea • Pancreatitis • Asthenia • Hyperlipidemia (especially hypertriglyceridemia) • Serum transaminase elevation • Hyperglycemia • Insulin resistance/diabetes mellitus • Fat maldistribution • Possible increased bleeding episodes in patients with hemophilia • PR interval prolongation • QT interval prolongation and torsades de pointes have been reported; however, causality could not be established.
Nelfinavir (NFV)/ Viracept	• 250-, 625-mg tablets • 50-mg/g oral powder	1,250 mg BID or 750 mg TID May dissolve tablets in a small amount of water; once dissolved, patients should mix the cloudy liquid well and consume it immediately. Take with food	CYP2C19 and 3A4 substrate—metabolized to active M8 metabolite; CYP 3A4 inhibitor	3.5–5 hrs	Room temperature (15º–30ºC/ 59º–86ºF)	• Diarrhea • Hyperlipidemia • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in patients with hemophilia • Serum transaminase elevation

Appendix B, Table 3. Characteristics of Protease Inhibitors (PIs)
Page 3 of 3

Generic Name (abbreviation)/ Trade Name	Formulations	Dosing Recommendations (For dosage adjustment in hepatic insufficiency, see Appendix B, Table 7)	Elimination	Serum Half-life	Storage	Adverse Events (Also see Table 13)
Ritonavir (RTV)/ Norvir	• 100-mg soft gel capsules • 100-mg tablets • 80-mg/mL oral solution Oral solution contains 43% alcohol	As pharmacokinetic booster for other PIs: 100–400 mg per day in 1–2 divided doses (refer to other PIs for specific dosing recommendations) *Tablet*: Take with food *Capsule and oral solution*: Take with food, if possible, to improve tolerability.	CYP3A4 >2D6 substrate; potent 3A4, 2D6 inhibitor	3–5 hrs	Refrigerate capsules. Capsules can be left at room temperature (up to 25ºC or 77ºF) for up to 30 days. Tablets do not require refrigeration. Oral solution should **not** be refrigerated; store at room temperature 20º–25ºC (68º–77ºF).	• GI intolerance, nausea, vomiting, diarrhea • Paresthesias—circumoral and extremities • Hyperlipidemia (especially hypertriglyceridemia) • Hepatitis • Asthenia • Taste perversion • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in patients with hemophilia
Saquinavir tablets and hard gel capsules (SQV)/ Invirase	• 500-mg tablets • 200-mg hard gel capsules	(SQV 1,000 mg + RTV 100 mg) BID Unboosted SQV is **not** recommended. Take with meals or within 2 hours after a meal	CYP3A4 inhibitor and substrate	1–2 hrs	Room temperature (15º–30ºC/ 59º–86ºF)	• GI intolerance, nausea, and diarrhea • Headache • Serum transaminase elevation • Hyperlipidemia • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in patients with hemophilia • PR interval prolongation • QT interval prolongation, torsades de pointes have been reported. Patients with pre-SQV QT interval >450 msec should not receive SQV (See Table 5b.).
Tipranavir (TPV)/ Aptivus	• 250-mg capsules • 100-mg/mL oral solution	(TPV 500 mg + RTV 200 mg) BID Unboosted TPV is **not** recommended. TPV taken with RTV **tablets**: Take with meals TPV taken with RTV **capsules** or **solution**: Take without regard to meals	Cytochrome P450 3A4 inducer and substrate Net effect when combined with RTV (CYP 3A4, 2D6 inhibitor)	6 hrs after single dose of TPV/r	Refrigerate capsules. Capsules can be stored at room temperature (25ºC or 77ºF) for up to 60 days. Oral solution should **not** be refrigerated or frozen and should be used within 60 days after opening the bottle.	• Hepatotoxicity: Clinical hepatitis (including hepatic decompensation and hepatitis-associated fatalities) has been reported; monitor closely, especially in patients with underlying liver diseases. • Skin rash (3%–21%): TPV has a sulfonamide moiety; use with caution in patients with known sulfonamide allergy. • Rare cases of fatal and nonfatal intracranial hemorrhages have been reported. Risks include brain lesion, head trauma, recent neurosurgery, coagulopathy, hypertension, alcoholism,, use of anti-coagulant or anti-platelet agents including vitamin E. • Hyperlipidemia • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in patients with hemophilia

Appendix B, Table 4. Characteristics of Integrase Inhibitor (Updated January 10, 2011)

Generic Name (abbreviation)/ Trade Name	Formulations	Dosing Recommendations (For dosage adjustment in hepatic insufficiency, see Appendix, Table 7.)	Serum half-life	Route of Metabolism	Adverse Events (Also see Table 13)
Raltegravir (RAL)/ Isentress	400 mg tablets	400 mg BID With rifampin: 800 mg BID Take without regard to meals	~9 hrs	UGT1A1-mediated glucuronidation	• Nausea • Headache • Diarrhea • Pyrexia • CPK elevation, muscle weakness and rhabdomyolysis

Appendix B, Table 5. Characteristics of Fusion Inhibitor (Updated January 29, 2008)

Generic Name (abbreviation)/ Trade Name	Formulations	Dosing Recommendation	Serum half-life	Elimination	Storage	Adverse Events (Also see Table 13)
Enfuvirtide (T20)/ Fuzeon	• Injectable—supplied as lyophilized powder • Each vial contains 108 mg of T20; reconstitute with 1.1mL of sterile water for injection for delivery of approximately 90mg/1mL.	90 mg (1mL) subcutaneously BID	3.8 hrs	Expected to undergo catabolism to its constituent amino acids, with subsequent recycling of the amino acids in the body pool	Store at room temperature (up to 25ºC or 77ºF). Reconsti-tuted solution should be refrigerated at 2ºC–8ºC (36ºF–46Fº) and used within 24 hours.	• Local injection site reactions in almost 100% of patients (pain, erythema, induration, nodules and cysts, pruritus, ecchymosis) • Increased bacterial pneumonia • Hypersensitivity reaction (<1%): Symptoms may include rash, fever, nausea, vomiting, chills, rigors, hypotension, or elevated serum transaminases. Rechallenge is not recommended.

Appendix B, Table 6. Characteristics of CCR5 Antagonist (Updated January 29, 2008)

Generic Name (abbreviation)/ Trade Name	Formulation	Dosing Recommendations (For dosage adjustment in hepatic insufficiency, see Appendix, Table 7.)	Serum Half-life	Elimination	Adverse Events (Also see Table 13)
Maraviroc (MVC)/ Selzentry	150-, 300-mg tablets	• **150 mg BID** when given with strong CYP3A inhibitors (with or without CYP3A inducers) including PIs (except TPV/r) • **300 mg BID** when given with NRTIs, T-20, TPV/r, NVP, RAL, and other drugs that are not strong CYP3A inhibitors or inducers • **600 mg BID** when given with CYP3A inducers, including EFV, ETR, etc. (without a CYP3A inhibitor) Take without regard to meals	14–18 hrs	CYP3A4 substrate	• Abdominal pain • Cough • Dizziness • Musculoskeletal symptoms • Pyrexia • Rash • Upper respiratory tract infections • Hepatotoxicity • Orthostatic hypotension

Appendix B, Table 7. Antiretroviral Dosing Recommendations in Patients with Renal or Hepatic Insufficiency (Updated January 10, 2011)

See reference section following tables for creatinine clearance (CrCl) calculation formulas and criteria for Child-Pugh classification.

Antiretrovirals Generic Name (abbreviation)/ Trade Name	Usual Daily Dose (Refer to Appendix B Tables 1-6 for additional dosing information)	Dosing in Renal Insufficiency (Including with chronic ambulatory peritoneal dialysis [CAPD] and hemodialysis [HD])	Dosing in Hepatic Impairment
Nucleoside Reverse Transcriptase Inhibitors **Use of fixed-dose combination NRTI (+/- NNRTI) of Atripla, Combivir, Trizivir, or Epzicom is not recommended in patients with CrCl <50 mL/min. Use of Truvada is not recommended in patients with CrCl <30 mL/min.**			
Abacavir (ABC)/ Ziagen	300 mg PO BID	No dosage adjustment necessary	**Child-Pugh Score** — **Dose** 5–6 — 200 mg BID (use oral solution) > 6 — Contraindicated
Didanosine enteric coated (ddI)/ Videx EC	**Body weight ≥60 kg**: 400 mg PO once daily **Body weight <60 kg**: 250 mg PO once daily	**Dose (once daily)** **CrCl (mL/min)** — **≥60 kg** — **<60 kg** 30–59 — 200 mg — 125 mg 10–29 — 125 mg — 125 mg <10, HD, CAPD — 125 mg — use oral solution	No dosage adjustment necessary
Didanosine oral solution (ddI)/ Videx	**Body weight ≥60 kg**: 200 mg PO BID or 400 mg PO once daily **Body weight <60 kg**: 250 mg PO once daily or 125 mg PO BID	**Dose (once daily)** **CrCl (mL/min)** — **≥60 kg** — **<60 kg** 30–59 — 200 mg — 150 mg 10–29 — 150 mg — 100 mg <10, HD, CAPD — 100 mg — 75 mg	No dosage adjustment necessary
Emtricitabine (FTC)/ Emtriva	200mg oral capsule PO once daily; or 240 mg (24 mL) oral solution PO once daily	**Dose** **CrCl (mL/min)** — **Capsule** — **Solution** 30–49 — 200 mg q48h — 120 mg q24h 15–29 — 200 mg q72h — 80 mg q24h <15 or HD — 200 mg q96h — 60 mg q24h Take dose after HD session on dialysis days	No dosage recommendation
Lamivudine (3TC)/ Epivir	300 mg PO once daily; or 150 mg PO BID	**CrCl (mL/min)** — **Dose** 30–49 — 150 mg q24h 15–29 — 1 x 150 mg, then 100 mg q24h 5–14 — 1 x 150 mg, then 50 mg q24h <5 or HD — 1 x 50 mg, then 25 mg q24h Take dose after HD session on dialysis days	No dosage adjustment necessary
Stavudine (D4T)/ Zerit	**Body weight ≥60 kg**: 40 mg PO BID **Body weight <60 kg**: 30 mg PO BID	**Dose** **CrCl (mL/min)** — **≥60 kg** — **<60 kg** 26–50 — 20 mg q12h — 15 mg q12h 10–25 or HD — 20 mg q24h — 15 mg q24h Take dose after HD session on dialysis days	No dosage recommendation
Tenofovir (TDF)/ Viread	300 mg PO once daily	**CrCl (mL/min)** — **Dose** 30–49 — 300 mg q48h 10–29 — 300 mg twice weekly <10 not on HD — no recommendation HD — 300 mg q7d Take dose after HD session on dialysis days	No dosage adjustment necessary
Emtricitabine (FTC) + **Tenofovir** (TDF)/ Truvada	1 tablet PO once daily	**CrCl (mL/min)** — **Dose** 30–49 — 1 tablet q48h <30 or HD — not recommended	No dosage recommendation
Zidovudine (AZT, ZDV)/ Retrovir	300 mg PO BID	**CrCl (mL/min)** — **Dose** < 15 or HD — 100 mg TID or 300 mg once daily	No dosage recommendation

Appendix B, Table 7. Antiretroviral Dosing Recommendations in Patients with Renal or Hepatic Insufficiency

Antiretrovirals Generic Name (abbreviation)/ Trade Name	Daily Dose	Dosing in Renal Insufficiency (Including with chronic ambulatory peritoneal dialysis [CAPD] and hemodialysis [HD])	Dosing in Hepatic Impairment
Non-Nucleoside Reverse Transcriptase Inhibitors			
Delavirdine (DLV)/ Rescriptor	400 mg PO TID	No dosage adjustment necessary	No dosage recommendation; use with caution in patients with hepatic impairment
Efavirenz (EFV)/ Sustiva	600 mg PO at or before bedtime	No dosage adjustment necessary	No dosage recommendation; use with caution in patients with hepatic impairment
Efavirenz (EFV) + **Emtricitabine** (FTC) + **Tenofovir** (TDF)/ Atripla	1 tablet PO once daily	Atripla not recommended if CrCl <50 mL/min	
Etravirine (ETR)/ Intelence	200 mg PO BID	No dosage adjustment necessary	Child-Pugh Class A or B: no dosage adjustment Child-Pugh Class C: no dosage recommendation
Nevirapine (NVP)/ Viramune	200 mg PO BID	HD patients: limited data; no dosage recommendation	Child-Pugh Class B or C: contraindicated
Protease Inhibitors			
Atazanavir (ATV)/ Reyataz	400 mg PO once daily or (ATV 300 mg + RTV 100 mg) PO once daily	No dosage adjustment for patients with renal dysfunction not requiring HD ARV-naïve patients on HD: (ATV 300 mg + RTV 100 mg) once daily ARV-experienced patients on HD: ATV or RTV-boosted ATV not recommended	**Child-Pugh Score** **Dose** 7–9 300 mg once daily >9 not recommended RTV boosting is **not** recommended in patients with hepatic impairment (Child-Pugh Score ≥7).
Darunavir (DRV)/ Prezista	(DRV 800 mg + RTV 100 mg) PO once daily (ARV-naïve patients) or (DRV 600 mg + RTV 100 mg) PO BID	No dosage adjustment necessary	Mild to moderate hepatic impairment: no dosage adjustment Severe hepatic impairment: not recommended
Fosamprenavir (FPV)/ Lexiva	1,400 mg PO BID or (FPV 1,400 mg + RTV 100–200 mg) PO once daily or (FPV 700 mg + RTV 100 mg) PO BID	No dosage adjustment necessary	**Child-Pugh Score** **Dose** PI-naïve patients only: 5–9 700 mg BID 10–15 350 mg BID PI-naïve or PI-experienced patients: 5–6 700 mg BID + RTV 100 mg once daily 7–9 450 mg BID + RTV 100 mg once daily 10–15 300 mg BID + RTV 100 mg once daily
Indinavir (IDV)/ Crixivan	800 mg PO q8h	No dosage adjustment necessary	Mild to moderate hepatic insufficiency because of cirrhosis: 600 mg q8h
Lopinavir/ritonavir (LPV/r) Kaletra	400/100 mg PO BID or 800/200 mg PO once daily	Avoid once daily dosing in patients on HD	No dosage recommendation; use with caution in patients with hepatic impairment
Nelfinavir (NFV)/ Viracept	1,250 mg PO BID	No dosage adjustment necessary	Mild hepatic impairment: no dosage adjustment Moderate to severe hepatic impairment: do not use
Ritonavir (RTV)/ Norvir	As a PI-boosting agent: 100–400 mg per day	No dosage adjustment necessary	Refer to recommendations for the primary PI
Saquinavir (SQV)/ Invirase	(SQV 1,000 mg + RTV 100 mg) PO BID	No dosage adjustment necessary	Mild to moderate hepatic impairment: use with caution Severe hepatic impairment: contraindicated
Tipranavir (TPV)/ Aptivus	(TPV 500 mg + RTV 200 mg) PO BID	No dosage adjustment necessary	Child-Pugh Class A: use with caution Child-Pugh Class B or C: contraindicated

Appendix B, Table 7. Antiretroviral Dosing Recommendations in Patients with Renal or Hepatic Insufficiency
Page 3 of 3

Antiretrovirals Generic Name (abbreviation)/ Trade Name	Daily Dose	Dosing in Renal Insufficiency	Dosing in Hepatic Impairment
Fusion Inhibitor			
Enfuvirtide (T20)/ Fuzeon	90 mg subcutaneous BID	No dosage adjustment necessary	No dosage adjustment necessary
CCR5 Antagonist			
Maraviroc (MVC)/ Selzentry	The recommended dose differs based on concomitant medications because of drug interactions. See **Appendix B, Table 6** for detailed dosing information.	**CrCl <30 mL/min or HD** Without potent CYP3A inhibitors or inducers: 300 mg BID; reduce to 150 mg BID if postural hypotension occurs With potent CYP3A inducers or inhibitors: not recommended	No dosage recommendations. Concentrations will likely be increased in patients with hepatic impairment.
Integrase Inhibitor			
Raltegravir (RAL)/ Isentress	400 mg BID	No dosage adjustment necessary	Mild to moderate hepatic insufficiency: no dosage adjustment necessary Severe hepatic insufficiency: no recommendation

Creatinine Clearance Calculation	
Male: $\frac{(140 - \text{age in years}) \times \text{weight (kg)}}{72 \times \text{Serum Creatinine}}$	Female: $\frac{(140 - \text{age in years}) \times \text{weight (kg)} \times 0.85}{72 \times \text{Serum Creatinine}}$

Child-Pugh Score			
Component	**Points Scored**		
	1	**2**	**3**
Encephalopathy*	None	Grade 1–2	Grade 3–4
Ascites	None	Mild or controlled by diuretics	Moderate or refractory despite diuretics
Albumin	>3.5 g/dL	2.8–3.5 g/dL	<2.8 g/dL
Total bilirubin or	<2 mg/dL (<34 μmol/L)	2–3 mg/dL (34 μmol/L to 50 μmol/L)	>3 mg/dL (>50 μmol/L)
Modified total bilirubin†	<4 mg/dL	4–7 mg/dL	>7 mg/dL
Prothrombin time (seconds prolonged) or	<4	4–6	>6
International normalized ratio (INR)	<1.7	1.7–2.3	>2.3

* Encephalopathy Grades
Grade 1: Mild confusion, anxiety, restlessness, fine tremor, slowed coordination
Grade 2: Drowsiness, disorientation, asterixis
Grade 3: Somnolent but rousable, marked confusion, incomprehensible speech, incontinence, hyperventilation
Grade 4: Coma, decerebrate posturing, flaccidity
† Modified total bilirubin used to score patients who have Gilbert's syndrome or who are taking indinavir or atazanavir

Child-Pugh Classification	Total Score*
Class A	5–6 points
Class B	7–9 points
Class C	>9 points

* Sum of points for each component

MMWR™
Morbidity and Mortality Weekly Report
www.cdc.gov/mmwr

Recommendations and Reports | April 10, 2009 / Vol. 58 / No. RR-4

Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents

Recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America

INSIDE: Continuing Education Examination

DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTERS FOR DISEASE CONTROL AND PREVENTION

The *MMWR* series of publications is published by the Coordinating Center for Health Information and Service, Centers for Disease Control and Prevention (CDC), U.S. Department of Health and Human Services, Atlanta, GA 30333.

Suggested Citation: Centers for Disease Control and Prevention. [Title]. MMWR 2009;58(No. RR-#):[inclusive page numbers].

Centers for Disease Control and Prevention

Richard E. Besser, MD
(Acting) Director

Tanja Popovic, MD, PhD
Chief Science Officer

James W. Stephens, PhD
Associate Director for Science

Steven L. Solomon, MD
Director, Coordinating Center for Health Information and Service

Jay M. Bernhardt, PhD, MPH
Director, National Center for Health Marketing

Katherine L. Daniel, PhD
Deputy Director, National Center for Health Marketing

Editorial and Production Staff

Frederic E. Shaw, MD, JD
Editor, MMWR *Series*

Susan F. Davis, MD
(Acting) Assistant Editor, MMWR *Series*

Teresa F. Rutledge
Managing Editor, MMWR *Series*

David C. Johnson
(Acting) Lead Technical Writer-Editor

Suzanne M. Hewitt, MPA
Project Editor

Martha F. Boyd
Lead Visual Information Specialist

Malbea A. LaPete
Stephen R. Spriggs
Visual Information Specialists

Kim L. Bright, MBA
Quang M. Doan, MBA
Phyllis H. King
Information Technology Specialists

Editorial Board

William L. Roper, MD, MPH, Chapel Hill, NC, Chairman
Virginia A. Caine, MD, Indianapolis, IN
David W. Fleming, MD, Seattle, WA
William E. Halperin, MD, DrPH, MPH, Newark, NJ
Margaret A. Hamburg, MD, Washington, DC
King K. Holmes, MD, PhD, Seattle, WA
Deborah Holtzman, PhD, Atlanta, GA
John K. Iglehart, Bethesda, MD
Dennis G. Maki, MD, Madison, WI
Sue Mallonee, MPH, Oklahoma City, OK
Patricia Quinlisk, MD, MPH, Des Moines, IA
Patrick L. Remington, MD, MPH, Madison, WI
Barbara K. Rimer, DrPH, Chapel Hill, NC
John V. Rullan, MD, MPH, San Juan, PR
William Schaffner, MD, Nashville, TN
Anne Schuchat, MD, Atlanta, GA
Dixie E. Snider, MD, MPH, Atlanta, GA
John W. Ward, MD, Atlanta, GA

CONTENTS

Summary 1
Introduction 2
History of the Guidelines 2
Guidelines Process 2
Major Changes in Guidelines Since Last Publication 3
How to Use the Information in this Report 3
Effect of ART on the Management of OIs 4
Initiation of ART in the Setting of an Acute OI (Treatment-Naïve Patients) 4
Management of Acute OIs in Patients Receiving ART 5
Special Considerations During Pregnancy 5
Disease Specific Recommendations 6
- *Pneumocystis* Pneumonia 6
- *Toxoplasma gondii* Encephalitis 10
- Cryptosporidiosis 14
- Microsporidiosis 17
- *Mycobacterium tuberculosis* Infection and Disease 19
- Disseminated *Mycobacterium avium* Complex Disease 28
- Bacterial Respiratory Disease 31
- Bacterial Enteric Infections 36
- Bartonellosis 39
- Syphilis 41
- Mucocutaneous Candidiasis 45
- Cryptococcosis 48
- Histoplasmosis 50
- Coccidioidomycosis 52
- Aspergillosis 54
- Cytomegalovirus Disease 55
- Herpes Simplex Virus Disease 61
- HHV-6 and HHV-7 Disease 63
- Varicella-Zoster Virus Diseases 64
- Human Herpesvirus-8 Disease 66
- Human Papillomavirus Disease 68
- Hepatitis B Virus Infection 75
- Hepatitis C Virus Infection 84
- Progressive Multifocal Leukoencephalopathy/JC Virus Infection 91

Geographic OIs of Specific Consideration 94
- Malaria 94
- *Penicilliosis marneffei* 98
- Leishmaniasis 99
- Chagas Disease 103
- Isosporiasis 105

References 107
Tables 145
Figures 197
Appendix 199
List of Abbreviations Used in this Report 204
Contributors 206
Continuing Education Activity CE-1

Disclosure of Relationship

CDC, our planners, and our content specialists wish to disclose they have no financial interests or other relationships with the manufacturers of commercial products, suppliers of commercial services, or commercial supporters, with the exception of Constance Benson and King K. Holmes. Dr. Benson discloses being on the Advisory Board for Merck, GlaxoSmithKline, and Boehringer Ingelheim; being a grant recipient for Gilead; and being a Data Safety Monitoring Board (DSMB) member for Achillion and JJR Australia. Her spouse also is a consultant for Merck, Gilead, Achillion, Monogram, and Vertex. Dr. Holmes discloses being a DSMB member of Merck, receiving an honorarium at the 2005 Infectious Diseases Society of America Conference, and serving on the Mycology Research Laboratories scientific advisory board. Presentations will not include any discussion of the unlabeled use of a product or a product under investigational use.

Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents

Recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America

Prepared by
Jonathan E. Kaplan, MD[1]
Constance Benson, MD[2]
King K. Holmes, MD, PhD[3]
John T. Brooks, MD[1]
Alice Pau, PharmD[4]
Henry Masur, MD[4]
[1]*CDC, Atlanta, Georgia*
[2] *University of California San Diego, San Diego, California*
[3]*University of Washington, Seattle, Washington*
[4]*National Institutes of Health, Bethesda, Maryland*

Summary

This report updates and combines earlier versions of guidelines for the prevention and treatment of opportunistic infections (OIs) in HIV-infected adults (i.e., persons aged ≥18 years) and adolescents (i.e., persons aged 13–17 years), last published in 2002 and 2004, respectively. It has been prepared by the Centers for Disease Control and Prevention (CDC), the National Institutes of Health (NIH), and the HIV Medicine Association (HIVMA) of the Infectious Diseases Society of America (IDSA). The guidelines are intended for use by clinicians and other health-care providers, HIV-infected patients, and policy makers in the United States. These guidelines address several OIs that occur in the United States and five OIs that might be acquired during international travel. Topic areas covered for each OI include epidemiology, clinical manifestations, diagnosis, prevention of exposure; prevention of disease by chemoprophylaxis and vaccination; discontinuation of primary prophylaxis after immune reconstitution; treatment of disease; monitoring for adverse effects during treatment; management of treatment failure; prevention of disease recurrence; discontinuation of secondary prophylaxis after immune reconstitution; and special considerations during pregnancy.

These guidelines were developed by a panel of specialists from the United States government and academic institutions. For each OI, a small group of specialists with content-matter expertise reviewed the literature for new information since the guidelines were last published; they then proposed revised recommendations at a meeting held at NIH in June 2007. After these presentations and discussion, the revised guidelines were further reviewed by the co-editors; by the Office of AIDS Research, NIH; by specialists at CDC; and by HIVMA of IDSA before final approval and publication.

The recommendations are rated by a letter that indicates the strength of the recommendation and a Roman numeral that indicates the quality of evidence supporting the recommendation, so that readers can ascertain how best to apply the recommendations in their practice environments.

Major changes in the guidelines include 1) greater emphasis on the importance of antiretroviral therapy for the prevention and treatment of OIs, especially those OIs for which no specific therapy exists; 2) information regarding the diagnosis and management of immune reconstitution inflammatory syndromes; 3) information regarding the use of interferon-gamma release assays for the diagnosis of latent Mycobacterium tuberculosis (TB) infection; 4) updated information concerning drug interactions that affect the use of rifamycin drugs for prevention and treatment of TB; 5) the addition of a section on hepatitis B virus infection; and 6) the addition of malaria to the list of OIs that might be acquired during international travel.

This report includes eleven tables pertinent to the prevention and treatment of OIs, a figure that pertains to the diagnois of tuberculosis, a figure that describes immunization recommendations, and an appendix that summarizes recommendations for prevention of exposure to opportunistic pathogens.

The material in this report originated in the National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention, Kevin Fenton, MD, Director.
Corresponding preparer: John T. Brooks, M.D., Division of HIV/AIDS Prevention, NCHHSTP, CDC, 1600 Clifton Road NE, MS E-45, Atlanta, GA 30333, Telephone: 404-639-3894, Fax: 404-639-6127, Email: zud4@cdc.gov.

Introduction

Before the widespread use of potent combination antiretroviral therapy (ART), opportunistic infections (OIs), which have been defined as infections that are more frequent or more severe because of immunosuppression in HIV-infected persons, were the principal cause of morbidity and mortality in this population. In the early 1990s, the use of chemoprophylaxis, immunization, and better strategies for managing acute OIs contributed to improved quality of life and improved survival (*1*). However, the widespread use of ART starting in the mid-1990s has had the most profound influence on reducing OI-related mortality in HIV-infected persons in those countries in which these therapies are accessible and affordable (*1–8*).

Despite the availability of ART in the United States and other industrialized countries, OIs continue to cause considerable morbidity and mortality for three primary reasons: 1) many patients are unaware of their HIV infection and seek medical care when an OI becomes the initial indicator of their disease; 2) certain patients are aware of their HIV infection, but do not take ART because of psychosocial or economic factors; and 3) certain patients are prescribed ART, but fail to attain adequate virologic and immunologic response because of factors related to adherence, pharmacokinetics, or unexplained biologic factors (*4,9,10*). Thus, although hospitalizations and deaths have decreased since the implementation of ART, OIs remain a leading cause of morbidity and mortality in HIV-infected persons (*11–19*). Clinicians must be knowledgeable about optimal strategies for prevention and management of OIs to provide comprehensive high-quality care for these patients.

Recognizing that the relation between OIs and HIV infection is bidirectional is important. HIV leads to immunosuppression that allows opportunistic pathogens to cause disease in HIV-infected persons. OIs and other coinfections that might be common in HIV-infected persons, such as sexually transmitted infections, can also have adverse effects on the natural history of HIV infection. Certain OIs are associated with reversible increases in circulating viral load (*20–25*), and these increases could lead to accelerated HIV progression or increased transmission of HIV (*26*). Thus, although chemoprophylaxis and vaccination directly prevent pathogen-specific morbidity and mortality, they might also contribute to reduced rate of progression of HIV disease. For instance, randomized trials using trimethoprim-sulfamethoxazole (TMP-SMX) have documented that chemoprophylaxis can both decrease OI-related morbidity and improve survival. The survival benefit is likely to be partially attributable to reduced progression of HIV infection (*27–31*). Reduced progression of HIV infection would also indirectly delay or reduce the occurrence of subsequent OIs.

History of the Guidelines

In 1989, the Guidelines for Prophylaxis against *Pneumocystis carinii* Pneumonia for persons infected with the human immunodeficiency virus became the first HIV-related treatment guideline published by the U.S. Public Health Service (*32*). This report was followed by a guideline on prevention of *Mycobacterium avium* complex (MAC) disease in 1993 (*33*). In 1995, these guidelines were expanded to include the prevention of all HIV-related OIs and the Infectious Diseases Society of America (IDSA) joined as a cosponsor (*34*). These prevention guidelines were revised in 1997, 1999, and 2002 and have been published in *MMWR* (*35–37*), *Clinical Infectious Diseases* (*38–40*), *the Annals of Internal Medicine* (*41,42*), *American Family Physician* (*43,44*), and *Pediatrics* (*45*); accompanying editorials have appeared in the *Journal of the American Medical Association* (*46,47*).

In 2004, CDC, the National Institutes of Health (NIH), and the HIV Medicine Association (HIVMA) of the IDSA published a new guideline including recommendations for treating HIV-infected adults and adolescents with OIs (*48*). Companion guidelines were published for HIV-infected children (*49*).

Responses to these guidelines (e.g., numbers of requests for reprints, website contacts, and observations from health-care providers) have demonstrated that these guidelines have served as valuable references for HIV health-care providers. Because the guidelines include ratings indicating the strength of each recommendation and the quality of supporting evidence, readers have been able to assess the importance of each recommendation. The present report includes recommendations for both prevention and treatment of OIs in HIV-infected adults and adolescents; an accompanying report includes recommendations for HIV-exposed and -infected children.

These guidelines are intended for clinicians, other health-care providers, HIV-infected patients, and policy makers residing in the United States; guidelines pertinent to other regions of the world, especially countries with limited resources, might differ regarding the spectrum of OIs of interest and their diagnostic and therapeutic capacity.

Guidelines Process

These guidelines were prepared by the Opportunistic Infections Working Group under the auspices of the Office of AIDS Research Advisory Council (OARAC) of NIH. Group leaders and team members with expertise in specific OIs were selected from the membership of the Working Group; each group reviewed the literature since the last publication of the prevention and treatment guidelines, conferred for several months, and produced draft revised guidelines.

Recommendations were reviewed and discussed by the Working Group at a meeting in Bethesda, Maryland, on June 25–26, 2007. A draft version of these recommendations was posted at AIDSInfo (http://aidsinfo.nih.gov/contentfiles/Adult_OI.pdf) on June 18, 2008. Since the June 18, 2008 posting, the draft recommendations were reviewed and updated for this report by Working Group members and subject matter experts. Suggested updates were reviewed by the co-editors, who amended the report, as warranted. The final version of the report was further reviewed by the co-editors, the Office of AIDS Research, NIH; experts at CDC; and the HIVMA of IDSA before final approval and publication.

The current guidelines share key features with prior versions. They are labeled as guidelines, indicating that the recommendations should be considered in the context of the individual patient situation and the community where the patient is being managed. They are evidence based. For each recommendation, the strength and quality of the evidence supporting it are indicated using a revised version of the rating system of the IDSA. As noted above, they have been developed by a broadly based panel that included representatives from academic medical centers, federal governmental agencies, community-based practices, and consumer advocates; representatives from Europe, Latin America, and Asia also took part in the process. The guidelines are available in print media and on the Internet. They are written for physicians and other health-care providers who care for HIV-infected persons in the United States and Western Europe where access is available to a full range of up-to-date medical services; however, these recommended strategies might not be feasible or appropriate in all settings where the spectrum of HIV-related complications and diagnostic capacity differ from those observed in the United States and Western Europe. Final versions of the guidelines were reviewed by respective members of each panel to ensure the recommendations were complete and appropriate. They are endorsed by CDC, the NIH, and the HIVMA of the IDSA. They are intended to complement more comprehensive textbooks, journals, and other relevant informational materials. Information is summarized in 11 tables.

Major Changes in Guidelines Since Last Publication

Major changes include 1) additional emphasis on the importance of ART for prevention and treatment of OIs, especially those for which specific chemoprophylaxis and treatment do not exist; 2) information on diagnosis and management of immune reconstitution inflammatory syndromes (IRIS); 3) information on interferon-gamma release assays (IGRAs) for the detection of latent *Mycobacterium tuberculosis* infection; 4) updated information on drug interactions affecting use of rifamycin drugs for prevention and treatment of tuberculosis (TB); 5) addition of a section on hepatitis B virus (HBV) infection; and 6) addition of a section on malaria to the OIs of geographic interest.

How to Use the Information in this Report

For each of the OIs discussed in this report, recommendations are provided that address 1) preventing exposure to opportunistic pathogens, 2) preventing disease, 3) discontinuing primary prophylaxis after immune reconstitution, 4) treating patients with disease, 5) monitoring for adverse effects (including IRIS), 6) managing treatment failure, 7) preventing

BOX. System used to rate the strength of recommendations and quality of supporting evidence

Rating	Strength of recommendation
A	Both strong evidence for efficacy and substantial clinical benefit support recommendation for use. Should always be offered.
B	Moderate evidence for efficacy—or strong evidence for efficacy but only limited clinical benefit—supports recommendation for use. Should generally be offered.
C	Evidence for efficacy is insufficient to support a recommendation for or against use. Or evidence for efficacy might not outweigh adverse consequences (e.g. drug toxicity, drug interactions) or cost of the treatment or alternative approaches. Optional.
D	Moderate evidence for lack of efficacy or for adverse outcome supports a recommendation against use. Should generally not be offered.
E	Good evidence for lack of efficacy or for adverse outcome supports a recommendation against use. Should never be offered.
Rating	**Quality of the evidence supporting the recommendation**
I	Evidence from at least one properly-designed randomized, controlled trial.
II	Evidence from at least one well-designed clinical trial without randomization, from cohort or case-controlled analytic studies (preferably from more than one center), or from multiple time-series studies, or dramatic results from uncontrolled experiments.
III	Evidence from opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees.

disease recurrence ("secondary prophylaxis" or chronic maintenance therapy), 8) discontinuing secondary prophylaxis after immune reconstitution, and 9) special considerations during pregnancy. Recommendations are rated by a revised version of the IDSA rating system (Box). In this system, the letters A–E signify the strength of the recommendation for or against a preventive or therapeutic measure, and Roman numerals I–III indicate the quality of evidence supporting the recommendation. The guidelines include eleven tables pertinent to the prevention and treatment of OIs (Tables 1–11), a figure that pertains to the diagnosis of tuberculosis (Figure 1), a figure that describes immunization recommendations (Figure 2), and an appendix that summarizes recommendations pertinent to prevention of exposure to opportunistic pathogens.

Effect of ART on the Management of OIs

Clinicians treating HIV-infected patients often have to consider two questions related to OIs and ART: 1) when to initiate ART in ART-naïve persons who experience an acute OI, and 2) how ART should be managed for persons who are on ART but who experience an acute OI.

Initiation of ART in the Setting of an Acute OI (Treatment-Naïve Patients)

When an acute OI is present, initiation of ART is usually expected to improve immune function and contribute to faster resolution of the OI. Initiation of ART has been documented to be effective for OIs for which effective therapy does not exist; cryptosporidiosis, microsporidiosis, and progressive multifocal leukoencephalopathy (PML) might resolve or at least stabilize after the institution of effective ART (50–*52*). For Kaposi's sarcoma (KS), initiation of ART has been documented to lead to resolution of lesions in the absence of specific therapy for the sarcoma (*53*). The initiation of ART in the setting of an acute OI also has preventive benefit; a second OI is less likely to occur if ART is started promptly rather than delaying the initiation of ART.

Starting ART in the setting of an acute OI has several potential disadvantages. Severely ill patients might not absorb ART drugs, leading to subtherapeutic serum levels and the development of antiretroviral drug resistance. ART toxicities might be confused with disease manifestations or toxicities associated with drugs used for treating patients with an OI. Drug-drug interactions among ART and anti-OI drugs might be difficult to manage. Renal or hepatic dysfunction during acute OIs might make dosing of ART drugs difficult to estimate. Finally, IRIS events can occur and cause manifestations that are difficult to distinguish from other clinical conditions.

The term IRIS has been used to describe a group of clinical syndromes associated with immune reconstitution that have been observed most commonly for mycobacterial infections (TB and disseminated MAC disease), but also for other OIs, including *Pneumocystis jirovecii* pneumonia (PCP), toxoplasmosis, hepatitis B and hepatitis C viruses, cytomegalovirus (CMV) infection, varicella-zoster virus (VZV) infection, cryptococcal infection, histoplasmosis, and PML (*54–65*). IRIS manifestations are diverse and have not been defined precisely; they are usually characterized by fever and worsening of the clinical manifestations of the underlying OI. These clinical manifestations might be at the site of previously recognized opportunistic disease or might "unmask" disease at new sites not previously known to be infected by the pathogen. They also might represent a response to a previously unrecognized additional pathogen. The majority of patients who manifest IRIS do so within the first 4–8 weeks after starting ART, and have had high viral loads and low $CD4^+$ T-lymphocyte ($CD4^+$) counts. However, IRIS has occurred weeks after ART was started and in sequestered sites such as bone.

Diagnosis of IRIS is clinically challenging and involves differentiation from progression of the initial OI (including the possibility of antimicrobial resistance and treatment failure), development of a new OI, unrelated organ dysfunction, or drug toxicity. Therapy for IRIS has been empiric. No well-controlled trials exist to help decide when nonsteroidal drugs or corticosteroids are needed or when ART should be suspended. The inflammation might take weeks or months to subside. IRIS does not appear to have favorable or unfavorable implications about patient survival, with the possible exception of IRIS associated with cryptococcal meningitis (*66, 67*).

For these reasons, no consensus has been reached concerning the optimal time to start ART in the setting of a recently diagnosed OI. However, one recently completed randomized clinical trial has demonstrated a clinical and survival benefit of starting ART early, within the first 2 weeks, of initiation of treatment for an acute OI, excluding TB (*68*). The majority of OIs represented in this study were PCP and invasive bacterial infections, although cryptococcal, other fungal diseases, and disseminated MAC disease occurred in substantial numbers; the results suggest that unless other individual compelling contraindications are present, early initiation of ART near the time of initiating OI treatment should be considered for most patients with an acute OI, excluding TB. Other elements that should be considered when making this decision are degree of immunosuppression, availability of effective therapy for the OI, risk for drug interactions, overlapping drug toxicities, risk for the consequences of the development of IRIS, and

willingness of the patients to adhere to their drug regimens. In cases of cryptosporidiosis, microsporidiosis, PML, KS, PCP, and invasive bacterial infections, the early benefits of ART outweigh increased risk related to these other factors and ART should be started as soon as possible. In the setting of TB disease, awaiting a response to OI therapy might be warranted before initiating ART.

Management of Acute OIs in Patients Receiving ART

OIs that occur after patients have been started on ART can be categorized into three groups. The first group includes OIs that occur shortly after initiating ART (within 12 weeks). These cases might be subclinical infections that have been unmasked by early immune reconstitution or simply OIs that occurred because of advanced immunosuppression and are not considered to represent early failure of ART. Many of these cases represent IRIS *(54,56,69–72)*.

The second group includes OIs that occur >12 weeks after initiation of ART among patients with suppressed HIV ribonucleic acid (RNA) levels and sustained $CD4^+$ counts >200 cells/μL (*73,74*). Determining whether these represent a form of IRIS rather than incomplete immunity with the occurrence of a new OI is difficult. The third group includes OIs that occur among patients who are experiencing virologic and immunologic failure while on ART. These represent clinical failure of ART.

When an OI occurs within 12 weeks of starting ART, treatment for the OI should be started and ART should be continued. When an OI occurs despite complete virologic suppression (i.e., late OI), therapy for the OI should be initiated and ART should be continued. If the $CD4^+$ response to ART has been suboptimal, modification of the ART regimen may be considered, although no evidence exists to indicate that changing the ART regimen in this setting will improve the $CD4^+$ response. When an OI occurs in the setting of virologic failure, OI therapy should be started, antiretroviral resistance testing should be performed, and the ART regimen should be modified, if possible, to achieve better virologic control.

Special Considerations During Pregnancy

No large studies have been conducted concerning the epidemiology or manifestations of HIV-associated OIs among pregnant women. No data demonstrate that the spectrum of OIs differs from that among nonpregnant women with comparable $CD4^+$ counts.

Physiologic changes during pregnancy can complicate the recognition of OIs and complicate pharmacokinetics. Factors to consider include the following (*75*):

- Increased cardiac output by 30%–50% with concomitant increase in glomerular filtration rate and renal clearance.
- Increased plasma volume by 45%–50% while red cell mass increases only by 20%–30%, leading to dilutional anemia.
- Tidal volume and pulmonary blood flow increase, possibly leading to increased absorption of aerosolized medications. The tidal volume increase of 30%–40% should be considered if ventilatory assistance is required.
- Placental transfer of drugs, increased renal clearance, altered gastrointestinal absorption, and metabolism by the fetus might affect maternal drug levels.
- Limited pharmacokinetic data are available; use usual adult doses based on current weight, monitor levels if available, and consider the need to increase doses if the patient is not responding as expected.

Fetal risk is not increased with cumulative radiation doses below 5 rads; the majority of imaging studies result in radiation exposure to the fetus that is lower than the 5-rad recommended limit. In humans, the primary risks associated with high-dose radiation exposure are growth restriction, microcephaly, and developmental disabilities. The most vulnerable period is 8–15 menstrual weeks of gestation with minimal risk before 8 weeks and after 25 weeks. The apparent threshold for development of mental retardation is 20–40 rads, with risk of more serious mental retardation increasing linearly with increasing exposures above this level. Among children, risk for carcinogenesis might be increased approximately 1 per 1,000 or less per rad of in utero radiation exposure (*76*). Therefore, pregnancy should not preclude usual diagnostic evaluation when an OI is suspected (*76–78*). Abdominal shielding should be used when feasible to further limit radiation exposure to the fetus. Experience with use of magnetic resonance imaging (MRI) in pregnancy is limited, but no adverse fetal effects have been noted (*76*).

Other procedures necessary for diagnosis of suspected OIs should be performed in pregnancy as indicated for nonpregnant patients. A pregnant women who is >20 weeks of gestation should not lie flat on her back but should have her left hip elevated with a wedge to displace the uterus off the great vessels and prevent supine hypotension. Oxygenation should be monitored when pregnant patients are positioned such that ventilation or perfusion might be compromised.

For pregnant women who have had an OI diagnosed and are not on ART, immediate initiation of ART with OI therapy should be encouraged to minimize the risk for perinatal transmission of HIV (*79*). Decisions about immediate versus delayed initiation of ART in pregnancy should include con-

sideration of gestational age, maternal HIV RNA levels and clinical condition, and potential toxicities and interactions between ART and OI drugs.

After first-trimester exposure to agents of uncertain teratogenic potential, a detailed ultrasound examination at 18–20 weeks should be conducted to detect possible major anomalies. For women who receive drugs that have not been extensively evaluated during pregnancy, an ultrasound should be conducted every 4–6 weeks to assess fetal growth and fluid volume, with antepartum testing if growth lag or decreased fluid are noted. Women in the third trimester of pregnancy should be instructed in daily fetal movement counting to detect decreased activity that might indicate fetal compromise (*80*).

Disease Specific Recommendations

Pneumocystis Pneumonia

Epidemiology

Pneumocystis pneumonia (PCP) is caused by *Pneumocystis jirovecii,* a ubiquitous organism that is classified as a fungus but that also shares biologic characteristics with protozoa. The taxonomy of the organism has been changed; *Pneumocystis carinii* now refers only to the pneumocystis that infects rodents, and *Pneumocystis jirovecii* refers to the distinct species that infects humans. The abbreviation PCP is still used to designate *Pneumocystis* pneumonia. Initial infection with *P. jirovecii* usually occurs in early childhood; two thirds of healthy children have antibody to *P. jirovecii* by age 2–4 years (*81*). Rodent studies and case clusters among immunosuppressed patients suggest that *Pneumocystis* spreads by the airborne route. Disease probably occurs by new acquisition of infection and by reactivation of latent infection (*82–84*). Before the widespread use of primary PCP prophylaxis and ART, PCP occurred in 70%–80% of patients with AIDS (*85*); the course of treated PCP was associated with a mortality of 20%–40% in persons with profound immunosuppression. Approximately 90% of cases occurred among patients with $CD4^+$ counts of <200 cells/μL. Other factors associated with a higher risk for PCP included $CD4^+$ cell percentage <14%, previous episodes of PCP, oral thrush, recurrent bacterial pneumonia, unintentional weight loss, and higher plasma HIV RNA (*86,87*).

Incidence of PCP has declined substantially with widespread use of prophylaxis and ART; recent incidence among patients with AIDS in Western Europe and the United States is 2–3 cases per 100 person-years (*88*). The majority of cases occur among patients who are unaware of their HIV infection or are not receiving ongoing HIV care (*89*) or among those with advanced immunosuppression ($CD4^+$ counts <100 cells/μL) (*90*).

Clinical Manifestations

The most common manifestations of PCP among HIV-infected persons are the subacute onset of progressive dyspnea, fever, nonproductive cough, and chest discomfort that worsens within days to weeks. The fulminant pneumonia observed among non-HIV-infected patients is less common (*91,92*).

In mild cases, pulmonary examination is usually normal at rest. With exertion, tachypnea, tachycardia, and diffuse dry ("cellophane") rales might be observed (*92*). Oral thrush is a common coinfection. Fever is apparent in the majority of cases and might be the predominant symptom among some patients. Extrapulmonary disease is rare but can occur in any organ and has been associated with use of aerosolized pentamidine prophylaxis.

Hypoxemia, the most characteristic laboratory abnormality, might range from mild (room air arterial oxygen [pO2] of $\geq$70 mm Hg or alveolar-arterial O2 difference, [A-a] DO2 <35 mm Hg) to moderate ([A-a] DO2 >35 and <45 mm Hg) to severe levels ([A-a] DO2 >45 mm Hg). Oxygen desaturation with exercise is indicative of an abnormal A-a gradient but is nonspecific (*93*). Elevation of lactate dehydrogenase levels to >500 mg/dL is common but nonspecific (*94*). The chest radiograph typically demonstrates diffuse, bilateral, symmetrical interstitial infiltrates emanating from the hila in a butterfly pattern (*92*); however, patients with early disease might have a normal chest radiograph (*95*). In addition, atypical presentations with nodules, blebs and cysts, asymmetric disease, upper lobe localization, and pneumothorax occur. Pneumothorax in a patient with HIV infection should raise the suspicion of PCP (*96,97*). Cavitation, intrathoracic adenopathy, and pleural effusion are uncommon in the absence of other pulmonary pathogens or malignancy, and their presence might indicate an alternative diagnosis. Approximately 13%–18% of patients with documented PCP have another concurrent cause of pulmonary dysfunction (e.g., TB, KS, or bacterial pneumonia) (*98,99*).

Thin-section computerized tomography (CT) demonstrating patchy ground-glass attenuation (*100,101*) or a gallium scan indicating increased pulmonary uptake *(102*) increases the likelihood that a diagnostic study such as bronchoscopy would demonstrate PCP in patients with mild-to-moderate symptoms and a normal chest radiograph and might be useful as adjunctive studies.

Diagnosis

Because the clinical presentation, blood tests, or chest radiographs are not pathognomonic for PCP and the organism cannot be cultivated routinely, histopathologic demonstration of organisms in tissue, bronchoalveolar lavage fluid, or induced sputum samples (*98,99,103,104*) are required for a

definitive diagnosis. Spontaneously expectorated sputum has low sensitivity and should not be submitted to the laboratory to diagnose PCP. Giemsa, Diff-Quik, and Wright stains detect both the cyst and trophozoite forms but do not stain the cyst wall; Gomori methenamine silver, Gram-Weigert, cresyl violet, and toluidine blue stain the cyst wall. Certain laboratories prefer direct immunofluorescent staining. Nucleic acid tests have greater sensitivity but less specificity than colorimetric or immunologic stains and can be combined with noninvasive samples such as induced sputum or oral wash samples; however, their availability is limited (*105–107*). (1→3)ß-D-glucan (a component of fungal cell walls) might be elevated in patients with PCP, but the sensitivity and specificity of this assay to establish a diagnosis of PCP has not been adequately evaluated. (*108*).

Previous studies of stained respiratory tract samples obtained by various methods indicate the following relative diagnostic sensitivities: induced sputum <50%–>90% (the sensitivity and specificity depend on the quality of the specimens and the experience of the microbiologist or pathologist), bronchoscopy with bronchoalveolar lavage 90%–99%, transbronchial biopsy 95%–100%, and open lung biopsy 95%–100%.

Because of the potential for certain processes to have similar clinical manifestations, a specific diagnosis of PCP should be sought rather than relying on a presumptive diagnosis, especially in patients with moderate-to-severe disease. Treatment can be initiated before making a definitive diagnosis because organisms persist in clinical specimens for days or weeks after effective therapy is initiated (*104*).

Preventing Exposure

Certain authorities might recommend that persons who are at risk for PCP not share a hospital room with a patient who has PCP, a recommendations based on animal studies and anecdotal human experience. Data are insufficient to support this recommendation as standard practice **(CIII)**.

Preventing Disease

Initiating Primary Prophylaxis

HIV-infected adults and adolescents, including pregnant women and those on ART, should receive chemoprophylaxis against PCP if they have a $CD4^+$ count of <200 cells/μL **(AI)** or a history of oropharyngeal candidiasis **(AII)** (*32,85,86*). Persons who have a $CD4^+$ cell percentage of <14% or a history of an AIDS-defining illness, but do not otherwise qualify, should be considered for prophylaxis **(BII)** (*32,85,86*). When monitoring $CD4^+$ counts frequently (e.g., every 1–3 months) is not possible, initiating chemoprophylaxis at a $CD4^+$ count of >200, but <250 cells/μL, also should be considered **(BII)** (*86*).

TMP-SMX is the recommended prophylactic agent **(AI)** (*32,109–111*). One double-strength tablet daily is the preferred regimen **(AI)**. However, one single-strength tablet daily (*111*) also is effective and might be better tolerated than one double-strength tablet daily **(AI)**. One double-strength tablet three times weekly also is effective **(BI)** (*112*). TMP-SMX at a dose of one double-strength tablet daily confers cross-protection against toxoplasmosis (*113*) and selected common respiratory bacterial infections (*109,114*). Lower doses of TMP-SMX also likely confer such protection. For patients who have an adverse reaction that is not life threatening, chemoprophylaxis with TMP-SMX should be continued if clinically feasible; for those who have discontinued such therapy because of an adverse reaction, reinstituting TMP-SMX should be strongly considered after the adverse event has resolved **(AII)**. Patients who have experienced adverse events, including fever and rash, might better tolerate reintroduction of the drug with a gradual increase in dose (i.e., desensitization), according to published regimens **(BI)** (*115,116*) or reintroduction of TMP-SMX at a reduced dose or frequency **(CIII)**; as many as 70% of patients can tolerate such reinstitution of therapy (*114*).

If TMP-SMX cannot be tolerated, alternative prophylactic regimens include dapsone **(BI)** (*109*), dapsone plus pyrimethamine plus leucovorin **(BI)** (*117–119*), aerosolized pentamidine administered by the Respirgard II nebulizer (manufactured by Marquest, Englewood, Colorado) **(BI)** (*110*), and atovaquone **(BI)** (*120,121*). Atovaquone is as effective as aerosolized pentamidine (*120*) or dapsone **(BI)** (*121*) but is substantially more expensive than the other regimens. For patients seropositive for *Toxoplasma gondii* who cannot tolerate TMP-SMX, recommended alternatives to TMP-SMX for prophylaxis against both PCP and toxoplasmosis include dapsone plus pyrimethamine plus leucovorin **(BI)** (*117–119*) or atovaquone with or without pyrimethamine plus leucovorin **(CIII)**.

Oral pyrimethamine plus sulfadoxine also has activity in preventing PCP **(CIII)** (*122–124*). This combination should not be used in patients with hypersensitivity to sulfonamides. Pyrimethamine plus sulfadoxine has an increased risk for severe cutaneous reactions, including Stevens-Johnson syndrome (*125*), and the long half-life of both pyrimethamine and sulfadoxine will result in a delayed clearance when the drug is stopped. Largely because TMP-SMX has superior safety, widespread availability, and is low cost, oral pyrimethamine plus sulfadoxine should be used rarely in the United States **(CIII)**.

The following regimens cannot be recommended as alternatives because data regarding their efficacy for PCP prophylaxis are insufficient:

- Aerosolized pentamidine administered by other nebulization devices
- Intermittently administered parenteral pentamidine
- Oral clindamycin plus primaquine.

However, clinicians might consider using these agents in unusual situations in which the recommended agents cannot be administered **(CIII)**.

Discontinuing Primary Prophylaxis

Primary pneumocystis prophylaxis should be discontinued for adult and adolescent patients who have responded to ART with an increase in CD4+ counts to >200 cells/μL for >3 months **(AI)**. In observational and randomized studies supporting this recommendation, the majority of patients were taking antiretroviral regimens that included a protease inhibitor (PI), and the majority had a CD4+ count of >200 cells/μL for >3 months before discontinuing PCP prophylaxis (88,126–134). The median CD4+ count at the time prophylaxis was discontinued was >300 cells/μL, most had a CD4+ cell percentage of ≥14 %, and many patients had a sustained suppression of HIV plasma RNA levels below detection limits of the assay employed. Median follow-up was 6–19 months.

Discontinuing primary prophylaxis among these patients is recommended because prophylaxis adds limited disease prevention (i.e., for PCP, toxoplasmosis, or bacterial infections) (*127,133*) and because discontinuing drugs reduces pill burden, potential for drug toxicity, drug interactions, selection of drug-resistant pathogens, and cost.

Prophylaxis should be reintroduced if the $CD4^+$ count decreases to <200 cells/μL **(AIII)**.

Treatment of Disease

TMP-SMX is the treatment of choice **(AI)** (*135,136*)**.** The dose must be adjusted for abnormal renal function. Multiple randomized clinical trials indicate that TMP-SMX is as effective as parenteral pentamidine and more effective than other regimens. Adding leucovorin to prevent myelosuppression during acute treatment is not recommended because of questionable efficacy and some evidence for a higher failure rate **(DII)** (*137*)**.** Oral outpatient therapy of TMP-SMX is highly effective among patients with mild-to-moderate disease **(AI)** (*136*)**.**

Mutations associated with resistance to sulfa drugs have been documented, but their effect on clinical outcome is uncertain (*138–140*). Patients who have PCP despite TMP-SMX prophylaxis are usually effectively treated with standard doses of TMP-SMX **(BIII)**.

Patients with documented or suspected PCP and moderate-to-severe disease, as defined by room air pO_2 <70 mm Hg or arterial-alveolar O_2 gradient >35 mm Hg, should receive adjunctive corticosteroids as early as possible, and certainly within 72 hours after starting specific PCP therapy **(AI)** (*141–146*). If steroids are started at a later time, their benefits are unclear, although the majority of clinicians would use them in such circumstances for patients with moderate-to-severe disease **(BIII)**. Methylprednisolone at 75% of the respective prednisone dose can be used if parenteral administration is necessary.

Alternative therapeutic regimens for mild-to-moderate disease include 1) dapsone and TMP **(BI)** (*136,147*) (this regimen might have similar efficacy and fewer side effects than TMP-SMX but is less convenient because of the number of pills), 2) primaquine plus clindamycin **(BI)** (*148–150*) (the clindamycin component can be administered intravenously for more severe cases; however, primaquine is only available orally), and 3) atovaquone suspension **(BI)** (*135,151*) (this is less effective than TMP-SMX for mild-to-moderate disease but has fewer side effects). Patients should be tested for G6PD deficiency whenever possible before administration of primaquine. Alternative therapeutic regimens for patients with moderate-to-severe disease include clindamycin-primaquine or intravenous (IV) pentamidine **(AI)** (*150,152,153*) (usually the drug of second choice for severe disease). Certain clinicians prefer IV pentamidine because of convincing data regarding its high degree of efficacy. Other clinicians prefer clindamycin-primaquine because this combination is better tolerated than pentamidine, although data regarding efficacy are not as robust as the data supporting pentamidine. Aerosolized pentamidine should not be used for the treatment of PCP because of limited efficacy and more frequent relapse **(DI)** (*152,154,155*). Trimetrexate is no longer available commercially.

The recommended duration of therapy for PCP is 21 days **(AII)** (*91*)**.** The probability and rate of response to therapy depend on the agent used, number of previous PCP episodes, severity of illness, degree of immunodeficiency, and timing of initiation of therapy.

Although the overall prognosis of patients whose degree of hypoxemia requires intensive care unit (ICU) admission or mechanical ventilation remains poor, survival in up to 50% of patients requiring ventilatory support has been reported in recent years (*156–158*). Because long-term survival is possible for patients in whom ART is effective, certain patients with AIDS and severe PCP should be offered intensive care unit (ICU) admission or mechanical ventilation when appropriate (e.g., when they have reasonable functional status) **(AII)**.

Because of the potential for additive or synergistic toxicities associated with anti-PCP and antiretroviral therapies, certain health-care providers delay initiation of ART until after the completion of anti-PCP therapy, or until at least 2 weeks after initiating anti-PCP therapy, despite some suggestion of

potential benefit of early ART in the treatment of PCP **(CIII)** (*157,159*).

Monitoring and Adverse Events, Including Immune Reconstitution Inflammatory Syndrome (IRIS)

Careful monitoring during therapy is important to evaluate response to treatment and to detect toxicity as soon as possible. Follow-up after therapy includes assessment for early relapse, especially when therapy has been with an agent other than TMP-SMX or was shortened for toxicity. PCP prophylaxis should be initiated immediately upon completion of therapy and maintained until the $CD4^+$ count is >200 cells/μL.

Adverse reaction rates among patients with AIDS are high for TMP-SMX (20%–85%) (*135,136,147,149,153,161–165*). Common adverse effects are rash (30%–55%) (including Stevens-Johnson syndrome), fever (30%–40%), leukopenia (30%–40%), thrombocytopenia (15%), azotemia (1%–5%), hepatitis (20%), and hyperkalemia. Supportive care for common adverse effects should be attempted before discontinuing TMP-SMX **(AIII)**. Rashes can often be "treated through" with antihistamines, nausea can be controlled with antiemetics, and fever can be managed with antipyretics.

The most common adverse effects of alternative therapies include methemoglobinemia and hemolysis with dapsone or primaquine (especially in those with G6PD deficiency); rash and fever with dapsone (*136,147*); azotemia, pancreatitis, hypo- or hyperglycemia, leukopenia, electrolyte abnormalities, and cardiac dysrhythmia with pentamidine (*151–153,164*); anemia, rash, fever, and diarrhea with primaquine and clindamycin (*136,148,149*); and headache, nausea, diarrhea, rash, and transaminase elevations with atovaquone (*135,163*).

IRIS has been reported following PCP. Most cases have occurred within weeks of the episode of PCP. Reported cases are not sufficient to provide guidance on the optimal time to start ART following a mild or severe case of PCP (*160,166*).

Management of Treatment Failure

Clinical failure is defined as lack of improvement or worsening of respiratory function documented by arterial blood gases (ABGs) after at least 4–8 days of anti-PCP treatment. Treatment failure attributed to treatment-limiting toxicities occurs in up to one third of patients (*136*). Switching to another regimen is the appropriate management for treatment-related toxicity **(BII)**. Failure attributed to lack of drug efficacy occurs in approximately 10% of those with mild-to-moderate disease. No convincing clinical trials exist on which to base recommendations for the management of treatment failure attributed to lack of drug efficacy. Clinicians should wait at least 4–8 days before switching therapy for lack of clinical improvement **(BIII)**. In the absence of corticosteroid therapy, early and reversible deterioration within the first 3–5 days of therapy is typical, probably because of the inflammatory response caused by antibiotic-induced lysis of organisms in the lung. Other concomitant infections must be excluded as a cause for clinical failure (*98,99*); bronchoscopy with bronchoalveolar lavage should be strongly considered to evaluate for this possibility, even if it was conducted before initiating therapy.

If TMP-SMX has failed or must be avoided for toxicity in moderate-to-severe disease, the common practice is to use parenteral pentamidine or primaquine combined with clindamycin **(BII)** (*149,153,165*). As noted above, trimetrexate is no longer available commercially. For mild disease, atovaquone is a reasonable alternative **(BII)**. Although one meta-analysis concluded that the combination of clindamycin and primaquine might be the most effective regimen for salvage therapy (*150*), no prospective clinical trials have evaluated the optimal approach to patients who experience a therapy failure with TMP-SMX.

Preventing Recurrence

Patients who have a history of PCP should be administered chemoprophylaxis for life (i.e., secondary prophylaxis or chronic maintenance therapy) with TMP-SMX unless immune reconstitution occurs as a result of ART (*167*) **(AI)**. For patients who are intolerant of TMP-SMX, alternatives are dapsone, dapsone combined with pyrimethamine, atovaquone, or aerosolized pentamidine.

Discontinuing Secondary Prophylaxis (Chronic Maintenance Therapy)

Secondary prophylaxis should be discontinued for adult and adolescent patients whose $CD4^+$ count has increased from <200 cells/μL to >200 cells/μL for >3 months as a result of ART **(BII)**. Reports from observational studies (*126,132,168,169*) and from two randomized trials (*133,170*) and a combined analysis of eight European cohorts being followed prospectively (*171*) support this recommendation. In these studies, patients had responded to ART with an increase in $CD4^+$ counts to $\geq$200 cells/μL for >3 months. The majority of patients were taking PI-containing regimens. The median $CD4^+$ count at the time prophylaxis was discontinued was >300 cells/μL and most had a $CD4^+$ cell percentage of >14%. The majority of patients had sustained suppression of plasma HIV RNA levels below the detection limits of the assay employed; the longest follow-up was 40 months. If the episode of PCP occurred at a $CD4^+$ count of >200 cells/μL, continuing PCP prophylaxis for life, regardless of how high the $CD4^+$ count rises as a consequence of ART, would be prudent **(CIII)**; however, data regarding the most appropriate approach in this setting are limited.

Discontinuing secondary prophylaxis for patients is recommended because prophylaxis adds limited disease prevention (i.e., for PCP, toxoplasmosis, or bacterial infections) and because discontinuing drugs reduces pill burden, potential for drug toxicity, drug interactions, selection of drug-resistant pathogens, and cost.

Prophylaxis should be reintroduced if the CD4+ count decreases to <200 cells/μL **(AIII)**. If PCP recurs at a CD4+ count of ≥200 cells/μL, lifelong prophylaxis should be administered **(CIII)**.

Special Considerations During Pregnancy

PCP diagnostic considerations for pregnant women are the same as for nonpregnant women. Indications for therapy are the same as for nonpregnant women. The preferred initial therapy during pregnancy is TMP-SMX, although alternate therapies can be used if patients are unable to tolerate or are unresponsive to TMP-SMX (*172*) **(AI)**. In case-control studies, trimethoprim has been associated with an increased risk for neural tube defects and cardiovascular, urinary tract, and multiple anomalies after first-trimester exposure (*173–175*). Epidemiologic data suggest that folic acid supplementation might reduce this risk (*174,175*), but no controlled studies have been done. In a small study, an increased risk for birth defects among infants born to women receiving antiretrovirals and folate antagonists, primarily trimethoprim, was reported, whereas no increase was observed among those with either antiretroviral or folate antagonist exposure alone (*176*). Although first-trimester exposure to trimethoprim might be related to a small increased risk for birth defects, pregnant women in their first trimester with PCP should be treated with TMP-SMX **(AIII)**. Although folic acid supplementation of 0.4 mg/day is routinely recommended for all pregnant women (*177*), data do not indicate if higher levels of supplementation, such as the 4 mg/day recommended for pregnant women with a previous infant with a neural tube defect, would provide added benefit in this situation. Follow-up ultrasound to assess fetal anatomy at 18–20 weeks is recommended **(BIII)**.

Neonatal-care providers should be informed of maternal sulfa or dapsone therapy if used near the delivery date because of the theoretical increased risk for hyperbilirubinemia and kernicterus (*178*).

Pentamidine is embryotoxic but not teratogenic among rats and rabbits (*179*). Adjunctive corticosteroid therapy should be used as indicated in nonpregnant adults (*180–183*) **(AIII)**. Maternal fasting and postprandial glucose levels should be monitored closely when corticosteroids are used in the third trimester because the risk for glucose intolerance is increased.

Rates of preterm labor and preterm delivery are increased with pneumonia during pregnancy. Pregnant women with pneumonia after 20 weeks of gestation should be monitored for evidence of contractions **(BII)**.

Chemoprophylaxis for PCP should be administered to pregnant women the same as for other adults and adolescents **(AIII)**. TMP-SMX is the recommended prophylactic agent; dapsone is an alternative. Because of theoretical concerns regarding possible teratogenicity associated with drug exposures during the first trimester, health-care providers might withhold prophylaxis during the first trimester. In such cases, aerosolized pentamidine can be considered because of its lack of systemic absorption and the resultant lack of exposure of the developing embryo to the drug **(CIII)**.

Toxoplasma gondii Encephalitis

Toxoplasmic encephalitis (TE) is caused by the protozoan *Toxoplasma gondii*. Disease appears to occur almost exclusively because of reactivation of latent tissue cysts (*184–187*). Primary infection occasionally is associated with acute cerebral or disseminated disease.

Epidemiology

Seroprevalence varies substantially among different communities (e.g., approximately 15% in the United States and 50%–75% in certain European countries) (*187,188*). In the pre-ART era, for patients with advanced immunosuppression who were seropositive for *T. gondii* and not receiving prophylaxis with drugs active against *T. gondii*, the 12-month incidence of TE was approximately 33%. The incidence of toxoplasmosis in patients who are seronegative for *T. gondii* is low. If well-documented cases did occur among seronegative patients, they would presumably represent either primary infection, reactivation of latent disease in patients unable to produce detectable antibody, or patients who were tested with insensitive assays. The incidence and associated mortality in Europe and the United States have decreased substantially with the initiation of ART and the broad use of prophylaxis regimens active against *T. gondii (189,190)*.

Clinical disease is rare among patients with CD4+ counts >200 cells/μL. The greatest risk occurs among patients with a CD4+ count <50 cells/μL (*184–186,190*). Primary infection occurs after eating undercooked meat containing tissue cysts or ingesting oocysts that have been shed in cat feces and have sporulated in the environment (sporulation requires at least 24 hours). No transmission of the organism occurs by person-to-person contact.

Clinical Manifestations

The most common clinical presentation of *T. gondii* infection among patients with AIDS is focal encephalitis with headache, confusion, or motor weakness and fever (*184–186*). Physical

examination might demonstrate focal neurological abnormalities, and in the absence of treatment, disease progression results in seizures, stupor, and coma. Retinochoroiditis, pneumonia, and evidence of other multifocal organ system involvement can be observed after dissemination of infection but are rare manifestations in this patient population. CT scan or MRI of the brain will typically show multiple contrast-enhancing lesions, often with associated edema (*184,185,191–193*). However, toxoplasmosis also can manifest as single lesions in the brain.

Diagnosis

HIV-infected patients with TE are almost uniformly seropositive for anti-toxoplasma immunoglobulin G (IgG) antibodies (*184–186,194*). The absence of IgG antibody makes a diagnosis of toxoplasmosis unlikely but not impossible. Anti-toxoplasma immunoglobulin M (IgM) antibodies are usually absent. Quantitative antibody titers are not diagnostically useful.

Definitive diagnosis of TE requires a compatible clinical syndrome; identification of one or more mass lesions by CT, MRI, or other radiographic testing; and detection of the organism in a clinical sample. For TE, this requires a brain biopsy, which is most commonly performed by a stereotactic CT-guided needle biopsy. Organisms are demonstrable with hematoxylin and eosin stains, although immunoperoxidase staining by experienced laboratories might increase sensitivity (*195*). Detection of *T. gondii* by polymerase chain reaction (PCR) in cerebrospinal fluid (CSF) has produced disappointing results; although specificity is high (96%–100%), sensitivity is low (50%) and the results usually are negative once specific anti-toxoplasma therapy has been started (*196,197*).

The differential diagnosis of focal neurological disease in patients with AIDS includes central nervous system (CNS) lymphoma; mycobacterial infection (especially TB); fungal infection (e.g., cryptococcosis); Chagas disease; bacterial abscess; and rarely PML, which can be distinguished on the basis of imaging studies (PML lesions typically involve white matter rather than gray matter, are noncontrast enhancing, and produce no mass effect).

The majority of clinicians rely initially on an empiric diagnosis, which can be established as an objective response, on the basis of clinical and radiographic improvement, to specific anti-*T. gondii* therapy in the absence of a likely alternative diagnosis. Brain biopsy is reserved for patients who fail to respond to specific therapy. In patients with contrast-enhancing mass lesions, detection of Epstein-Barr virus (EBV) by PCR in CSF is highly suggestive of CNS lymphoma (*198,199*). Positron emission tomography (PET) (*192*) or single-photon emission computed tomography (SPECT) scanning (*193*) might be helpful for distinguishing between TE and primary CNS lymphoma, but no imaging technique is completely specific.

Preventing Exposure

HIV-infected persons should be tested for IgG antibody to *Toxoplasma* soon after the diagnosis of HIV infection to detect latent infection with *T. gondii* **(BIII)**.

HIV-infected persons, including those who lack IgG antibody to *Toxoplasma*, should be counseled regarding sources of *Toxoplasma* infection. To minimize risk for acquiring toxoplasmosis, HIV-infected persons should be advised not to eat raw or undercooked meat, including undercooked lamb, beef, pork, or venison **(BIII)**. Specifically, lamb, beef, venison, and pork should be cooked to an internal temperature of 165ºF–170ºF (*200*); meat cooked until it is no longer pink inside usually has an internal temperature of 165ºF–170ºF and therefore, from a more practical perspective, satisfies this requirement. To minimize the risk for acquiring toxoplasmosis, HIV-infected persons should wash their hands after contact with raw meat and after gardening or other contact with soil; in addition, they should wash fruits and vegetables well before eating them raw **(BIII)**. If the patient owns a cat, the litter box should be changed daily, preferably by an HIV-negative, nonpregnant person; alternatively, patients should wash their hands thoroughly after changing the litter box **(BIII)**. Patients should be encouraged to keep their cats inside and not to adopt or handle stray cats **(BIII)**. Cats should be fed only canned or dried commercial food or well-cooked table food, not raw or undercooked meats **(BIII)**. Patients need not be advised to part with their cats or to have their cats tested for toxoplasmosis **(EII)**.

Preventing Disease

Initiating Primary Prophylaxis

Toxoplasma-seropositive patients who have a $CD4^+$ count of <100 cells/μL should be administered prophylaxis against TE **(AII)** (*113*). The double-strength tablet daily dose of TMP-SMX recommended as the preferred regimen for PCP prophylaxis also is effective against TE and is therefore recommended **(AII)** (*113*). TMP-SMX, one double-strength tablet three times weekly, is an alternative **(BIII)**. If patients cannot tolerate TMP-SMX, the recommended alternative is dapsone-pyrimethamine plus leucovorin, which is also effective against PCP **(BI)** (*117–119*)**.** Atovaquone with or without pyrimethamine/leucovorin also can be considered **(CIII)**. Prophylactic monotherapy with dapsone, pyrimethamine, azithromycin, or clarithromycin cannot be recommended on the basis of available data **(DII)**. Aerosolized pentamidine does not protect against TE and is not recommended **(EI)** (*109,113*)**.**

Toxoplasma-seronegative persons who are not taking a PCP prophylactic regimen known to be active against TE (e.g., aerosolized pentamidine) should be retested for IgG antibody to *Toxoplasma* when their CD4+ counts decline to <100 cells/μL to determine whether they have seroconverted and are therefore at risk for TE **(CIII)**. Patients who have seroconverted should be administered prophylaxis for TE as described previously **(AII)**.

Discontinuing Primary Prophylaxis

Prophylaxis against TE should be discontinued among adult and adolescent patients who have responded to ART with an increase in CD4+ counts to >200 cells/μL for >3 months **(AI)**. Multiple observational studies (*126,132,201*) and two randomized trials (*127,202*) have reported that primary prophylaxis can be discontinued with minimal risk for developing TE among patients who have responded to ART with an increase in CD4+ count from <200 cells/μL to >200 cells/μL for >3 months. In these studies, the majority of patients were taking PI-containing regimens and the median CD4+ count at the time prophylaxis was discontinued was >300 cells/μL. At the time prophylaxis was discontinued, the majority of patients had sustained suppression of plasma HIV RNA levels below the detection limits of available assays; the median follow-up was 7–22 months. Although patients with CD4+ counts of <100 cells/μL are at greatest risk for having TE, the risk for TE occurring when the CD4+ count has increased to 100–200 cells/μL has not been studied as rigorously as an increase to >200 cells/μL. Thus, the recommendation specifies discontinuing prophylaxis after an increase to >200 cells/μL. Discontinuing primary TE prophylaxis is recommended because prophylaxis at CD4+ count >200 cells/ μL adds limited disease prevention for toxoplasmosis and because discontinuing drugs reduces pill burden, potential for drug toxicity, drug interaction, selection of drug-resistant pathogens, and cost. Prophylaxis for TE should be reintroduced if the CD4+ count decreases to <100–200 cells/μL **(AIII)**.

Treatment of Disease

The initial therapy of choice for TE consists of the combination of pyrimethamine plus sulfadiazine plus leucovorin **(AI)** (*203–206*)**.** Pyrimethamine penetrates the brain parenchyma efficiently even in the absence of inflammation (*207*). Use of leucovorin reduces the likelihood of the hematologic toxicities associated with pyrimethamine therapy (*208,209*). The preferred alternative regimen for patients with TE who are unable to tolerate or who fail to respond to first-line therapy is pyrimethamine plus clindamycin plus leucovorin **(AI)** (*203,204*)**.**

TMP-SMX was reported in a small (77 patients) randomized trial to be effective and better tolerated than pyrimethamine-sulfadiazine (*210*). On the basis of less in vitro activity and less experience with TMP-SMX, treatment with this drug may be considered an option **(BI)**. For patients who cannot take an oral regimen, no well-studied options exist. No parenteral formulation of pyrimethamine exists; the only widely available parenteral sulfonamide is the sulfamethoxazole component of TMP-SMX. Certain specialists will treat severely ill patients initially requiring parenteral therapy for TE with parenteral TMP-SMX or oral pyrimethamine plus parenteral clindamycin **(CIII)**.

The following regimens have been show to be effective in the treatment of TE in at least two nonrandomized, uncontrolled trials, although their relative efficacy compared with the previous regimens is unknown: atovaquone (with meals or oral nutritional supplements) plus either pyrimethamine plus leucovorin or sulfadiazine or, for patients intolerant of both pyrimethamine and sulfadiazine, as a single agent **(BII)** (*211–214*) (if atovaquone is used alone, clinicians should be aware that different patients experience a high variability of absorption of the drug; plasma levels of >18.5 μg/mL are associated with an improved response rate but measurements are not routinely available) (*212–214*); and azithromycin plus pyrimethamine plus leucovorin daily **(BII)** (*215,216*).

The following regimens have been reported to have activity in the treatment of TE in small cohorts of patients or in case reports of one or several patients: clarithromycin plus pyrimethamine **(CIII)** (*217*); 5-fluorouracil plus clindamycin **(CIII)** (*218*), dapsone plus pyrimethamine plus leucovorin **(CIII)** (*219*); and minocycline or doxycycline combined with either pyrimethamine plus leucovorin, sulfadiazine, or clarithromycin **(CIII)** (*220,221*). Although the clarithromycin dose used in the only published study was 1g twice a day, doses >500 mg have been associated with increased mortality in HIV-infected patients treated for disseminated MAC. Doses >500 mg twice a day should not be used **(DIII)**.

Acute therapy for TE should be continued for at least 6 weeks, if there is clinical and radiologic improvement **(BII)** (*184–187*). Longer courses might be appropriate if clinical or radiologic disease is extensive or response is incomplete at 6 weeks. CNS lesions must not have contrast enhancement on CT/MRI. Adjunctive corticosteroids (e.g., dexamethasone) should be administered to patients with TE when clinically indicated only for treatment of a mass effect associated with focal lesions or associated edema **(BIII)**. Because of the potential immunosuppressive effects of corticosteroids, they should be discontinued as soon as clinically feasible. Patients receiving corticosteroids should be monitored closely for the

development of other OIs, including cytomegalovirus (CMV) retinitis and TB disease.

Anticonvulsants should be administered to patients with TE who have a history of seizures **(AIII)**, but should not be administered as prophylactics to all patients **(DIII)**. Anticonvulsants, if administered, should be continued at least through the period of acute therapy.

Monitoring and Adverse Events, Including Immune Reconstitution Inflammatory Syndrome (IRIS)

Changes in antibody titers are not useful for monitoring responses to therapy. Patients with TE should be monitored routinely for adverse events and clinical and radiologic improvement **(AIII)**. Common pyrimethamine toxicities include rash, nausea, and bone marrow suppression (neutropenia, anemia, and thrombocytopenia) that can often be reversed by increasing the dose of leucovorin to 50–100 mg/day administered in divided doses **(CIII)**.

Common sulfadiazine toxicities include rash, fever, leukopenia, hepatitis, nausea, vomiting, diarrhea, and crystalluria. Common clindamycin toxicities include fever, rash, nausea, diarrhea (including pseudomembranous colitis or diarrhea related to *Clostridium difficile* toxin), and hepatotoxicity. Common TMP-SMX toxicities include rash, fever, leukopenia, thrombocytopenia, and hepatotoxicity. Drug interactions between anticonvulsants and antiretroviral agents should be evaluated carefully and doses adjusted according to established guidelines.

Several cases of neurologic disease have been attributed to immune reconstitution and toxoplasmosis, but more data are needed to verify that such cases are IRIS related to *T. gondii* (*222*).

Management of Treatment Failure

A brain biopsy, if not previously performed, should be strongly considered for patients who fail to respond to initial therapy for TE **(BII)** as defined by clinical or radiologic deterioration during the first week despite adequate therapy or lack of clinical improvement within 2 weeks. For those who undergo brain biopsy and have confirmed histopathologic evidence of TE, a switch to an alternative regimen as previously described should be considered **(BIII)**. Recurrence of disease during secondary maintenance therapy following an initial clinical and radiographic response is unusual if patients adhere to their regimens.

Preventing Recurrence

Patients who have completed initial therapy for TE should be administered lifelong suppressive therapy (i.e., secondary prophylaxis or chronic maintenance therapy) **(AI)** (*203,204*) unless immune reconstitution occurs as a consequence of ART, in which case discontinuation of treatment is indicated. The combination of pyrimethamine plus sulfadiazine plus leucovorin is highly effective as suppressive therapy for patients with TE **(AI)** and provides protection against PCP **(AII)**. Although sulfadiazine is routinely dosed as a four times a day regimen, a pharmacokinetic study suggests bioequivalence when using the same total daily dose in a twice a day or four times a day regimen (*223*), and limited clinical experience suggests that twice a day dosing is effective (*224*). A commonly used regimen as suppressive therapy for patients with TE who cannot tolerate sulfa drugs is pyrimethamine plus clindamycin **(BI)**. Because of the high failure rate observed with lower doses (*203*), a dose of 600 mg clindamycin every 8 hours is recommended **(CIII)**. However, this regimen does not provide protection against PCP **(AII)**, and thus an additional agent (e.g., aerosol pentamidine) must be used. Atovaquone with or without pyrimethamine or sulfadiazine is also active against both TE and PCP **(BII)** but is substantially more expensive (*121*). A small uncontrolled study in patients who had been receiving ART for a median of 13 months suggested that TMP-SMX could be used as a suppressive regimen to reduce pill burden (*225*).

Discontinuing Secondary Prophylaxis (Chronic Maintenance Therapy)

Adult and adolescent patients receiving secondary prophylaxis (i.e., chronic maintenance therapy) for TE are at low risk for recurrence of TE when they have successfully completed initial therapy for TE, remain asymptomatic with regard to signs and symptoms of TE, and have a sustained increase in their $CD4^+$ counts of >200 cells/μL after ART (e.g., >6 months) (*132,168,202,226*). Although the numbers of patients who have been evaluated in observational studies and in one randomized clinical trial remain limited, and occasional recurrences have been reported, on the basis of these observations and inference from more extensive cumulative data indicating the safety of discontinuing secondary prophylaxis for other OIs during advanced HIV disease, discontinuing chronic maintenance therapy among such patients is a reasonable consideration **(BI)**. Certain specialists recommend obtaining an MRI of the brain as part of their evaluation to determine whether discontinuing therapy is appropriate by assessing whether the brain lesions had resolved.

Secondary prophylaxis (chronic maintenance therapy) for TE should be reintroduced if the $CD4^+$ count decreases to <200 cells/μL **(AIII)**.

Special Considerations During Pregnancy

Documentation of maternal *T. gondii* serologic status should be obtained during pregnancy. Indications for treatment of *T. gondii* during pregnancy should be based on confirmed or

suspected symptomatic disease in the mother. Pediatric-care providers should be informed if the HIV-infected mother is seropositive for *T. gondii* infection to allow evaluation of the neonate for evidence of congenital infection. Pregnant HIV-infected women with suspected or confirmed primary *T. gondii* infection during pregnancy should be managed in consultation with a maternal-fetal medicine or other appropriate specialist **(BIII)** (*227*)**.**

Treatment should be the same as in nonpregnant adults (**BIII**). Although pyrimethamine has been associated with birth defects in animals, limited human data have not suggested an increased risk for defects and, therefore, it can be administered to pregnant women (*228–230*). Pediatric providers should be notified if sulfadiazine is continued until delivery because its use might increase the risk for neonatal hyperbilirubinemia and kernicterus *(230*).

Although perinatal transmission of *T. gondii* normally occurs only with acute infection in the immunocompetent host, case reports have documented occurrences of transmission with reactivation of chronic infection in HIV-infected women with severe immunosuppression (*229,231*). Pregnant, HIV-infected women who have evidence of primary toxoplasmic infection or active toxoplasmosis, including TE, should be evaluated and managed during pregnancy in consultation with appropriate specialists **(BIII)**. Because the risk for transmission with chronic infection appears low, routine evaluation of the fetus for infection with amniocentesis or cordocentesis is not indicated. Detailed ultrasound examination of the fetus specifically evaluating for hydrocephalus, cerebral calcifications, and growth restriction should be done for HIV-infected women with suspected primary or symptomatic reactivation of *T. gondii* during pregnancy.

TMP-SMX can be administered for primary prophylaxis against TE as described for PCP **(AIII)**. Secondary prophylaxis should be provided using the same indications as for nonpregnant women. The risks of TMP-SMX in the first trimester, as discussed for PCP, must be balanced against the risk for recurrent TE.

Cryptosporidiosis

Epidemiology

Cryptosporidiosis is caused by various species of the protozoan parasite *Cryptosporidium*, which infect the small bowel mucosa, and in immunosuppressed persons, the large bowel and extra-intestinal sites. Persons at greatest risk for disease have advanced immunosuppression, typically $CD4^+$ counts of <100 cells/μL (*232*). The three most common species infecting humans are *C. hominis*, *C. parvum*, and *C. meleagridis*. Infections are usually caused by one species but might be mixed (*233*).

In developed countries with low rates of environmental contamination where potent ART is widely available, cryptosporidiosis occurs at an incidence of <1 per 100 person-years among persons with AIDS. Infection occurs through ingestion of *Cryptosporidium* oocysts. Viable oocysts in feces can be transmitted directly through contact with infected humans or animals, particularly those with diarrhea. Oocysts can contaminate recreational water sources (e.g., swimming pools, lakes) and public water supplies and might persist despite standard chlorination (see Appendix: Food and Water-Related Exposures). Person-to-person transmission is common, especially among sexually active men who have sex with men (MSM). Young children with cryptosporidial diarrhea might infect adults during diapering and cleaning after defecation.

Clinical Manifestations

Patients with cryptosporidiosis most commonly have acute or subacute onset of profuse, nonbloody, watery diarrhea, accompanied often by nausea, vomiting, and lower abdominal cramping (*234*). Fever is present in approximately one third of patients and malabsorption is common. The epithelium of the biliary tract and the pancreatic duct can be infected with *Cryptosporidium,* leading to sclerosing cholangitis and to pancreatitis secondary to papillary stenosis, particularly among patients with prolonged disease and low $CD4^+$ counts (*235–238*). Pulmonary infections also have been reported (*239,240*).

Diagnosis

Cryptosporidium species can be cultivated in vitro, but not as a routine diagnostic procedure. Diagnosis of cryptosporidiosis can be made by microscopic identification of the oocysts in stool or tissue. Acid-fast staining methods, with or without stool concentration, are most frequently used in clinical laboratories. Oocysts stain varying intensities of red with a modified acid-fast technique, permitting their differentiation from yeasts, which are of similar size and shape but are not acid fast. *Cryptosporidium* oocysts also can be detected by direct immunofluorescence, which offers the greatest sensitivity and specificity, or by enzyme-linked immunosorbent assays (ELISAs) (*241*). Molecular methods such as PCR are predicted to enhance sensitivity further. Cryptosporidial enteritis also can be diagnosed from small intestinal biopsy sections. The organism, which appears basophilic with hematoxylin and eosin staining, occurs alone or in clusters in various developmental stages on the brush border of the mucosal epithelial surfaces.

Among persons with profuse diarrheal illness, a single stool specimen is usually adequate for diagnosis. Among persons

with milder disease, repeat stool sampling is recommended, although no controlled studies have demonstrated the utility of three consecutive stool samples as is the case in *Giardia duodenalis* infection.

Preventing Exposure

HIV-infected persons should be educated and counseled concerning the different ways that *Cryptosporidium* can be transmitted **(BIII)**. Modes of transmission include having direct contact with infected adults, diaper-aged children, and infected animals; coming into contact with contaminated water during recreational activities; drinking contaminated water; and eating contaminated food.

Scrupulous handwashing can reduce the risk for diarrhea in HIV-infected persons, including diarrhea caused by *Cryptosporidium (242)*. HIV-infected persons should be advised to wash their hands after potential contact with human feces (including after diapering small children) and after the following activities: handling pets or other animals, gardening or other contact with soil, before preparing food, before eating, and before and after sex **(BIII)**. HIV-infected persons should avoid unprotected sex practices, especially practices that could lead to direct (e.g., oral-anal) or indirect (e.g., penile-anal) contact with feces. Patients should be advised to use barriers during sex to reduce such exposures (e.g., condoms, dental dams) **(BIII)**.

HIV-infected persons (particularly those with $CD4^+$ counts < 200 cells/μL), should avoid direct contact with diarrhea or stool from pets, particularly any stray pets, or dogs and cats aged <6 months **(BIII)**. Gloves should be worn when handling feces or cleaning areas that might have been contaminated by feces from pets **(BIII)**. HIV-infected persons should limit or avoid direct exposure to calves and lambs (e.g., farms, petting zoos) **(BII)**. Paying attention to hygiene and avoiding direct contact with stool are important when visiting premises where these animals are housed or exhibited.

HIV-infected persons should not drink water directly from lakes or rivers **(AIII)**. Waterborne infection also can result from swallowing water during recreational activities. HIV-infected persons should be aware that lakes, rivers, and salt water beaches and some swimming pools, recreational water parks, and ornamental water fountains might be contaminated with human or animal waste that contains *Cryptosporidium*. They should avoid swimming in water that is likely contaminated and should avoid swallowing water while swimming or playing in recreational water **(BIII)**.

Outbreaks of cryptosporidiosis have been linked to drinking water from municipal water supplies. During outbreaks or in other situations that impose a community advisory to boil water, boiling water for at least 3 minutes will eliminate the risk for cryptosporidiosis **(AIII)**. Using submicron personal-use water filters (home/office types) or bottled water might also reduce the risk for infection from municipal and well water **(CIII)**.

The magnitude of the risk for acquiring cryptosporidiosis from drinking water in a non-outbreak setting is uncertain, and available data are inadequate to recommend that all HIV-infected persons boil water or avoid drinking tap water in non-outbreak settings. However, HIV-infected persons who wish to take independent action to reduce the risk for waterborne cryptosporidiosis might take precautions similar to those recommended during outbreaks. Persons who opt to use a personal-use filter or bottled water should be aware of the complexities involved in selecting appropriate products, the lack of enforceable standards for the destruction or removal of oocysts, the costs of the products, and the logistic difficulty of using these products consistently.

Persons who take precautions to avoid acquiring cryptosporidiosis from drinking water should be advised that ice made from contaminated tap water also can be a source of infection. Such persons also should be aware that fountain beverages served in restaurants, bars, theaters, and other places also might pose a risk because these beverages, and the ice they contain, are usually made from tap water. Nationally distributed brands of bottled or canned carbonated soft drinks are safe to drink. Commercially packaged noncarbonated soft drinks and fruit juices that do not require refrigeration until after they are opened (i.e., can be stored unrefrigerated on grocery shelves) are also safe. Nationally distributed brands of frozen fruit juice concentrate are safe if the user reconstitutes them with water from a safe water source. Fruit juices that must be kept refrigerated from the time they are processed to the time of consumption might be either fresh (i.e., unpasteurized) or heat-treated (i.e., pasteurized); only those juices labeled as pasteurized should be considered free of risk from *Cryptosporidium*. Other pasteurized beverages and beers also are considered safe to drink.

HIV-infected persons should avoid eating raw oysters because cryptosporidial oocysts can survive in oysters for >2 months and have been found in oysters taken from certain commercial oyster beds **(BIII)**. In a hospital, standard precautions (i.e., use of gloves and handwashing after removal of gloves) should be sufficient to prevent transmission of cryptosporidiosis from an infected patient to a susceptible HIV-infected person **(BIII)**. However, because of the potential for fomite transmission, some specialists recommend that HIV-infected persons, specifically persons who are severely immunocompromised, should not share a room with a patient with cryptosporidiosis **(CIII)**.

If HIV-infected persons travel in developing countries, they should be warned to avoid drinking tap water or using tap water to brush their teeth **(BIII)**. Ice that is not made from bottled water also should be avoided. Raw fruits or vegetables that might have been washed in tap water also should be avoided

(BIII). HIV-infected persons also should avoid other sources of *Cryptosporidium* oocytes as much as possible **(BIII)**. These include working directly with people with diarrhea; with farm animals, cattle, and sheep; and with domestic pets that are very young or have diarrhea. If exposure is unavoidable, then the use of gloves and good hand hygiene is recommended.

Preventing Disease

Because chronic cryptosporidiosis occurs primarily in persons with advanced immunodeficiency, appropriate initiation of ART before the patient becomes severely immunosuppressed should prevent this disease **(AIII)**. Rifabutin (RIF) or clarithromycin, when taken for MAC prophylaxis, have been found to protect against cryptosporidiosis (*243,244*). However, data are insufficient to warrant a recommendation for using rifabutin or clarithromycin as chemoprophylaxis for cryptosporidiosis.

Treatment of Disease

In the setting of severe immunosuppression, ART with immune restoration to a $CD4^+$ count >100 cells/μL leads to resolution of clinical cryptosporidiosis (*50,245*) and is the mainstay of treatment. Therefore, patients with cryptosporidiosis should be offered ART as part of the initial management of their infection **(AII)**. Management should include symptomatic treatment of diarrhea **(AIII)**. Rehydration and repletion of electrolyte losses by either the oral or IV route are important. Severe diarrhea can exceed >10 L/day among patients with AIDS, often requiring intensive support. Oral rehydration should be pursued aggressively with oral rehydration solutions **(AIII)**.

Multiple agents have been investigated in small randomized controlled clinical trials of HIV-infected adults, including nitazoxanide, paromomycin, spiramycin, bovine hyperimmune colostrum, and bovine dialyzable leukocyte extract. No pharmacologic or immunologic therapy directed specifically against *C. parvum* has been shown to be consistently effective when used without ART (*246,247*).

Nitazoxanide is an orally administered nitrothiazole benzamide with in vivo activity against a broad range of helminths, bacteria, and protozoa (*248–250*). It has been approved by the Food and Drug Administration (FDA) for treatment of *C. parvum* in children and adults. When administered for 3 days at 500 mg twice daily to HIV-uninfected adults with cryptosporidiosis, nitazoxanide resulted in higher rates of diarrhea resolution and oocyst-free stools than placebo (*248*). HIV-infected adults with cryptosporidiosis with $CD4^+$ >50 cells/μL treated with 500–1,000 mg twice daily of nitazoxanide for 14 days experienced substantially higher rates of parasitological cure and resolution of diarrhea than persons receiving placebo treatment (*249*). Data from a compassionate use program before the advent of combination ART, which included primarily white male adults with a median $CD4^+$ count ≤50 cells/μL, reported that a majority of patients experienced some degree of clinical response (reduction in frequency of total stool and of liquid stools), usually within the first week of treatment (*251*). Adverse events associated with nitazoxanide are limited and typically mild, and no important drug-drug interactions have been reported. Because of the clinical significance of cryptosporidiosis, a trial of nitazoxanide in conjunction with ART, but never instead of ART, may be considered **(CIII)**.

Paromomycin is a nonabsorbable aminoglycoside indicated for the treatment of intestinal amebiasis but not specifically approved for cryptosporidiosis. It is effective in high doses for the treatment of cryptosporidiosis in animal models (*252*). A meta-analysis of 11 published studies of paromomycin in humans reported a response rate of 67%; however, relapses were common, with long-term success rates of only 33%. A Cochrane review and a meta-analysis of the two randomized controlled trials comparing paromomycin with placebo among patients with AIDS found the drug was no more effective than placebo at reducing diarrheal frequency or parasite burden (*246,247,253,254*). In persons with $CD4^+$ counts <100 cells/μL, a substantial clinical response to paromomycin is rare. Therefore, data do not support a recommendation for the use of paromomycin for cryptosporidiosis **(DII)**.

Treatment with antimotility agents (e.g., loperamide, tincture of opium) can palliate symptoms by reducing diarrheal frequency and volume, but these agents are not consistently effective **(BIII)**. Octreotide, a synthetic octapeptide analog of naturally occurring somatostatin that is approved for the treatment of secreting tumor-induced diarrhea, is no more effective than other oral antidiarrheal agents and is usually not recommended **(DII)** (*250*).

Monitoring and Adverse Events, Including Immune Reconstitution Inflammatory Syndrome (IRIS)

Patients should be monitored closely for signs and symptoms of volume depletion, electrolyte and weight loss, and malnutrition. Total parenteral nutrition might be indicated in certain patients **(CIII)**.

IRIS has not been described in association with treatment of cryptosporidiosis.

Management of Treatment Failure

Supportive treatment and optimizing ART to achieve full virologic suppression are the only feasible approaches to the management of treatment failure **(AIII)**.

Preventing Recurrence

No pharmacologic interventions are known to be effective in preventing the recurrence of cryptosporidiosis.

Special Considerations During Pregnancy

As with nonpregnant women, initial treatment should rely on rehydration and initiation of ART **(AII)**. Pregnancy should not preclude the use of ART. Nitazoxanide is not teratogenic in animals but human data on use in pregnancy are not available. Nitazoxanide may be used in pregnancy after the first trimester in severely symptomatic pregnant women **(CIII)**.

Microsporidiosis

Epidemiology

Microsporidia are protists related to fungi, defined by the presence of a unique invasive organelle consisting of a single polar tube that coils around the interior of the spore (*255,256*). They are ubiquitous organisms and are likely zoonotic and/or waterborne in origin (*257,258*). The microsporidia reported as pathogens in humans include *Encephalitozoon cuniculi*, *Encephalitozoon hellem*, *Encephalitozoon* (*syn Septata*) *intestinalis*, *Enterocytozoon bieneusi*, *Trachipleistophora hominis*, *Trachipleistophora anthropophthera*, *Pleistophora species*, *P. ronneafiei*, *Vittaforma* (*syn Nosema*) *corneae*, *Microsporidium sp.*, *Nosema ocularum*, *Anncaliia* (*syns Brachiola/Nosema*) *connori*, *Anncaliia* (*syn Brachiola*) *vesicularum*, and *Anncaliia* (*syns Brachiola/Nosema*) *algerae (255–257,259–262*). In the pre-ART era, reported prevalence rates of microsporidiosis varied between 2% and 70% among HIV-infected patients with diarrhea, depending on the diagnostic techniques employed and the patient population described (*255–257,259*). The incidence of microsporidiosis has declined with the widespread use of effective ART, but is still being detected in HIV-infected persons unable to access or continue with ART. Among non-HIV-infected persons, microsporidiosis is being increasingly recognized in children, travelers, organ transplant recipients, and the elderly. In the immunosuppressed host, clinical signs related to microsporidiosis are most commonly observed when the $CD4^+$ count is <100 cells/μL (*255-257,259*).

Clinical Manifestations

The most common manifestation of microsporidiosis is gastrointestinal tract infection with diarrhea; however, encephalitis, ocular infection, sinusitis, myositis, and disseminated infection also are described (*255–257,259*).

Clinical syndromes can vary by infecting species. *E. bieneusi* is associated with malabsorption, diarrhea, and cholangitis. *E. cuniculi* is associated with hepatitis, encephalitis, and disseminated disease. *E. intestinalis* is associated with diarrhea, disseminated infection, and superficial keratoconjunctivitis. *E. hellem* is associated with superficial keratoconjunctivitis, sinusitis, respiratory disease, prostatic abscesses, and disseminated infection. *Nosema*, *Vittaforma*, and *Microsporidium* are associated with stromal keratitis following trauma in immunocompetent hosts. *Pleistophora*, *Anncaliia*, and *Trachipleistophora* are associated with myositis. *Trachipleistophora* is associated with encephalitis and disseminated disease.

Diagnosis

Although microsporidia belonging to the genera *Encephalitozoon*, *Anncaliia*, *Vittaforma*, and *Trachipleistophora* have been cultivated in vitro, *E. bieneusi* has not been successfully cultivated in vitro. Effective morphologic demonstration of microsporidia by light microscopy can be accomplished by staining methods that produce differential contrast between the spores of the microsporidia and the cells and debris in clinical samples (e.g., stool). In addition, because of the small size of the spores (1–5 mm), adequate magnification (e.g., 1,000X) is required for visualization. Chromotrope 2R, calcofluor white (a fluorescent brightener), and Uvitex 2B (a fluorescent brightener) are useful as selective stains for microsporidia in stool and other body fluids (*262*).

In biopsy specimens, microsporidia can be visualized with Giemsa, tissue Gram stains (Brown-Hopps Gram stain), calcofluor white or Uvitex 2B (fluorescent brighteners) staining, Warthin-Starry silver staining, hematoxylin and eosin, or Chromotrope 2A (*262*). In gastrointestinal disease**,** examination of three stools with chromotrope and chemofluorescent stains is often sufficient for diagnosis. If stool examination is negative and microsporidiosis is suspected, a small bowel biopsy should be performed. If the etiologic agent is *Encephalitozoon* or *Trachipleistophora spp.*, examination of urine often also reveals the organism. Determination of the species of microsporidia causing disease can be made by the morphology of the organism demonstrated by transmission electron microscopy, by staining with species-specific antibodies, or by PCR using species- or genus-specific primers (*262*). Assistance of specialists familiar with the species differentiation of microsporidia should be sought.

Preventing Exposure

Patients with AIDS (e.g., $CD4^+$ count <200 cells/μL) should avoid untreated water sources **(AIII).** Otherwise, other than general attention to handwashing and other personal hygiene measures, no precautions to reduce exposure to microsporidia are recommended.

Preventing Disease

No chemoprophylactic regimens are known to be effective in preventing microsporidiosis.

Treatment of Disease

ART with immune restoration (an increase of $CD4^+$ count to >100 cells/μL) is associated with resolution of symptoms of enteric microsporidiosis, including that caused by *E. bieneusi (245,263-265*). All patients should be offered ART as part of the initial management of microsporidial infection **(AII)**. Data suggest that following successful ART, immune reconstitution occurs and enables the patient's own defenses to eradicate microsporidia (*245,264*).

No specific therapeutic agent is available for *E. bieneusi* infection. A controlled clinical trial suggested that *E. bieneusi* might respond to oral fumagillin (60 mg/day), a water-insoluble antibiotic made by *Aspergillus fumigatus* **(BII)** (*266,267*), or to its synthetic analog TNP-470 **(BIII)** (*268*). However, fumagillin and TNP-470 are not available for systemic use in the United States. One report indicated that treatment with nitazoxanide for 60 days might resolve chronic diarrhea caused by *E. bieneusi* in the absence of ART (*269*); however, the effect appeared to be minimal among patients with low $CD4^+$ counts. Therefore, this drug cannot be recommended with confidence **(CIII).**

Albendazole, a benzimidazole that binds to β-tubulin, has activity against many species of microsporidia, but it is not effective against *Enterocytozoon* infections or *V. corneae.* The tubulin genes of both *E. bieneusi (270*) and *V. corneae (271*) have amino acid residues associated with albendazole resistance. Therefore, albendazole is recommended for initial therapy of intestinal and disseminated microsporidiosis caused by microsporidia other than *E. bieneusi* and *V. corneae* **(AII)** (*272–274*).

Itraconazole might be useful in disseminated disease when combined with albendazole, especially in infections caused by *Trachipleistophora* or *Anncaliia* **(CIII).**

Ocular infections caused by microsporidia should be treated with topical Fumidil B (fumagillin bicylohexylammonium) in saline (to achieve a concentration of 70 μg/mL of fumagillin) **(BII)** (*273*). Topical fumagillin is the only formulation available for treatment in the United States and is investigational. Although clearance of microsporidia from the eye can be demonstrated, the organism often is still present systemically and can be detected in urine or in nasal smears. Therefore, the use of albendazole as a companion systemic agent to fumagillin is recommended in ocular infections **(BIII).**

Metronidazole and atovaquone are not active in vitro or in animal models and should not be used to treat microsporidiosis **(DII)**. Fluid support should be offered if diarrhea has resulted in dehydration **(AIII)**. Patients with malnutrition and wasting should be treated with nutritional supplementation **(AIII)**. Antimotility agents can be used if required for diarrhea control **(BIII).**

Monitoring and Adverse Events, Including Immune Reconstitution Inflammatory Syndrome (IRIS)

Albendazole side effects are rare but hypersensitivity (rash, pruritis, fever), neutropenia (reversible), CNS effects (dizziness, headache), gastrointestinal disturbances (abdominal pain, diarrhea, nausea, vomiting), hair loss (reversible), and elevated hepatic enzymes (reversible) have been reported. Albendazole is not known to be carcinogenic or mutagenic. Topical fumagillin has not been associated with substantial side effects. Oral fumagillin has been associated with thrombocytopenia, which is reversible on stopping the drug.

An IRIS has not been described in association with treatment for *E. bieneusi* or non-*E. bieneusi* microsporidiosis.

Management of Treatment Failure

Supportive treatment and optimizing ART to attempt to achieve full virologic suppression are the only feasible approaches to the management of treatment failure **(AIII).**

Preventing Recurrence

Treatment for ocular microsporidiosis should be continued indefinitely because recurrence or relapse might follow discontinuation of treatment **(BIII).** Whether treatment of other manifestations can be safely discontinued after immune restoration with ART is unknown; however, such a practice is reasonable, based on experience with discontinuation of secondary prophylaxis (chronic maintenance therapy) for other OIs present during advanced HIV disease. Therefore, certain specialists recommend discontinuing chronic maintenance therapy if patients no longer have signs and symptoms of microsporidiosis and have a sustained (e.g., >6 months) increase in their $CD4^+$ counts to levels >200 cells/μL after ART **(BIII)** (*245*).

Special Considerations During Pregnancy

The primary approach to treatment of microsporidiosis in pregnancy should be initiation of ART to restore immune function. Among animals (i.e., rats and rabbits), albendazole is embryotoxic and teratogenic at dosages of 20 mg/kg body weight. Therefore, albendazole is not recommended for use among pregnant women **(DIII).** However, well-controlled studies in human pregnancy have not been performed. Systemic fumagillin has been associated with increased resorption and growth retardation in rats. No data on use in human pregnancy are available. However, because of the

antiangiogenic effect of fumagillin, this drug should not be used among pregnant women **(EIII).** Topical fumagillin has not been associated with embryotoxic or teratogenic effects among pregnant women and may be considered when therapy with this agent is appropriate **(CIII).**

Mycobacterium tuberculosis Infection and Disease

Epidemiology

The World Health Organization (WHO) estimates that TB is the cause of death for 13% of persons with AIDS (*275*). TB infection occurs when a susceptible person inhales droplet nuclei containing *Mycobacterium tuberculosis* organisms, generated when persons with pulmonary or laryngeal TB disease cough, sneeze, shout, or sing (*276*). Usually within 2–12 weeks after infection, the immune response limits multiplication of tubercle bacilli. However, viable bacilli persist for years, a condition referred to as latent TB infection (LTBI). Persons with LTBI are asymptomatic and are not infectious. TB disease can develop immediately after exposure (primary disease) or after reactivation of LTBI (reactivation disease). Primary disease accounts for one third or more of cases of TB disease in HIV-infected populations (*277*).

Overall case rates of TB in the United States are declining, with 4.4 new cases of TB disease per 100,000 population (a total of 13,299 cases) reported in 2007 *(278*) and an estimated 4.0% prevalence of LTBI in the general population (*279*). Similarly, health-care–associated outbreaks of TB are now uncommon in the United States, partly because of improved public health and hospital TB-control programs (*280*). The percentage of patients with TB and with known HIV infection also decreased from 15.0% in 2003 to 12.4% in 2006, although the percentage of TB cases with unknown HIV status increased from 28.7% in 2005 to 31.7% in 2006 *(281*), which might reflect either a lack of HIV testing or incomplete reporting of HIV test results (*278*).

The estimated annual risk for active TB among persons with LTBI in the general population is 12.9 per 1,000 person-years of observation. In contrast, rates of progression to active TB among HIV-infected persons with LTBI have ranged from 35 to 162 per 1,000 person-years of observation (*282–284*). Unlike other AIDS-related OIs, $CD4^+$ count is not a reliable predictor of increased risk for TB disease in HIV-infected persons. In both TB-endemic and non-TB-endemic areas, patients can have relatively high $CD4^+$ counts at the time HIV-related TB disease develops. As with HIV-uninfected persons, HIV-infected persons who live or work in high-risk congregate settings such as correctional facilities, health-care facilities, drug-treatment units, or homeless shelters are at increased risk for acquiring TB.

Clinical Manifestations

Persons with LTBI are, by definition, asymptomatic. Among HIV-infected persons, the presentation of active TB disease is influenced by the degree of immunodeficiency (*285,286*). In addition, early after initiating ART in severely immunosuppressed patients, previously unrecognized subclinical TB can be unmasked by reconstitution of the immune system (*287,288*).

In HIV-infected patients without pronounced immunodeficiency (e.g., $CD4^+$ count >350 cells/μL), HIV-related TB clinically resembles TB among HIV-uninfected persons. The majority of patients have disease limited to the lungs, and common chest radiographic manifestations include upper lobe fibronodular infiltrates with or without cavitation (*289*). However, extrapulmonary disease is more common in HIV-infected persons than in HIV-uninfected persons, regardless of $CD4^+$ counts, although clinical manifestations are not substantially different from those described in HIV-uninfected persons. TB must be ruled out in diseases of every organ (*290*) but especially those related to CNS or meningeal symptoms in which early TB treatment is essential to improve outcomes (*291,292*).

In advanced HIV disease, the chest radiographic findings of pulmonary TB are markedly different compared with those among patients with less severe immunosuppression. Lower lobe, middle lobe, interstitial, and miliary infiltrates are common and cavitation is less common (*285,289,293*). Marked mediastinal lymphadenopathy also can be found. Even with normal chest radiographs, patients with HIV infection and pulmonary TB might have acid fast bacilli (AFB)-positive sputum smear and culture results.

With increasing degrees of immunodeficiency, extrapulmonary TB (e.g., lymphadenitis, pleuritis, pericarditis, and meningitis), with or without pulmonary involvement, is more common, and found in the majority of TB patients with $CD4^+$ counts <200 cells/μL. Among such patients, TB can be a severe systemic disease with high fevers, rapid progression, and sepsis syndrome.

Histopathologic findings also are affected by the degree of immunodeficiency. Patients with relatively intact immune function have typical granulomatous inflammation associated with TB disease. With progressive immunodeficiency, granulomas become poorly formed or can be completely absent (*286*).

In severely immunodeficient patients with a high mycobacterial load, TB disease may be subclinical or oligo-symptomatic. After initiation of ART, immune reconstitution might unmask

active TB, resulting in pronounced inflammatory reactions at the sites of infection (*294–298*). This type of IRIS can manifest as early as 7 days after starting ART. Signs and symptoms include fever; weight loss; and signs of local inflammatory reactions such as lymphadenitis, pulmonary consolidation, infiltrates, nodules, and effusions. Histologically, a vigorous granulomatous reaction, with or without caseation, but with suppuration, necrotising inflammation, and AFB might be evident; cultures of this material are almost invariably positive for *M. tuberculosis*.

Diagnosis

Diagnosis of Latent Tuberculosis Infection (LTBI)

All persons should be tested for LTBI at the time of HIV diagnosis regardless of their TB risk category **(AII)**. Persons with negative diagnostic tests for LTBI, advanced HIV infection ($CD4^+$ count <200 cells/μL), and without indications for initiating empiric LTBI treatment should be re-tested for LTBI once they start ART and attain a $CD4^+$ count ≥200 cells/μL **(AIII)**. In general, annual testing for LTBI is recommended for HIV-infected persons who are or remain in a "high-risk" category for repeated or ongoing exposure to persons with active TB, i.e., persons who are or who have been incarcerated, live in congregate settings, are active drug users, or have other sociodemographic risk factors for TB **(AIII)**. All HIV-infected persons with a positive diagnostic test for LTBI should undergo chest radiography and clinical evaluation to rule out active TB **(AI)**.

Diagnosis of LTBI can be accomplished with one of two approaches. The tuberculin skin test (TST), placed by the Mantoux method, is considered positive in HIV-infected persons if induration of ≥5 mm is demonstrated 48–72 hours after the intradermal placement of 0.1 mL purified protein derivative (PPD). Recently, new in vitro assays that detect IFN-γ release in response to *M. tuberculosis*-specific peptides have been developed for diagnosing LTBI (*299*). Given the high risk for progression to active disease in HIV-infected persons, any HIV-infected person with reactivity on any of the current LTBI diagnostic tests should be considered infected with *M. tuberculosis* (Figure 1) (*300*).

Evidence suggests that the IGRAs have more consistent and higher specificity (92%–97%) compared with TST (56%–95%), better correlation with surrogate measures of exposure to *M. tuberculosis*, and less cross reactivity because of Bacillus Calmette-Guérin (BCG) vaccination or other nontuberculous mycobacteria exposure than the TST (*299,301*). Three IGRAs are FDA-approved and available in the United States: the QuantiFERON®-TB Gold and the QuantiFERON®-TB Gold In-Tube (Cellestis Limited), and the T-SPOT™.*TB* test (Oxford Immunotec) is awaiting final FDA approval (Table 10). For both the TST and IGRAs, however, HIV-related immunosuppression might be associated with false-negative results (*302*). The frequency of false-negative and indeterminate IGRA results increases with advancing immunodeficiency (*303,304*).

Results from comparative studies of TST and IGRAs in HIV-infected patients indicate that concordance between the tests is not complete *(305,306*). The TST remains useful for diagnosing LTBI, particularly for patients who have not been vaccinated for BCG and in settings with cost constraints. The optimal application of IGRAs in HIV-infected persons will be better defined when the results of ongoing studies become available *(301*). IGRAs might be used in combination with TST to improve sensitivity and specificity for detection of LTBI (*301*).

Fibrotic lesions consistent with TB might be incidentally noted on a chest radiograph obtained for other reasons. Persons with fibrotic lesions should undergo diagnostic testing for LTBI and be evaluated for active disease. Unless the patient has a known history of prior adequate treatment for active TB, sputum samples for AFB smear and culture should be obtained even if the patient is asymptomatic. HIV-infected persons with $CD4^+$ counts <200 cells/μL who have fibrotic lesions consistent with TB on a chest radiograph and no prior history of treatment should be considered as having *M. tuberculosis* infection irrespective of the results of LTBI diagnostic tests. In situations with moderate-to-high suspicion of active TB regardless of the results of LTBI tests, empiric treatment for active TB should be initiated while awaiting the results of further diagnostic tests **(AII).**

Diagnosis of Active Tuberculosis

The evaluation of suspected HIV-related TB should include a chest radiograph regardless of the possible anatomic site of disease. Sputum samples for AFB smear and culture should be obtained from patients with pulmonary symptoms and chest radiographic abnormalities. A normal chest radiograph does not exclude the possibility of active pulmonary TB and when suspicion for disease is high, sputum samples should still be obtained (*289,307*). Obtaining three unique specimens, preferably in the morning of different days, increases the yield for both smear and culture (*308*). TST and IGRAs should not be relied upon for the diagnosis of TB disease. Approximately one fourth of HIV-infected persons with pulmonary TB disease have false-negative results (*301*).

HIV serostatus does not affect the yield from sputum smear and culture examinations; positive smear results are more common in cavitary pulmonary disease (*309*). The yield of AFB smear and culture of specimens from extrapulmonary sites is greater among patients with advanced immunodeficiency

compared with HIV-uninfected adults (*310-312*). Nucleic acid amplification (NAA) tests, also called "direct amplification tests," can be applied directly to clinical specimens such as sputum and help to evaluate persons with a positive AFB smear. A positive NAA result in an AFB smear-positive patient likely reflects active TB. In persons with AFB smear-negative sputum or extrapulmonary disease, however, NAA tests have lower sensitivity and negative predictive value and should be used and interpreted with caution (*299*).

For patients with signs of extrapulmonary TB, needle aspiration or tissue biopsy of skin lesions, lymph nodes, or pleural or pericardial fluid should be performed. Mycobacterial blood cultures might be helpful for patients with signs of disseminated disease or worsening immunodeficiency.

A positive AFB smear result in any specimen (sputum, needle aspirate, tissue biopsy) represents some form of mycobacterial disease but does not always represent TB. Because TB is the most virulent mycobacterial pathogen and can be spread from person to person, patients with smear-positive results should be considered to have TB disease until definitive mycobacterial species identification is made. Automated liquid media culture systems might indicate growth of *M. tuberculosis* within 1–3 weeks compared with 3–8 weeks in solid media.

Drug-susceptibility testing and adjustment of the treatment regimen based on results are critical to the successful treatment of patients with TB and to curbing transmission of drug-resistant *M. tuberculosis*. For all patients with TB disease, testing for susceptibility to first-line agents (isoniazid [INH], rifampin [RIF], ethambutol [EMB], and pyrazinamide [PZA]) should be performed, regardless of the source of the specimen. Drug susceptibility tests should be repeated if sputum cultures remain positive for *M. tuberculosis* after 3 months of treatment or become positive after 1 month or longer of negative cultures (*308*). Second-line drug susceptibility testing should be performed only in reference laboratories and should be limited to specimens from patients who 1) have had previous therapy, 2) are contacts of patients with drug-resistant TB disease, 3) have demonstrated resistance to RIF or to other first-line drugs, 4) have positive cultures after 3 months of treatment, or, 5) are from regions with a high prevalence of multiple drug-resistant (MDR) or extensively drug-resistant (XDR) TB (*313*).

Molecular beacons, phage-based assays, and line probe assays are three methods for rapidly detecting the presence of drug resistance, specifically to INH and RIF. These assays are expensive, require sophisticated laboratory support, need further study, and are not yet FDA-approved for use in the United States. Published results on the performance of the two assays suitable for direct use on samples, the INNO-LiPA Rif. TB kit (Innogenetics, Gent, Belgium) and FASTPlaque-TB (Biotec Laboratories Ltd., Ipswich, United Kingdom), have been inconsistent. Until results of ongoing validation and field testing of these rapid tests are available, conventional laboratory methods for culture and susceptibility testing should be pursued on all suspect clinical specimens.

Preventing Exposure

HIV-infected persons should be advised that time spent in congregate settings or other environments identified as possible sites of TB transmission (e.g., correctional facilities, homeless shelters, nursing homes) might increase the likelihood of contracting *M. tuberculosis* infection **(BIII)** (*277*)**.** Factors known to increase contagiousness include anatomical site of TB disease (pulmonary or laryngeal), AFB smear-positive sputum, cavities evident on chest radiograph, and aerosolization by coughing or singing. HIV-infected patients who have pulmonary or laryngeal TB are, on average, as contagious as patients who are not HIV-infected. Exposure to patients with known TB, but who have AFB smear-negative sputum results, poses a lower but not nonexistent risk for *M. tuberculosis* transmission (*276,314*).

In health-care facilities and other environments with a high risk for transmission, all patients with known or presumed infectious TB should be physically separated from other patients, but especially from those with HIV infection **(AII)** (*276*). A patient with infectious TB returning to a congregate living setting or to any setting in which susceptible persons might be exposed should be receiving or should have completed treatment and have three consecutive negative AFB smear results from good quality sputum samples collected ≥8 hours apart (with one specimen collected during the early morning), be on adequate treatment for >2 weeks, and demonstrate clinical improvement before being considered noninfectious **(AIII)** (*276,280,315*). Certain specialists recommend that patients with MDR-TB have a negative sputum culture before returning to a congregate setting.

Treatment of LTBI is effective in reducing TB incidence among populations who reside in areas of low, medium, and high TB transmission (*316–318*). All possible strategies should be pursued to ensure that HIV-infected persons with risk factors for TB are tested for *M. tuberculosis* infection and those with LTBI receive and complete a course of LTBI treatment **(AII)** (*319*). Persons infected with HIV should be treated presumptively for LTBI when the history of TB exposure is substantial, regardless of the results of diagnostic testing for LTBI **(BII)** (*276,282,283*)**.** Use of BCG vaccine is not recommended as a means to control TB in the United States because of the unproven efficacy of the vaccine in the U.S. population and the success of other measures in reducing TB incidence (*319*). BCG vaccination for HIV-infected persons is

contraindicated because of its potential to cause disseminated disease **(EII).**

Preventing Disease (Treatment of LTBI)

All HIV-infected persons with suspected LTBI or who have symptoms indicating TB should promptly undergo chest radiography and clinical evaluation to rule out active TB regardless of the results of diagnostic tests for LTBI (*320*).

HIV-infected persons, regardless of age, should be treated for LTBI if they have no evidence of active TB and exhibit the following characteristics: 1) a positive diagnostic test for LTBI and no prior history of treatment for active or latent TB **(AI)**; 2) a negative diagnostic test for LTBI but are close contacts of persons with infectious pulmonary TB **(AII)**; and 3) a history of untreated or inadequately treated healed TB (i.e., old fibrotic lesions on chest radiography) regardless of diagnostic tests for LTBI **(AII)** (*321*).

The efficacy of LTBI treatment has not been documented for HIV-infected persons with negative diagnostic tests for LTBI without known exposure to *M. tuberculosis.* Persons from groups or geographic areas with a high prevalence of *M. tuberculosis* infection might be at increased risk for primary or reactivation TB and, in this situation, decisions to treat for LTBI must include consideration of $CD4^+$ count and other factors **(BIII)** (*282,283,320*)**.**

Treatment options for LTBI include INH daily **(AII)** or twice weekly **(BII)** for 9 months (*282,283,322*). Results from a randomized clinical trial comparing INH daily therapy for 9 months with 12 doses of once-weekly INH-rifapentine are pending (*323*). Because of an increased risk for fatal and severe hepatotoxicity, a 2-month regimen of daily RIF and PZA is not recommended for LTBI treatment regardless of HIV status **(DI)** (*277*). HIV-infected persons receiving INH should receive pyridoxine **(BIII)** to minimize the risk for developing peripheral neuropathy. Alternatives for persons who cannot take INH or who have been exposed to a known INH-resistant index patient include either RIF or rifabutin alone for 4 months **(BIII).** Decisions to use a regimen containing either RIF or rifabutin should be made after considering potential drug interactions (see the section on ART in the Management of TB Disease). For persons exposed to INH- and/or RIF-resistant TB, decisions to treat with one or two drugs other than INH, RIF, or rifabutin should be based on the relative risk for exposure to organisms broadly resistant to other antimycobacterial drugs and should be made in consultation with public health authorities **(AII).** Directly observed therapy (DOT) should be used with intermittent dosing regimens **(AI)** when otherwise feasible to maximize regimen-completion rates (*282,283*)**.**

No evidence suggests that LTBI treatment should be continued beyond the recommended duration in persons with HIV infection. Therefore, LTBI treatment should be discontinued after completing the appropriate number of doses **(AII).**

Treatment of Disease

Considering the variability of yield from smear microscopy and NAA tests, empiric treatment should be initiated and continued in HIV-infected persons in whom TB is suspected until all diagnostic work-up (smears, cultures, or other identification results) is complete **(AII)**. When active TB is diagnosed or suspected, a multi-drug anti-TB treatment regimen should be started immediately **(AI)**. This approach promotes rapid killing of tubercle bacilli, prevents the emergence of drug resistance, and decreases the period of contagion (*48*). DOT is recommended for all patients with HIV-related TB **(AII)**. Likelihood of treatment success is further enhanced by DOT with support for other social and medical needs of HIV-infected patients **(BII)** (enhanced DOT) (*48*). A treatment plan should be based on completion of the total number of recommended doses ingested rather than the duration of treatment administration **(AIII)** (*277*). The following text summarizes both duration-based and total number-based dosing recommendations.

Recommendations for anti-TB treatment regimens in HIV-infected adults follow the same principles as for adults without HIV infection **(AI)** (*48*). Treatment of drug-susceptible TB disease should include a 6-month regimen with an initial phase of INH, RIF or rifabutin, PZA, and EMB administered for 2 months, followed by INH and RIF (or rifabutin) for 4 additional months **(AI)**. When drug-susceptibility testing confirms the absence of resistance to INH, RIF, and PZA, EMB may be discontinued before 2 months of treatment have been completed **(AI)** (*277*). For patients with cavitary lung disease and cultures positive for *M. tuberculosis* after completion of 2 months of therapy, treatment should be extended with INH and RIF for an additional 3 months for a total of 9 months **(AII)**. All HIV-infected patients treated with INH should receive pyridoxine supplementation **(BIII)**. For patients with extrapulmonary TB, a 6- to 9-month regimen (2 months of INH, RIF, PZA, and EMB followed by 4–7 months of INH and RIF) is recommended **(AII)**. Exceptions to the recommendation for a 6- to 9-month regimen for extrapulmonary TB include CNS disease (tuberculoma or meningitis) and bone and joint TB, for which many experts recommend 9–12 months **(AII)** (*277*). Adjuvant corticosteroids should be added when treating CNS and pericardial disease **(AII)**. Treatment with corticosteroids should be started intravenously as early as possible with change to oral therapy individualized according to clinical improvement (Table 3). Recommended corticosteroid regimens are dexamethasone 0.3–0.4 mg/kg tapered over 6–8 weeks (*324*) or prednisone 1 mg/kg for 3 weeks, then tapered for 3–5 weeks**.**

The optimal way to prevent relapse has not been determined. How the CD4+ count relates to likelihood of treatment failure and relapse remains uncertain. Some recent observational studies suggest that 9 months of therapy result in a lower rate of relapse than shorter or 6-month anti-TB regimens (*325–327*). While awaiting definitive results of randomized comparisons of treatment duration in HIV-infected patients with TB disease, 6 months of therapy are probably adequate for the majority of patients, but prolonged therapy (up to 9 months) is recommended (as in HIV-uninfected patients) for patients with a delayed response to therapy, with cavitary disease on chest radiograph, and for those with extrapulmonary or CNS disease **(BII)** (*48*)**.**

Intermittent dosing (i.e., twice or thrice weekly) facilitates DOT by decreasing the number of encounters required, might provide more effective peak serum concentrations, and is preferable to complete the regimen. For HIV-infected patients, the initial 8-week phase of therapy should be administered daily by DOT (7 days per week for 56 doses or 5 days per week for 40 doses) **(AII)** or 3 times weekly by DOT for 24 doses **(BII)** (*277*). Because twice-weekly administration of the continuation phase of therapy is associated with an increased risk for relapse with acquired rifamycin-resistant M. tuberculosis strains (*277*,*328–330*), for patients with CD4+ counts <100 cells/μL the continuation phase of either 4 months or 7 months should be administered either daily or three times weekly by DOT **(AIII)**. Twice-weekly continuation-phase therapy may be considered in patients with CD4+ counts ≥100 cells/μL **(CIII)**. Once-weekly administration of INH-rifapentine in the continuation phase should not be used for any patient with HIV infection **(EI)**.

Monitoring and Adverse Events, Including Immune Reconstitution Inflammatory Syndrome (IRIS)

Monitoring of LTBI Treatment

All patients with a diagnosis of LTBI should be counseled about risk for TB, adherence to treatment regimens, benefits and risks of treatment, interactions with other drugs, and an optimal follow-up plan. HIV-infected patients receiving treatment for LTBI also should have baseline laboratory testing, including an evaluation of hepatic function (serum aspartate aminotransferase [AST], bilirubin, and alkaline phosphatase) for patients treated with INH and a complete blood count and platelet count for patients taking RIF or rifabutin (*282,283*).

Patients being treated for LTBI should be monitored at least monthly with a history and physical assessment designed to detect hepatitis and neuropathy. Patients should be advised to stop treatment and promptly seek medical evaluation if symptoms suggesting hepatitis occur, such as nausea, vomiting, jaundice, or dark urine. Clinicians in all settings should consider dispensing no more than a 1-month supply of medication (*331,332*). Routine laboratory monitoring is indicated in HIV-infected patients with abnormal baseline liver-function tests, with chronic liver disease, or in those receiving treatment with ART **(***282,283,333*).

Monitoring of Active TB Disease Treatment

A baseline evaluation and monthly follow-up consisting of clinical, bacteriologic, and periodic laboratory and radiographic evaluations are essential to ensure treatment success. Clinical history and baseline tests to evaluate hepatic function (AST, bilirubin, and alkaline phosphatase), renal function (serum creatinine), complete blood count (including platelet count), and CD4+ counts are recommended for all patients (*277*). HIV-infected patients being treated for active TB should have a clinic-based evaluation at least monthly. For patients with extrapulmonary TB, the frequency and types of evaluations will depend on the sites involved and the ease with which specimens can be obtained. For patients with pulmonary TB, at least one sputum specimen for AFB smear and mycobacterial culture should be obtained monthly until two consecutive specimens are culture negative. Sputum specimens should be obtained after 8 weeks of treatment to inform clinical decision-making about the duration of the continuation phase. For patients with positive AFB smears at initiation of treatment, follow-up smears may be obtained at more frequent intervals (e.g., every 2 weeks until two consecutive specimens are negative) to provide an early assessment of the treatment response (*277*).

For patients with positive *M. tuberculosis* cultures after 3 months of treatment, drug-susceptibility tests should be repeated on newly acquired sputum specimens. Patients with positive *M. tuberculosis* cultures after 4 months of treatment should be considered as treatment failures and managed accordingly (*44*). At each visit, patients should be questioned about adherence and possible adverse effects of anti-TB medications; those taking EMB should be asked about blurred vision or scotomata and tested for visual acuity and color discrimination. Routine laboratory monitoring during treatment, even when baseline laboratory abnormalities are not present, could be considered **(***333*).

In HIV-infected persons with active TB, serum concentrations of the first-line anti-TB drugs are frequently lower than published normal ranges (*334*). However, routine drug-level monitoring is not recommended (*277*). For those with a slow response to treatment, drug concentration measurements might provide objective information on which to base modifications of treatment (*335*).

Management of Common Adverse Events

Although the reported frequency of anti-TB drug-related toxicity in patients with HIV infection varies, for most adverse events, rates are not different than for HIV-uninfected patients (*333,336–339*). Because alternative drugs often have less efficacy and more toxicities than first-line anti-TB drugs and diagnosing a drug reaction and determining the responsible agent can be difficult, the first-line drugs (especially INH, RIF, or rifabutin) should not be stopped permanently without strong evidence that the specific anti-TB drug was the cause of the reaction. In such situations, consultation with a specialist in treating LTBI or TB in persons with HIV infection is recommended (*48*).

Gastrointestinal reactions are common with many of the anti-TB medications (*340*). If gastrointestinal symptoms occur, AST and bilirubin should be measured, and if the AST level is less than three times the upper limit of normal (ULN) or the baseline for the patient, the symptoms are assumed not to be caused by hepatic toxicity. Typically, gastrointestinal symptoms should be managed without discontinuing TB medications; initial approaches should include either changing the hour of administration or administering drugs with food.

Skin rashes are common with all of the anti-TB drugs. If rash is minor, affects a limited area, or causes pruritis, antihistamines should be administered for symptomatic relief and all anti-TB medications continued. If the rash is severe, all TB medications should be stopped until the rash is substantially improved, and TB drugs restarted one by one at intervals of 2–3 days. RIF or rifabutin should be restarted first (because they are least likely to cause rash and their role in treatment is critical). If the rash recurs, the last drug added should be stopped. If a petechial rash thought to be caused by thrombocytopenia occurs, the RIF or rifabutin should be stopped permanently (*341*). If a generalized rash associated with either fever or mucous membrane involvement occurs, all drugs should be stopped immediately, the patient should be switched to alternative anti-TB agents, and LTBI or TB treatment should be managed in consultation with a specialist.

Fever in an HIV-infected patient who has been receiving effective TB therapy for several weeks might represent drug fever, a paradoxical reaction, or IRIS (*342*). If superinfection or worsening TB is excluded as a potential cause, all TB drugs should be stopped**.** Once the fever has resolved, the general guidelines described for restarting/stopping drugs in the presence of a rash should be followed.

An increase in AST concentration occurs in approximately 20% of patients treated with the standard four-drug anti-TB regimen (*343*). Drug-induced liver injury can be caused by INH, rifamycins, or PZA and is defined as an AST elevation to ≥3 times the ULN in the presence of symptoms, or >5 times the ULN in the absence of symptoms (*344*). In addition to AST elevation, disproportionate increases in bilirubin and alkaline phosphatase occur occasionally. This latter pattern is more consistent with rifamycin hepatotoxicity than with INH or PZA hepatotoxicity. In most patients, asymptomatic aminotransferase elevations resolve spontaneously.

In the absence of symptoms, elevations of AST <3 times ULN should not prompt changes of TB therapy, but the frequency of clinical and laboratory monitoring should be increased. If AST levels are ≥5 times the ULN regardless of symptoms, >3 times the ULN with symptoms, or if a significant increase in bilirubin and/or alkaline phosphatase occurs, hepatotoxic drugs should be stopped, and the patient should be evaluated immediately. For any substantial new transaminase or bilirubin elevation, serologic testing for hepatitis A, B, and C should be performed and the patient questioned regarding symptoms suggestive of biliary tract disease and exposures to alcohol and other hepatotoxins.

If anti-TB drugs must be stopped for hepatotoxicity, substituting ≥3 nonhepatotoxic anti-TB drugs is prudent until the specific cause of hepatotoxicity can be determined and an alternative longer-term regimen constructed. The suspected anti-TB medications should be restarted one at a time after the AST level returns to <2 times the ULN or to near baseline for patients with pre-existing abnormalities. Because the rifamycins are a critical part of the TB regimen and are less likely to cause hepatotoxicity than INH or PZA (*343*), they should be restarted first. If no increase in AST occurs after 1 week, INH may be restarted. PZA may be restarted 1 week after INH if AST does not increase. If symptoms recur or AST increases, the last drug added should be stopped. If RIF and INH are tolerated and hepatitis was severe, PZA should be assumed responsible and should be discontinued. In this last circumstance, depending on the number of doses of PZA taken, severity of disease, and bacteriological status, therapy might be extended to 9 months with RIF and INH alone.

For HIV-infected patients on LTBI therapy who have hepatotoxicity, most of the general guidelines described for restarting/stopping drugs for patients on therapy for active TB apply. The ultimate decision regarding resumption of therapy with the same or a different agent for LTBI treatment should be made after weighing the risk for additional hepatic injury against the benefit of preventing progression to TB disease (*333*) and always in consultation with an expert in treating LTBI in persons with HIV infection.

ART in the Management of TB Disease

The treatment of TB can be complicated by drug interactions with the rifamycins and overlapping toxicities associated with

antiretrovirals (ARVs) and anti-TB drugs when therapy for both HIV and TB infections is concomitantly administered. Both RIF and rifabutin induce CYP3A enzymes, and although rifabutin is not as potent an inducer as RIF, it is a substrate, leading to drug interactions with the PIs and non-nucleoside reverse transcriptase inhibitors (NNRTIs) when these agents are concomitantly administered with the rifamycins; such administration might result in increased metabolism and suboptimal levels of ARVs (*345*).

Compared with PI-based regimens, NNRTI-based regimens have fewer interactions with RIF-based TB therapy (*346*). Rifabutin is an alternative to RIF and can be administered with PIs or NNRTIs with appropriate dose adjustments (*346*). Concomitant use of RIF with ritonavir-boosted PIs has been shown to result in subtherapeutic levels of the PI. Use of ritonavir-boosted saquinavir with RIF was associated with a high incidence of hepatotoxicity in a pharmacokinetic study using healthy volunteers (*347*). RIF should not be used in patients on PI-based regimens, with or without ritonavir-boosting **(EII)**. For patients undergoing treatment for active TB, starting ART with either an efavirenz- or nevirapine-based regimen is preferred because these NNRTIs have fewer interactions with RIF **(BII)**; dosage adjustments for these NNRTIs might be needed for persons weighing more than 60 kg **(BII)** (*348,349*). Delavirdine should not be used with either RIF or rifabutin (*350*).

If rifabutin is used in place of RIF, dosage reduction is required with boosted-PI regimens. Efavirenz decreases the levels of rifabutin, and the dose of the latter might have to be increased. Nevirapine does not affect the levels of rifabutin sufficiently to merit adjustment of the rifabutin dose. Underdosing of ARVs or rifabutin can result in selection of HIV drug-resistant mutants or acquired rifamycin resistance, respectively, whereas overdosing of rifabutin might result in dose-related toxicities such as neutropenia and uveitis. Because interpatient variations in the degree of enzyme induction or inhibition can occur, the use of therapeutic drug monitoring for levels of rifabutin, PIs, or NNRTIs might help to adjust dosing for individual patients.

HIV nucleos(tide) analogs and the fusion inhibitor enfuvirtide are not affected by the CYP enzymes and can be used with the rifamycins. Results of ongoing drug-drug interaction studies predict that the combination of RIF (and possibly rifabutin) will result in decreased levels of maraviroc, raltegravir, and elvitegravir. Until data are available to guide dose adjustment, these drugs in combination should be avoided or used with extreme caution. Available NNRTIs and PIs do not have clinically significant drug interactions with other first- and second-line anti-TB drugs; thus, when rifamycins cannot be administered because of toxicity or resistance (MDR or XDR *M. tuberculosis* strains), ART regimens should be selected on the basis of other factors appropriate to the patient **(AIII).**

Optimal Timing of Initiation of ART in ART-Naïve Patients with Active TB

For ART-naïve, HIV-infected persons who are diagnosed with active TB, anti-TB treatment must be started immediately **(AIII)**. The optimal timing of initiation of ART in this setting is not clear. Options include simultaneous TB and ART or treatment of TB first with delay of ART by several weeks to months. A positive aspect of starting both regimens simultaneously is the possible prevention of progressive HIV disease and reduction in morbidity or mortality associated with TB or other OIs. A negative of this approach is the possibility of overlapping toxicities, drug interactions, a high pill burden, and the possibility of developing IRIS or a paradoxical reaction. These factors must be weighed carefully when choosing the best time to start ART in individual patients.

Several randomized clinical trials are under way to address the optimal timing of initiation of ART in persons being treated for active TB, but the results will not be known for several years. Pending these results, certain specialists determine when to start ART based on the immunologic status of the patients (*339*,*351*,*352*). For patients with a $CD4^+$ count <100 cells/μL, ART should be started after ≥2 weeks of TB treatment **(BII)** to reduce confusion about overlapping toxicities, drug interactions (*339*), and the occurrence of paradoxical reactions or IRIS (*353*). For persons with a $CD4^+$ count of 100–200 cells/μL, certain specialists would delay ART until the end of the 2-month intensive phase of anti-TB treatment **(BII)**. In those with a sustained $CD4^+$ count >200 cells/μL, ART could be started during the anti-TB maintenance phase and for those with a $CD4^+$ count >350 cells/μL, after finishing anti-TB treatment **(BII)**. In one study, paradoxical reactions occurred in almost all HIV-infected patients with TB and a $CD4^+$ count <100 cells/μL who started ART within the first 30 days of TB therapy (*222*). However, other studies suggest this approach might prevent HIV disease progression or death (*222*,*339*,*353*). In a small, prospective, nonrandomized study of 49 HIV-infected patients from Brazil (*348*) treated with a RIF-based anti-TB regimen and efavirenz-based ART, morbidity and side effects of medications in patients who started ART 3 weeks after initiation of TB treatment were reduced, compared with those who started ART and anti-TB treatment simultaneously. Furthermore, simultaneous anti-TB and anti-HIV treatment did not reduce overall mortality.

When TB occurs in patients already on ART, treatment for TB must be started immediately **(AIII),** and ART should be modified to reduce the risk for drug interactions and maintain virologic suppression. When TB occurs in the setting of viro-

logic failure, ART drug-resistance testing should be performed and a new ART regimen constructed to achieve virologic suppression and avoid drug interactions with the anti-TB regimen administered **(AIII).**

Immune Reconstitution and Paradoxical Reactions

IRIS or a paradoxical reaction occurring after the initiation of ART is thought to be the result of recovery of immune responses to previously recognized TB antigens, reconstituted by ART or by TB treatment itself (*48*). The immune response might be an exaggerated inflammatory response during TB treatment in a patient known to have TB, referred to as paradoxical TB-associated IRIS, or might unmask previously undiagnosed TB, referred to as unmasking TB-associated IRIS.

TB-associated paradoxical reactions or IRIS usually occur in the first 1–3 months after starting ART in patients receiving TB treatment (*294*). The risk for IRIS is greater when ART is started within the first 2 months of TB therapy (*222,354*) and when the $CD4^+$ count is <100 cells/μL (*295-298*). Signs of a paradoxical reaction or IRIS can include, but are not limited to, high fevers, worsening respiratory status, increase in size and inflammation of involved lymph nodes or new lymphadenopathy, breakthrough meningitis or new or expanding CNS lesions, radiologic worsening of pulmonary parenchymal infiltrations, and increasing pleural effusions. Such findings should be attributed to a paradoxical or IRIS reaction only after a thorough evaluation has excluded other possible causes, especially failure of TB therapy.

IRIS or paradoxical reactions are usually self-limited but if symptoms are severe, supportive treatment might be required, depending on the nature of the complications. Typically, a paradoxical or IRIS reaction that is not severe should be treated symptomatically with nonsteroidal anti-inflammatory agents without a change in anti-TB treatment or ART **(BIII).** Approaches to the management of severe reactions (e.g., high fever, airway compromise from enlarging lymph nodes, enlarging serosal fluid collections, increased intracranial pressure [ICP], or sepsis syndrome) have not been studied but might require invasive interventions such as surgical decompression, and although no specific treatment is recommended for severe reactions, improvement has been observed with the use of prednisone or methylprednisolone used at a dose of approximately 1 mg/kg body weight gradually reduced after 1–2 weeks **(BIII)** (*48*)**.**

Management of Treatment Failure

Drug-resistant TB continues to be a substantial clinical and public health problem. Predisposing factors include cavitary disease with a large bacillary load, use of an inadequate drug regimen, or a combined failure of both the patient and the provider to ensure compliance with the prescribed regimen (*277*). Ongoing transmission of drug-resistant strains is a source of new drug-resistant cases (*355*). The recommended treatment for drug-resistant TB is the same for HIV-infected as for non-HIV-infected patients **(AII)** (*277,355*). The optimal duration of treatment for highly resistant strains has not been established.

For patients with *M. tuberculosis* strains resistant to INH, INH should be discontinued and the patient treated with a 6-month regimen of RIF, PZA, and EMB, which is nearly as effective as the conventional INH-containing regimen **(BII)**. A fluoroquinolone may be added for those with more severe or extensive disease **(CIII)**. Alternatively, treatment with RIF and EMB for 12 months can be used, with PZA added during at least the initial 2 months **(BII).**

Treatment regimens for TB disease caused by RIF mono-resistant strains are less effective, and patients infected with these strains are at increased risk for relapse and treatment failure. A minimum of 12–18 months of treatment with INH, EMB, and a fluoroquinolone (e.g., levofloxacin, moxifloxacin) with PZA administered during the first 2 months is recommended **(BIII)**. An injectable agent (e.g., amikacin or capreomycin) might be included in the first 2–3 months for patients with RIF mono-resistance and severe or extensive disease **(CIII).**

Patients with *M. tuberculosis* resistant to both INH and RIF (MDR-TB) are at high risk for treatment failure and further acquired resistance and require close follow-up during and after treatment. Treatment regimens for MDR-TB should be individualized based on drug-resistance test results, relative activities of available anti-TB agents, the extent of disease, potential interaction with ARVs, and presence of other comorbid conditions **(AIII).** Treatment regimens should consist of at least four effective drugs **(AIII)** (*277,355*). The management of MDR-TB is complex and should be undertaken only by an experienced specialist or in close consultation with specialized treatment centers **(AIII).**

Reports of highly resistant *M. tuberculosis* strains have occurred during the past two decades (*356,357,358, 359,360*). The emergence of *M. tuberculosis* with extensive drug resistance was first reported on a global level in 2006 (*361*). The WHO Emergency Global Task Force on XDR-TB has defined XDR-TB as resistance to at least INH and RIF among the first-line anti-TB drugs, and resistance to any fluoroquinolone and at least one of three injectable second-line drugs (kanamycin, amikacin, capreomycin) (*362*). XDR-TB has been reported in the United States and every region of the world (*363–365*). Community transmission of XDR-TB and a high and rapid mortality rate among HIV-infected patients with XDR-TB

have been documented in South Africa (*366*). Poor TB treatment outcomes and high mortality among HIV-infected persons with XDR-TB also have been reported from New York City (*367*). Patients with *M. tuberculosis* resistant to RIF or any two first-line drugs should be tested for susceptibility to a full panel of anti-TB drugs **(BIII).** Repeat drug-susceptibility testing should be considered for HIV-infected patients with MDR-TB who are not responding to treatment to rapidly identify drug resistance that occurs during treatment **(BIII).** Contact investigation and strict infection- control precautions should be implemented according to national guidelines **(BIII)** (*368*). The management of XDR-TB should be undertaken only by an experienced specialist in close consultation with specialized treatment centers **(AIII).**

Preventing Recurrence

For patients with a low ongoing risk for exposure and transmission of *M. tuberculosis* infection, chronic suppressive therapy after successful completion of a recommended treatment regimen for LTBI or active TB is unnecessary **(DII).** However, recurrence of TB disease can result from either endogenous relapse or exogenous reinfection. Even in low TB burden countries, reinfection is a risk for HIV-infected residents of institutions that pose an ongoing high risk for exposure to *M. tuberculosis* (e.g., prisons, jails, and homeless shelters) (*282,283*). Recurrence of TB disease is also substantially increased in HIV-infected persons in geographic areas with a high TB burden (*344,369–375*). In these settings, treatment of LTBI resulting from presumed reinfection among persons previously treated for TB has been documented to reduce recurrence of TB disease (*370,372,376*). The reported incidence of TB disease for persons immigrating to the United States from settings with high TB burden (especially Sub-Saharan Africa and Asia) who have been in the United States <1 year is often greater than the estimated case rate in their country of origin (*377*). Recent molecular epidemiology studies suggest that the majority of TB cases among foreign-born persons in the United States are caused by or related to activation of latent infection (*377–381*). These findings suggest that recent immigrants might be at high risk for recent infection or reinfection in their countries of origin. Close monitoring of recent immigrants at such risk is necessary.

Special Considerations During Pregnancy

HIV-infected pregnant women who do not have documentation of a negative TST result during the preceding year should be tested during pregnancy. The frequency of anergy is not increased during pregnancy, and routine anergy testing for HIV-1-infected pregnant women is not recommended (*382–385*). No data are available on the performance of the IGRAs for diagnosis of LTBI in pregnant women.

The diagnostic evaluation for TB disease in pregnant women is the same as for nonpregnant adults. Chest radiographs with abdominal shielding result in minimal fetal radiation exposure. An increase in pregnancy complications and undesirable outcomes (including preterm birth), low birthweight, and intrauterine growth retardation might be observed among pregnant women with either pulmonary or extrapulmonary TB not confined to the lymph nodes, especially when treatment is not begun until late in pregnancy (*382–389*). Congenital TB infection of the infant might occur but appears to be rare (390).

Treatment of TB disease for pregnant women should be the same as for nonpregnant women, but with attention given to the following considerations **(BIII):**

- Although INH is not teratogenic in animals or humans, hepatotoxicity caused by INH might occur more frequently in pregnancy and the postpartum period (*391*). Monthly monitoring of liver transaminases during pregnancy and the postpartum period is recommended (**CIII**).
- RIF is not teratogenic in humans. Because of a potential increased risk for RIF-related hemorrhagic disease among neonates born to women who receive anti-TB therapy during pregnancy, prophylactic vitamin K, in a single 10 mg dose, should be administered to the neonate (**BIII**).
- PZA is not teratogenic among animals. Experience is limited with use in human pregnancy. Although WHO and the International Union Against Tuberculosis and Lung Diseases (*392,393*) have made recommendations for the routine use of PZA in pregnant women, it has not been recommended for general use during pregnancy in the United States because data characterizing its effects in this setting are limited (*394*). If PZA is not included in the initial treatment regimen, the minimum duration of TB therapy should be 9 months. The decision regarding whether to include PZA for treatment should be made after consultation among obstetricians, TB specialists, and women, taking into account gestational age and likely susceptibility pattern of the infecting strain (**CIII**).
- EMB is teratogenic among rodents and rabbits at doses that are much higher than those used among humans. No evidence of teratogenicity has been observed among humans. Ocular toxicity has been reported among adults taking EMB, but changes in visual acuity have not been detected in infants born after exposure in utero.

Experience with using the majority of the second-line drugs for TB during pregnancy is limited. MDR-TB in pregnancy should be managed in consultation with a specialist. Therapy should not be withheld because of pregnancy **(AIII).** The fol-

lowing concerns should be considered when selecting second-line anti-TB drugs for use among pregnant women:

- Streptomycin use has been associated with a 10% rate of VIII nerve toxicity in infants exposed in utero; its use during pregnancy should be avoided if possible (**DIII**).
- Hearing loss has been detected in approximately 2% of children exposed to long-term kanamycin therapy in utero; like streptomycin, this agent should typically be avoided if possible (**DIII**). The fetus is at a theoretical risk for ototoxicity with in utero exposure to amikacin and capreomycin, but this risk has not been documented and these drugs might be alternatives when an aminoglycoside is required for treatment of MDR-TB (**CIII**).
- Because arthropathy has been noted in immature animals exposed in utero to quinolones, quinolones are typically not recommended for pregnant women and among children aged <18 years (**CIII**). However, >400 cases of quinolone use in human pregnancies have been reported to various pregnancy registries, and use has not been associated with human arthropathy or birth defects after in utero exposure. Thus, quinolones can be used in pregnancy for drug-resistant TB, if they are required on the basis of susceptibility testing (**CIII**) *(395)*.
- Para-aminosalicylic acid (PAS) is not teratogenic among rats or rabbits *(394)*. In one study, a possible increase in limb and ear anomalies was reported among 143 infants delivered by woman who were exposed during the first trimester of their pregnancies (*396*). No specific pattern of defects and no increase in rate of defects have been detected among subjects in other human studies, indicating that this agent can be used with caution if needed (**CIII**).
- Ethionamide has been associated with an increased risk for several anomalies among mice, rats, and rabbits after high-dose exposure; no increased risk for defects was noted with doses similar to those used among humans, but experience is limited with use during human pregnancy. Thus, ethionamide should be avoided unless its use is necessary (**CIII**).
- No data are available from animal studies or reports of cycloserine use in humans during pregnancy.

If LTBI is diagnosed during pregnancy and active TB has been ruled out, treatment should be initiated during pregnancy whenever possible **(BIII)**. If the woman is receiving ART only for prophylaxis of perinatal HIV transmission and will stop ARVs after delivery, deferral of treatment for LTBI until after delivery or use of a triple nucleoside regimen to allow use of RIF is reasonable. For women who require long-term ART for their own health, initiation of INH prophylaxis during pregnancy is recommended **(BIII)**.

ART is indicated for all pregnant women either for treatment of maternal infection, or if not indicated for maternal therapy, for prevention of perinatal transmission of HIV (*397*). Pregnant women on ART who have a diagnosis of active TB should have their ARV regimens adjusted as needed to accommodate their TB drugs. For women whose diagnosis includes concurrent active TB and HIV infection during pregnancy, TB therapy should be initiated immediately and ART should be initiated as soon as possible thereafter, usually according to the principles described for nonpregnant adults. Efavirenz use is not recommended during the first trimester because of 1) substantial CNS and cleft defects seen in cynomolgous monkeys treated in the first trimester with efavirenz at doses similar to those used in humans and 2) because of case reports of neural tube defects in humans after first-trimester exposure. Efavirenz can be used after the first trimester, if indicated, to avoid drug interactions between anti-TB drugs and PIs. Initiation of nevirapine is not recommended for women with $CD4^+$ counts >250 cells/μL because of an increased risk for potentially fatal liver toxicity. For women who require ART strictly for prophylaxis of perinatal HIV transmission, use of a triple nucleoside regimen, including abacavir, could be considered to avoid interactions with TB drugs.

Disseminated *Mycobacterium avium* Complex Disease

Epidemiology

Organisms of the *Mycobacterium avium* complex (MAC) are ubiquitous in the environment (*398–400*). *M. avium* is the etiologic agent in >95% of patients with AIDS who acquire disseminated MAC disease (*398,401–406*). An estimated 7%–12% of adults have been previously infected with MAC, although rates of disease vary in different geographic locations (*398,402,405,406*). Although epidemiologic associations have been identified, no environmental exposure or behavior has been consistently linked to a subsequent risk for developing MAC disease.

The mode of transmission is thought to be through inhalation, ingestion, or inoculation via the respiratory or gastrointestinal tract. Household or close contacts of those with MAC disease do not appear to be at increased risk for disease, and person-to-person transmission is unlikely.

In the absence of effective ART or chemoprophylaxis in those with AIDS-associated immunosuppression, the incidence of disseminated MAC disease is 20%–40% (*407,408*). For persons with a $CD4^+$ count <100 cells/μL who are receiving effective prophylaxis or have responded to ART with a sustained increase in $CD4^+$ count to levels >100–200 cells/μL, the overall incidence has been estimated at 2 cases per 100

person-years. MAC disease typically occurs among persons with CD4+ counts <50 cells/μL. Other factors that are associated with increased susceptibility to MAC disease are high plasma HIV RNA levels (>100,000 copies/mL), previous OIs, previous colonization of the respiratory or gastrointestinal tract with MAC, and reduced in vitro lymphoproliferative immune responses to *M. avium* antigens, possibly reflecting defects in T-cell repertoire.

Clinical Manifestations

In persons with AIDS not on ART, MAC disease is typically a disseminated multi-organ infection (*409–412*). Early symptoms might be minimal and might precede detectable mycobacteremia by several weeks. Symptoms include fever, night sweats, weight loss, fatigue, diarrhea, and abdominal pain (*402*).

Localized manifestations of MAC disease have been reported most frequently among persons who are receiving and have responded to ART. Localized syndromes include cervical or mesenteric lymphadenitis, pneumonitis, pericarditis, osteomyelitis, skin or soft tissue abscesses, genital ulcers, or CNS infection.

Laboratory abnormalities particularly associated with disseminated MAC disease include anemia (often out of proportion to that expected for the stage of HIV disease) and elevated liver alkaline phosphatase (*398,399,401–408,413,414*). Hepatomegaly, splenomegaly, or lymphadenopathy (paratracheal, retroperitoneal, para-aortic, or less commonly peripheral) might be identified on physical examination or by radiographic or other imaging studies. Other focal physical findings or laboratory abnormalities might occur in the context of localized disease.

IRIS, initially characterized by focal lymphadenitis with fever, has subsequently been recognized as a systemic inflammatory syndrome with signs and symptoms that are clinically indistinguishable from active MAC infection. Its occurrence with MAC disease is similar to IRIS or paradoxical reactions observed with TB disease (*415–418*). Bacteremia is absent. The syndrome has been described among patients with subclinical ("unmasking IRIS") or established MAC disease and advanced immunosuppression who begin ART and have a rapid and marked increase in CD4+ count (≥100 cells/μL). As with TB, the syndrome might be benign and self-limited or might result in severe unremitting symptoms that are improved with the use of systemic anti-inflammatory therapy or corticosteroids in doses similar to those described for TB-associated IRIS.

Diagnosis

A confirmed diagnosis of disseminated MAC disease is based on compatible clinical signs and symptoms coupled with the isolation of MAC from cultures of blood, lymph node, bone marrow, or other normally sterile tissue or body fluids (*408,411,419,420*). Species identification should be performed using specific DNA probes, high performance liquid chromatography, or biochemical tests.

Other ancillary studies provide supportive diagnostic information, including AFB smear and culture of stool or tissue biopsy material, radiographic imaging, or other studies aimed at isolation of organisms from focal infection sites.

Preventing Exposure

MAC organisms commonly contaminate environmental sources (e.g., food and water). Available information does not support specific recommendations regarding avoidance of exposure.

Preventing Disease

Initiating Primary Prophylaxis

HIV-infected adults and adolescents should receive chemoprophylaxis against disseminated MAC disease if they have a CD4+ count of <50 cells/μL **(AI)**. Azithromycin (*421*) or clarithromycin (*399,422*) are the preferred prophylactic agents **(AI)**. The combination of clarithromycin and rifabutin is no more effective than clarithromycin alone for chemoprophylaxis, is associated with a higher rate of adverse effects than either drug alone, and should not be used **(EI)** (*399*). The combination of azithromycin with rifabutin is more effective than azithromycin alone; however, the additional cost, increased occurrence of adverse effects, potential for drug interactions, and absence of a survival difference compared with azithromycin alone do not warrant a routine recommendation for this regimen **(CI)** (*421*). Azithromycin and clarithromycin also each confer protection against respiratory bacterial infections **(BII)**. If azithromycin or clarithromycin cannot be tolerated, rifabutin is an alternative prophylactic agent for MAC disease, although drug interactions might complicate the use of this agent **(BI)** (*423,424*). Before prophylaxis is initiated, disseminated MAC disease should be ruled out by clinical assessment, which might include obtaining a blood culture for MAC. Because treatment with rifabutin could result in RIF resistance among persons who have active TB, active TB also should be excluded before rifabutin is used for prophylaxis.

Although detecting MAC organisms in the respiratory or gastrointestinal tract might predict disseminated MAC infection, no data are available regarding efficacy of prophylaxis with clarithromycin, azithromycin, rifabutin, or other drugs among asymptomatic patients harboring MAC organisms at these sites in the presence of a negative blood culture. Therefore, routine screening of respiratory or gastrointestinal specimens for MAC is not recommended **(DIII)**.

Discontinuing Primary Prophylaxis

Primary MAC prophylaxis should be discontinued among adult and adolescent patients who have responded to ART with an increase in $CD4^+$ counts to >100 cells/μL for ≥3 months **(AI)**. Two randomized, placebo-controlled trials and observational data have demonstrated that such patients can discontinue primary prophylaxis with minimal risk for acquiring MAC disease (*126,425–428*). Discontinuing primary prophylaxis among patients who meet these criteria is recommended to reduce pill burden, the potential for drug toxicity, drug interactions, selection of drug-resistant pathogens, and cost. Primary prophylaxis should be reintroduced if the $CD4^+$ count decreases to <50 cells/μL **(AIII)**.

Treatment of Disease

Initial treatment of MAC disease should consist of two or more antimycobacterial drugs to prevent or delay the emergence of resistance **(AI)** (*400,405,406,429–436*). Clarithromycin is the preferred first agent **(AI);** it has been studied more extensively than azithromycin in patients with AIDS and appears to be associated with more rapid clearance of MAC from the blood (*400,429,431,435–437*). However, azithromycin can be substituted for clarithromycin when drug interactions or clarithromycin intolerance preclude the use of clarithromycin **(AII)**. Testing MAC isolates for susceptibility to clarithromycin or azithromycin is recommended for all patients **(BIII)** (*438,439*)**.**

EMB is the recommended second drug **(AI)**. Some clinicians add rifabutin as a third drug **(CI)**. One randomized clinical trial demonstrated that the addition of rifabutin to the combination of clarithromycin and EMB improved survival, and in two randomized clinical trials, this approach reduced emergence of drug resistance (*400,431*) in persons with AIDS and disseminated MAC disease. These studies were completed before the availability of effective ART. The addition of a third or fourth drug should be considered in persons with advanced immunosuppression ($CD4^+$ count <50 cells/μL), high mycobacterial loads (>2 $\log_{10}$ colony forming units/mL of blood), or in the absence of effective ART, settings in which mortality is increased and emergence of drug resistance is most likely **(CIII)**. On the basis of data in non-HIV-infected patients, the third or fourth drug might include an injectable agent such as amikacin or streptomycin **(CIII)** (*438*)**.**

Patients who have disseminated MAC disease and have not been treated previously with or are not receiving effective ART should generally typically have ART withheld until after the first 2 weeks of antimycobacterial therapy have been completed to reduce risk for drug interactions, pill burden, and complications associated with the occurrence of IRIS **(CIII)**. If ART has already been instituted, it should be continued and optimized unless drug interactions preclude the safe concomitant use of antiretroviral and antimycobacterial drugs **(CIII)**.

Monitoring and Adverse Events, Including Immune Reconstitution Inflammatory Syndrome (IRIS)

A repeat blood culture for MAC should be obtained 4–8 weeks after initiating antimycobacterial therapy only for patients who fail to have a clinical response to their initial treatment regimen. Improvement in fever and a decline in quantity of mycobacteria in blood or tissue can be expected within 2–4 weeks after initiation of appropriate therapy; however, for those with more extensive disease or advanced immunosuppression, clinical response might be delayed.

Adverse effects with clarithromycin and azithromycin include nausea, vomiting, abdominal pain, abnormal taste, and elevations of liver transaminase levels or hypersensitivity reactions. Doses of clarithromycin >1 g/day for treatment of disseminated MAC disease have been associated with increased mortality and should not be used **(EI)** (*440*). Rifabutin doses of ≥450 mg/day have been associated with higher risk for adverse drug interactions when used with clarithromycin or other drugs that inhibit cytochrome P450 isoenzyme 3A4 and might be associated with a higher risk for experiencing uveitis, arthralgias, or other adverse drug reactions (*441,442*).

Persons who develop moderate to severe symptoms typical of IRIS during ART, should receive initial treatment with nonsteroidal, anti-inflammatory agents **(CIII)**. If IRIS symptoms do not improve, short-term (4–8 weeks) systemic corticosteroid therapy, in doses equivalent to 20–40 mg of oral prednisone daily, has been successful in reducing symptoms and morbidity **(CIII)** (*416,443,444*).

Rifabutin should not be administered to patients receiving certain PIs and NNRTIs because the complex interactions have been incompletely studied and the clinical implications of those interactions are unclear (*423,424*). PIs can increase clarithromycin levels, but no recommendation to adjust the dose of either clarithromycin or PIs can be made on the basis of existing data. Efavirenz can induce metabolism of clarithromycin. This can result in reduced serum concentration of clarithromycin but increased concentration of the 14-OH active metabolite of clarithromycin. Although the clinical significance of this interaction is unknown, the efficacy of clarithromycin for MAC prophylaxis could be reduced because of this interaction. Azithromycin metabolism is not affected by the cytochrome P450 (CYP450) system; azithromycin can be used safely in the presence of PIs or NNRTIs without concerns of drug interactions.

Management of Treatment Failure

Treatment failure is defined by the absence of a clinical response and the persistence of mycobacteremia after 4–8 weeks of treatment. Repeat testing of MAC isolates for susceptibility to clarithromycin or azithromycin is recommended for patients who relapse after an initial response. The majority of patients who experience failure of clarithromycin or azithromycin primary prophylaxis in clinical trials had isolates susceptible to these drugs at the time MAC disease was detected (*400,405,406,429,445,446*).

Because the number of drugs with demonstrated clinical activity against MAC is limited, results of susceptibility testing should be used to construct a new multi-drug regimen. The regimen should consist of at least two new drugs not used previously, to which the isolate is susceptible and selected from among the following: EMB, rifabutin, amikacin, or a quinolone (moxifloxacin, ciprofloxacin, or levofloxacin), although data supporting a survival or microbiologic benefit when these agents are added have not been compelling **(CIII)** (*33,405,406,430-434,437,447–450*). On the basis of data related to non-HIV-infected patients being treated for MAC, an injectable agent such as amikacin or streptomycin should be considered **(CIII)** (*438*)**.** Whether continuing clarithromycin or azithromycin despite resistance provides additional benefit is unknown. Clofazimine should not be used because randomized trials have demonstrated lack of efficacy and an association with increased mortality **(EII)** (*430,432,448*)**.** Other second-line agents (e.g., ethionamide, thiacetazone [not available in the United States], or cycloserine) have been anecdotally combined with clarithromycin and azithromycin as salvage regimens. However, their role in this setting is not well defined. Among patients whose initial treatment for MAC disease has not been successful or who have antimycobacterial drug-resistant MAC disease, optimizing ART is an important adjunct to second-line or salvage therapy for MAC disease **(AIII)**.

Adjunctive treatment of MAC disease with immunomodulators has not been thoroughly studied, and data are insufficient to support a recommendation for use **(DIII)**.

Preventing Recurrence

Adult and adolescent patients with disseminated MAC disease should receive lifelong secondary prophylaxis (chronic maintenance therapy) **(AII)**, unless immune reconstitution occurs as a result of ART (*425,426*).

Discontinuing Secondary Prophylaxis (Chronic Maintenance Therapy)

Patients are at low risk for recurrence of MAC when they have completed a course of ≥12 months of treatment for MAC, remain asymptomatic with respect to MAC signs and symptoms, and have a sustained increase (e.g., >6 months) in their $CD4^+$ counts to >100 cells/μL after ART. Although the numbers of patients who have been evaluated remain limited and recurrences could occur, based on the limited number of patients who have been evaluated and the inferences from more extensive data indicating the safety of discontinuing secondary prophylaxis for other OIs, discontinuing chronic maintenance therapy is reasonable **(BII)** (*121,426,434,451*). Secondary prophylaxis should be reintroduced if the $CD4^+$ count decreases to <100 cells/μL **(AIII)**.

Special Considerations During Pregnancy

Chemoprophylaxis for MAC disease should be administered to pregnant women the same as for nonpregnant women and adolescents **(AIII)**. Because of an increased risk for birth defects evident in certain animal studies, clarithromycin is not recommended as the first-line agent for prophylaxis or treatment of MAC in pregnancy **(DIII)**. Two studies, each with slightly more than 100 women with first-trimester exposure to clarithromycin, did not demonstrate an increase in or specific pattern of defects, although an increased risk for spontaneous abortion was noted in one study (*452,453*). Azithromycin did not produce defects in animal studies, but experience for use in humans during the first trimester is limited. Azithromycin is recommended for primary prophylaxis in pregnancy **(BIII)**. For secondary prophylaxis (chronic maintenance therapy), azithromycin plus EMB are the preferred drugs **(BIII)**.

Diagnostic considerations and indications for treatment of pregnant women are the same as for nonpregnant women. On the basis of animal data discussed previously, azithromycin is preferred over clarithromycin as the second agent with EMB **(BIII)**. Use of EMB should minimize concerns regarding drug interactions, allowing initiation of ART as soon as possible during pregnancy to decrease the risk for perinatal transmission of HIV. Pregnant women whose treatment failed on their primary regimen should be managed in consultation with infectious disease and obstetrical specialists.

Bacterial Respiratory Disease

Epidemiology

Bacterial pneumonia is a common cause of HIV-associated morbidity. The incidence of bacterial pneumonia among HIV-infected persons is greater than that in the noninfected population (*454*). In the precombination ART era, the Pulmonary Complications of HIV Infection Study reported that the incidence of bacterial pneumonia ranged was 3.9–7.3 episodes per 100 person-years (*455*). In the current era, the incidence of bacterial pneumonia in HIV-infected persons has declined (*4,456,457*).

Bacterial pneumonia might be the first manifestation of underlying HIV infection and can occur at any stage of HIV disease and at any CD4+ count. The high rates of bacterial pneumonia in HIV-infected persons probably result from multiple factors, including qualitative B-cell defects that impair ability to produce pathogen-specific antibody, impaired neutrophil function or numbers or both, and factors (e.g., injection drug use) that are associated with underlying HIV infection. Risk factors associated with an increased risk for bacterial pneumonia, include low CD4+ count, injection-drug use, and cigarette smoking (*454*).

Similar to persons without HIV infection, *Streptococcus pneumoniae* and *Haemophilus* species are the most frequently identified causes of community-acquired bacterial pneumonia in HIV-infected persons (*458–464*). Similar to the noninfected population, drug-resistant *Streptococcus pneumoniae* is an increasing concern and is associated with increased mortality (*465*).

Although atypical bacterial pathogens such as *Legionella pneumophila*, *Mycoplasma pneumoniae*, and *Chlamydophila* species have been reported as infrequent causes of community-acquired bacterial pneumonia in HIV-infected persons (*461,466*), they are important considerations in decisions regarding antibiotic treatment.

In contrast to the noninfected population, *Pseudomonas aeruginosa* and *Staphylococcus aureus* are both reported as community-acquired pathogens with an increased frequency among persons with HIV infection (*462,467*).

Compared with persons without HIV infection, HIV-infected persons have an increased incidence of bacteremia accompanying pneumonia, especially if they are infected with *S.pneumoniae*. (*468–470*). In one study, the estimated rate of pneumococcal bacteremia (9.4 cases per 1,000 patient-years) in AIDS patients was approximately 100-fold greater than in HIV-uninfected historical controls (*468*).

Bacterial pneumonia is associated with an increased mortality among HIV-infected persons (*462,471,472*). Among HIV-infected persons with community-acquired bacterial pneumonia, a prospective, multicenter study documented that a CD4+ count <100 cells/μL, radiographic progression of disease, and the presence of shock were independent predictors of increased mortality (*473*). In this study, multilobar infiltrates, cavitary infiltrates, and pleural effusion at baseline were all independent predictors of radiographic progression of HIV.

Clinical Manifestations

The clinical and radiographic presentation of bacterial pneumonia in HIV-infected persons is similar to that in persons without HIV infection. Persons with pneumonias caused by *Streptococcus pneumoniae* and *Haemophilus* species characteristically have an acute onset (3–5 days) of symptoms, including fevers, chills, rigors, chest pain, cough productive of purulent sputum, and dyspnea (*92*). On examination of vital signs, patients are often febrile. The presence of tachycardia or hypotension is an indicator of the systemic inflammatory response syndrome (SIRS). Tachypnea and decreased arterial oxygen saturation indicate moderate-to-severe pneumonia and clinicians should strongly consider hospitalizing such patients.

Persons with bacterial pneumonia typically have evidence of focal consolidation and/or pleural effusion on lung examination, as contrasted to persons with PCP, in which the lung examination is often normal or, if abnormal, reveals inspiratory crackles.

The white blood cell (WBC) count is usually elevated in persons with bacterial pneumonia. In persons with advanced HIV disease, the elevation might be relative to the persons's baseline WBC. A left shift also might be present.

Persons with bacterial pneumonia characteristically exhibit unilateral, focal, segmental, or lobar consolidation on chest radiograph. However, the frequency of these typical radiographic findings might depend on the underlying bacterial pathogen. HIV-infected persons might present with multifocal or multilobar involvement and with parapneumonic effusions more frequently than persons without HIV infection (*474*).

Diagnosis

Guidelines for the management of community-acquired pneumonia (CAP) in persons without HIV infection also apply to HIV-infected persons (*475*). Persons with clinical symptoms and signs suggestive of CAP should have a chest radiograph. When available, previous radiographs should be reviewed to assess for the presence of new findings. The clinical diagnosis of bacterial pneumonia requires a demonstrable infiltrate.

Given the increased incidence of *Mycobacterium tuberculosis* in HIV-infected persons, the diagnosis of TB should always be suspected in HIV-infected persons who have pneumonia. Those persons with a clinical and radiographic evidence suggestive of TB should be managed as potential TB (e.g., respiratory isolation if hospitalized), and three sputum specimens should be obtained for AFB smear and culture. Dual therapy for both bacterial pneumonia and TB is appropriate for patients for whom both of these diagnoses are considerations and where diagnostic studies are undertaken.

Standard recommendations for routine testing for bacterial pneumonia remain controversial (*475*). Usually, the differential diagnosis of pneumonia in HIV-infected persons is broad and a confirmed microbiologic diagnosis might allow clinicians to target the specific pathogen and to discontinue broad spectrum antibiotic therapy and/or empiric therapy that targets nonbacterial pathogens (e.g., empiric PCP therapy). The increased incidence of bacteremia in HIV-infected persons (especially

at low CD4+ count) and the high specificity of blood cultures argue for their collection in HIV-infected persons. Although the low sensitivity of sputum and blood cultures and the infrequency that these results alter clinical management in HIV-uninfected patients with CAP argue against their routine collection, patients with HIV infection are at increased risk for infection with drug-resistant *Streptococcus pneumococci* (drug-resistant *S. pneumoniae*) and identification of this organism could lead to changes in management.

HIV-infected persons with suspected CAP should undergo investigation for specific pathogens that would significantly alter standard (empirical) management decisions when the presence of such pathogens is suspected on the basis of epidemiologic, clinical, or radiologic clues. *Pseudomonas aeruginosa* should be considered in HIV-infected persons with advanced HIV disease (i.e., CD4+ count ≤50 cells/μL); those with pre-existing lung disease (i.e., bronchiectasis); underlying neutropenia, corticosteroid therapy, or severe malnutrition; those who have been hospitalized within 90 days or reside in a health-care facility or nursing home; and those on chronic hemodialysis. Given the frequency of cavitary infiltrates in persons with *P. aeruginosa*, this radiographic finding should also prompt an investigation for this pathogen. *Staphylococcus aureus* should be considered in persons with recent viral (or influenza) infection; history of injection-drug use; or severe, bilateral, necrotizing pneumonia.

Routine diagnostic tests to identify an etiologic diagnosis are optional for persons with CAP who are well enough to be treated as outpatients, especially true if microbiologic studies cannot be performed promptly.

A pretreatment expectorated sputum specimen for Gram stain and culture and two blood cultures should be obtained from persons with CAP who are hospitalized, especially if intensive care is required. Gram stain and culture of expectorated sputum should be performed only if a good-quality specimen can be obtained and quality performance measures for collection, transport, and processing of samples can be met. Correlation of the sputum culture with the Gram stain can help in the interpretation of sputum culture data. For intubated patients, an endotracheal aspirate sample should be obtained. In addition to the above tests, urinary antigen tests for *Legionella pneumophila* and *Streptococcus pneumoniae* should be considered.

Diagnostic thoracentesis should be considered in any person with pleural effusion, especially if a concern exists for accompanying empyema, and a therapeutic thoracentesis should be performed to relieve respiratory distress secondary to a moderate- to large-sized effusion.

Preventing Exposure

No effective means exist to reduce exposure to *Streptococcus pneumoniae* and *Haemophilus influenzae*, which are common in the community.

Preventing Disease

HIV-infected adults and adolescents who have a CD4+ count of >200 cells/μL should be administered a single dose of 23-valent polysaccharide pneumococcal vaccine (PPV) unless they have received this vaccine during the previous 5 years **(AII)** (*157,476–479*). One randomized placebo-controlled trial of pneumococcal vaccine in Africa paradoxically determined that an increased risk for pneumonia was associated with vaccination (*480*). Follow-up of this cohort confirmed the increase in pneumonia in vaccinated subjects but also reported a decrease in all-cause mortality (*481*). In contrast, multiple observational studies of pneumococcal vaccine in the United States have reported benefits from vaccination (*157,476–479,482*). Studies also have documented that vaccination is associated with a lower risk for pneumococcal bacteremia (*482,483*). The majority of HIV specialists believe that the potential benefit of pneumococcal vaccination in the United States outweighs the risk.

HIV-infected adults and adolescents who have a CD4+ count of <200 cells/μL can be offered PPV **(CIII)**. Clinical evidence has not confirmed efficacy in this group, but evidence documents the benefit for those who also start ART (*482*). Revaccination can be considered for persons who were initially vaccinated when their CD4+ counts were <200 cells/μL and whose CD4+ counts have increased to >200 cells/μL in response to ART **(CIII)**.

The duration of the protective effect of primary pneumococcal vaccination is unknown; revaccination every 5 years may be considered **(CIII)** (*479*). No evidence confirms clinical benefit from revaccination. Nevertheless, the recommendation to vaccinate is increasingly pertinent because of the increasing incidence of invasive infections with drug-resistant (including TMP-SMX-, macrolide-, and ß-lactam-resistant) strains of *S. pneumoniae*.

The incidence of *H. influenzae* type b (Hib) infection among HIV-infected adults is low. Therefore, Hib vaccine is not usually recommended for adult use **(DIII)**.

Several factors are associated with a decreased risk for bacterial pneumonia, including the use of combination ART and TMP-SMX used for PCP prophylaxis (*472*). The use of antimicrobial prophylaxis to prevent bacterial pneumonia has been explored. In many studies, TMP-SMX, when administered daily for PCP prophylaxis, reduces the frequency of bacterial respiratory infections (*30*, *114,454*). This should be considered in selecting an agent for PCP prophylaxis **(AII)**. However,

indiscriminate use of this drug (when not indicated for PCP prophylaxis or other specific reasons) might promote development of TMP-SMX-resistant organisms. Thus, TMP-SMX should not be prescribed solely to prevent bacterial respiratory infection **(DIII)**. Similarly, clarithromycin administered daily or azithromycin administered weekly for MAC prophylaxis might be effective in preventing bacterial respiratory infections (*421,484*). This should be considered in selecting an agent for prophylaxis against MAC (**BII**). However, these drugs should not be prescribed solely for preventing bacterial respiratory infection **(DIII)**.

An absolute neutrophil count that is depressed because of HIV disease or drug therapy is associated with an increased risk for bacterial infections, including pneumonia. To reduce the risk for such bacterial infections, health-care providers might consider taking steps to reverse neutropenia, either by stopping myelosuppressive drugs **(CII)** or by administering granulocyte-colony stimulating factor (G-CSF) **(CII)**.

Modifiable factors associated with an increased risk for bacterial pneumonia include smoking cigarettes and other drugs, injection-drug use (IDU), and alcohol use (*138,454,485,486*). Clinicians should encourage cessation of these behaviors, although no data exist to indicate that cessation decreases risk **(CIII)**.

Inactivated influenza vaccine should be administered annually to all HIV-infected persons during influenza season **(AIII)**. This recommendation is pertinent to prevention of bacterial pneumonia, which might occur as a complication of influenza illness. Live attenuated influenza vaccine is contraindicated for HIV-infected persons **(EIII)**.

Treatment of Disease

The principles of the treatment of community-acquired bacterial pneumonia are the same for HIV-infected persons as for HIV-uninfected persons (*475*). Usually, collection of specimens for microbiologic studies should be performed before the initiation of antibiotic therapy. However, antibiotic therapy should be administered promptly, without waiting for the results of diagnostic testing.

An assessment of disease severity and arterial oxygenation should be performed in all persons with pneumonia. Noninvasive measurement of arterial oxygen saturation via pulse oximetry is an appropriate screening test. However, ABG analysis is indicated for persons with evidence of hypoxemia suggested by noninvasive assessment and for persons with tachypnea and/or respiratory distress. Criteria that were developed to assess CAP disease severity in HIV-uninfected persons have been found to be valid for HIV-infected persons (*473*). Unlike recommendations for CAP therapy in non-HIV patients, no HIV-infected patient should receive macrolide monotherapy because of the increased risk for drug-resistant *Streptococcus pneumoniae* in the HIV-infected patient.

Outpatient Treatment

HIV-infected persons who are being treated as outpatients should receive an oral beta-lactam plus an oral macrolide **(AII).** Preferred beta-lactams are high-dose amoxicillin and amoxicillin-clavulanate; cefpodoxime and cefuroxime are alternatives. Preferred macrolides are azithromycin and clarithromycin. Oral doxycycline is an alternative to the macrolide **(CIII)**.

For persons who are allergic to penicillin or who have received a beta-lactam within the previous 3 months, an oral respiratory fluoroquinolone (moxifloxacin, levofloxacin [750 mg/day], or gemifloxacin) should be used **(AII)**. Respiratory fluoroquinolones are active against *Mycobacterium tuberculosis.* Thus, persons with TB who are treated with fluoroquinolone monotherapy might respond initially, but this response might be misleading, might delay the diagnosis of TB and the initiation of appropriate multi-drug therapy, and might increase the risk for transmission of TB. Thus, fluoroquinolones should be used with caution in patients in whom TB is suspected but who are not being treated with concurrent standard four-drug TB therapy. Because HIV-infected persons have an increased incidence of TB and the presentation of TB can be varied in HIV-infected persons, fluoroquinolones should be used only when the presentation strongly suggests bacterial pneumonia.

Increasing pneumococcal resistance rates have suggested that empirical therapy with a macrolide alone cannot be routinely recommended **(DIII)**. Patients who are receiving a macrolide for MAC prophylaxis should never receive macrolide monotherapy for empiric treatment of bacterial pneumonia.

Non-ICU Inpatient Treatment

HIV-infected persons who are being treated as inpatients should receive an IV beta-lactam plus a macrolide **(AII)**. Preferred beta-lactams are ceftriaxone, cefotaxime, or ampicillin-sulbactam. Doxycycline is an alternative to the macrolide **(CIII)**.

For persons who are allergic to penicillin or who have received a beta-lactam within the previous 3 months, an IV respiratory fluoroquinolone (moxifloxacin or levofloxacin [750 mg/day]) should be used **(AII)**. Because of the activity of fluoroquinolones against *Mycobacterium tuberculosis* and the dangers of monotherapy in persons with TB, fluoroquinolones should be used with caution in patients in whom TB is suspected but is not being treated with concurrent standard four-drug TB therapy.

Increasing pneumococcal resistance rates have suggested that empirical therapy with a macrolide alone cannot be recommended routinely **(DIII)**. Patients who are receiving a

macrolide for MAC prophylaxis should never receive macrolide monotherapy for empiric treatment of bacterial pneumonia.

ICU Treatment

Persons with severe pneumonia who require intensive care should be treated with an IV beta-lactam plus either IV azithromycin **(AII)** or an IV respiratory fluoroquinolone (moxifloxacin or levofloxacin [750 mg/day]) **(AII)**. Preferred beta-lactams are ceftriaxone, cefotaxime, or ampicillin-sulbactam.

For persons who are allergic to penicillin or who have received a beta-lactam within the previous 3 months, aztreonam plus an IV respiratory fluoroquinolone (moxifloxacin or levofloxacin [750 mg/day]) should be used **(BIII)**.

Infections with the overwhelming majority of CAP pathogens will be treated adequately by use of the recommended empirical regimens. The increased incidence of *P. aeruginosa* and *S. aureus* as a cause of CAP is the exception. These pathogens occur in specific epidemiologic patterns with distinct clinical presentations, for which empirical antibiotic coverage might be warranted. Diagnostic tests (sputum Gram stain and culture) are likely to be of high yield for these pathogens, allowing early discontinuation of empirical treatment if results are negative.

Empiric Pseudomonas aeruginosa *Treatment*

If risk factors for *Pseudomonas* infection are present, an antipneumococcal, antipseudomonal beta-lactam plus either ciprofloxacin or levofloxacin (750 mg dose) should be used **(BIII)**. Preferred beta-lactams are piperacillin-tazobactam, cefepime, imipenem, or meropenem. An antipneumococcal, antipseudomonal beta-lactam plus an aminoglycoside and azithromycin **(BIII)** or an antipneumococcal, antipseudomonal beta-lactam plus an aminoglycoside and an antipneumococcal fluoroquinolone **(BIII)** are alternatives. For persons who are allergic to penicillin or who have received a beta-lactam within the previous 3 months, aztreonam can be used in place of the beta-lactam **(BIII)**.

Empiric Staphylococcus aureus *Treatment*

If risk factors for *Staphylococcus aureus* infection, including community-acquired methicillin-resistant *S. aureus*, are present, vancomycin (possibly in combination with clindamycin) or linezolid alone should be added to the antibiotic regimen **(BIII)**.

Pathogen-Directed Therapy

When the etiology of pneumonia has been identified on the basis of reliable microbiological methods, antimicrobial therapy should be directed at that pathogen **(BIII)**.

Switch from Intravenous to Oral Therapy

For patients with CAP who begin IV antibiotic therapy, switching to oral therapy should be considered when they are improving clinically, are able to swallow and tolerate oral medications, and have intact gastrointestinal function. Suggested criteria for clinical stability include oral temperature <37.8 °C, heart rate <100 beats/minute, respiratory rate <24 breaths/minute, systolic blood pressure ≥90 mm Hg, and room air oxygen saturation >90% or partial pressure of oxygen in arterial blood (PaO2) >60 mm Hg (475).

Monitoring and Adverse Events, Including Immune Reconstitution Inflammatory Syndrome (IRIS)

The clinical response to appropriate antimicrobial therapy is similar in HIV-infected and non-HIV-infected persons (*487*). A clinical response (i.e., a reduction in fever and improvement in respiratory symptoms, physical findings, and laboratory studies) is typically observed within 48–72 hours after the initiation of appropriate antimicrobial therapy. Usually, radiographic improvement might lag behind clinical improvement. If a patient has progressive pneumonia in spite of therapy, leading to severe CAP, adjunctive therapy with corticosteroids might be appropriate to ameliorate the inflammatory reaction to killing bacteria in the lung parenchyma **(CIII)**.

IRIS has not been described in association with bacterial respiratory disease and treatment with ART in HIV-infected persons.

Management of Treatment Failure

Persons who fail to respond to appropriate antimicrobial therapy should undergo further evaluation to search for other infectious and noninfectious causes of pulmonary dysfunction. The possibility of TB should always be considered in HIV-infected persons with pulmonary disease.

Preventing Recurrence

HIV-infected persons should receive pneumococcal and influenza vaccine as recommended. Clinicians can administer antibiotic chemoprophylaxis to HIV-infected patients who have frequent recurrences of serious bacterial respiratory infections **(CIII)**. TMP-SMX, administered for PCP prophylaxis, and clarithromycin or azithromycin, administered for MAC prophylaxis, are appropriate for drug-sensitive organisms. However, health-care providers should be cautious when using antibiotics solely for preventing the recurrence of serious bacterial respiratory infections because of the potential development of drug-resistant microorganisms and drug toxicity.

Special Considerations During Pregnancy

The diagnosis of bacterial respiratory-tract infections among pregnant women is the same as for nonpregnant women, with appropriate shielding of the abdomen during radiographic procedures. Bacterial respiratory-tract infections should be managed as in nonpregnant women, with certain exceptions. Because of an increased risk for birth defects evident in some animal studies, clarithromycin is not recommended as the first-line agent among macrolides. Two studies, each involving at least 100 women with first-trimester exposure to clarithromycin, did not document a clear increase in or specific pattern of birth defects, although an increased risk for spontaneous abortion was noted in one study (*452,453*). Azithromycin did not produce birth defects in animal studies, but experience with human use in the first trimester is limited. Azithromycin is recommended when a macrolide is indicated in pregnancy **(BIII)**. Arthropathy has been noted in immature animals exposed in utero to quinolones. However, approximately 400 cases of quinolone use in human pregnancies have been reported to various pregnancy registries, and use has not been associated with human arthropathy or birth defects after in utero exposure. Thus, quinolones can be used in pregnancy for serious respiratory infections when indicated **(CIII)** (*395*). Doxycycline is not recommended for use during pregnancy because of increased hepatotoxicity and staining of fetal teeth and bones. Beta-lactam antibiotics have not been associated with teratogenicity or increased toxicity in pregnancy. Aminoglycosides may be used as needed. Although a theoretical risk for fetal renal or eighth nerve damage can occur with exposure during pregnancy, this finding has not been documented in humans except with streptomycin (10% risk) and kanamycin (2% risk). Experience with linezolid in human pregnancy has been limited, but it was not teratogenic in mice, rats, and rabbits.

Rates for preterm labor and preterm delivery are increased with pneumonia during pregnancy. Pregnant women with pneumonia after 20 weeks of gestation should be monitored for evidence of contractions **(BII)**.

Pneumococcal vaccine can be administered during pregnancy **(AIII)**. Although its safety during the first trimester of pregnancy has not been evaluated, no adverse consequences have been reported among newborns whose mothers were inadvertently vaccinated during pregnancy. Inactivated influenza vaccine also can be administered during pregnancy, and influenza vaccine is recommended for all pregnant women who will be pregnant during influenza season **(AIII)**. Live attenuated influenza vaccine should not be used during pregnancy **(EIII)**. Because administration of vaccines might be associated with a transient rise in plasma HIV RNA levels, vaccination of pregnant women is recommended after ART has been initiated to minimize increases in plasma HIV RNA levels that might increase the risk for perinatal HIV transmission.

Bacterial Enteric Infections

Epidemiology

Incidence rates of gram-negative bacterial enteric infections are 20- to 100-fold higher among HIV-infected adults than in the general population (*488-492*). The most common causes among adults in the United States are *Salmonella* (particularly *Salmonella* serotypes Typhimurium and Enteritidis), *Shigella*, and *Campylobacter*. As with non-HIV-associated bacterial enteric infections, the probable source for most HIV-infected associated infections is ingestion of contaminated food or water (*490*). Sexual activity with the potential for fecal-oral exposure also increases risk for infections, especially with *Shigella (493*) and *Campylobacter (494*). Acquisition of enteric bacterial infections might be facilitated by HIV-associated gastric achlorhydria, by treatment with agents that decrease gastric acid secretion, and by HIV-associated alterations in mucosal immunity. Although diarrheagenic *Escherichia coli*, especially enteroaggregative *E. coli*, are a frequent cause of diarrhea among HIV-infected persons in resource-limited settings, they do not appear to cause more morbidity in HIV-infected patients than in other persons in more developed regions (*495*).

Clinical Manifestations

The three major clinical syndromes of infection with gram-negative enteric bacteria among HIV-infected patients include the following:

- Self-limited gastroenteritis;
- A more severe and prolonged diarrheal disease, associated with fever, bloody diarrhea, weight loss, and possible bacteremia (bloody diarrhea is more frequent with *Shigella* but also can occur with *Campylobacter* or *Salmonella* (*496,497*); and
- Septicemia, which can exhibit extra-intestinal involvement with or without concurrent or preceding gastrointestinal illness (*498–501*).

The risk for more profound illness increases with the degree of immunosuppression (*488,490,491,502*). Relapses in infections with *Salmonella* and other gram-negative bacterial enteric pathogens after appropriate treatment have been well-documented in HIV-infected patients (*497,503,504*). *Salmonella* is a particularly common cause of septicemia, which is prone to relapse. Recurrent *Salmonella* septicemia constitutes an AIDS-defining illness and might require chronic suppressive therapy (*488*). The development of antimicrobial resistance during therapy, often associated with clinical deterioration

or relapse, can also occur among HIV-infected persons with gram-negative enteridities (*500,501*).

Diagnosis

The diagnosis of gram-negative bacterial enteric infection is established through cultures of stool and blood. Because of the high rate of bacteremia associated with *Salmonella* gastroenteritis in HIV-infected patients, in particular patients with advanced disease, blood cultures should be obtained from any patient with diarrhea and fever.

HIV-infected persons are notably at risk for infection with non-jejuni non-coli *Campylobacter* species, including *C. fetus, C. upsaliensis, C. lari,* and the enterohepatic *Helicobacter* species, *H. cineadi*, and *H. fennelliae* (originally described as *Campylobacter* species). Although blood culture systems will typically grow these bacteria, routine stool cultures performed by most laboratories will fail to identify these more fastidious organisms, which require special conditions for stool culture. Clinicians might wish to notify their clinical laboratory service of a patient's HIV status and to consider evaluation of stool specimens for non-jejuni non-coli *Campylobacter* if initial microbiological evaluation is unrevealing. Endoscopy can be diagnostically useful. If lower endoscopy is performed, ulcerations similar to those seen with CMV colitis might be evident and can only be distinguished through histopathologic examination and culture. Clinicians should notify their microbiology laboratories if they suspect infection with diarrheagenic *E. coli* so that appropriate molecular diagnostic methods can be used or the specimen can be sent to a reference laboratory.

Preventing Exposure

Scrupulous handwashing can reduce risk for diarrhea in HIV-infected persons, including diarrhea caused by enteric bacteria (*242*). HIV-infected persons should be advised to wash their hands after potential contact with human feces (e.g., defecation, cleaning feces from infants), after handling pets or other animals, after gardening or other contact with soil, before preparing food, before eating, and before and after sex **(AIII)**. HIV-infected persons should avoid unprotected sex practices that might result in oral exposure to feces (e.g., anal sex, oral-anal contact) and in addition to hand-washing they should be advised to use barriers during sex to reduce exposures when possible (e.g., condoms, dental dams) **(AIII)**.

Food

Health-care providers should advise HIV-infected persons, particularly those with a $CD4^+$ count <200 cells/μL, not to eat raw or undercooked eggs, including specific foods that might contain raw eggs (e.g., certain preparations of hollandaise sauce, Caesar and other salad dressings, certain mayonnaises (e.g., homemade), uncooked cookie and cake batter, and eggnog); raw or undercooked poultry, meat, and seafood (raw shellfish in particular); unpasteurized dairy products; unpasteurized fruit juices; and raw seed sprouts (e.g., alfalfa sprouts or mung bean sprouts) **(BIII)**. Poultry and meat are safest when adequate cooking is confirmed by thermometer (i.e., internal temperature of 180º F (82º C) for poultry and 165º F (74º C) for red meats). If a thermometer is not used when cooking meats, the risk for illness is decreased by eating poultry and meat that have no trace of pink color. However, color change of the meat (e.g., absence of pink) does not always correlate with internal temperature. Produce should be washed thoroughly before being eaten **(BIII)**.

Health-care providers should advise HIV-infected persons to avoid cross-contamination of foods. Uncooked meats, including hot dogs, and their juices should not come into contact with other foods **(BIII)**. Hands, cutting boards, counters, knives, and other utensils should be washed thoroughly after contact with uncooked foods **(BIII)**.

Health-care providers should advise HIV-infected persons that, although the incidence of listeriosis is low, it is a serious disease that occurs with unusually high frequency among severely immunosuppressed HIV-infected persons. Immunosuppressed, HIV-infected persons who wish to reduce the risk for acquiring listeriosis should adhere to the following precautions **(CIII)**:

- Avoid soft cheeses (e.g., feta, Brie, Camembert, blue-veined, and Mexican-style cheese such as queso fresco); hard cheeses, processed cheeses, cream cheese (including slices and spreads), cottage cheese, or yogurt need not be avoided.
- Cook leftover foods or ready-to-eat foods (e.g., hot dogs) until steaming hot before eating.
- Avoid foods from delicatessen counters (e.g., prepared salads, meats, cheeses) or heat/reheat these foods until steaming before eating.
- Avoid refrigerated pâtés and other meat spreads or heat/reheat these foods until steaming; canned or shelf-stable pâté and meat spreads need not be avoided.
- Avoid raw or unpasteurized milk (including goat's milk) or milk products or foods that contain unpasteurized milk or milk products.

Pets

HIV-infected persons should avoid direct contact with stool from new pets, dogs or cats aged <6 months, or stray pets **(BIII)**. Gloves should always be worn when handling feces or cleaning areas that might have been contaminated by feces from pets **(BIII)**. Persons should avoid or limit contact with reptiles (e.g., snakes, lizards, iguanas, and turtles) and chicks and ducklings because of the risk for salmonellosis **(BIII)**.

Travel

The risk for foodborne and waterborne infections among immunosuppressed, HIV-infected persons is magnified during travel to economically developing countries. Persons who travel to such countries should avoid foods and beverages that might be contaminated, including raw fruits and vegetables, raw or undercooked seafood or meat, tap water, ice made with tap water, unpasteurized milk and dairy products, and items sold by street vendors **(AII)**. Foods and beverages that are usually safe include steaming hot foods, fruits that are peeled by the traveler, bottled (including carbonated) beverages, hot coffee and tea, beer, wine, and water that is brought to a rolling boil for 1 minute. Treating water with iodine or chlorine might not be as effective as boiling and will not prevent infection with *Cryptosporidium* but can be used when boiling is not practical **(BIII)**.

Preventing Disease

Prophylactic antimicrobial agents are not usually recommended for travelers **(DIII)**. The effectiveness of these agents depends on gastrointestinal pathogens' local antimicrobial resistance patterns, which are seldom known. Moreover, these agents can elicit adverse reactions, promote the emergence of resistant organisms, and increase risk for enteric *Clostridium difficile* infection. However, for HIV-infected travelers, antimicrobial prophylaxis can be considered, depending on the level of immunosuppression and the region and duration of travel **(CIII)**. Use of fluoroquinolones or rifaximin can be considered when prophylaxis is deemed necessary **(CIII)**. As an alternative (e.g., for pregnant women and persons already taking TMP-SMX for PCP prophylaxis), TMP-SMX might offer limited protection against traveler's diarrhea **(BIII)**. Risk for toxicity should be considered before treatment with TMP-SMX is initiated solely because of travel.

Treatment of Disease

Immunocompetent hosts without HIV infection often do not require treatment for *Salmonella* gastroenteritis; the condition is self-limited and treatment might prolong the carrier state. However, no treatment trials have examined the strategy of watchful waiting for spontaneous resolution among patients with HIV infection, and the risk for bacteremia is sufficiently high that most specialists recommend treatment of all HIV-associated *Salmonella* infections **(BIII)**.

The initial treatment of choice for *Salmonella* infection is a fluoroquinolone **(AIII)** (*505*). Ciprofloxacin is the preferred agent **(AIII)** (*505*); other fluoroquinolones (levofloxacin and moxifloxacin) also would likely be effective in treatment of salmonellosis among HIV-infected persons, but these agents have not been well-evaluated in clinical studies **(BIII)**. Depending on antibiotic susceptibility, alternatives to the fluoroquinolones might include TMP-SMX or expanded spectrum cephalosporins (e.g., ceftriaxone or cefotaxime) **(BIII)**.

The length of therapy for HIV-related Salmonella infection is poorly defined. For patients with $CD4^+$ counts ≥200 cells/μL and mild gastroenteritis, with or without bacteremia, 7–14 days of treatment for salmonellosis is reasonable **(BIII)**; among patients with advanced HIV disease ($CD4^+$ count <200 cells/μL), a longer course of antibiotics (e.g., 2–6 weeks) is often recommended **(CIII)**.

Therapy for shigellosis is indicated both to shorten the duration of illness and to prevent spread of the infection to others **(AIII)** (*505*). The recommended treatment is with a fluoroquinolone for 3–7 days **(AIII)**. Depending on antibiotic susceptibilities, alternatives to this treatment may include TMP-SMX for 3–7 days or azithromycin for 5 days **(BIII)**. Cases of shigellosis acquired internationally have high rates of TMP-SMX resistance; in addition, HIV-infected persons have higher rates of adverse effects related to this agent. As a result, fluoroquinolones are preferred as first-line treatment. Treating patients who have *Shigella* bacteremia is less well defined. Depending on the severity of infection, extending treatment to 14 days is reasonable, using the agents described previously **(BIII)**.

As with non-HIV-infected patients, the optimal treatment of campylobacteriosis among persons with HIV infection is poorly defined. Among patients with mild disease, some clinicians might opt to withhold therapy unless symptoms persist for more than several days. Increasing resistance to fluoroquinolones makes the choice of therapy especially problematic. For mild-to-moderate campylobacteriosis, initiating therapy with a fluoroquinolone (e.g., ciprofloxacin) or a macrolide (e.g., azithromycin), pending susceptibility test results, and treating for 7 days is a reasonable approach **(BIII)**. Patients with bacteremia should be treated for ≥2 weeks **(BIII)**, and adding a second active agent (e.g., an aminoglycoside) might be prudent **(CIII)**.

Monitoring and Adverse Events, Including Immune Reconstitution Inflammatory Syndrome (IRIS)

Patients should be monitored closely for response to treatment, as defined clinically by improvement in systemic signs and symptoms and resolution of diarrhea. A follow-up stool culture to demonstrate clearance of the organism is not generally required if a complete clinical response has been demonstrated, but should be considered for those patients who fail to respond clinically to appropriate antimicrobial therapy or when public health considerations dictate the need to ensure microbiologic cure (e.g., health-care or food service workers). If after a diagnosis of gram-negative bacterial enteritis and diarrhea

persists or recurs after intervention, other enteric infections should be considered, particularly *Clostridium difficile*.

IRIS has not been described in association with treatment for bacterial enteric diarrhea.

Management of Treatment Failure

Treatment failure is defined by the lack of improvement in clinical signs and symptoms of diarrheal illness and the persistence of organisms in stool, blood, or other relevant body fluids or tissue after completion of appropriate antimicrobial therapy for the recommended duration. Some patients with *Salmonella* bacteremia might remain febrile for 5–7 days despite effective therapy. Therefore, careful observation is required to determine the adequacy of the response.

Treatment should be guided by drug susceptibility testing of isolates recovered in culture. An evaluation of other factors that might contribute to failure or relapse, such as malabsorption of oral antibiotics, a sequestered focus of infection (e.g., an undrained abscess), adverse drug reactions that interfere with antimicrobial activity, or infection with other agents (e.g., *C. difficile*) should be undertaken as indicated.

Preventing Recurrence

HIV-infected persons with *Salmonella* septicemia, which typically occurs in those with advanced HIV disease (e.g., $CD4^+$ count <200 cells/μL), should be monitored clinically for recurrence after treatment **(BIII)**. For persons with recurrent *Salmonella* septicemia, 6 months or more of antibiotics treatment of acute disease should be considered as secondary prophylaxis, although the value of this intervention has not been established and must be weighed against the risks of long-term antibiotic exposure **(CIII)**. In patients who have responded to ART, secondary prophylaxis can probably be stopped. Chronic suppressive or maintenance therapy is not recommended for *Campylobacter* or *Shigella* infections among persons with HIV infection **(EIII)**. Household contacts of HIV-infected persons who have salmonellosis or shigellosis should be evaluated for persistent asymptomatic carriage of *Salmonella* or *Shigella* so that strict hygienic measures or antimicrobial therapy can be instituted and recurrent transmission to the HIV-infected person prevented **(BIII)**.

Special Considerations During Pregnancy

The diagnosis of bacterial enteric infections among pregnant women is the same as among nonpregnant women. Bacterial enteric infections in the pregnant woman should be managed as in the nonpregnant woman, with several considerations. Arthropathy has been noted in immature animals when quinolones are used during pregnancy. However, approximately 400 cases of quinolone use in pregnancy have been reported to various pregnancy registries, and use has not been associated with arthropathy or birth defects after in utero exposure. Thus, quinolones can be used in pregnancy for bacterial enteric infections in HIV-infected pregnant women as indicated **(CIII)** (*395*). Alternate agents for use in pregnancy include expanded spectrum cephalosporins, TMP-SMX, or azithromycin, depending on the organism and the results of susceptibility testing **(CIII)**. Neonatal-care providers should be informed if maternal sulfa therapy is used near delivery because of the theoretical increased risk for hyperbilirubinemia and kernicterus to the newborn.

Bartonellosis

Epidemiology

Bartonella species cause infections that include cat scratch disease, trench fever, relapsing bacteremia, endocarditis, bacillary angiomatosis (BA), and bacillary peliosis hepatis (*506*). The latter two manifestations occur only in immunocompromised persons. BA is caused by either *B. quintana* or *B. henselae* (*506,507*). Nineteen species of *Bartonella* have been identified, and five have been isolated from humans. However, only *B. henselae* and *B. quintana* infections have been identified in HIV-infected persons (*507*). BA most often occurs late in HIV infection, in patients with a median $CD4^+$ count of <50 cells/μL (*507*). In HIV-infected patients, bartonellosis is often a chronic illness, lasting for months to years, with BA lesions and intermittent bacteremia.

Development of BA lesions caused by *B. henselae* is statistically linked to cat exposure in patients with HIV infection (*507*). In contrast, BA caused by *B. quintana* is associated with body louse infestation and homelessness (*507*). The body louse serves as the vector of *B. quintana* among humans. The cat flea is the vector of *B. henselae* among cats. However, the cat is the most common vector (via a scratch) that is responsible for transmitting *B. henselae* to humans, most likely when claws become contaminated with feces from *B. henselae*-infected fleas. In some areas of the United States, the prevalence of *B. henselae* bacteremia in pet cats approaches 50% (*508*). Control of cat flea infestation and avoidance of cat scratches are therefore critical strategies for prevention of *B. henselae* infections in HIV-infected persons. To avoid exposure to *B. quintana*, HIV-infected patients should avoid and treat infestation with body lice.

Clinical Manifestations

BA lesions have been associated with nearly every organ system, but cutaneous lesions are the most readily identified. BA lesions can be clinically indistinguishable from KS. BA also can cause subcutaneous nodules. Osteomyelitis is usually caused by *B. quintana*, and only *B. henselae* can cause bacillary peliosis

hepatis. Although isolated organs can appear to be the principal focus of disease, BA represents a hematogenously disseminated infection, and systemic symptoms of fever, night sweats, and weight loss often accompany BA. *Bartonella* infection is a major cause of unexplained fever in late-stage AIDS patients and should be considered in the differential diagnosis of patients with fever and a $CD4^+$ count of <100 cells/μL (*509*).

Diagnosis

Diagnosis can be confirmed by histopathologic examination of biopsied tissue (*510*). BA lesions are characterized by vascular proliferation, and a modified silver stain (e.g., Warthin-Starry stain) usually demonstrates numerous bacilli. Tissue Gram staining and acid-fast staining are negative.

A well-characterized serologic test was developed at CDC (*511*) and is also available at some state health labs. In addition, several private laboratories offer serological testing, but none of these private laboratory tests has been evaluated for sensitivity or specificity with sera from HIV-infected patients. In immunocompetent patients, anti-*Bartonella* antibodies might not be detectable for 6 weeks after acute infection; in contrast, by the time *Bartonella* infection is suspected in patients with late-stage HIV infection, they usually have been infected for months or even >1 year. Note that as many as 25% of *Bartonella* culture-positive patients might never develop antibodies in the setting of advanced HIV infection (*509*). In those patients who do develop anti-*Bartonella* antibodies, monitoring of antibody levels might correlate with resolution and recrudescence of *Bartonella* infection.

Bartonella species can be isolated (with difficulty) from blood, using EDTA tubes. The organisms have been isolated from tissue in only a few laboratories because of the fastidious nature of *Bartonella (507*). PCR methods have been developed for identification and speciation of *Bartonella,* but are not widely available.

Preventing Exposure

HIV-infected persons, specifically those who are severely immunocompromised ($CD4^+$ counts <100 cells/μL), are at high risk for severe disease caused by *B. quintana* and *B. henselae*. The major risk factors for acquisition of *B. henselae* are contact with cats infested with fleas and receiving cat scratches. Immunocompromised persons should consider the potential risks of cat ownership **(AIII)**. Persons who acquire a cat should acquire an animal aged >1 year and in good health **(BII)**. Cats should be acquired from a known environment, have a documented health history, and be free of fleas. Stray cats and cats with flea infestation should be avoided. Declawing is not advised, but HIV-infected persons should avoid rough play with cats and situations in which scratches are likely **(AII)**. Patients should avoid contact with flea feces ("flea dirt"), and any cat-associated wound should be washed promptly **(BIII)**. Care of cats should include a comprehensive, ongoing flea-control program under the supervision of a veterinarian **(BIII)**. No evidence indicates any benefits to cats or their owners from routine culture or serologic testing of the pet for *Bartonella* infection or from antibiotic treatment of healthy, serologically positive cats **(DII)**. The major risk factor for *B. quintana* infection is body lice infestation. Homeless or marginally housed persons should be informed that body louse infestation can be associated with serious illness and provided with appropriate measures to eradicate body lice, if present **(AII)**.

Preventing Disease

Primary chemoprophylaxis for *Bartonella*-associated disease is not recommended **(DIII)**. However, note that in a retrospective case-control study, MAC prophylaxis using a macrolide or rifamycin was protective against developing *Bartonella* infection (*507*).

Treatment of Disease

Guidelines for treatment of Bartonella infections have been published (*512*). No randomized, controlled clinical trials have evaluated antimicrobial treatment of bartonellosis in HIV-infected patients. Erythromycin and doxycycline have been used successfully to treat BA, peliosis hepatis, bacteremia, and osteomyelitis and are considered first-line treatment for bartonellosis, on the basis of reported experience in case series **(AII)** (*506*,*507*). Therapy should be administered for ≥3 months **(AII)**. Doxycycline, with or without RIF, is the treatment of choice for bartonellosis infection involving the central nervous system (CNS) and other severe bartonellosis infections **(AIII)**.

Clarithromycin or azithromycin treatment has been associated with clinical response and either of these can be an alternative for *Bartonella* treatment **(BIII)**. Azithromycin is recommended for patients who are less likely to comply with the more frequent dosing schedule for doxycycline or erythromycin. Penicillins and first-generation cephalosporins have no in vivo activity and should not be used for treatment of bartonellosis **(DII)**. Quinolones and TMP-SMX have variable in vitro activity and an inconsistent clinical response in case reports and are not recommended **(DIII)**.

IRIS has not been described in association with *Bartonella* infection, but patients with *Bartonella* CNS or ophthalmic lesions should probably be treated with doxycycline and RIF for 2–4 weeks before instituting ART.

Monitoring and Adverse Effects, Including Immune Reconstitution Inflammatory Syndrome (IRIS)

Patients treated with oral doxycycline should be cautioned about pill-associated ulcerative esophagitis that occurs most often when a dose is taken with only a small amount of liquid or at night just before retiring **(AIII)** (*513*).

No immune inflammatory response syndrome has been described in association with Bartonellosis and treatment with ART in HIV-infected persons.

Management of Treatment Failure

Among patients who fail to respond to initial treatment, one or more of the second-line alternative regimens should be considered **(AIII)**.

Preventing Recurrence

Relapse can occur after a course of primary treatment. In this setting, long-term suppression of infection with doxycycline or a macrolide is recommended, as long as the $CD4^+$ count remains <200 cells/μL **(AIII)**.

Long-term suppression can be discontinued after the patient has received 3–4 months of therapy and when the $CD4^+$ count remains >200 cells/μL for ≥6 months **(CIII)**. Certain specialists would discontinue therapy only if the *Bartonella* titers have also decreased by fourfold **(CIII)**.

Special Considerations During Pregnancy

Infection with *B. bacilliformis* in immunocompetent patients during pregnancy has been associated with increased complications and risk for death (*514*). No data are available on the effect of *B. henselae* or *B. quintana* infections in pregnant women with concomitant HIV infection.

The approach to diagnosis of *Bartonella* infections in pregnant women is the same as in nonpregnant women. Erythromycin treatment should be used **(AIII)** rather than tetracyclines **(EII)** during pregnancy because of the increased risk for hepatotoxicity and the accumulation of tetracycline in fetal teeth and bones, resulting in dark, permanent staining of fetal teeth. Third-generation cephalosporins (e.g., ceftizoxime (*515*) or ceftriaxone) might have efficacy against *Bartonella* in the pregnant HIV-infected woman, but should be considered second-line therapy after a macrolide. First- and second-generation cephalosporins are not recommended because of their lack of efficacy against *Bartonella* **(EII)**.

Syphilis

Epidemiology

Syphilis is associated with increased risk for HIV sexual acquisition and transmission (*516,517*). Recent reports indicate a resurgence of syphilis among men in several U.S. cities and in Western Europe (*518–524*). Although coexistent HIV infection, particularly in the advanced stages, can modify the diagnosis, natural history, or management of *Treponema pallidum* infection, the principles of syphilis management are the same for persons with and without coexistent HIV infection (*525–529*). Recent syphilis treatment recommendations are available in the 2006 CDC STD Treatment Guidelines (*529,530*).

Clinical Manifestations

Despite multiple case reports and small case series, limited large studies have documented the effect of coexistent HIV on the protean manifestations of syphilis. The few larger studies suggest that HIV infection might shift the clinical manifestations of syphilis, making clinical lesions more apparent, and might accelerate progression of syphilitic disease (*526,527*). Early syphilis in HIV-infected persons may also cause a transient decrease in $CD4^+$ count and increase in HIV viral load that improves with standard treatment regimens (*531–533*).

Primary syphilis commonly exhibits a single painless nodule at the site of contact that rapidly ulcerates to form a classic chancre; however, among HIV-infected persons, multiple or atypical chancres occur and primary lesions might be absent or missed (*526,534*).

Progression to secondary syphilis typically follows 2–8 weeks after primary inoculation. Although more rapid progression or severe disease might occur among HIV-infected persons with advanced immunosuppression, the clinical manifestations are similar to those among HIV-uninfected persons. The manifestations of secondary syphilis involve virtually all organ systems. The most common manifestations, macular, maculopapular, papulosquamous, or pustular skin lesions, usually begin on the trunk and spread peripherally, involving palms and soles and accompanied by generalized lymphadenopathy and fever, malaise, anorexia, arthralgias, and headache (*527–529*). Condyloma lata, moist, flat, papular lesions in warm intertrigenous regions, might resemble papilloma virus infection. Secondary syphilis, particularly acute syphilitic meningitis, can resemble acute primary HIV infection; constitutional symptoms, along with nonfocal CNS symptoms and CSF abnormalities (e.g., lymphocytic pleocytosis with a mildly elevated CSF protein), are common to both (*534–539*).

Signs and symptoms of secondary syphilis can persist from a few days to several weeks before resolving and evolving to latent or later stages. Latent syphilis lacks overt clinical signs and symptoms, but relapse of manifestations of secondary syphilis might occur, most commonly during the first 1–4 years following infection.

Manifestations of "late" syphilis generally include neurosyphilis, cardiovascular syphilis, and gummatous syphilis or

a slowly progressive disease that can affect any organ system. Neurosyphilis can occur at any stage of syphilis. Asymptomatic neurosyphilis is defined as one or more CSF abnormalities (i.e., elevated protein, lymphocytic pleocytosis, or positive VDRL) in the absence of symptoms or signs. Manifestations of symptomatic neurosyphilis (i.e., meningitis or meningovascular or parenchymatous disease) among HIV-infected persons are similar to those in the HIV-uninfected persons. However, clinical manifestations of neurosyphilis, such as concomitant uveitis and meningitis, might be more common among HIV-infected persons (*538*).

Diagnosis

The diagnosis of syphilis depends on direct detection of the organism (e.g., by darkfield microscopy, direct fluorescent antibody-*Treponema pallidum*, biopsy with silver stain), or on presumptive serologic diagnosis based upon nontrepomenal tests (e.g., Venereal Disease Research Laboratory [VDRL] and rapid plasma reagin [RPR]) and treponemal tests (e.g., FTA-ABS and TP-PA). The serologic diagnosis of syphilis traditionally has involved screening for nontreponemal antibodies with confirmation of reactive tests by treponemal-based assays (*529,540*). Recently, some laboratories have initiated a testing algorithm using treponemal-based enzyme immunoassay (EIA) as a screening test with nontreponemal testing for confirmation. This latter strategy may more often identify those with a previous syphilis infection along with those having untreated infection (*541*). Clinical experience suggests that concurrent HIV infection probably does not change the performance of standard tests for the diagnosis of syphilis. However, false-positive nontreponemal serologic tests that are not confirmed by treponemal serologic tests might be more common among HIV-infected persons (*542,543*).

Early-stage disease (i.e., primary, secondary, and early-latent syphilis) among HIV-infected persons is confirmed by the identical procedures used for the HIV-uninfected person (e.g., darkfield microscopy of a mucocutaneous lesion and standard serologic tests). HIV infection does not decrease the sensitivity or specificity of darkfield microscopy. Responses to nontreponemal serologic tests (i.e., VDRL and RPR) might be atypical (i.e., higher, lower, or delayed) among HIV-infected versus HIV-uninfected persons with early-stage syphilis (*543,544*). No data indicate that treponemal tests perform differently among HIV-infected compared with -uninfected patients (*545*). Similar to HIV-uninfected persons, false-negative serologic tests for syphilis can occur both among HIV-uninfected and HIV-infected persons with documented *T. pallidum* infection (*546,547*). Therefore, if serologic tests do not confirm the diagnosis of suspected syphilis, other diagnostic procedures (e.g., repeat serology in 1–2 weeks, exclusion of prozone phenomenon, biopsy, darkfield examination, or direct fluorescent antibody staining of lesion material) should be pursued. By definition, persons with latent syphilis have serological evidence of syphilis in the absence of clinical or other laboratory abnormalities (i.e., normal CSF profiles). Patients with early-latent syphilis have documented infection of <1 year; persons with late-latent syphilis have documented infection for >1 year or the duration of infection is not known. The diagnostic testing recommended for detection of late-stage syphilis (e.g., cardiovascular and gummatous syphilis) among HIV-infected persons is the same as for the HIV-uninfected person.

All persons with syphilis, regardless of disease stage, should be evaluated for clinical evidence of CNS or ocular involvement. CSF abnormalities (elevated protein and mononuclear pleocytosis) are common in early syphilis and in persons with HIV infection. However, whether the prognostic significance of such CSF abnormalities differs between HIV-infected persons and HIV-uninfected persons with primary, secondary, or early-latent syphilis is unknown.

CSF examination should be performed in persons with neurologic or ocular signs or symptoms, active tertiary syphilis, and treatment failure. CSF examination is also recommended for HIV-infected persons with late-latent syphilis, including those with syphilis of unknown duration. Some specialists recommend CSF examination for all HIV-infected persons with syphilis regardless of stage, particularly if serum RPR is 1:32 or with a $CD4^+$ count of <350 cells/μL *(537,539)*. The risk for developing clinical neurosyphilis in this circumstance is unknown. CSF abnormalities consistent with neurosyphilis should be treated using standard neurosyphilis treatment regimens.

Among persons without HIV infection, diagnosis of neurosyphilis is established by CSF examination, which might indicate mild mononuclear pleocytosis (e.g., 10–200 cells/μL), normal or mildly elevated protein concentration, or a reactive CSF-VDRL (*529,537,539*). The CSF-VDRL is specific but not sensitive, and a reactive test establishes the diagnosis of neurosyphilis, but a nonreactive test does not exclude the diagnosis. In comparison, CSF treponemal tests (e.g., the CSF FTA-ABS) are sensitive but not specific, with a nonreactive test excluding the diagnosis of neurosyphilis. Calculated indices (e.g., TPHA-index) are of limited value in establishing the diagnosis of neurosyphilis. PCR-based diagnostic methods are not currently recommended as a diagnostic test for neurosyphilis. A reactive CSF-VDRL and a CSF WBC >10 cells/μL support the diagnosis of neurosyphilis; the majority of specialists would not base the diagnosis solely on elevated CSF protein concentrations in the absence of these other abnormalities.

Establishing the diagnosis of neurosyphilis can be more difficult among persons with HIV infection, because HIV infection itself might be associated with mild mononuclear CSF pleocytosis (5–15 cells/μL), particularly among persons with peripheral blood CD4$^+$ counts >500 cells/μL. If neurosyphilis cannot be excluded by a nonreactive CSF treponemal test, such persons should be treated for neurosyphilis, despite the acknowledged uncertainty of the diagnosis.

Preventing Exposure

The resurgence of syphilis among persons with HIV infection in the United States underscores the importance of primary prevention of syphilis among persons with HIV infection. This should begin with routine discussion of sexual behaviors. Providers should discuss client-centered risk reduction messages and provide specific actions that can reduce the risk for acquiring sexually transmitted infections and for transmitting HIV (*529,548–550*). Routine serologic screening for syphilis is recommended at least annually for all sexually active HIV-infected persons, with more frequent screening (every 3–6 months) for those with multiple partners, unprotected intercourse, sex in conjunction with illicit drug use, methamphetamine use, or partners who participate in such activities (*529,551*). The occurrence of syphilis in an HIV-infected person is an indication of high-risk behavior and should prompt intensified counseling messages and strong consideration of referral for behavioral intervention. Persons undergoing screening or treatment for syphilis also should be evaluated for all common sexually transmitted diseases (STDs) (*529*).

Preventing Disease

The same measures that apply to preventing exposure apply to preventing disease.

Treatment of Disease

Management of syphilis in HIV-infected persons is similar to the management in HIV-uninfected persons (*529,530,544*). However, closer follow-up is recommended to detect potential treatment failure or disease progression.

Penicillin remains the treatment of choice for syphilis regardless of HIV status. HIV-infected persons with early-stage (i.e., primary, secondary, or early-latent) syphilis should receive a single intramuscular (IM) injection of 2.4 million units of benzathine penicillin G **(AII)**. Although most HIV-infected persons with early syphilis respond appropriately to standard benzathine penicillin, some specialists recommend two additional weekly benzathine penicillin injections. The benefit of this treatment approach remains unproven. Enhanced penicillin therapy (i.e., standard benzathine penicillin with high-dose oral amoxicillin and probenecid) did not improve clinical outcome in early-stage syphilis (*544*) and is not recommended **(DII)** .

The efficacy of alternative nonpenicillin regimens in HIV-infected persons with early syphilis, including oral doxycycline, ceftriaxone, and azithromycin, has not been evaluated sufficiently in HIV-infected persons to warrant use as first-line treatment. Regardless of HIV infection status, the use of any alternative penicillin treatment regimen should be undertaken only with close clinical and serologic monitoring **(BIII)**. Similarly, although some evidence suggests that a single 2-gram oral dose of azithromycin might have efficacy for treating early syphilis (*552,553*), molecular resistance of *T. pallidum* to macrolides and clinical treatment failures with azithromycin have been reported (*554–556*); such treatment should be used only with close clinical and serologic monitoring to detect treatment failure **(CII)**.

In HIV-infected persons with late-latent syphilis for whom the CSF examination excludes the diagnosis of neurosyphilis, treatment with three weekly IM injections of 2.4 million units benzathine penicillin G is recommended **(AIII)**. Alternative therapy with doxycycline 100 mg by mouth twice a day for 28 days has not been sufficiently evaluated in HIV-infected persons to warrant use as first-line treatment **(BIII)**. If the clinical situation requires the use of an alternative to penicillin, treatment should be undertaken with close clinical and serologic monitoring.

HIV-infected persons with clinical evidence of late-stage (tertiary) syphilis (cardiovascular or gummatous disease) should have a CSF examination to rule out neurosyphilis before initiating therapy. The complexity of tertiary syphilis management is beyond the scope of these guidelines and providers are advised to consult an infectious disease specialist.

HIV-infected persons with clinical or laboratory evidence of neurosyphilis (i.e., CNS, otic, or ocular disease) should receive IV aqueous crystalline penicillin G, 18–24 million units daily, administered 3–4 million units IV every 4 hours or by continuous infusion for 10–14 days **(AII)** or procaine penicillin 2.4 million units IM once daily plus probenecid 500 mg orally four times a day for 10–14 days **(BII)** (*529,537,539*). HIV-infected persons who are allergic to sulfa-containing medications should not be administered probenecid because of potential allergic reaction **(DIII)**.

Because neurosyphilis treatment regimens are of shorter duration than those used in late-latent syphilis, some specialists recommend 2.4 million units IM once per week for up to 3 weeks after completion of neurosyphilis treatment to provide a comparable duration of therapy **(CIII)** (*529*). Among patients who are allergic to penicillin, penicillin desensitization is the preferred approach to treating neurosyphilis **(BIII)**. However, limited data indicate that ceftriaxone (2 g daily IV for 10–14

days) might be an acceptable alternative regimen **(CIII)** (*557*). Other alternative regimens for neurosyphilis have not been evaluated adequately.

Monitoring and Adverse Events, Including Immune Reconstitution Inflammatory Syndrome (IRIS)

Clinical and serologic responses to treatment of early-stage (i.e., primary, secondary, and early-latent) disease should be monitored at 3, 6, 9, 12, and 24 months after therapy. Serologic responses to treatment are similar in persons with and without HIV infection; however, subtle variations might occur, including the temporal pattern of response (*529,530,544,558*).

After successful treatment for syphilis (HIV-infected and -uninfected persons), 15%–20% of persons might remain "serofast," meaning that serum nontreponemal test titers remain reactive at low and unchanging titers, usually <1:8, for prolonged periods *(529,544)*. This serofast state probably does not represent treatment failure. Serologic detection of potential reinfection should be based on an at least a fourfold increase in titer above the established serofast baseline.

Response to therapy of late-latent syphilis should be monitored using nontreponemal serologic tests at 6, 12, 18, and 24 months to ensure at least a fourfold decline in titer. Some retrospective studies have documented concomitant HIV infection associated with poorer CSF and serologic responses to neurosyphilis therapy (*559,560*). CSF examination should be repeated at 6 months after completion of therapy. If clinical symptoms develop or nontreponemal titers rise fourfold, a repeat CSF examination should be performed and treatment administered accordingly. The earliest CSF indicator of response to neurosyphilis treatment is a decline in CSF lymphocytosis. The CSF VDRL might respond more slowly. Nontreponemal serum titers should be monitored during the next 12–24 months and if the titers do not decline fourfold, consultation with an infectious disease specialist is recommended (*529*).

No IRIS has been described in association with syphilis and treatment with ART in HIV-infected persons.

Management of Treatment Failure

Retreatment of persons with early-stage syphilis should be considered for those who 1) have a sustained fourfold increase in serum nontreponemal titers after an initial reduction after treatment, or 2) have persistent or recurring clinical signs or symptoms of disease **(BIII)**. Certain specialists recommend retreating persons with early syphilis who do not experience at least a fourfold decrease in serum nontreponemal titers 6–12 months after therapy **(BIII)**. If CSF examination does not confirm the diagnosis of neurosyphilis, such persons should receive 2.4 million units IM benzathine penicillin G administered at 1-week intervals for 3 weeks **(BIII)**. Certain specialists also recommend a course of aqueous penicillin G administered IV or procaine penicillin administered IM plus probenecid for treatment of neurosyphilis in this setting, although data to support this practice are lacking **(CIII)**. If titers do not respond appropriately after retreatment, the value of repeated CSF examination or additional therapy has not been established. Persons with HIV infection might be at increased risk for treatment failure and neurologic complications; the magnitude of these risks is not precisely defined but is likely low (*536,561*).

Persons with late-latent syphilis should have a repeat CSF examination and be retreated if they have clinical signs or symptoms of syphilis, have a fourfold increase in serum nontreponemal test titer, or experience an inadequate serologic response (less than four-fold decline in nontreponemal test titer) within 12–24 months of therapy **(BIII)**. If the CSF examination is consistent with CNS involvement, retreatment should follow the neurosyphilis recommendations **(AIII)**. Persons with latent syphilis and a normal CSF examination should be treated with benzathine penicillin, 2.4 million units IM weekly for 3 weeks **(BIII)**; certain specialists also recommend adding a neurosyphilis regimen in this setting **(CIII)**. Retreatment for neurosyphilis should then be considered if the CSF WBC count has not decreased 6 months after completion of treatment or if the CSF-VDRL remains reactive 2 years after treatment **(BIII)**.

Preventing Recurrence

No recommendations indicate the need for secondary prophylaxis or prolonged chronic maintenance antimicrobial therapy for syphilis in HIV-infected persons. Targeted mass treatment of high-risk populations has not been demonstrated to be effective and is not recommended. Azithromycin is not recommended as secondary prevention because of azithromycin treatment failures reported in HIV-infected persons and reports of macrolide-resistant *T. pallidum (554–556)*.

Special Considerations During Pregnancy

Pregnant women should be screened for syphilis at the first prenatal visit. In areas where syphilis prevalence is high or among women at high risk (e.g., uninsured, women living in poverty, commercial sex workers, and IDUs), testing should be repeated at 28–32 weeks of gestation and at delivery. All women delivering a stillborn infant after 20 weeks of gestation also should be tested for syphilis. Syphilis screening should also be offered at sites providing episodic care to pregnant women at high risk, including emergency departments, jails, and prisons. No infant should leave the hospital without documentation of maternal syphilis-serology status during pregnancy (*562*).

The rate of transmission to the fetus and adverse pregnancy outcomes of untreated syphilis are highest with primary, secondary, and early-latent syphilis during pregnancy and decrease with increasing duration of infection thereafter. Pregnancy does not appear to alter the clinical course, manifestations, or diagnostic test results of syphilis infection among adults. Concurrent syphilis infection has been associated with increased risk for perinatal transmission of HIV to the infant (*563–568*).

Treatment during pregnancy should consist of the same penicillin regimen as recommended for the given disease stage among nonpregnant, HIV-infected adults. Because of treatment failures reported after single injections of benzathine penicillin G among HIV-uninfected pregnant women (*569*), certain specialists recommend a second injection 1 week after the initial injection for pregnant women with early syphilis (*529,570*). Because of additional concerns about the efficacy of standard therapy in HIV-infected persons, a second injection in 1 week for HIV-infected pregnant women should be considered **(BIII)**.

No alternatives to penicillin have been proven effective and safe for treatment of syphilis during pregnancy or for prevention of fetal infection. Pregnant women who have a history of penicillin allergy should be referred for skin testing and desensitization and treatment with penicillin **(AIII)** (*529*). Erythromycin does not reliably cure fetal infection; tetracyclines should not be used during pregnancy because of hepatotoxicity and staining of fetal bones and teeth **(EIII)**. However, because of insufficient information regarding the use of azithromycin (*571*) or ceftriaxone (*572*) treatment in pregnancy, routine use is not a recommended **(DIII)**.

A Jarisch-Herxheimer reaction that occurs during the second half of pregnancy might precipitate preterm labor or fetal distress (*573*). Women should be advised to seek obstetric attention after treatment if they notice contractions or a decrease in fetal movement during the first 24 hours after treatment. During the second half of pregnancy, syphilis management may be facilitated by a sonographic fetal evaluation for congenital syphilis, but this evaluation should not delay therapy. Sonographic signs of fetal or placental syphilis indicate a greater risk for fetal treatment failure. Such cases should be managed in consultation with obstetric specialists. Evidence is insufficient to recommend specific regimens for these situations. After >20 weeks of gestation, fetal and contraction monitoring for 24 hours after initiation of treatment for early syphilis should be considered when sonographic findings indicate fetal infection.

Repeat serologic titers should be performed in the third trimester and at delivery for women treated for syphilis during pregnancy. Data related to serologic response to syphilis in HIV-infected women are insufficient. Titers can be conducted monthly for women at high risk for reinfection. Clinical and antibody response should be appropriate for the stage of disease, although the majority of women will deliver before their serologic response can be definitively assessed. Maternal treatment is likely to be inadequate if delivery occurs within 30 days of therapy, if clinical signs of infection are present at delivery or if the maternal antibody titer is fourfold higher than the pretreatment titer.

Mucocutaneous Candidiasis

Epidemiology

Oropharyngeal and esophageal candidiasis are common (*574*). The majority of infection is caused by *Candida albicans*. Fluconazole (or azole) resistance is predominantly the consequence of previous exposure to fluconazole (or other azoles), particularly repeated and long-term exposure (*575–577*). In this setting, *C. albicans* resistance has been accompanied by a gradual emergence of non-*albicans Candida* species, particularly *C. glabrata*, as a cause of refractory mucosal candidiasis, particularly in patients with advanced immunosuppression (*575,578*).

The occurrence of oropharyngeal or esophageal candidiasis is recognized as an indicator of immune suppression, and these are most often observed in patients with $CD4^+$ counts <200 cells/μL (*574*). In contrast, vulvovaginal candidiasis is common among healthy, adult women and is unrelated to HIV status. Recurrent vulvovaginal candidiasis alone should not be considered a sentinel of HIV infection among women. The introduction of ART has led to a dramatic decline in the prevalence of oropharyngeal and esophageal candidiasis and a marked diminution in cases of refractory disease.

Clinical Manifestations

Oropharyngeal candidiasis is characterized by painless, creamy white, plaque-like lesions of the buccal or oropharyngeal mucosa or tongue surface. Lesions can be easily scraped off with a tongue depressor or other instrument. Less commonly, erythematous patches without white plaques can be seen on the anterior or posterior upper palate or diffusely on the tongue. Angular chelosis is also noted on occasion and might be caused by *Candida*.

Esophageal candidiasis is occasionally asymptomatic but retrosternal burning pain or discomfort and odynophagia are often present. Endoscopic examination reveals whitish plaques similar to those observed with oropharyngeal disease that might progress to superficial ulceration of the esophageal mucosa, with central or surface whitish exudates.

Candida vulvovaginitis might be mild to moderate and sporadic, similar to that in normal hosts, and be characterized by a

white adherent vaginal discharge associated with mucosal burning and itching. In those with advanced immunosuppression, episodes might be more severe and more frequently recurrent. Compared with oropharyngeal candidiasis, vaginal candidiasis is less frequent and rarely refractory to azole therapy.

Diagnosis

Diagnosis of oropharyngeal candidiasis is usually clinical and based on the appearance of lesions. The feature that distinguishes these from oral hairy leukoplakia is the ability to scrape off the superficial whitish plaques. If laboratory confirmation is required, a scraping for microscopic examination for yeast forms using a potassium hydroxide (KOH) preparation provides supportive diagnostic information. Cultures of clinical material identify the species of yeast present.

The diagnosis of esophageal candidiasis requires endoscopic visualization of lesions with histopathologic demonstration of characteristic *Candida* yeast forms in tissue and culture confirmation of the presence of *Candida* species. The diagnosis of vulvovaginal candidiasis is based on the clinical presentation coupled with the demonstration of characteristic pseudohyphal yeast forms in vaginal secretions examined microscopically after KOH preparation. Culture confirmation is rarely required but might provide supportive information. Because self-diagnosis of vulvovaginitis is unreliable, microscopic and culture confirmation is required to avoid unnecessary exposure to inappropriate treatments.

Preventing Exposure

Candida organisms are common commensals on mucosal surfaces in healthy persons. No measures are available to reduce exposure to these fungi.

Preventing Disease

Data from prospective controlled trials indicate that fluconazole can reduce the risk for mucosal (e.g., oropharyngeal, esophageal, and vaginal) candidiasis among patients with advanced HIV disease (*579–582*). However, routine primary prophylaxis is not recommended because mucosal disease is associated with very low attributable mortality, acute therapy is highly effective, prophylaxis can lead to disease caused by drug-resistant species, prophylactic agents can produce drug interactions, and prophylaxis is expensive (**DIII**). ART does reduce the likelihood of mucosal candidiasis **(AI)**.

Treatment of Disease

Oral fluconazole is as effective and, in certain studies, superior to topical therapy for oropharyngeal candidiasis. In addition, it is more convenient and typically better tolerated. Therefore, oral fluconazole is considered the drug of choice **(AI)** (*583*).

Initial episodes of oropharyngeal candidiasis can be adequately treated with topical therapy, including clotrimazole troches, nystatin suspension or pastilles, or once-daily miconazole mucoadhesive tablets **(BII)** (*584*).

Itraconazole oral solution for 7–14 days is as effective as oral fluconazole but less well tolerated **(AI)**. Posaconazole oral solution (*585*) is also as effective as fluconazole and is generally better tolerated than itraconazole **(AI).** They are alternatives to oral fluconazole, although few situations require that these drugs would be used in preference to fluconazole solely to treat mucosal candidiasis. In a multicenter, randomized study, posaconazole was proven more effective than fluconazole in sustaining clinical success after antifungal therapy was discontinued (*585*). Ketoconazole and itraconazole capsules are less effective than fluconazole because of their more variable absorption. Using these agents to treat mucosal candidiasis is not reasonable if the other options are available **(DIII)**.

Systemic antifungals are required for effective treatment of esophageal candidiasis **(AI)**. A 14–21-day course of either fluconazole (oral or IV) or oral itraconazole solution is highly effective **(AI)**. As with oropharyngeal candidiasis, oral ketoconazole or itraconazole capsules are less effective than fluconazole because of variable absorption **(DII)**. Although IV caspofungin **(BI)** or IV voriconazole **(BI)** are effective in treating esophageal candidiasis among HIV-infected patients, oral or IV fluconazole remain the preferred therapies **(AI)**.

Two additional parenteral echinocandins, micafungin and anidulafungin, also are approved for the treatment of esophageal candidiasis. Although the three echinocandins are as effective as fluconazole in the treatment of esophageal candidiasis, they all appear to have a greater relapse rate when compared with fluconazole (*586,587*). Although symptoms of esophageal candidiasis might be mimicked by other pathogens, a diagnostic trial of antifungal therapy is usually appropriate before endoscopy is used to identify causes of esophagitis **(CII)**.

Vulvovaginal candidiasis in HIV-infected women is usually uncomplicated (90%) and responds readily to short-course oral or topical treatment with any of several therapies, including the following regimens:

- Oral fluconazole **(AII)**
- Topical azoles (clotrimazole, butaconazole, miconazole, ticonazole, or terconazole **(AII)**
- Itraconazole oral solution **(BII)**

Severe or recurrent episodes of vaginitis require oral fluconazole or topical antifungal therapy for ≥7 days **(AIII)**.

ART reduces the frequency of mucosal candidiasis. Refractory cases of mucosal candidiasis typically resolve when immunity improves in response to ART.

IRIS has not been reported in association with episodes of mucosal candidiasis in HIV-positive persons.

Monitoring and Adverse Events, Including Immune Reconstitution Inflammatory Syndrome (IRIS)

For the majority of patients with mucocutaneous candidiasis, response to therapy is rapid, with improvement in signs and symptoms within 48–72 hours. Short courses of topical therapy rarely result in adverse effects, although patients might experience cutaneous hypersensitivity reactions, characterized rash, and pruritus. Oral azole therapy can be associated with nausea, vomiting, diarrhea, abdominal pain, or transaminase elevations. If prolonged azole therapy is anticipated (>21 days), periodic monitoring of liver chemistry studies should be considered **(CIII)**.

The echinocandins thus far appear to be safe and free of substantial side effects; histamine-related infusion toxicity, elevation of transaminase, and rash have been attributed to these drugs. No dose adjustments are required in renal failure.

IRIS has not been described because of *Candida*.

Management of Treatment Failure or Refractory Mucosal Candidiasis

Refractory oral or esophageal candidiasis is still reported in approximately 4%–5% of HIV-infected persons, typically in those patients with $CD4^+$ counts <50 cells/μL who have received multiple courses of azole antifungals.

Treatment failure is typically defined as signs and symptoms of oropharyngeal or esophageal candidiasis that persist after more than 7–14 days of appropriate therapy. Oral itraconazole solution is effective at least transiently in approximately two thirds of persons with fluconazole-refractory mucosal candidiasis **(AII).** Posaconazole immediate-release oral suspension (400 mg bid for 28 days) is effective in 75% of patients with azole refractory oropharyngeal and/or esophageal candidiasis **(AII)** (*588*).

IV amphotericin B is usually effective and can be used among patients with refractory disease **(BII)**. Both conventional amphotericin B and lipid complex and liposomal amphotericin B have been used **(BII)**.

Amphotericin B oral suspension (1 mL four times daily of the 100 mg/mL suspension) is sometimes effective among patients with oropharyngeal candidiasis who do not respond to itraconazole **(CIII)**. However, this product is not available in the United States.

Azole-refractory esophageal candidiasis also can be treated with posaconazole **(AII)**, anidulafungin **(BII)**, caspofungin **(CII)**, micafungin **(CII)**, or voriconazole **(CIII)**.

Preventing Recurrence

As with primary prophylaxis, the majority of HIV specialists do not recommend secondary prophylaxis (chronic maintenance therapy) for recurrent oropharyngeal or vulvovaginal candidiasis because of the effectiveness of therapy for acute disease, the low mortality associated with mucosal candidiasis, the potential for resistant *Candida* organisms to develop, the possibility of drug interactions, and the cost of prophylaxis **(DIII)**. However, if recurrences are frequent or severe, oral fluconazole can be used for either oropharyngeal **(BI)** or vulvovaginal **(CI)** candidiasis (*579–581*). A recent randomized clinical trial (*582*) has documented that the number of episodes of oropharyngeal candidiasis and other invasive fungal infections was statistically significantly lower in HIV patients with $CD4^+$ count <150 cells/μL when receiving continuous (three times a week) fluconazole versus episodic treatment of recurrences. This clinical trial also proved that the development of clinically significant resistance was not higher in the group of continuous prophylaxis than in the group with episodic administration of Fluconazole, provided that patients received ART.

The decision to use secondary prophylaxis should take into account the effect of recurrences on the patient's well-being and quality of life; the need for prophylaxis for other fungal infections; cost, toxicities, and most importantly, drug interactions (*589*).

For recurrent esophageal candidiasis, daily fluconazole can be used **(BI).** Oral posaconazole bid is also effective **(BII)**. However, potential azole resistance should be considered when long-term azoles are considered.

Secondary prophylaxis should be instituted in those patients with fluconazole-refractory oropharyngeal or esophageal candidiasis who have responded to echinocandins, voriconazole, or posaconazole therapy because of high relapse rate until ART produces immune reconstitution **(CI)**.

Discontinuing Secondary Prophylaxis (Chronic Maintenance Therapy)

In situations where secondary prophylaxis is instituted, no data support a recommendation regarding discontinuation. On the basis of experience with other OIs, discontinuing secondary prophylaxis when the $CD4^+$ count has risen to 200 cells/μL because of ART would be reasonable **(CIII)**.

Special Considerations During Pregnancy

Pregnancy increases the risk for vaginal colonization with *Candida* species. Diagnosis of oropharyngeal, esophageal, and vulvovaginal candidiasis is the same as among nonpregnant women.

Topical therapy is preferred for treatment of oral or vaginal candidiasis in pregnancy when possible **(BIII).** Single-dose, episodic treatment with fluconazole has not been associated with birth defects in humans. However, with chronic use of doses of fluconazole of 400 mg or higher in pregnancy, five cases of a syndrome of craniosynostosis, characteristic facies, digital synostosis, and limb contractures have been reported ("fluconazole embryopathy") (*590*). On the basis of these data, substitution of amphotericin B for high-dose fluconazole in the first trimester is recommended for invasive or refractory esophageal candidal infections **(AIII).** Neonates born to women on chronic amphotericin B at delivery should be evaluated for renal dysfunction and hypokalemia. Itraconazole has been teratogenic in animals at high doses, but the metabolic mechanism accounting for these defects is not present in humans, so data are not applicable. Case series in humans do not suggest an increased risk for birth defects with itraconazole, but experience is limited. Posaconazole was associated with skeletal abnormalities in rats at doses similar to human levels and was embryotoxic in rabbits. No human data are available for posaconazole. Voriconazole is FDA category D because of cleft palate and renal defects seen in rats and embryotoxicity in rabbits. No human data on use of voriconazole are available, so use in the first trimester is not recommended. Multiple anomalies are seen in animals with micafungin; ossification defects have been seen with anidulafungin and caspofungin. No human data are available for these drugs, and their use in human pregnancy is not recommended **(DIII).**

Chemoprophylaxis, either primary or secondary, against oropharyngeal, esophageal, or vaginal candidiasis using systemically absorbed azoles should not be initiated during pregnancy **(DIII),** and prophylactic azoles should be discontinued for HIV-infected women who become pregnant (**AIII).**

Cryptococcosis

Epidemiology

The majority of HIV-associated cryptococcal infections are caused by *Cryptococcus neoformans*; rarely, infection because of *Cryptococcus neoformans var. gattii* is recognized in the United States. Before the advent of potent ART, approximately 5%–8% of HIV-infected patients in developed countries acquired disseminated cryptococcosis (*591*). The incidence has declined substantially since then (*592*). The majority of cases are observed among patients who have $CD4^+$ counts of <50 cells/μL.

Clinical Manifestations

Among patients with HIV infection, cryptococcosis most commonly occurs as a subacute meningitis or meningoencephalitis with fever, malaise, and headache (*591*). Classic meningeal symptoms and signs, such as neck stiffness and photophobia, occur in only one fourth to one third of patients. Encephalopathic symptoms, including lethargy, altered mentation, personality changes, and memory loss, usually resulting from elevated intracranial pressure, occurs in small groups of patients.

Analysis of CSF usually demonstrates a mildly elevated serum protein; glucose ranging from low to normal; a pleocytosis consisting mostly of lymphocytes, although some patients have no cells; and a positive Gram or India ink stain for numerous yeasts. The opening pressure in the CSF is usually elevated, with pressures >20 cm H_2O occurring in up to 75% of patients. When cryptococcosis occurs in the HIV-infected patient, disseminated disease is common. Virtually any organ can be involved, and skin lesions mimicking molluscum contagiosum are frequently observed. In addition, isolated pulmonary infection is evident; symptoms and signs include cough and dyspnea in association with an abnormal chest radiograph.

Diagnosis

Cryptococcal antigen is almost invariably detected in CSF at high titer in patients with meningitis or meningoencephalitis. The serum cryptococcal antigen is also almost always positive in cases of CNS disease and in other instances of disseminated infection. As such, testing for serum cryptococcal antigen is a useful initial screening tool in diagnosing cryptococcosis in HIV-infected patients (*593*). Up to 75% of patients with HIV-associated cryptococcal meningitis have routine blood cultures positive for *C. neoformans*.

Preventing Exposure

HIV-infected persons cannot completely avoid exposure to *C. neoformans*. Limited epidemiologic evidence suggests that specific activities, including exposure to bird droppings, lead to an increased risk for infection.

Preventing Disease

Because the incidence of cryptococcal disease is low, routine testing of asymptomatic persons for serum cryptococcal antigen is not recommended **(DIII).**

Prospective, controlled trials indicate that fluconazole and itraconazole can reduce the frequency of primary cryptococcal disease among patients who have $CD4^+$ counts <50 cells/μL (*579,594*). However, the majority of HIV specialists recommend that antifungal prophylaxis not be used routinely to prevent cryptococcosis because of the relative infrequency of cryptococcal disease, lack of survival benefits associated with prophylaxis, possibility of drug interactions, potential antifungal drug resistance, and cost **(DIII).** The need for primary prophylaxis or suppressive therapy for other fungal infections

(e.g., candidiasis, histoplasmosis, or coccidioidomycosis) should be considered when making decisions concerning primary prophylaxis for cryptococcosis.

Treatment of Disease

The recommended initial standard treatment is amphotericin B deoxycholate, at a dose of 0.7 mg/kg daily, combined with flucytosine, at a dose of 100 mg/kg daily in four divided doses, for ≥2 weeks for those with normal renal function **(AI)**. Renal function should be monitored closely and the flucytosine dose adjusted appropriately for patients with renal impairment. The addition of flucytosine to amphotericin B during acute treatment is associated with more rapid sterilization of CSF (*595*,*596*). The combination of amphotericin B deoxycholate with fluconazole, 400 mg daily **(BII)**, is inferior to amphotericin B combined with flucytosine for clearing Cryptococcus from CSF but is more effective than amphotericin B alone **(BII)** (*597*).

Lipid formulations of amphotericin B also are effective and should be considered for patients who experience renal dysfunction during therapy or have a likelihood of having renal failure. The optimal dose of lipid formulations of amphotericin B has not been determined. An unpublished study demonstrated that liposomal amphotericin B (AmBisome®) at a dose of 6 mg/kg daily had an improved outcome over 3 mg/kg daily (*598*). The noncomparative CLEAR study used a mean dose of amphotericin B lipid complex (ABLC) of 4.4 mg/kg daily to treat cryptococcosis (*599*). In an Australian study, a 3-week course of liposomal amphotericin B (AmBisome®) at 4 mg/kg daily resulted in more rapid sterilization of CSF than amphotericin B deoxycholate at 0.7 mg/kg daily (*600*). On the basis of these data, a dose of 4–6 mg/kg daily for lipid formulations of amphotercin B is recommended **(AII).**

Fluconazole (400–800 mg daily) combined with flucytosine is an alternative to amphotericin B plus flucytosine (*598*), but is inferior to amphotericin B (*601*) and is recommended only for persons who are unable to tolerate or unresponsive to standard treatment **(CII).**

After at least a 2-week period of successful induction therapy, defined as substantial clinical improvement and a negative CSF culture after repeat lumbar puncture, amphotericin B and flucytosine may be discontinued and follow-up therapy initiated with fluconazole 400 mg daily **(AI).** This therapy should continue for 8 weeks **(AI)** (*595,596,602*). Itraconazole is an acceptable though less effective alternative **(BI)** (*602*). Limited data are available for the newer triazoles, voriconazole and posaconazole, as either primary or follow-up therapy for patients with cryptococcosis. Voriconazole should be used cautiously with HIV PIs and efavirenz.

Monitoring and Adverse Events, Including Immune Reconstitution Inflammatory Syndrome (IRIS)

Increased ICP can cause clinical deterioration despite a microbiologic response and is more likely if the CSF opening pressure is >20 cm H_2O (*596,603*). In one large clinical trial, 93% of deaths that occurred within the first 2 weeks of therapy and 40% of deaths that occurred within weeks 3–10 were associated with increased ICP (*603*).

At time of diagnosis, all patients with cryptococcal meningitis should have their opening pressure measured in the lateral decubitus position with good manometrics assured; normal values are <25 cm H_20. Patients with confusion, blurred vision, papilledema, lower extremity clonus, or other neurologic signs of increased ICP should be managed using measures to decrease ICP. Daily lumbar punctures are usually recommended for initial management. One approach is to remove a volume (typically 20–30 mL) of CSF that halves the opening pressure (*604*). CSF shunting should be considered for patients in whom daily lumbar punctures are no longer tolerated or whose signs and symptoms of cerebral edema are not being relieved **(BIII).** Corticosteroids, mannitol, and acetazolamide are not recommended **(DIII).**

After the initial 2 weeks of treatment, a repeat lumbar puncture should be performed to ensure the organism has been cleared from the CSF, even among those who have improved after the initial 2 weeks of treatment. Positive CSF cultures after 2 weeks of therapy are predictive of future relapse and typically less favorable clinical outcomes. If new symptoms or clinical findings occur later, a repeat lumbar puncture, with measurement of opening pressure and CSF culture, should be performed.

Patients treated with amphotericin B should be monitored for dose-dependent nephrotoxicity and electrolyte disturbances. Preinfusion administration of 500 mL of normal saline appears to reduce the risk for nephrotoxicity during treatment. Infusion-related adverse reactions may be ameliorated by pretreatment with acetaminophen and diphenhydramine; in rare cases, glucocorticosteroids administered approximately 30 minutes before the infusion might be required **(CIII).**

Patients receiving flucytosine should have flucytosine blood levels monitored to prevent bone marrow suppression and gastrointestinal toxicity; peak serum levels, which occur 2 hours after an oral dose, should not exceed 75 μg/mL. Persons treated with fluconazole should be monitored for hepatotoxicity.

An estimated 30% of patients with cryptococcal meningitis and HIV infection experience IRIS after initiation or reinitiation of ART (*605*). Patients who have cryptococcal IRIS are more likely to be antiretroviral naïve and have higher HIV RNA levels. Appropriate management of IRIS is to continue

ART and antifungal therapy **(AII).** In patients with severely symptomatic IRIS, short-course glucocorticosteroids are recommended by certain specialists **(BIII).** Delaying the initiation of potent ART might be prudent, at least until the completion of induction therapy (the first 2 weeks) for severe cryptococcosis, especially if patients have elevated ICP **(CIII).**

Management of Treatment Failure

Treatment failure is defined as either the lack of clinical improvement after 2 weeks of appropriate therapy, including management of increased ICP, or relapse after an initial clinical response, defined as either a positive CSF culture and/or a rising CSF cryptococcal antigen titer with an associated compatible clinical picture. Although fluconazole resistance has been reported with *C. neoformans,* it is rare in the United States (*606*). At this time, susceptibility testing is not recommended routinely **(DII).**

The optimal therapy for patients with treatment failure has not been established. For those initially treated with fluconazole, therapy should be changed to amphotericin B, with or without flucytosine, and continued until a clinical response occurs (**BIII**). Liposomal amphotericin B (4–6 mg/kg/day) might have improved efficacy over the deoxycholate formulation (*600,607*) and should be considered in treatment failures **(AII)**. Higher doses of fluconazole in combination with flucytosine also might be useful **(BIII)**. Caspofungin and other echinocandins have no in vitro activity against *Cryptococcus spp*. and no role in the clinical management of these patients. The newer triazoles, posaconazole and voriconazole, have activity against *Cryptococcus spp*. in vitro and might have a role in therapy.

Preventing Recurrence

Patients who have completed the initial 10 weeks of therapy for acute cryptococcosis should be administered chronic maintenance therapy with fluconazole 200 mg daily, either lifelong or until immune reconstitution occurs as a consequence of ART (**AI**). Itraconazole is inferior to fluconazole for preventing relapse of cryptococcal disease **(BI)** (*608,609*)**.**

Discontinuing Secondary Prophylaxis (Chronic Maintenance Therapy)

The risk for recurrence of cryptococcosis appears low when patients have successfully completed a course of initial therapy, remain asymptomatic with regard to signs and symptoms of cryptococcosis, and have a sustained increase (i.e., >6 months) in their CD4+ counts to ≥200 cells/μL after ART. The numbers of such patients who have been evaluated remain limited. In a European study, none of 39 subjects whose antifungal therapy was discontinued had a recurrence of cryptococcosis. The median CD4+ count of this cohort was 239 cells/μL, the median HIV RNA concentration was <500 copies/mL, and the median time on potent ART was 25 months (610). A prospective randomized study of 60 patients in Thailand documented no cases of recurrence after 48 weeks when the CD4+ count was >100 cells/μL and HIV RNA was undetectable for 3 months (*611*). On the basis of two published studies and inference from data regarding safety of discontinuing secondary prophylaxis for other OIs during advanced HIV disease, discontinuing chronic maintenance therapy among such patients who have successfully completed a course of intial therapy when the CD4+ count is consistently >200 cells/μL is reasonable **(BII)** (*612*). Certain HIV specialists would perform a lumbar puncture to determine if the CSF is culture negative and antigen negative before stopping therapy even if patients are asymptomatic **(CIII)**. Maintenance therapy should be reinitiated if the CD4+ count decreases to <200 cells/μL **(AIII)**.

Special Considerations During Pregnancy

The diagnosis and treatment of cryptococcal infections during pregnancy is similar to that in nonpregnant adults with the following considerations regarding the use of antifungal during pregnancy. Because of their risk for teratogenicity, azole antifungals should be avoided during the first trimester of pregnancy **(EII).** Neonates born to women on chronic amphotericin B at delivery should be evaluated for renal dysfunction and hypokalemia.

Histoplasmosis

Epidemiology

Histoplasmosis is caused by the dimorphic fungus *Histoplasma capsulatum*. In the United States, infection is common in several regions where the disease is endemic, especially the Ohio and Mississippi River Valleys. It is also endemic in Latin America, including Puerto Rico. Among persons with HIV infection residing in areas in which histoplasmosis is endemic, symptomatic disease occurs at an annual incidence approaching 5%. Environmental exposure, positive *Histoplasma* serology, and a CD4+ count ≤150 cells/μL are associated with an increased risk for symptomatic illness (*613*).

Virtually all cases of primary histoplasmosis are acquired by inhalation of microconidia from the mycelial phase of the organism. Asymptomatic dissemination of infection beyond the lungs is common and cellular immunity is critical in controlling infection. Reactivation of a silent focus of infection that was acquired years earlier can occur when cellular immunity wanes and is the presumed mechanism for disease occurrence in nonendemic areas. The incidence of symptomatic

histoplasmosis in patients with HIV infection appears to have declined since the use of potent ART.

Clinical Manifestations

Disseminated histoplasmosis usually occurs in patients with CD4⁺ counts ≤150 cells/μL (*614*). Common clinical manifestations include fever, fatigue, weight loss, hepatosplenomegaly, and lymphadenopathy (*615*). Cough, chest pain, and dyspnea occur in approximately 50% of patients (*614*). CNS, gastrointestinal, and cutaneous manifestations occur in a smaller percentage (*670*), and <10% of patients experience shock and multi-organ failure. Other anatomic sites are less commonly involved. Patients with CNS histoplasmosis typically experience fever, headache, and, if brain involvement is present, seizures, focal neurological deficits, and changes in mental status (*614,616*). Gastrointestinal disease usually is manifested by diarrhea, fever, abdominal pain, and weight loss (*617*). For patients with CD4⁺ counts >300 cells/μL, symptoms and signs of histoplasmosis are often limited to the respiratory tract.

Diagnosis

Detection of *Histoplasma* antigen in blood or urine is a sensitive method for rapid diagnosis of disseminated histoplasmosis but is insensitive for pulmonary infection. Antigen is detected in the urine of 95% and serum of 85% of AIDS patients with disseminated histoplasmosis (*618*). In patients with severe disseminated histoplasmosis, peripheral blood smears can show the organisms engulfed by WBCs. Histopathologic examination of biopsy material from involved tissues demonstrates the characteristic 2–4 μm budding yeast and can provide a rapid diagnosis.

H. capsulatum can be cultured from blood, bone marrow, respiratory secretions, or other involved sites in >85% of patients with AIDS, but organisms might require several weeks to grow (*614,618*). Serologic tests are less useful than antigen assays in AIDS patients with disseminated histoplasmosis, but might be helpful in patients who have intact immune responses.

The diagnosis of meningitis can be difficult. A lymphocytic pleocytosis is usually associated with elevated protein and low glucose. Fungal stains are usually negative, and CSF cultures are positive in a minority of cases (*619*). *Histoplasma* antigen or anti-*Histoplasma* antibodies can be detected in CSF in up to 70% of cases and either is diagnostic. For some patients, none of these tests are positive, and a presumptive diagnosis of *Histoplasma* meningitis is appropriate if the patient has disseminated histoplasmosis and findings of CNS infection not explained by another cause.

Preventing Exposure

Although HIV-infected persons living in or visiting areas in which histoplasmosis is endemic cannot completely avoid exposure, those whose CD4⁺ counts are ≤150 cells/μL should avoid activities known to be associated with increased risk **(CIII).** Such activities include creating dust when working with surface soil; cleaning chicken coops that are contaminated with droppings; disturbing areas contaminated with bird or bat droppings; cleaning, remodeling, or demolishing old buildings; and exploring caves **(CIII).**

Preventing Disease

Initiating Primary Prophylaxis

Data from a prospective, randomized, controlled trial indicate that itraconazole can reduce the frequency of histoplasmosis among patients who have advanced HIV infection and who live in areas in which histoplasmosis is highly endemic (*594*). However, no survival benefit was observed among persons receiving itraconazole.

Prophylaxis with itraconazole at a dose of 200 mg daily can be considered for patients with CD4⁺ counts ≤150 cells/μL who are at high risk because of occupational exposure or who live in a community with a hyperendemic rate of histoplasmosis (>10 cases/100 patient-years) **(CI).**

Discontinuing Primary Prophylaxis

If used, primary prophylaxis can be discontinued once peripheral blood CD4⁺ counts are >150 cells/μL for 6 months in patients on potent ART **(BIII).** Prophylaxis should be restarted if the CD4⁺ counts fall to ≤150 cells/μL **(CIII).**

Treatment of Disease

Patients with moderately severe to severe disseminated histoplasmosis should be treated with an IV lipid formulation of amphotericin B for ≥2 weeks (or until they improve clinically) followed by oral itraconazole (200 mg three times daily for 3 days and then 200 mg twice daily for a total of >12 months) **(AI)** (*620,621*).

In a randomized clinical trial, liposomal amphotericin B at 3.0 mg/kg daily was more effective than standard amphotericin B deoxycholate at 0.7 mg/kg daily (*620*), inducing a more rapid and more complete response, lowering mortality, and reducing toxicity. Substitution with ABLC at 5.0 mg/kg daily may be an alternative because of cost or tolerability **(CIII).**

In patients with less severe disseminated histoplasmosis, oral itraconazole at 200 mg three times daily for 3 days followed by 200 mg twice daily is appropriate initial therapy **(AII)** (*622*). The liquid formulation of intraconazole is preferred, owing to better absorption and fewer food interactions.

For persons with confirmed meningitis, liposomal amphotericin B should be administered as initial therapy for 4–6 weeks at a dosage of 5 mg/kg daily. This should be followed by maintenance therapy with itraconazole at a dose of 200 mg two or three times daily for a total of ≥1 year and until resolution of abnormal CSF findings **(AII)** (*616*).

Posaconazole has been reported in some salvage studies to be of some benefit (*623*). Fluconazole has limited to no activity against histoplasmosis and should not be used. The role of other azoles, including voriconazole, is not clear. Voriconazole should be used cautiously with HIV PIs and efavirenz. No published data exist regarding the use of echinocandins for treating patients with histoplasmosis.

Acute pulmonary histoplasmosis in an HIV-infected patient with intact immunity, as indicated by a CD4⁺ count >300 cells/μL, should be managed in a manner similar to that used for a nonimmunocompromised host **(AIII)** (*621*).

Monitoring and Adverse Events, Including Immune Reconstitution Inflammatory Syndrome (IRIS)

Serial monitoring of serum or urine for *Histoplasma* antigen is useful for determining response to therapy. A rise in level is suggestive of a relapse **(AIII).** Because absorption of itraconazole can be erratic, serum itraconazole levels should be obtained at least once in all patients to ensure adequate absorption **(AIII).** The serum concentration should be >1 μg/mL, ideally drawn for reasons of consistency as a trough level after at least 7 days on the current regimen. Itraconazole solution is recommended over the capsule formulation because absorption is improved, but this has not been studied specifically in AIDS patients.

IRIS has been reported uncommonly in patients with histoplasmosis (*605,624,625*). ART should not be withheld because of concern for the possible development of IRIS **(AIII).**

Management of Treatment Failure

Posaconazole solution at 800 mg daily was recently reported to be successful in three patients with HIV infection whose other previous therapies had failed (*623*). Voriconazole has been used in several transplant recipients and in one patient with AIDS who failed or could not tolerate therapy with other agents (*626,627*). Cross resistance between fluconazole and voriconazole has been noted in vitro *(628*).

Preventing Recurrence

Long-term suppressive therapy with itraconazole (200 mg daily) should be administered for patients with severe disseminated or CNS infection **(AII)** and in patients who relapse despite receipt of appropriate therapy **(CIII).** Fluconazole 800 mg daily is less effective than itraconazole **(CII)** (*629*). The role of voriconazole and posaconazole is not clear, but both have been used successfully in patients with histoplasmosis (*623,626*).

Discontinuing Secondary Prophylaxis (Chronic Maintenance Therapy)

An AIDS Clinical Treatment Group (ACTG)-sponsored study reported that discontinuing itraconazole was safe for patients who have been treated for histoplasmosis and who have a good immunologic response to ART (*630*). In that trial, patients had received ≥1 year of itraconazole therapy, had negative blood cultures, Histoplasma serum antigen <2 units, CD4⁺ counts >150 cells/μL, and had been on ART for 6 months. No relapses were evident in 32 subjects who were followed for a median of 24 months (*630*). Thus, discontinuing suppressive azole therapy appears to be safe for patients who meet the criteria described above **(AI)**. Suppressive therapy should be resumed if the CD4⁺ count decreases to <150 cells/μL **(BIII)**.

Special Considerations During Pregnancy

Because of their risk for teratogenicity, azoles should not be used during the first trimester of pregnancy **(EII).** Neonates born to women on chronic amphotericin B at delivery should be evaluated for renal dysfunction and hypokalemia.

Coccidioidomycosis

Epidemiology

Coccidioidomycosis is caused by a soil-dwelling fungus that consists of two species, *Coccidioides immitis* and *C. posadasii*. Most cases in persons with HIV infection have been from the areas in which the disease is endemic, including the Southwestern United States and parts of Central and South America (*631*). However, sporadic cases have been diagnosed outside those areas, presumably as a result of reactivation of a previous infection.

Cellular immunity is critical in controlling coccidioidomycosis. Symptomatic coccidioidomycosis can occur in persons with normal CD4⁺ concentrations. In patients with no discernible immunodeficiency, disseminated disease occurs in <1%. Black and Filipino men appear to be at higher risk for disseminated disease, as do pregnant women who acquire coccidioidal infection in the second or third trimester.

In patients with HIV infection, immune response to *Coccidioides spp*. appears to wane with declining CD4⁺ counts and the risk for developing symptomatic disease in areas in which the disease is endemic increases when this count is <250 cells/μL or with a diagnosis of AIDS (*632*). Retrospective studies have suggested a decline in the incidence of coccidioidomycosis in the areas in which the disease is endemic since the introduction of ART (*633*).

Clinical Manifestations

Among persons with HIV infection, six common syndromes have been described (*634*). These are focal pneumonia, diffuse pneumonia (presenting as apparent PCP), cutaneous involvement, meningitis, liver or lymph node involvement, and positive coccidioidal serology tests without evidence of localized infection. Focal pneumonia is most common in those with $CD4^+$ counts >250 cells/μL, whereas the other syndromes usually occur in more immunosuppressed patients. Symptoms of meningitis are headache and progressive lethargy. The CSF profile demonstrates a low glucose with elevated protein and a lymphocytic pleocytosis.

Diagnosis

The diagnosis of coccidioidomycosis is confirmed by culture of the organism from clinical specimens or by demonstration of the typical spherule on histopathologic examination of involved tissue. Blood cultures are positive in a minority of patients, usually in those with diffuse pulmonary disease. Coccidioidal IgM and IgG serology, performed by EIA, immunodiffusion, or classical tube precipitin or complement fixation methodology, is useful in diagnosis although it may be less frequently positive among patients with low $CD4^+$ counts than among immunocompetent persons. Complement fixation IgG antibody is frequently detected in the CSF in coccidioidal meningitis and is useful in establishing this diagnosis. Culture of the CSF is positive in fewer than one third of patients with meningitis.

Preventing Exposure

Although HIV-infected persons cannot completely avoid activities involving extensive exposure to infection while living in or visiting areas in which *Coccidioides spp*. is endemic, they should avoid activities involving extensive exposure to disturbed native soil, such as occurs at building excavation sites or during dust storms **(CIII).**

Preventing Disease

Initiating Primary Prophylaxis

Within an area where the disease is endemic, a positive IgM or IgG serologic test indicates an increased risk for the development of active infection (*635*) and specialists would recommend treatment if the $CD4^+$ count is <250 cells/μL **(BIII).** Yearly testing for seronegative HIV-infected persons living in such regions is reasonable **(CIII).**

Although highly immunosuppressed patients (*633*) might benefit from primary prophylaxis, such therapy for HIV-infected persons without a positive IgM or IgG serologic test who live in the area where disease is endemic is not recommended **(DIII).** However, several clinicians would empirically provide chemoprophylaxis with either oral fluconazole 400 mg daily or itraconazole 200 mg bid if there were a positive IgM or IgG serologic test and the CD4 cell count was <250 cells/μL **(CIII).** Outside the region in which coccidiodomycosis is endemic, routine testing does not appear to be useful and should not be performed **(DIII).**

Discontinuing Primary Prophylaxis

If used, primary prophylaxis can be discontinued once peripheral blood $CD4^+$ counts are $\geq$250 cells/μL for 6 months **(CIII)**. Primary prophylaxis should be restarted if the $CD4^+$ count is <250 cells/μl **(BIII)**.

Treatment of Disease

For patients with clinically mild infection, such as focal pneumonia, or who have a positive coccidioidal serologic test alone, initial therapy with a triazole antifungal is appropriate **(BII).** Fluconazole or itraconazole at doses of 400 mg daily is recommended (*636,637*). Data are limited with regard to the newer triazoles, posaconazole and voriconazole, but these agents might be useful in cases that fail to respond to fluconazole or itraconazole. Voriconazole should be used cautiously with HIV PIs and efavirenz.

For patients with either diffuse pulmonary involvement or severely ill patients with extrathoracic disseminated disease, amphotericin B is the preferred initial therapy **(AII)** (*636*). Most experience has been with the deoxycholate formulation using 0.7–1.0 mg/kg daily as an initial dose. Data regarding lipid formulations of amphotericin B are limited, but these formulations are likely as effective.

Therapy with amphotericin B should continue until clinical improvement is observed. Certain specialists would use a triazole antifungal concurrently with amphotericin B and continue the triazole once amphotericin B is stopped **(BIII)** (*636*).

Treatment of patients with coccidioidal meningitis requires consultation with a specialist. Therapy should begin with a triazole antifungal. Fluconazole at a dose of 400–800 mg daily is preferred **(AII)** (*638*), but itraconazole has also been used successfully (*639*). Successful therapy with voriconazole (*640,641*) and posaconazole (*642*) has been described in case reports. Despite successful antifungal therapy, patients might develop hydrocephalus and require CSF shunting. In some instances, triazole antifungals are not effective. In such cases, intrathecal amphotericin B is recommended **(AIII).**

Monitoring and Adverse Events, Including Immune Reconstitution Inflammatory Syndrome (IRIS)

Monitoring the titer of the complement-fixing (CF) antibody is useful in assessing clinical response to therapy. This should be obtained every 12 weeks **(AIII).** A rise suggests

recurrence of clinical disease. IRIS has not been observed in coccidioidomycosis.

Management of Treatment Failure

Patients whose therapy with fluconazole or itraconazole fails might be candidates for newer triazoles, but data regarding both posaconazole and voriconazole are limited. In most such instances, IV amphotericin B, in combination with triazole therapy, is recommended.

Preventing Recurrence

Patients who complete initial therapy for coccidioidomycosis should be considered for lifelong suppressive therapy using either fluconazole 400 mg daily or itraconazole 200 mg twice daily **(AII).**

Discontinuing Secondary Prophylaxis (Chronic Maintenance Therapy)

Patients with focal coccidioidal pneumonia who have clinically responded to antifungal therapy appear to be at low risk for recurrence of coccidioidomycosis if their $CD4^+$ counts are >250 cells/μL and they are receiving ART. A reasonable plan for treating such patients is to discontinue secondary prophylaxis after 12 months of therapy **(CIII)** with continued monitoring for recurrence using serial chest radiographs and coccidioidal serology.

In patients with diffuse pulmonary disease or nonmeningeal disseminated coccidioidomycosis, relapses occur even in patients without HIV infection in 25%–33% of cases (*643,644*). Even in patients with $CD4^+$ counts >250 cells/μL on potent ART, therapy should be continued indefinitely **(AIII).** For patients with meningitis, relapses have occurred in 80% of patients in whom triazoles have been discontinued (*645*). On the basis of this evidence, therapy for coccidioidal meningitis should be lifelong **(AII).**

Special Considerations During Pregnancy

Coccidioidomycosis is more likely to disseminate if acquired during the second or third trimester of pregnancy (*646*). Because of their risk for teratogenicity, azoles should not be used during the first trimester of pregnancy **(EII).** Neonates born to women on chronic amphotericin B at delivery should be evaluated for renal dysfunction and hypokalemia. One problematic area is coccidioidal meningitis, in which the only alternative treatment is intrathecal amphotericin B. For such situations, the decision regarding choice of treatment should be made in consultation with the mother, infectious diseases consultant, and obstetrician.

Aspergillosis

Epidemiology

Invasive aspergillosis in the HIV-infected person is rare. It is most frequently caused by *Aspergillus fumigatus*, although certain cases are caused by *A. flavus*, *A. niger,* and *A. terreus*. Invasive aspergillosis occurs among patients with advanced HIV infection and was more common before the advent of ART (*647,648*). Specific risk factors include neutropenia, use of corticosteroids, exposure to broad-spectrum antibacterial therapy, and previous pneumonia or other underlying lung disease. Patients who have had HIV-associated aspergillosis typically have $CD4^+$ counts <100 cells/μL, a history of other AIDS-defining OIs, and are not receiving ART (*649*).

Clinical Manifestations

Invasive aspergillosis in the HIV-infected patient is evidenced most commonly as a respiratory illness that can be a necrotizing pneumonia or a tracheobronchitis (*650*). Symptoms of invasive pneumonia are fever, cough, dyspnea, chest pain, hemoptysis, and hypoxemia; the chest radiograph might demonstrate a diffuse, focal, or cavitary infiltrate. A "halo" of low attentuation surrounding a pulmonary nodule or an "air-crescent" on CT scan of the lung is suggestive of disease. Tracheobronchitis is associated with fever, cough, dyspnea, stridor, and wheezing. Bronchoscopic examination demonstrates multiple ulcerative or plaque-like lesions adherent to the tracheal wall (*651*). Extrapulmonary forms of invasive aspergillosis include sinusitis, cutaneous disease, osteomyelitis, and CNS infection (*652*).

Diagnosis

The diagnosis of pulmonary aspergillosis is usually based on either 1) the repeated isolation of *Aspergillus spp*. from cultures or respiratory secretions or 2) the finding of dichotomously branching septate hyphae consistent with *Aspergillus spp*. in respiratory or other samples in association with a compatible clinical syndrome. Histological evidence of tissue invasion by hyphae with a positive culture for *Aspergillus spp*. represents a definite diagnosis.

Newer tests based on circulating fungal antigen have been employed to diagnose aspergillosis. These have not been formally evaluated in patients with HIV infection. A sandwich ELISA test for galactomannan, a major fungal cell wall antigen, can be used on serum and bronchoalveolar lavage fluid (*653*). Although sensitivity and specificity appear reasonable, the test has yielded both false-positive and -negative results and is currently recommended for screening for invasive aspergillosis primarily in stem-cell transplant recipients.

Preventing Exposure

Aspergillus spp. are ubiquitous in the environment, and exposure is unavoidable. Avoiding particularly dusty environments is prudent, especially in areas such as those created by construction because spore counts might be higher in such settings.

Preventing Disease

No data on the prevention of primary aspergillosis in HIV-infected patients exists, although posaconzaole has been reported to be effective among patients with hematologic malignancy and neutropenia (*654*).

Treatment of Disease

Treatment of aspergillosis in the HIV-infected population has not been examined systematically. The recommended treatment for invasive aspergillosis in patients without HIV infection is voriconazole (*655*). Voriconazole is the drug of choice but should be used cautiously with HIV PIs and efavirenz **(BIII).** Amphotericin B deoxycholate at 1 mg/kg daily or lipid-formulation amphotericin B at 5 mg/kg daily are alternatives **(AIII),** as is caspofungin at 50 mg daily (**BII**) and posaconazole **(BII).** Other echinocandins, such as micafungin and anidulafungin, are reasonable alternatives. Posaconazole also has proven to be useful in patients with invasive aspergillosis without HIV infection (*656*) but is not approved for treatment of aspergillosis. The length of therapy is not established but should continue at least until the peripheral blood CD4$^+$ count is >200 cells/μL and there is evidence of clinical response.

Monitoring and Adverse Events, Including Immune Reconstitution Inflammatory Syndrome (IRIS)

IRIS has rarely been reported to occur in patients with invasive aspergillosis (*657*).

Management of Treatment Failure

The overall prognosis is poor among patients with advanced immunosuppression and in the absence of effective ART. No data are available to guide recommendations for the management of treatment failure. If voriconazole was used initially, substitution with amphotericin B, posaconazole, or echinocandins might be considered; the amphotericin B or echinocandins would be a reasonable choice for those who began therapy with voriconazole or posaconazole **(BIII).**

Preventing Recurrence

No data are available to base a recommendation for or against chronic maintenance or suppressive therapy among patients who have successfully completed an initial course of treatment **(CIII).**

Special Considerations During Pregnancy

Because of their risk for teratogenicity, azoles should not be used during the first trimester of pregnancy **(EII).** (See mucocutaneous candidiasis). Neonates born to women on chronic amphotericin B at delivery should be evaluated for renal dysfunction and hypokalemia.

Cytomegalovirus Disease

Epidemiology

Cytomegalovirus (CMV) is a double-stranded DNA virus in the Herpesvirus family that can cause disseminated or localized end-organ disease among patients with advanced immunosuppression. Most clinical disease occurs in previously infected (seropositive) persons and so represents either reactivation of latent infection or reinfection with a novel strain.

End-organ disease caused by CMV occurs among persons with advanced immunosuppression, typically those with CD4$^+$ counts <50 cells/μL, who are either not receiving or have failed to respond to ART (*658–660*). Other risk factors include previous OIs and high plasma HIV RNA levels (>100,000 copies/mL).

Before potent ART, an estimated 30% of patients with AIDS experienced CMV retinitis some time between the diagnosis of AIDS and death (*658–660*). The incidence of new cases of CMV end-organ disease has declined by 75%–80% with the advent of ART and now is estimated to be <6 cases per 100 person-years (*661*). For those with established CMV retinitis, recurrence of active lesions occurs at a rate of 0.58/person-year for those with CD4$^+$ cells <50 cells/μL, a rate substantially lower than that seen in the pre-ART era. However, even for those with immune recovery sufficient to discontinue anti-CMV therapy (i.e., >100 cells/μL), relapse of the retinitis occurs at a rate of 0.03/person-year and can occur at CD4$^+$ counts as high as 1,250 cells/μL (*662*). Therefore, whether anti-CMV therapy is continued, regular ophthalmologic follow-up is needed.

Clinical Manifestations

Retinitis is the most common clinical manifestation of CMV end-organ disease. CMV retinitis occurs as unilateral disease in two thirds of patients at presentation, but in the absence of therapy or immune recovery, viremic dissemination results in bilateral disease in the majority of patients (*663*). For patients with unilateral CMV retinitis and CD4$^+$ count <50 cells/μL, rates of contralateral disease approach those of the pre-ART era (*663*).

Peripheral retinitis might be asymptomatic or present with floaters, scotomata, or peripheral visual field defects. Central retinal lesions or lesions impinging on the macula or optic

nerve are associated with decreased visual acuity or central field defects. CMV retinitis is a full-thickness necrotizing retinitis, and the characteristic ophthalmologic appearance is that of fluffy yellow-white retinal lesions, with or without intraretinal hemorrhage, and with little inflammation of the vitreous unless immune recovery with potent ART intervenes (*658*). Blood vessels near the lesions might appear to be sheathed. Occasionally, CMV retinitis lesions, particularly peripheral lesions, might have a more granular appearance.

In the absence of ART or specific anti-CMV therapy, retinitis invariably progresses, usually within 10–21 days after presentation. Progression of retinitis occurs in "fits and starts" and causes a characteristic brushfire pattern, with a granular, white leading edge advancing before an atrophic gliotic scar (*672*).

Colitis occurs in 5%–10% of persons with AIDS and CMV end-organ disease (*659*). The most frequent clinical manifestations are fever, weight loss, anorexia, abdominal pain, debilitating diarrhea, and malaise. Extensive mucosal hemorrhage and perforation can be life-threatening complications.

Esophagitis caused by CMV, which occurs in <5%–10% of persons with AIDS who experience CMV end-organ disease, causes fever, odynophagia, nausea, and occasionally mid-epigastric or retrosternal discomfort. CMV pneumonitis is uncommon. CMV neurologic disease causes dementia, ventriculoencephalitis, or ascending polyradiculomyelopathy (*664*). Patients with dementia typically have lethargy, confusion, and fever, mimicking that of HIV dementia. CSF typically demonstrates lymphocytic pleocytosis (although a mixture of neutrophils and lymphocytes might be evident), low-to-normal glucose levels, and normal-to-elevated protein levels. Patients with ventriculoencephalitis have a more acute course, with focal neurologic signs, often including cranial nerve palsies or nystagmus, and rapid progression to death. Periventricular enhancement of CT or MRI images is indicative of CMV ventriculoencephalitis rather than HIV-related neurologic disease. CMV polyradiculomyelopathy causes a Guillian-Barre–like syndrome characterized by urinary retention and progressive bilateral leg weakness. The clinical symptoms usually progress during several weeks to include loss of bowel and bladder control and to flaccid paraplegia. A spastic myelopathy has been reported and sacral paresthesia might occur. The CSF usually demonstrates a neutrophilic pleocytosis (usually 100–200 neutrophils/μL and some erythrocytes) accompanied by hypoglycorrhachia and elevated protein levels.

Diagnosis

CMV viremia can be detected by PCR or antigen assays and is usually observed in end-organ disease, but viremia also might be present in the absence of end-organ disease (*664-669*). The presence of serum antibodies to CMV is not diagnostically useful, although a negative IgG antibody level indicates that CMV is unlikely to be the cause of the disease process.

The diagnosis of CMV retinitis is usually made based on recognition of characteristic retinal changes observed through a dilated pupil during an ophthalmoscopic examination performed by an experienced ophthalmologist. Diagnosis by such clinical examination has a 95% positive predictive value. In rare cases, diagnosis might be difficult and PCR of vitreous for CMV and other pathogens might be valuable in the differential diagnosis.

Demonstration of mucosal ulcerations on endoscopic examination combined with colonoscopic or rectal biopsy with histopathologic demonstration of characteristic intranuclear and intracytoplasmic inclusions is required for the diagnosis of CMV colitis (*659*). The diagnosis of CMV esophagitis is established by the presence of extensive large, shallow ulcers of the distal esophagus and biopsy evidence of intranuclear inclusion bodies in the endothelial cells with an inflammatory reaction at the edge of the ulcer (*659*).

Culturing CMV from a biopsy or cells brushed from the colon or the esophagus is not sufficient to establish the diagnosis of CMV colitis or esophagitis in the absence of histopathologic changes because certain persons with low $CD4^+$ counts might be viremic and have positive cultures for CMV in the absence of clinical disease (*669*).

Diagnosis of CMV pneumonitis should take into account pulmonary interstitial infiltrates, identification of multiple CMV inclusion bodies in lung tissue, and the absence of other pathogens that are more commonly associated with pneumonitis evident in this population (*667*). CMV neurologic disease is diagnosed on the basis of a compatible clinical syndrome and the presence of CMV in CSF or brain tissue (*660,668*). Detection of CMV is enhanced by PCR (*665,668*).

Preventing Exposure

HIV-infected persons who belong to groups at risk with relatively low seroprevalence rates for CMV and who, therefore, cannot be presumed to be seropositive should be tested for antibody to CMV **(BIII)**. These groups include patients who have not had contact with MSM or used injection drugs. HIV-infected adolescents and adults should be advised that CMV is shed in semen, cervical secretions, and saliva and that latex condoms must always be used during sexual contact to reduce the risk for exposure to CMV and to other sexually transmitted pathogens **(AII)**.

HIV-infected adults and adolescents who provide child care or parents of children in day care facilities should be informed that they are at increased risk for acquiring CMV infection **(BI).** Similarly, parents and other caretakers of HIV-infected children should be advised of the increased risk to children at

these centers **(BIII).** Risk for acquiring CMV infection can be diminished by optimal hygienic practices (e.g., hand-washing and use of latex gloves) **(AII).**

HIV-exposed infants and infected children, adolescents, and adults who are seronegative for CMV and who require blood transfusion should be administered only CMV antibody-negative or leukocyte-reduced cellular blood products in nonemergency situations **(BIII).**

Preventing Disease

CMV end-organ disease is best prevented using ART to maintain the $CD4^+$ count >100 cells/μL. Although oral valganciclovir would likely prevent the occurrence of CMV retinititis in patients with $CD4^+$ counts <50 cells/μL, such therapy is not usually recommended because of cost, the potential to induce CMV resistance, the utility of treating disease when it occurs, and the lack of demonstrated survival advantage **(DI)**. The primary method for preventing severe CMV disease is recognizing the early manifestations of the disease. Patients should be made aware of the importance of increased floaters in the eye and should be advised to assess their visual acuity regularly by using simple techniques (e.g., reading newsprint) **(BIII).** Regular funduscopic examinations performed by an ophthalmologist are recommended by certain specialists for patients with low (e.g., <50 cells/μL) $CD4^+$ counts **(CIII).**

Natural history studies in the era of ART indicate that CMV viremia can be detected by PCR on at least one occasion in approximately 30% of those whose $CD4^+$ counts remain <100 cells/μL (*669*). Such detection of CMV infection by PCR correlates with the development of future CMV disease and death (*669*). Furthermore, evidence from a cohort study indicates that patients with CMV retinitis administered systemic therapy had substantially reduced mortality (*671*). These observations suggest that pre-emptive anti-CMV treatment administered to patients who have evidence of active infection but who have not yet exhibited end-organ disease could be a therapeutic strategy for preventing CMV end-organ disease. Unless future studies document that clinical benefit can be obtained from pre-emptive therapy, the treatment of patients with CMV viremia in the absence of organ system involvement is not recommended **(DII).**

Treatment of Disease

Oral valganciclovir, IV ganciclovir, IV ganciclovir followed by oral valganciclovir, IV foscarnet, IV cidofovir, and the ganciclovir intraocular implant coupled with valganciclovir are all effective treatments for CMV retinitis **(AI)** (*672–677*). Systemic therapy has been documented to reduce morbidity in the contralateral eye (*710*). This therapy should be considered when choosing among oral, IV, and local options. The choice of initial therapy for CMV retinitis should be individualized based on the location and severity of the lesion(s), the level of underlying immune suppression, and other factors such as concomitant medications and ability to adhere to treatment (**AIII**). No one regimen has been proven in a clinical trial to have superior efficacy related to protecting vision, and thus clinical judgment must be used when choosing a regimen (*673–677*). Forms of ganciclovir most often are the first choice for CMV infection or disease. Certain clinical trials were conducted with oral ganciclovir, a preparation that was poorly bioavailable and is no longer marketed. Instead, the prodrug valganciclovir, which is the valine ester of ganciclovir, is administered orally to deliver ganciclovir. In these guidelines, references to oral ganciclovir have been deleted and the equivalent dose of valganciclovir has been substituted.

The ganciclovir intraocular implant plus oral valganciclovir is superior to once-daily IV ganciclovir (and presumably to once-daily oral valganciclovir) for preventing relapse of retinitis **(AI)** (*673–677*). For this reason, certain HIV specialists recommend the intraocular implant plus valganciclovir as the preferred initial therapy for patients with immediate sight- threatening lesions (adjacent to the optic nerve or fovea); for patients with small peripheral lesions oral valganciclovir alone may be adequate **(BII).** Certain ophthalmologists recommend an initial intravitreous injection of ganciclovir at the time CMV retinitis is diagnosed to deliver a high local concentration of ganciclovir to the eye immediately, until the ganciclovir implant can be placed **(CIII).**

Because ART can control CMV retinitis without anti-CMV therapy in patients who experience immune recovery, some clinicians might consider not treating small peripheral CMV lesions with anti-CMV therapy in ART-naïve patients. However, complications of CMV retinitis, including immune recovery retinitis and retinal detachment, are more common in patients with larger CMV lesions, and ART might take 3–6 months to fully control HIV replication and stimulate sufficient immune recovery to control the retinitis. Furthermore, consistent with natural history studies that associated CMV viremia with increased mortality in the pre- and current ART era (*669,678,679*), evidence indicates that anti-CMV therapy decreases mortality among patients with CMV retinitis and immune compromise (*671*). Therefore, even in ART-naïve patients with small peripheral lesions, treatment with systemic anti-CMV therapy, such as valganciclovir for the initial 3–6 months until ART has induced immune recovery, will likely be beneficial **(BII).**

For patients who have colitis or esophagitis, a majority of HIV specialists would recommend IV ganciclovir or foscarnet (or with oral valganciclovir if symptoms are not severe enough to interfere with oral absorption) for 21–28 days or until signs

and symptoms have resolved **(BII)**. Certain HIV specialists also would withhold therapy unless moderate-to-severe symptoms justify the use of systemic treatment if ART is to be initiated soon or can be optimized **(BIII)**.

Criteria for establishing that CMV is the cause of pneumonitis and pulmonary dysfunction have been difficult to establish. If CMV is considered the cause of pulmonary dysfunction based on histology or cytology, treatment with IV ganciclovir, foscarnet, or cidofovir is logical, although few data establish that such therapy affects outcome **(CIII).**

For neurological disease, initiating therapy promptly is critical for an optimal clinical response. Although combination treatment with ganciclovir and foscarnet might be preferred as initial therapy to stabilize disease and maximize response (**BII**), this approach is associated with substantial rates of adverse effects, and optimal treatment for neurologic disease if ART can be optimized has not been established.

No data are available to demonstrate that starting ART among treatment-naïve patients with CMV retinitis would have an adverse effect on retinitis, gastrointestinal disease, or pneumonitis. Therefore, initiation of appropriate ART should be administered to those with acute CMV retinitis, gastrointestinal disease, or pneumonitis **(BIII).** Although no data indicate that IRIS worsens CMV neurologic disease syndromes, because of the localized morbidity that might occur with such an inflammatory reaction, a delay in initiating ART in this setting until clinical improvement occurs might be prudent **(CIII).**

Monitoring and Adverse Events, Including Immune Reconstitution Inflammatory Syndrome (IRIS)

Management of CMV retinitis requires close monitoring by an experienced ophthalmologist and the primary clinician. Consideration should be given to both treating the infected eye and preventing infection in the contralateral eye using systemic treatment (*663,680*).

Indirect ophthalmoscopy through a dilated pupil should be performed at the time of diagnosis of CMV retinitis, after completion of induction therapy, 1 month after the initiation of therapy, and monthly thereafter while the patient is on anti-CMV treatment **(AIII).** Monthly fundus photographs, using a standardized photographic technique that documents the appearance of the retina, provide the optimum method for following patients and detecting early relapse **(AIII).** For patients who have experienced immune recovery, the frequency of ophthalmologic follow-up can be decreased to every 3 months **(AIII).** Because relapse of retinitis might still occur among some patients with immune recovery, ophthalmologic follow-up might be indicated; however, the optimal timing and interval of such follow-up has not been established.

Adverse effects of ganciclovir include neutropenia, thrombocytopenia, nausea, diarrhea, and renal dysfunction. Adverse effects of foscarnet include anemia, nephrotoxicity, and electrolyte abnormalities. For patients receiving ganciclovir or foscarnet, monitoring of complete blood counts and serum electrolytes and renal function should be performed twice weekly during induction therapy and once weekly thereafter **(AIII).** Cidofovir is associated with dose-related nephrotoxicity and hypotony. For patients receiving IV cidofovir, blood urea nitrogen, creatinine, and urinalysis should be performed before each infusion; administration of the drug is contraindicated if renal dysfunction or proteinuria is detected. Even in the absence of retinitis with other CMV end-organ disease, periodic ophthalmologic examinations are needed to monitor for cidofovir-associated uveitis when this agent is used.

Immune recovery uveitis (IRU) is an ocular form of IRIS caused by an immunologic reaction to CMV, characterized by inflammation in the anterior chamber or vitreous in the setting of immune recovery after initiation of ART and is usually observed among those patients with a substantial rise in $CD4^+$ counts in the first 4–12 weeks after initiation of ART (*681–685*). Ocular complications of uveitis include macular edema and the development of epiretinal membranes, which can cause loss of vision. Treatment usually requires periocular corticosteroids or short courses of systemic corticosteroids. Estimated response rates are 50%. One uncontrolled case series suggested that IRU (or CMV retinitis-associated IRIS) might respond to oral valganciclovir (*686*).

Management of Treatment Failure

For patients without immune recovery after initiation of ART and who are receiving chronic maintenance therapy with systemic anti-CMV drugs, relapse of retinitis is likely to occur. Although drug resistance might be responsible for some episodes of relapse, early relapse is most often caused by the limited intraocular penetration of systemically administered drugs (*687–689*). Because it results in greater drug levels in the eye, the placement of a ganciclovir implant in a patient who has relapsed while receiving systemic treatment (IV ganciclovir or oral valganciclovir) is usually recommended and often will control the retinitis for 6–8 months until the implant requires replacement **(BIII)** (*690,691*)**.**

When patients relapse while receiving maintenance therapy, reinduction with the same drug followed by reinstitution of maintenance therapy can control retinitis, although for progressively shorter periods (*692*), and the majority of specialists recommend this approach for initial treatment of patients who experience relapsed disease (**AII**). Changing to an alternative drug at the time of first relapse typically does not result in superior control of the retinitis but should be

considered if drug resistance is suspected or if side effects or toxicities interfere with optimal courses of the initial agent (**AIII**) (*692*). The combination of ganciclovir and foscarnet is usually superior to systemic therapy with either agent alone and might be considered for patients with relapsed retinitis (*692*); however, this combination of drugs is accompanied by greater toxicity (**BI**).

Drug resistance occurs among patients receiving long-term therapy (*693–696*). Reported rates in the pre-ART era were approximately 25% per person-year (*693,697,698*) and reported rates are similar for ganciclovir, foscarnet, and cidofovir (*693,694*). In the ART era, the rate of resistance appears to be less, approximately 10% per person-year. Low-level resistance to ganciclovir occurs through mutations in the CMV UL97 (phosphotransferase) gene, and high-level resistance to ganciclovir typically occurs because of mutations in both the CMV UL97 and UL54 (DNA polymerase) genes (*699–704*). Resistance to foscarnet or cidofovir each occurs because of mutations in the CMV UL54 gene. High-level resistance to ganciclovir is frequently associated with cross resistance to cidofovir (*701*) and occasionally to foscarnet (*703*).

Although early relapse is typically not a result of resistance, later relapse often is. Because patients with resistant CMV nearly always have mutations in the CMV UL97 gene, and because a limited number of mutations are responsible for most drug resistance, susceptibility testing in peripheral blood using a CMV DNA PCR assay and sequencing for CMV UL97 mutations or using a point mutation assay (*705,706*) might be reasonable for patients who relapse on therapy (*707*). Virus in the eye and in the blood are identical in >90% of cases (*708*), so evaluating the blood for resistance is reasonable, and the detection of resistance in the blood or urine correlates with clinical behavior of the retinitis (*709*). Sequencing the UL97 gene from PCR-amplified specimens from blood can be accomplished in <48 hours, correlates well with conventional drug susceptibility testing and clinical outcomes (*707*), and, therefore, has clinical utility **(BII)** when conventional methods of culture and susceptibility testing and viral sequencing are not available or are too time consuming or costly. Conversely, CMV viral load measurements are of limited utility clinically because of their poor positive predictive value, but do have reasonable negative predictive value and might have utility in excluding resistance when sequencing is not available **(BII).** UL97 mutants usually respond to foscarnet, as do most UL54 mutants (except those associated with resistance to foscarnet).

Patients with low-level ganciclovir-resistant isolates in the eye might respond to a ganciclovir implant because of the higher local levels of ganciclovir resulting from this form of therapy. However, patients with high-level ganciclovir-resistant isolates typically will not respond and will require a switch to alternative therapy.

Preventing Recurrence

After induction therapy, secondary prophylaxis (i.e., chronic maintenance therapy) is recommended for life **(AI)** (*664,668,673,674,710*), unless immune reconstitution occurs as a result of ART. Regimens demonstrated to be effective for chronic suppression in randomized, controlled clinical trials include parenteral ganciclovir or valganciclovir, parenteral foscarnet, combined parenteral ganciclovir and foscarnet, parenteral cidofovir, and (for retinitis only) ganciclovir administration through intraocular implant **(AI).** Repetitive intravitreous injections of fomivirsen also have been demonstrated to be effective in randomized clinical trials, but this drug is no longer available in the United States.

Repetitive intravitreous injections of ganciclovir, foscarnet, and cidofovir have been effective for secondary prophylaxis of CMV retinitis in uncontrolled case series. Because of the risk for hypotony and uveitis, the intravitreal administration of cidofovir should be reserved for extraordinary cases. Intraocular therapy alone does not provide protection to the contralateral eye or to other organ systems and typically should be combined with oral valganciclovir.

The choice of a chronic maintenance regimen for patients treated for CMV disease should be made in consultation with a specialist. For patients with retinitis, this decision should be made in consultation with an ophthalmologist and should consider the anatomic location of the retinal lesion, vision in the contralateral eye, the immunologic and virologic status of the patient, and the patient's response to ART.

Patients with lesions that immediately threaten vision need prompt anti-CMV therapy because progression of the retinitis can occur during the time in which immune recovery is occurring (*674,675*). Patients with retinitis that immediately threatens sight still might benefit most from the use of the ganciclovir implant because of its ability to deliver high concentrations of drug locally and its superior ability to control retinitis progression **(BI).** However, replacement of the ganciclovir implant at 6–8 months might not be necessary for those with sustained immune recovery. If the ganciclovir implant is used, it should be combined with oral valganciclovir until immune recovery occurs **(BIII).**

Chronic maintenance therapy is not routinely recommended for gastrointestinal disease but should be considered if relapses occur **(BII).** A role for maintenance therapy for CMV pneumonitis has not been established **(CIII).**

Discontinuing Secondary Prophylaxis (Chronic Maintenance Therapy)

Multiple case series have reported that maintenance therapy can be discontinued safely among adult and adolescent patients with CMV retinitis whose CD4+ counts have indicated a sustained (e.g., 3–6 months) increase to >100 cells/μL in response to ART (*711-716*). Such patients have remained disease free for >30–95 weeks in clinical trials and case series, whereas during the pre-ART era, retinitis typically reactivated in <6–8 weeks after stopping CMV therapy. Plasma HIV RNA levels were varied among these patients, demonstrating that the CD4+ count is the primary determinant of immune recovery to CMV. Discontinuing secondary prophylaxis (chronic maintenance therapy) is reasonable for patients with a sustained (3–6 months) increase in CD4+ counts >100 cells/μL in response to ART **(BII)** (*711–715,717,718*). Such decisions should be made in consultation with an ophthalmologist and should include magnitude and duration of CD4+ count increase, anatomic location of the retinal lesions, vision in the contralateral eye, and the feasibility of regular ophthalmologic monitoring **(BII).** The relapse rate among patients whose anti-CMV therapy has been discontinued for immune recovery is 0.03 per person-year (i.e., 3% per year) and no level of CD4+ count is absolutely safe (relapses have been reported at CD4+ counts of 1,250 cells/μL). Therefore, all patients who have had anti-CMV maintenance therapy discontinued should continue to undergo regular ophthalmologic monitoring for early detection of CMV relapse and for IRU, optimally every 3 months (**AII**). Monitoring CMV viral load has poor positive predictive value for relapse of the retinitis and, therefore, is not recommended **(DII).**

Relapse of CMV retinitis occurs frequently among patients whose anti-CMV maintenance therapies have been discontinued and whose CD4+ counts have decreased to <50 cells/μL (*717*). Therefore, reinstitution of secondary prophylaxis should occur when the CD4+ count has decreased to <100 cells/μL **(AIII).**

Special Considerations During Pregnancy

The diagnostic considerations among pregnant women are the same as for nonpregnant women. Indications for treatment of CMV infection during pregnancy are the same as for nonpregnant HIV-infected adults **(AIII).** For retinal disease, use of intraocular implants or intravitreous injections for local therapy should be considered in the first trimester, if possible, to limit fetal exposure to systemically administered antiviral drugs **(CIII).** Systemic antiviral therapy as discussed should then be started after the first trimester.

Ganciclovir is embryotoxic among rabbits and mice and teratogenic (i.e., cleft palate, anophthalmia, aplastic kidney and pancreas, and hydrocephalus) in rabbits (*719–721*). Safe use in human pregnancy after organ transplantation has been reported (*719,720*), and use in late pregnancy to treat fetal CMV infection in HIV-uninfected women has also been reported (*722*). Foscarnet is associated with an increase in skeletal anomalies or variants in rats and rabbits. No experience with use early in human pregnancy has been reported. A single case report of use in the third trimester described normal infant outcome (*723*). Cidofovir is embryotoxic and teratogenic (i.e., meningomyelocele and skeletal abnormalities) among rats and rabbits. No experience with use of cidofovir in human pregnancy has been reported; use in pregnancy is not recommended **(DIII).**

On the basis of limited data, toxicity reports and studies, and ease of use of the various drugs, valganciclovir is recognized as the treatment of choice during pregnancy **(BIII).** No experience has been reported with the use of valganciclovir in human pregnancy, but concerns are expected to be the same as with ganciclovir. The fetus should be monitored by fetal-movement counting in the third trimester and by periodic ultrasound monitoring after 20 weeks of gestation to look for evidence of hydrops fetalis indicating substantial anemia. Because toxicity of foscarnet is primarily renal, weekly monitoring of amniotic fluid volumes by ultrasound is recommended after 20 weeks of gestation to detect oligohydramnios if foscarnet is used.

Rarely, ultrasound findings in the fetus (e.g., cerebral calcifications, abdominal and liver calcifications, hydrops, microcephaly, ventriculomegaly, ascites, and echogenic fetal bowel) might indicate the possibility of in utero CMV infection among pregnant women with CMV end-organ disease (*724*). In this case, consideration of invasive testing (i.e., amniocentesis and fetal umbilical blood sampling) must be individualized on the basis of clinical history and serologic findings, gestational age, potential risk for HIV transmission, and maternal preference (*725*). Referral to a maternal-fetal medicine specialist for evaluation, counseling, and potential further testing is recommended.

On the basis of data in HIV-uninfected women, transmission of CMV from mother to infant might occur in utero. However, symptomatic infection in the newborn is usually related to primary CMV infection in the mother during pregnancy, and because >90% of HIV-infected pregnant women are CMV antibody positive in the majority of studies, the risk for symptomatic infection in the fetus is low (*726–730*). Therefore, treatment of asymptomatic maternal CMV infection during pregnancy solely to prevent infant infection is not indicated **(DIII).**

Herpes Simplex Virus Disease

Epidemiology

Infections with human herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2) are common, with a seroprevalence of HSV-1 among adults of approximately 60% and a seroprevalence of HSV-2 among persons aged ≥12 years in the United States of 17% (731). Approximately 70% of HIV-infected persons are HSV-2 seropositive and 95% are seropositive for either HSV-1 or HSV-2 (732). In most HSV-infected persons, HSV infections are unrecognized clinically. However, regardless of the clinical severity of infection, reactivation on mucosal surfaces occurs intermittently and can result in transmission. HSV-2 is a risk factor for HIV acquisition, and HSV-2 reactivation results in increases in HIV RNA levels in coinfected patients.

Clinical Manifestations

Orolabial herpes is the most common manifestation of HSV-1 infection. Classic manifestations include a sensory prodrome in the affected area, rapidly followed by the evolution of lesions from papule to vesicle, ulcer, and crust stages on the lips. The course of illness in untreated subjects is 7–10 days. Lesions recur 1–12 times per year and can be triggered by sunlight or physiologic stress.

Genital herpes is the most common manifestation of HSV-2 infection. Genital mucosal or skin lesions are similar to external orolabial lesions in appearance and evolution. Local symptoms might include a sensory prodrome consisting of pain and pruritis. Ulcerative lesions are usually the only stage observed on mucosal surfaces. Mucosal disease is occasionally accompanied by dysuria or vaginal or urethral discharge; inguinal lymphadenopathy, particularly in primary infection, is common with genital herpes *(733)*. These classic manifestations occur in certain patients, but most persons with genital herpes have mild and atypical lesions that are not brought to medical attention and that cannot be diagnosed by physical examination. In profoundly immunocompromised patients, extensive, deep, nonhealing ulcerations might occur. These lesions have been reported most often in those with $CD4^+$ counts of <100 cells/μL and also might be more commonly associated with acyclovir-resistant virus (*734*).

The episodes of genital HSV-1 infection are indistinguishable from genital HSV-2 infection but genital HSV-1 infection recurs less frequently than genital HSV-2 infection.

Nonmucosal HSV infections, such as HSV keratitis, HSV encephalitis, HSV hepatitis, and herpetic whitlow, are similar in presentation to those manifestations observed in HIV-seronegative persons; disseminated HSV infection is rare. HSV retinitis manifests as acute retinal necrosis (ARN) and can lead rapidly to loss of vision.

Diagnosis

Because mucosal HSV infections cannot be diagnosed accurately without laboratory confirmation, especially in HIV-seropositive patients, a laboratory diagnosis should be pursued in all cases (*529*). Viral culture, HSV DNA PCR, and HSV antigen detection are available methods for diagnosis of mucocutaneous HSV lesions caused by HSV. PCR is the most sensitive method, but is not widely available. The virus detected in genital lesions should be typed, because HSV-1 recurs less frequently than HSV-2 in the genital area. Type-specific serologic assays are commercially available and can be used in asymptomatic persons or those with atypical lesions. Because of the poor sensitivity and specificity of clinical diagnosis, extensive interactions between HIV and HSV-2, and the availability of effective therapy for HSV-2, routine type-specific serologic testing for HSV-2 should be considered in persons who seek HIV care. Diagnosis of HSV-2 should be accompanied by counseling that discusses the risk for transmission of infection to sex partners. Guidelines for counseling are provided in the 2006 CDC STD treatment guidelines (http://www.cdc.gov/std/treatment).

Preventing Exposure

The majority of HIV-infected persons have HSV-1 and -2 infections. However, prevention of acquisition of HSV is important for those who are uninfected. HSV-2-seronegative HIV-infected persons should ask their partners to be tested using type-specific serology before initiating sexual activity, because disclosure of HSV-2 in heterosexual HSV-2-discordant couples was associated with reduced risk for transmission of HSV-2 **(BII)** (*735*). Consistent use of latex condoms reduced HSV-2 acquisition from women to men and from men to women, and their use should be encouraged for prevention of transmission of HSV-2 and other sexually transmitted pathogens **(AII)** (*736*). HIV-infected persons should specifically avoid sexual contact when their partners have overt (genital or orolabial) herpetic lesions **(AII).** However, sexual transmission of HSV can occur during asymptomatic shedding. The use of suppressive antiviral therapy (valacyclovir 500 mg once daily) in persons with genital herpes reduced HSV-2 transmission to susceptible heterosexual partners by 50% (*737*); the effectiveness of this approach in reducing HSV-2 transmission from HIV-seropositive persons or to HIV-seropositive persons has not been evaluated.

Preventing Disease

The dose, duration, and efficacy of antiviral prophylaxis after exposure to HSV have not been evaluated.

Treatment of Disease

Patients with HSV infections can be treated with episodic therapy when lesions occur or with daily therapy to prevent recurrences. The management of genital HSV-2 in HIV-infected persons should include several factors, including frequency and severity of HSV recurrences, the risk for HSV-2 transmission to susceptible partners, and the potential for interactions between HIV and HSV-2 that might result in increased HIV in plasma and genital secretions. Treatment for individual recurrences does not influence the natural history of genital HSV-2 infection and does not reduce the risk for HSV-2 transmission to sex partners, a major concern of persons with genital herpes.

Patients with orolabial lesions can be treated with oral valacyclovir, famciclovir, or acyclovir for 5–10 days **(AII).** Severe mucocutaneous HSV lesions respond best to initial treatment with IV acyclovir **(AII)** (*734,738*). Patients may be switched to oral therapy after the lesions have begun to regress. Therapy should be continued until the lesions have completely healed. Genital HSV infection should be treated with oral valacyclovir, famciclovir, or acyclovir for 5–14 days **(AI).** Short-course therapy (1, 2, or 3 days) should not be used in patients with HIV infection.

Monitoring and Adverse Events, Including Immune Reconstitution Inflammatory Syndrome (IRIS)

Acyclovir, valacyclovir, and famciclovir are occasionally associated with nausea or headache. No laboratory monitoring is needed in patients receiving episodic or suppressive therapy unless the patient has substantial renal impairment. For patients receiving high-dose IV acyclovir, monitoring of renal function and dose adjustment as necessary are recommended at initiation of treatment and once or twice weekly for the duration of treatment. Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome has been reported among HIV-infected patients treated with high-dose (8 grams/day) valacyclovir but has not been reported at doses used for therapy of HSV infection (*742*).

Cutaneous lesions that are atypical and occasionally recalcitrant to therapy have been reported in persons initiating ART and have been attributed to IRIS

Management of Treatment Failure

Treatment failure related to resistance to anti-HSV drugs should be suspected if lesions do not begin to resolve within 7–10 days after initiation of therapy. Among immunocompromised patients with suspected acyclovir-resistant HSV, viral culture of the lesion should be obtained and, if virus is isolated, susceptibility testing performed to confirm drug resistance **(AII)** (*743*).

The treatment of choice for acyclovir-resistant HSV is IV foscarnet **(AI)** (*744,745*). Topical trifluridine, cidofovir, and imiquimod also have been used successfully for lesions on external surfaces, although prolonged application for 21–28 days or longer might be required **(CIII).**

Preventing Recurrence

Most recurrences of genital herpes can be prevented using daily anti-HSV therapy, and this is recommended for persons who have frequent or severe recurrences **(AI)** (*739*). The option for suppressive therapy should be discussed with every HSV-2-infected patient. Suppressive therapy with oral acyclovir, valacyclovir, or famciclovir is effective in preventing recurrences **(AI)** (*739–741*). Suppressive therapy with valacyclovir should be 500 mg twice daily in HIV-infected persons **(AI),** or twice-daily regimens with acyclovir or famciclovir should be used. Daily anti-HSV suppressive therapy in HIV-infected persons also results in a decrease in HIV concentration in plasma and anal and genital secretions. Whether this regimen results in clinical benefit or decreased infectiousness is not known.

HIV-infected patients receiving ART who have immune reconstitution often experience improvement in the frequency and severity of their clinical episodes of genital herpes. However, immune reconstitution does not reduce the frequency of genital HSV shedding.

Special Considerations During Pregnancy

Diagnosis of mucocutaneous HSV infections is the same for pregnant women as for nonpregnant women. Episodic therapy for first-episode HSV disease and for recurrences can be offered during pregnancy, but suppressive therapy is not used routinely. Visceral disease is more likely to occur during pregnancy and can be fatal. Acyclovir is the antiviral drug with the most reported experience in pregnancy and appears to be safe (*746*); therefore, acyclovir is the first choice for therapy of HSV infections in pregnancy **(AIII).**

An additional concern with HSV during pregnancy is the potential for HSV transmission to the fetus and neonate. The rate of HSV transmission to the newborn in HSV-2-seropositive pregnant women is low, unless the pregnant woman has acquired genital HSV in late pregnancy. The predominant risk for HSV transmission is maternal genital shedding of HSV at delivery. Cesarean delivery is recommended for women with a genital herpes prodrome or visible HSV genital lesions at the onset of labor **(BII)** (*724*). Maternal genital herpes is a risk factor for perinatal mother-to-child

HIV transmission (*747*). Whether HSV suppression reduces the risk for HIV transmission during pregnancy, birth, or breastfeeding is unknown.

Use of acyclovir in late pregnancy suppresses genital herpes outbreaks and reduces the need for Cesarean delivery for recurrent HSV in HIV-seronegative women (*748*) and is likely to have similar efficacy in HIV-seropositive women **(BII).** However, the use of acyclovir in HIV-infected pregnant women to reduce the risk for intrapartum HIV and HSV transmission to the neonate has not been evaluated.

HHV-6 and HHV-7 Disease

Epidemiology

The highest geometric mean titers of HHV-6 antibody occur during the first 3 years of life, indicating a clustering of primary infections in infants and toddlers (*749,750*). Approximately 90% of healthy children become infected with HHV-6 by 12 months of life (*751*), and virtually 100% acquire infection by 3 years of age (*750*). HHV-6 seroprevalence remains high throughout adulthood (*750,751*). Most children likely acquire infection through contact with the secretions of adult caretakers who shed the virus in saliva; approximately 85% of healthy or HIV-infected adults shed HHV-6 intermittently in their saliva (*752*).

Primary HHV-7 infection also usually occurs during early childhood. Most adults have serologic evidence of previous HHV-7 infection. (*753*). Eighty to ninety percent of HHV-7–infected adults, regardless of HIV status, shed HHV-7 intermittently in their saliva.

Clinical Manifestations

HHV-6B causes exanthem subitum (roseola), a common disease of childhood (*754*). In addition, HHV-6B is a major cause of emergency room visits and hospitalizations for infants and young children (*755*). HHV-6 also produces a spectrum of neurologic diseases, including encephalitis and febrile seizure (*756*). Although HHV-6 has been described as a cause of disease in other immunocompromised patients, it has not been identified as an important opportunistic pathogen in HIV-infected patients.

Both HHV-6 and HIV can simultaneously infect the same $CD4^+$ cells under experimental conditions. Studies evaluating the effect of HHV-6 coinfection on active HIV viral replication in vitro have yielded contradictory results, with some investigations documenting enhanced HIV replication (*757*), whereas others reported inhibition of HIV replication (*758*). In vivo studies have suggested a possible role for HHV-6 coinfection in the progression of HIV disease (*759,760*), but this remains unconfirmed.

HHV-7 has not been definitively documented to cause a specific disease, with no apparent correlation between HHV-7 and HIV plasma load, suggesting that HHV-7 infection might not be stimulated by or interact with HIV infection (*761*).

Diagnosis

A fourfold or greater rise in anti-HHV-6 antibody titer between acute and convalescent serum samples suggests that active viral replication has occurred. Detection of HHV-6 IgM in infants and young children is a reliable marker of primary infection, although extrapolation to adults is problematic because IgM can be detected during HHV-6 reactivation. Detection of HHV-6 DNA in cell-free plasma specimens by PCR suggests active HHV-6 replication (*762*).

Preventing Exposure

HHV-6 and HHV-7 are ubiquitous universal infections, and prevention of exposure is not feasible.

Preventing Disease

Because of the ubiquity of HHV-6 and -7 during early childhood and the lack of an effective vaccine, prevention of primary HHV-6 and -7 infections or HHV-6 disease is not feasible.

Treatment of Disease

Antiviral susceptibility patterns of HHV-6 resemble those of CMV. HHV-6 replication is readily inhibited by foscarnet, cidofovir, and ganciclovir at levels that are easily achievable in the human plasma. Indications for treatment of HHV-6 infection in HIV-seropositive patients are unclear. However, if disease in an HIV-infected person is determined to be caused by HHV-6, ganciclovir or foscarnet can be considered treatment options using treatment schedules and doses similar to those used for CMV disease **(CIII).** HHV-7 has not been recognized as a cause of disease in HIV-infected persons, and no recommendation for treatment can be made.

Monitoring and Adverse Events, Including Immune Reconstitution Inflammatory Syndrome (IRIS)

See CMV treatment recommendations for monitoring and adverse events. HHV-6 and -7 have not been demonstrated to be associated with IRIS.

Management of Treatment Failure

Mutations conferring resistance of HHV-6 to ganciclovir, cidofovir, and foscarnet have been described (*763*). Theoretically, treatment failures could be managed by switching classes of antiviral medications (e.g., changing from ganciclovir to foscarnet), but data are completely lacking **(CIII).**

Preventing Recurrence

No data exist on prevention of HHV-6 or HHV-7 reactivation from latency in HIV-infected patients. Use of antiviral medications for this indication is not recommended **(DIII).**

Special Considerations During Pregnancy

Given the epidemiology of HHV-6 infection, symptomatic infection and indications for treatment in pregnancy are expected to be rare. See special considerations for CMV for a discussion of concerns regarding use of ganciclovir and foscarnet in pregnancy. Treatment of HHV-7 during pregnancy is not indicated.

Varicella-Zoster Virus Diseases

Epidemiology

Approximately 95% of adults (aged ≥21 years) born in the United States have had primary varicella-zoster virus (VZV) infection, known as varicella (or chickenpox). Reactivation of latent VZV results in herpes zoster (or shingles). A person's lifetime risk for herpes zoster is 15%–20%, with the highest incidence occurring in the elderly and immunocompromised persons. The incidence of herpes zoster is >15-fold higher for HIV-infected adults than for age-matched controls (*764*). Herpes zoster can occur in HIV-infected adults at any $CD4^+$ count, but frequency of disease is highest with $CD4^+$ counts of <200 cells/μL and is not reduced by ART (*765–767*).

Clinical Manifestations

The varicella rash first appears on the head, then on the trunk, and finally on the extremities, evolving through stages of vesicles, pustules, and crusts. The rash is characterized by rapid evolution of lesions during the initial 8–12 hours and by successive crops of new lesions. New vesicle formation continues for 2–4 days, accompanied by pruritus, fever, headache, malaise, and anorexia. Varicella can cause substantial morbidity in HIV-seropositive adolescents and adults. Visceral dissemination, especially VZV pneumonitis, is well documented (*768*). Because most HIV-infected adults in the United States are VZV seropositive, varicella is an uncommon occurrence in this population.

Herpes zoster manifests as a painful cutaneous eruption in a dermatomal distribution, often preceded by prodromal pain. The most common sites for herpes zoster are the thoracic dermatomes (40%–50% of cases), followed by cranial nerve (20%–25%), cervical (15%–20%), lumbar (15%), and sacral (5%) dermatomes. Skin changes begin with an erythematous maculopapular rash, followed by the appearance of clear vesicles and accompanied by pain (which might be severe). New vesicle formation typically continues for 3–5 days, followed by lesion pustulation and scabbing. Crusts typically persist for 2–3 weeks and cutaneous dissemination might be as high as 25% to 50%. About 20%–30% of HIV-infected patients have one or more subsequent episodes of herpes zoster, which might involve the same or different dermatomes. The probability of a recurrence of herpes zoster within 1 year of the index episode is approximately 10% (*767,769*). Approximately 10%–15% of HIV-seropositive patients report post-herpetic neuralgia (PHN) as a complication following herpes zoster (*767,770*).

Most herpes zoster-related complications, including herpes zoster dissemination, occur in patients with $CD4^+$ counts of <200 cells/μL (*771*). The CNS is the primary target organ for herpes zoster dissemination in patients coinfected with HIV. Various VZV-related neurologic syndromes occur in HIV-infected patients, including CNS vasculitis, multifocal leukoencephalitis, ventriculitis, myelitis and myeloradiculitis, optic neuritis, cranial nerve palsies and focal brain-stem lesions, and aseptic meningitis.

ARN and progressive outer retinal necrosis (PORN) are variants of necrotizing retinopathy caused by VZV. Although ARN can occur in both immunocompetent and immunocompromised patients, PORN occurs almost exclusively in AIDS patients with $CD4^+$ count <100 cells/μL (*772*). In contrast to ARN, PORN is characterized by minimal inflammation in the aqueous and vitreous humor, absence of retinal vasculitis, and multiple discrete peripheral lesions in the outer retinal layer (*773*). PORN lesions rapidly coalesce, causing full-thickness retinal necrosis and subsequent retinal detachment (*774*). Both ARN and PORN are associated with high rates of visual loss.

Diagnosis

Varicella and herpes zoster are distinctive in appearance and can usually be diagnosed clinically. Varicella can be diagnosed retrospectively by documenting seroconversion. When lesions are atypical or the diagnosis is uncertain, swabs from a fresh lesion or tissue biopsies can be submitted for viral culture, direct fluorescent antigen testing, or PCR. Histopathology and PCR can aid with diagnosis of VZV infections of visceral organs (e.g., encephalitis, retinitis, and pneumonitis).

Preventing Exposure

HIV-infected persons who are susceptible to VZV (i.e., those who have not been vaccinated, have no history of varicella or herpes zoster, or are seronegative for VZV) should avoid exposure to persons with chickenpox or herpes zoster **(AII)**. VZV-susceptible household contacts of susceptible HIV-infected persons should be vaccinated to prevent acquisition of chickenpox and potential transmission of VZV to their susceptible HIV-infected contacts **(BIII).**

Preventing Disease

Postexposure Prophylaxis

For prophylaxis against chickenpox, HIV-infected children and adults who are susceptible to VZV should receive varicella-zoster immune globulin (VariZIG™) as soon as possible (but within 96 hours) after close contact with a person who has active varicella or herpes zoster **(AIII)**. As of June 2007, VariZIG can be obtained only under a treatment IND; contact FFF Enterprises, 800-843-7477. The duration of protection should last at least for 3 weeks. Patients receiving monthly high-dose immune globulin intravenous (IGIV) (>400 mg/kg) are likely to be protected and probably do not require VariZIG if the last dose of IGIV was administered <3 weeks before exposure. Risk for VZV transmission is higher from exposure to a patient with chickenpox than from exposure to localized herpes zoster.

Among VZV-susceptible immunocompetent children, postexposure varicella vaccination has been shown to reduce the risk for chickenpox developing in children and is more effective than pre-emptive therapy with acyclovir. Post-exposure varicella vaccination (for patients with $CD4^+$ counts of >200 cells/μL) or short-term post-exposure administration of acyclovir may be considered for preventing chickenpox among susceptible HIV-infected adolescents or adults, but has not been studied in this population **(CIII)**.

Long-term–drug prophylaxis for prevention of primary VZV infection in HIV-infected persons is not recommended **(DIII).**

Vaccination

The live attenuated varicella vaccine has been documented to be safe and immunogenic in HIV-infected children aged ≥8 years with $CD4^+$ counts ≥200 cells/μL ($CD4^+$ percentage is ≥15%) (*775*) and is recommended for those children (776). No studies have evaluated the vaccine in HIV-infected adolescents or adults, but varicella vaccination (two doses, administered 3 months apart) may be considered in HIV-seropositive/VZV-seronegative persons ≥8 years old with $CD4^+$ counts ≥200 cells/μL (**CIII**). If vaccination results in disease because of vaccine virus, therapy with acyclovir is recommended (**AIII**). Administration of varicella vaccine to more severely immunocompromised HIV-infected patients is not recommended (**DIII**). Because of the high prevalence of VZV seropositivity in adults, use of varicella vaccine in this population will be infrequent. Routine serologic testing to determine the VZV serologic status of HIV-infected adults is not recommended.

Treatment of Disease

No controlled prospective studies of antiviral therapy for chickenpox in HIV-infected adults have been reported. For uncomplicated varicella, recommended treatment options are oral acyclovir (20 mg/kg body weight up to a maximum dose of 800 mg five times daily), valacyclovir (1 g PO tid), or famciclovir (500 mg PO tid) for 5–7 days **(AII).** IV acyclovir for 7–10 days is the recommended initial treatment for HIV-infected patients with severe chickenpox **(AIII)** (*768,777,778*). If no evidence of visceral involvement with VZV is available, switching to oral antiviral therapy after the patient has defervesced may be permissible **(AIII)** (*779*).

Prompt antiviral therapy should be instituted in all immunosuppressed herpes zoster patients within 1 week of rash onset or any time before full crusting of lesions. The recommended treatment options for acute localized dermatomal herpes zoster in HIV-infected patients are oral valacyclovir, famciclovir, or acyclovir for 7–10 days **(AII),** although longer durations of therapy should be considered if lesions resolve slowly. Valacyclovir or famciclovir are preferred because of their improved pharmacokinetic properties and simplified dosing schedule. If cutaneous lesions are extensive or if visceral involvement is suspected, IV acyclovir should be initiated and continued until clinical improvement is evident **(AII)** (*780*). A switch from IV acyclovir to oral antiviral therapy (to complete a 10–14 day treatment course) is reasonable when formation of new cutaneous lesions has ceased and the signs and symptoms of visceral VZV infection are improving **(AIII)**. Because of the absence of data to support benefit in this population, adjunctive corticosteroid therapy for herpes zoster is not recommended (**DIII**).

Optimal antiviral therapy for PORN remains undefined (*774,781*). Prognosis for visual preservation in involved eyes is poor despite aggressive antiviral therapy. A treatment regimen recommended by certain specialists is a combination of IV ganciclovir and foscarnet, plus intravitreal injections of ganciclovir and/or foscarnet **(AIII).** Optimization of ART in HIV-infected patients with PORN is also recommended **(AIII).** Anecdotal reports have described success with IV cidofovir. ARN appears to be more responsive to antiviral therapy; one recommended treatment is high-dose IV acyclovir (10 mg/kg every 8 hours for 10–14 days), followed by prolonged oral valacyclovir (1 gram tid for 6 weeks) **(AIII).** Involvement of an experienced ophthalmologist in management of patients with VZV retinitis is strongly recommended **(AIII).**

The incidence of herpes zoster in HIV-infected adults does not appear to be affected by ART therapy. Optimization of ART is recommended in patients with VZV infections (e.g., PORN) **(AIII)** that are difficult to treat.

Monitoring and Adverse Events, Including Immune Reconstitution Inflammatory Syndrome (IRIS)

For monitoring and adverse event recommendations related to anti-herpesvirus drugs, see preceding sections on HSV and CMV. Providers should be aware of the increased incidence of herpes zoster after initiation of ART. Such episodes should be treated as other episodes of herpes zoster.

Immune reconstitution following initiation of ART might be associated with an increased frequenty of VZV reactivation (*782*,*783*). Between 4 and 16 weeks after beginning ART, the risk for herpes zoster increases two- to fourfold from baseline. During the 6 months after the start of combination ART, the incidence of herpes zoster exceeds 90 episodes per 1,000 person years. The percentage of $CD8^+$ lymphocytes at baseline and the magnitude of their increase at 1 month after initiation of drug therapy are strongly associated with an increased risk for herpes zoster. The clinical presentation and natural history of herpes zoster in the setting of immune reconstitution do not differ from those observed in other HIV-infected patients.

Management of Treatment Failure

Treatment failure caused by resistance of VZV to acyclovir (and related drugs) should be suspected if lesions do not improve within 10 days of initiation of therapy or if they have an atypical (e.g., verrucous) appearance. A viral culture should be obtained, and if VZV is isolated, susceptibility testing performed to establish antiviral drug susceptibility or resistance and to document the need for alternative therapy. Among patients with suspected or proven acyclovir-resistant VZV infections, treatment with IV foscarnet is recommended **(AII)** (*784*).

Preventing Recurrence

No intervention has been recognized as preventing the recurrence of herpes zoster among HIV-infected persons. An attenuated virus vaccine for prevention of herpes zoster has been approved for use in immunocompetent persons aged ≥60 years, but data regarding its use in HIV-infected persons are lacking. Prospective clinical trials to evaluate the safety and immunogenicity of herpes zoster vaccine in HIV-seropositive subjects are planned. Administration of herpes zoster vaccine to HIV-infected persons is not recommended **(DIII)**.

Special Considerations During Pregnancy

HIV-infected pregnant women who are susceptible to VZV and have close contact to a person with active varicella or herpes zoster should receive VariZIG as soon as possible (within 96 hours) after exposure to VZV **(AIII).** If oral acyclovir is used for post-exposure prophylaxis, VZV serology should be performed so that the drug can be discontinued if the patient is seropositive for VZV **(CIII).** Pregnant women should not receive varicella vaccine **(EIII).**

Specific risks among HIV-infected women with varicella during pregnancy have not been reported. For HIV-seronegative women with chickenpox, the risk for transmitting VZV to the infant resulting in congenital varicella syndrome is 0.4% when infection occurs at or before 12 weeks of gestation, 2.2% with infection at 13–20 weeks, and is negligible after 20 weeks (*785*). Women with varicella during the first half of pregnancy should be counseled about the risks and offered detailed ultrasound surveillance for findings indicative of fetal congenital varicella syndrome (*785*). Administration of varicella-zoster immune globulin does not alter the risk for congenital varicella syndrome. Infants born to women who have chickenpox from 5 days before until 2 days after delivery should receive VariZIG to reduce the severity and mortality of neonatal varicella acquired during maternal viremia **(AIII)** (*783*)**.**

Oral acyclovir or valacyclovir are the preferred treatments for HIV-infected pregnant women who have uncomplicated chickenpox during pregnancy **(BIII).** Pregnant women who have severe varicella or who exhibit signs or symptoms of VZV pneumonitis should be hospitalized and treated with IV acyclovir (10 mg/kg every 8 hours) **(AII).**

No controlled studies of antiviral therapy of herpes zoster during pregnancy have been reported. Recommended therapy for uncomplicated shingles in pregnant HIV-infected women is oral acyclovir or valacyclovir **(BIII).**

Human Herpesvirus-8 Disease

Epidemiology

Human herpesvirus-8 (HHV-8) seroprevalence among the general population in the United States is 1%–5%. The seroprevalence is greater among MSM (20%–77%) (*800*), regardless of HIV infection, and is also higher in certain Mediterranean countries (10%–20%) and in parts of sub-Saharan Africa (30%–80%). HHV-8 is associated with all forms of KS (i.e., classic, endemic, transplant-related, and AIDS-related) and certain rare neoplastic (e.g., primary effusion lymphoma [PEL]) and lymphoproliferative disorders (multicentric Castleman disease [MCD]). The precise pathogenesis is unclear even though seroconversion to HHV-8 precedes the development of these tumors (*786*). Patients who are HHV-8 seropositive and have HHV-8 viremia have an increased risk (approximately ninefold) for experiencing KS compared with HHV-8 seropositive men without HHV-8 viremia (*787*), and HHV-8 viremia almost always accompanies symptomatic episodes of MCD (*788*).

The overall incidence of KS was as high as 20% among patients with AIDS before the advent of effective ART.

However, even before the widespread use of ART, the incidence had declined, perhaps because of ganciclovir, foscarnet, and cidofovir use for treatment of CMV disease. These agents inhibit the replication of HHV-8 in vitro, (*789,790, 803*) and observational studies indicate that patients receiving ganciclovir or foscarnet (but not acyclovir) develop KS at a reduced rate (*710,791–793*). The incidence of KS has declined after the introduction of PIs and HAART (*794*). PEL and MCD remain rare (*795*).

KS and PEL are described most frequently among HIV-infected persons with more advanced immunosuppression ($CD4^+$ counts of <200 cells/μL), although they can occur at any $CD4^+$ count. Episodes of MCD might present at any $CD4^+$ count.

Clinical Manifestations

Most persons with chronic HHV-8 infection are asymptomatic (*796*). Acquisition of HHV-8 has been associated with a primary infection syndrome consisting of fever, rash, lymphadenopathy, bone marrow failure, and occasional rapid progression to KS (*797,798*). MCD manifests with generalized adenopathy and fever and can progress to multi-organ failure (*795*). KS symptoms vary widely, but most persons have nontender, purplish, indurated skin lesions. Intraoral lesions are common and visceral dissemination can occur, occasionally without the presence of skin lesions. Other manifestations of HHV-8 infection are beyond the scope of this report. Asymptomatic HHV-8 infection is often associated with HHV-8 shedding in the saliva and occasional shedding in genital secretions (*796,799,800*); viral shedding might result in HHV-8 transmission to uninfected partners.

Diagnosis

Routine screening for HHV-8 by PCR or serologic testing for HHV-8 antibody is not indicated for HIV-infected persons. Use of PCR to quantify HHV-8 in the peripheral blood is helpful in the diagnosis and management of persons with MCD (*788*).

Preventing Exposure

Recommendations related to preventing exposure to HHV-8 do not exist.

Preventing Disease

Despite observational evidence supporting a role for anti-HHV-8 therapy in preventing the development of KS, the toxicity of current anti-HHV-8 therapy outweighs the potential benefits of administration **(DIII).**

Treatment of Disease

Although ganciclovir, foscarnet, and cidofovir have in vitro activity against HHV-8, and limited studies indicate these agents might be associated with reduced KS disease progression or lesion regression, larger and more definitive studies are needed to determine whether antiviral therapy has a useful role in managing HHV-8-associated diseases. KS regression has been documented after ganciclovir or foscarnet therapy (*801–803*), although one study indicated cidofovir was ineffective (*804*). The use of IV ganciclovir or oral valganciclovir is, however, recommended in the treatment of MCD **(BII)** (*805*) and might be useful adjunctive therapy in the treatment of PEL **(BII)** (*806,807*). Highly active ART that suppresses HIV replication should be administered to all HIV-infected persons with KS, PEL, or MCD **(BII)**, although insufficient evidence exists to support using one HAART regimen over another. Chemotherapy, in combination with ART, should be considered for patients with PEL or visceral KS **(BII)** and might be a useful adjunctive therapy in persons with widely disseminated cutaneous KS (**CIII**). Rituximab also appears to be an effective alternative to antiviral therapy in the treatment of MCD **(BII)** (*808*).

Monitoring and Adverse Events, Including Immune Reconstitution Inflammatory Syndrome (IRIS)

Fatal IRIS has been reported in persons initiating ART with pre-existing KS and MCD. The frequency of HHV-8-associated IRIS is not known but suppression of HIV replication and immune reconstitution are key components of therapy and initiation of ART should not be delayed.

Preventing Recurrence

Effective suppression of HIV replication with ART among HIV-infected patients with KS might prevent KS progression or occurrence of new lesions and should be considered for all persons with evidence of active KS **(BII).** Suppression of HIV replication also is recommended for persons with MCD **(BII)** and those with malignant lymphoproliferative disorders.

Special Considerations During Pregnancy

The seroprevalence of HHV-8 infection among HIV-infected pregnant women varies by geographic area, ranging from 1.7% among U.S.-born and 3.6% among Haitian-born women in New York City to 11.6% among pregnant women from four other U.S. cities (*809*). Pregnancy does not appear to affect the prevalence of antibodies to HHV-8 or the antibody levels (*84*), although levels of HHV-8 DNA in the peripheral blood might increase late in pregnancy (*810*). HHV-8 seropositivity does not appear to influence pregnancy outcome. Routine screening for HHV-8 by PCR or serology is not indicated for

HIV-infected pregnant women **(DII).** In vitro models suggest that beta-human chorionic gonadotropin induces regression of KS tumors, but clinical reports on the incidence and natural history of KS in pregnancy are conflicting (*811–814*).

Diagnosis of KS or other HHV-8-associated neoplasms in pregnancy should be the same as in nonpregnant women. Recommendations for the treatment of HHV-8 malignancies are beyond the scope of these guidelines. Treatment should be undertaken in consultation with a specialist.

Perinatal transmission of HHV-8 might occur infrequently. Evidence supporting vertical transmission during pregnancy or the intrapartum period includes cases of KS occurring in the infant shortly after birth (*815,816*), higher risk for transmission with higher maternal antibody titer (and by inference higher maternal levels of HHV-8) (*817*), and detection of similar strains of HHV-8 DNA by PCR in specimens drawn at birth from HHV-8-seropositive mothers and their infants (*818*). Data indicate increased mortality through age 24 months among HIV-infected infants born to HHV-8-seropositive compared with HHV-8-seronegative mothers (*815–817,819–824*), but these studies could not completely account for other confounding factors affecting HIV-infected infants. The majority of studies document a substantially higher rate of HHV-8 seropositivity among children born to HHV-8 antibody-positive compared with HHV-8 antibody-negative women (*819–824*).

Human Papillomavirus Disease

Epidemiology

Human papillomavirus (HPV), a common sexually transmitted DNA virus (*825–830*), is the most frequent cause of cervical cancer (*831–833*). Most HPV infections, however, resolve or become latent and undetectable (*828,834,835*), whereas persistent infection with an oncogenic HPV type is required for tumorigenesis. Of more than 100 HPV types, more than 40 can infect the cervix, and at least 13 of these are considered oncogenic types, including HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 66 (*836*). HPV16 alone accounts for approximately 50% of cervical cancers in the general population and HPV18 for another 10%–15%, whereas the other oncogenic HPV types each individually account for <5% of tumors (*832,837*). HPV types 6 and 11 cause 90% of genital warts (*838*).

Cervical cancer is the second most common cause of cancer in women worldwide, with almost twofold higher incidence in developing countries than in industrialized countries (*839*). In the United States and Western Europe, women with HIV/AIDS have several-fold higher rates of cervical cancer compared with the general population, according to studies linking population-based cancer registries with registries for HIV/AIDS (*840–843*). In Africa, findings have varied (*844*), but the only African study with a prospective registry-based design reported substantially increased risk for cervical cancer in women with HIV/AIDS, and cervical cancer represented 10% of all tumors detected (*845*). Furthermore, HIV seropositivity is associated with a high prevalence of HPV infection, low-grade cervical intraepithelial neoplasia (CIN), and the precursor to cervical cancer, CIN 3 (*846–865*). Among HIV-infected women, rates of oncogenic HPV and high-grade CIN increase with diminished $CD4^+$ count and higher HIV RNA levels (*858,860,866–876*).

Other cancers caused by oncogenic HPV infection include most anal cancers and a subset of tumors of the vulva, vagina, penis, oral cavity, and oropharynx (*836,877*). HPV16 is the type present in the majority of these HPV-positive noncervical cancers. As with cervical cancer, the incidence of anal cancer and the other HPV-associated tumors is substantially higher in patients with HIV/AIDS than in the general population (*841,842,878*). Furthermore, high-grade anal intraepithelial neoplasia (AIN), the likely anal cancer precursor lesion, is more common in HIV-seropositive adults than in HIV-seronegative adults (*879–883*) as are anal and genital warts and, in women, vulvar intraepithelial neoplasia (VIN) and vaginal intraepithelial neoplasia (VAIN) (*884–886*).

Although ART has altered HIV natural history, its effect on HPV and HPV-associated neoplasia is less clear. Certain studies have found reduced persistence/progression of cervical intralepithelial neoplasia (CIN) with use of ART. Conversely, most studies have not reported reduced persistence/progression of high-grade anal intraepithelial neoplasia (AIN) (AIN 2 or AIN 3) among men using ART (*882,892–894*), and most studies of cancer incidence have failed to document decreases in either cervical or anal cancer incidence since the widespread introduction of ART (*882,892,894–899*). Similarly, the incidence of high-grade vulvar neoplasia was not reduced with ART use (*884*), even though rates of low-grade vulvar lesions and anal or genital warts did decrease with ART (*884,900).* Whether ART has an effect on warts among HIV-infected persons is unclear (*884,888,900*). With ART having limited or no effect on HPV-associated cancers, and HIV-seropositive persons living longer, HIV-seropositive women and men will increasingly enter middle age, when the incidence of cervical and other HPV-associated cancers typically increases (*901–903*). Future increases in HPV-associated cancer rates among these patients are possible, particularly for cancers for which no routine screening, such as anal cancer is available. Continued careful monitoring of cancer rates in HIV-positive patients during the highly aggressive antiretroviral therapy (HAART) era is warranted.

Clinical Manifestations

The principal clinical manifestations of mucosal HPV infection are genital, anal, and oral warts; CIN; VIN; VAIN; AIN; squamous cell cancers; and cervical adenocarcinomas. A subset of oropharyngeal cancers are caused by HPV (*877*). HPV6 and 11 also cause recurrent respiratory papillomatosis, a rare condition in which papillomas grow in the respiratory tract.

Genital, Anal, and Oral Warts

Warts (condyloma acuminata) are usually flat, papular, or pedunculated growths on the mucosa or epithelium. The lesions might be a few millimeters to 1–2 centimeters in diameter; multiple lesions might be present. Certain persons with warts are asymptomatic although some have genital itching or discomfort.

CIN, VIN, and Squamous Cell Cancers

No characteristic symptoms are associated with CIN. These lesions are often asymptomatic but might manifest with bleeding. Cervical cancer also might be asymptomatic or might manifest with bleeding, pain, or a palpable mass.

AIN, VAIN, VIN and Oral HPV-Related Disease

No characteristic symptoms are associated with VAIN, VIN, and AIN. These lesions are often asymptomatic but might manifest with bleeding or itching, and external lesions might be visible or palpable. Similarly, squamous cell cancers at these sites also might be asymptomatic or they might manifest with bleeding, pain, or a visible/palpable mass.

Diagnosis

Genital, Anal, and Oral Warts

Diagnosis of genital and oral warts is made by visual inspection and can be confirmed by biopsy, although biopsy is needed only under certain circumstances (e.g., if the diagnosis is uncertain; the lesions do not respond to standard therapy; the disease worsens during therapy; or warts are pigmented, indurated, fixed, bleeding, or ulcerated). No data support the use of HPV tests in the routine diagnosis or management of visible genital or oral warts (*529*).

CIN, VIN, and Squamous Cell Cancers

The same cytology (Papanicolaou or Pap test) and colposcopic techniques used to detect CIN among HIV-seronegative women should be used in HIV-seropositive patients (*904*). Clinicians should be aware of such cytology and histology terms (Table 11). The entire genitalia and anal canal should be inspected carefully for visual signs of warts, intraepithelial neoplasia, or invasive cancer. Cervical cytology, tissue histology, or both should be performed according to the schedule described in the following sections.

After the Pap test, a digital examination of the vaginal, vulvar, and perianal regions and the anal canal should be performed as part of routine evaluation to feel for masses.

After an abnormal Pap test, a colposcopically directed cervical biopsy is the principal means of identifying CIN so that the lesion can be treated to prevent development of cervical cancer and to determine appropriate follow-up. For further details, see the section on prevention of cervical cancer.

AIN, VAIN, VIN and Oral HPV-Related Disease

AIN might first be recognized using a combination of visual inspection and anal cytology (termed anal SIL or ASIL), but as with CIN the diagnosis of AIN is principally made using anoscopically directed biopsy. Similarly, VAIN, VIN, and oral dysplasia are recognized through visual inspection and biopsy as needed. See the section on prevention of anal cancer.

Role of HPV Testing

Although a clinical test is available to detect 13 types of oncogenic HPV infection, no recommendations exist for use of this test in HIV-seropositive women. HIV-seropositive women should be referred for colposcopy if their cervical Pap test is interpreted as ASC US, ASC-H (or atypical glandular cells [ACG]), low-grade squamous intraepithelial lesions (LSIL), or high-grade squamous intraepithelial lesions (HSIL) (368,904,905). HPV testing may be used in the management of HIV-seronegative women with a cytologic diagnosis of ASC-US. “is practice has been recommended for similar use in HIV-seropositive women in American Society for Colposcopy and Cervical Pathology (ASCCP) guidelines (906), but at present, insufficient data are available to support this practice. Unlike for HIV-seronegative women, no recommendations exist for the use of HPV testing for triage of HIV-seropositive women aged >30 years with normal cervical cytology (e.g., to less or more frequent Pap tests based on a hybrid capture test) or in follow-up of CIN after treatment. No recommendations are available for HPV testing of anal specimens or other noncervical specimens.

Preventing Exposure

Consistent and correct use of male latex condoms has been associated with 72% reduction in risk for acquisition of genital HPV infection among sexually active college age women (*907*). Evidence confirms that condom use might reduce the risk for HPV-associated disease, including warts, cervical cancer, and CIN in women (*908,909*). Fewer data are available on prevention of HPV infection and HPV-associated conditions among HIV-seropositive patients. Laboratory studies have indicated

that latex condoms provide a sufficient barrier to prevent passage of particles the size of HPV (*908,910*). Although condoms might not prevent transmission of HPV from skin outside the area of condom coverage, they should be used by sexually active HIV-seropositive patients to reduce the risk for transmission or acquisition of sexually transmitted infections **(AII).**

A vaccine targeted against HPV16 and HPV18 (the two HPV types responsible for 60%–70% of cervical cancers) and HPV6 and HPV11 (which cause most anogenital warts) was licensed and recommended for use in 2006 (*911,912*). This quadrivalent HPV vaccine was efficacious in preventing HPV infection and high-grade CIN associated with vaccine-related HPV types among young HIV-seronegative women (*913–916*). A second vaccine targeting HPV16 and 18 has had similar efficacy. No data are available regarding the safety, tolerability, immunogenicity, or efficacy in HIV-infected women, and specific recommendations for HIV-seropositive women await data from ongoing studies. However, given the safety of other noninfectious vaccines in HIV-seropositive patients, the HPV vaccine is not absolutely contraindicated in HIV-seropositive women, and it may be used in circumstances when the clinician believes clinical benefit can be derived. The HPV vaccine has not demonstrated therapeutic benefit to treat existing HPV-related lesions in either HIV-seropositive or HIV-seronegative women, and women who have already acquired one sexually transmitted infection (e.g., HIV infection) are presumably more likely to have acquired others (e.g., infections with various HPV types). No published studies support using the HPV vaccine to prevent HPV infection and associated lesions of the anus, penis, or oral cavity; the vaccine is not currently approved for use in men in the United States. As in HIV-seropositive women, no data on the safety or efficacy of the HPV vaccine in HIV-positive men are available.

Preventing Disease

Preventing Cervical Cancer

See the guidelines for the use of cytology and biopsy to diagnose CIN. Also see section regarding treatment of CIN.

After obtaining a complete medical history, including the history of previous cervical disease, HIV-seropositive women should have a pelvic examination and a Pap test. The Pap test should be obtained twice during the first year after diagnosis of HIV infection and, if the results are normal, annually thereafter **(AII).** If the results of the Pap test are abnormal, care should be provided according to the Guidelines for Management of Women with Abnormal Cervical Cancer Screening Tests by ASCCP (*904*).

Regardless of $CD4^+$ count, plasma HIV viral load, or antiretroviral treatment status, colposcopy and appropriate directed biopsy are recommended for HIV-seropositive women with cytological reports of "atypical squamous cells, cannot exclude high grade SIL" (ASC-H), **(BII),** LSIL **(AII),** HSIL **(AII),** or squamous cell carcinoma **(AII)** (*529*). HPV testing may be used in the management of HIV-seronegative women with a cytologic diagnosis of ASC-US. This has been recommended for similar use in HIV-seropositive women in recent ASCCP guidelines (*904*). However, published data are limited, conflicting, and insufficient to support the use of HPV DNA testing in triage of ASC-US among HIV-seropositive women **(DIII)**. A prudent plan is to perform routine colposcopy for HIV-seropositive women with ASC-US **(CIII).**

Among women with ASC-US on a Pap test, if a biopsy-confirmed CIN is absent and the colposcopic exam was adequate, follow-up with cervical cytology in 12 months is recommended **(BIII),** with referral back to colposcopy if results of ASC-US or greater are obtained. After two repeated results negative for intraepithelial lesion or malignancy, an affected woman can return to routine annual cytological screening **(AII).** ASCCP guidelines should be followed if the colposcopic exam is not adequate or when CIN is found.

If no CIN 2 or 3 lesion is identified at colposcopy among women with ASC-H, and a review of the results confirms the reading of ASC-H, cytological follow-up is recommended at 6 and 12 months **(CIII).** Women with ASC-US or greater on repeat cytology should again be referred for repeat colposcopy **(BII).**

For women referred to colposcopy for LSIL, if the colposcopy is satisfactory (entire squamocolumnar junction can be visualized with the colposcope) and no lesion or CIN is identified, follow-up with repeat cytological testing at 6 and 12 months is recommended **(BII).** ASCCP guidelines should be followed if the colposcopy is unsatisfactory or CIN is found.

A cytological result of HSIL identifies a woman at high risk for high-grade CIN or invasive cervical cancer. An immediate loop electrosurgical excision or colposcopy with endocervical assessment is an acceptable method for managing women with HSIL **(BII).** ASCCP guidelines should be followed if the colposcopy is satisfactory and no lesion or only CIN 1 is identified, or the colposcopy is unsatisfactory, or CIN 2 or 3 is found.

AGC on cytology is associated with greater risk for CIN and glandular neoplasia than ASC-US or LSIL. The Bethesda system has classified AGC into three categories: AGC, either endocervical, endometrial, or glandular cells not otherwise specified ("AGC NOS"); AGC, either endocervical or glandular cells favor neoplasia ("AGC favor neoplasia"); and endocervical adenocarcinoma in situ (AIS). Colposcopy with endocervical sampling is recommended for all the subcategories of AGC and AIS **(AII).** Endometrial sampling is recommended in

conjunction with colposcopy and endocervical sampling in women 35 years of age and older **(BII).** ASCCP guidelines should be followed for women under the age of 35 and for subsequent evaluation of AGC.

For women with "AGC favor neoplasia" or AIS, those with normal colposcopy should undergo a diagnostic excisional procedure (e.g., cold knife excision, loop electrosurgical excision) **(BII).** If the initial colposcopy is normal in a woman with "AGC NOS," repeat cytology is recommended at 4–6-month intervals until four consecutive tests negative for intraepithelial neoplasia are obtained before returning to routine cytological screening **(BIII).** If abnormal cytology, including ASC, is obtained on follow-up cytology, repeat colposcopic examination or referral to a specialist is recommended **(BIII).**

Preventing Vaginal and Vulvar Cancer

In keeping with recommendations for HIV-seronegative women, routine screening of HIV-seropositive women for vaginal cancer following a hysterectomy for benign disease is not recommended, but women with a history of high-grade CIN or invasive cervical cancer are at increased risk and should be followed with a regular vaginal cuff Pap test **(AIII)** (*917,918*). For patients with abnormal vaginal cuff Pap tests with no visible vaginal colposcopic abnormalities, vaginal colposcopy and use of Lugol's iodine to stain the vagina are recommended **(AIII).** Vaginal colposcopy is also indicated in the presence of concomitant cervical and vulvar lesions (*919,920*). Classification of VAIN parallels that of the cervix (i.e., VAIN 1, VAIN 2, and VAIN 3).

No screening procedure is available for vulvar cancer. However, for HIV-seropositive women with a past history of cervical or VAIN/cancer, an inspection of the vulva with or without colposcopy should be encouraged as part of their regular follow-up **(CIII).** Diagnosis of VIN/cancer should be confirmed with a biopsy **(AII).** A wedge biopsy under local anesthesia is usually done.

Preventing Anal Cancer

High-grade AIN (AIN 2 or 3) has the potential to progress to invasive anal cancer (*921,922*). Evidence from multiple studies demonstrates that HIV-seropositive MSM and HIV-seropositive women are at increased risk for AIN 2 or 3 and are at increased risk for anal cancer compared with the general population. The incidence of anal cancer has not declined since the widespread introduction of ART (*899*). This evidence and a cost-effectiveness analysis projecting that screening and treatment for anal precancerous lesions detected by Pap tests provide clinical benefits comparable to other OI prevention measures for HIV-seropositive persons (*923*), anal cytology screening of HIV-seropositive MSM and of women might be useful preventive strategies. However, studies of screening and treatment programs for AIN 2 or 3 should be implemented before definitive recommendations for anal cytology screening can be made. No national recommendations exist for routine screening for anal cancer (*529*). Until such time, certain specialists recommend an annual digital rectal examination as an important procedure to detect masses on palpation that might be anal cancer **(BIII)** (*924*). In addition, certain specialists recommend anal cytologic screening for HIV-seropositive men and women **(CIII).** If anal cytology is performed and indicates ASC-US or ASC-H, LSIL, or HSIL **(BIII)**, then it should be followed by high-resolution anoscopy (HRA). Visible lesions should be biopsied to determine the level of histologic changes and to rule out invasive cancer **(BIII).** See section on treatment for details of treatment of AIN.

Preventing Other HPV-Associated Cancers Among HIV-Seropositive Men and Woman

Other cancers that have been associated with HPV infection among HIV-seropositive men and women include oropharyngeal squamous cell and penile cancers (*841,897,925*). Prevention options for these cancers are unclear. Circumcision might reduce the risk for penile cancer as documented in one study (*926*); however, the benefits of circumcision to prevent HPV infection and penile cancer have not been studied in a randomized clinical trial or among HIV-seropositive men. No national recommendations exist for screening for oropharyngeal or penile cancer or precancerous lesions among those with HIV infection.

Treatment of HPV-Associated Genital and Anal Lesions

Treatment of Genital and Oral Warts

Treatments are available for genital warts, but none is uniformly effective (*529*). No single treatment has been demonstrated to be superior to any other, and no single treatment is ideal for all patients or all warts. Recurrences are common regardless of the modality (*927*). Data are limited on the response of HIV-seropositive patients to the available treatments for genital warts. In the absence of data specific to the HIV-seropositive population, guidelines for the treatment of STDs for HIV-seronegative patients should be followed (*529*). Data are insufficient to recommend a single treatment modality for all patients, and more than one treatment option might be required for refractory or recurrent lesions among patients with HIV infection.

Patient-applied treatments are generally recommended for uncomplicated external warts that can be easily identified by the patient and consist of the following options:

Podophyllotoxin (e.g., podofilox [0.5% solution or gel]) is an antimitotic agent that should be applied topically to warts twice daily for 3 days, followed by 4 days of no therapy. Treatment can be repeated weekly for up to four cycles **(BIII).** The efficacy is 40%–60% in immunocompetent subjects (*928,929*).

Imiquimod (5% cream) is a topical cytokine inducer that recruits an inflammatory response to the site of the wart. Patients should apply the cream once daily at bedtime three times a week for up to 16 weeks. The treatment area should be washed with soap and water 6–10 hours after the application **(BII).** The efficacy of imiquimod in immunocompetent persons is 30%–70%; the overall response in HIV-seropositive persons might be lower than in immunocompetent persons (*930–932*).

Provider-applied treatments are typically recommended for complex or multicentric lesions or those lesions inaccessible to patient-applied treatments. These include intra-anal and vaginal warts. Options are summarized as follows:

Cryotherapy (liquid nitrogen or cryoprobe) destroys lesions by thermal-induced cytolysis. Liquid nitrogen should be applied until each lesion is thoroughly frozen and repeated every 1–2 weeks. Certain specialists recommend allowing the lesion to thaw and freezing a second time in each session **(BIII).** The efficacy of cryotherapy is 60%–80%.

Trichloroacetic acid (TCA) or bichloroacetic acid (BCA) (80%–90%) act as caustic agents to kill wart tissue. Providers should apply a small amount to warts only and allow them to dry, at which time a white "frosting" develops. If an excess amount of acid is applied, the treated area should be powdered with talc, sodium bicarbonate, or liquid soap to remove unreacted acid. The treatment can be repeated weekly for 3–6 weeks **(BIII).** The expected efficacy is 60%–80%.

Surgical treatments (tangential scissor excision, tangential shave excision, curettage, electrosurgery, electrocautery, infrared coagulation) can be used for external genital and anal warts **(BIII).** Laser surgery also can be used, but is usually more expensive **(CIII).** The efficacy of surgical removal can approach 100%, depending on the location of the lesions.

Podophyllin resin is a crude extract that contains podophyllotoxin and other cytotoxins and induces wart necrosis after topical application. It is prepared as a 10%–25% suspension in tincture of benzoin. It is applied to all lesions by the provider (up to 10 cm^2 of skin area) and then removed by washing a few hours later. Applications can be repeated weekly for 3–6 weeks **(CIII).** Efficacy is 20%–80%. It is usually only applied to external lesions and use of podophyllotoxin is preferred over podophyllin resin.

Other treatments might be options, but because of limited available data, difficult administration, or possible side effects these treatments should be considered only if the treatments described above are ineffective. In limited, uncontrolled studies, topical application of cidofovir has reported activity against genital warts **(CIII)** (*933,934*). No topical formulation is commercially available. Intralesional interferon has been used for the treatment of genital warts but because of cost, difficult administration, and potential for systemic side effects (i.e., fever, fatigue, myalgias, and leukopenia) it is not recommended for first-line treatment **(DIII).** Among non-HIV–infected persons, the overall efficacy of interferon in treating genital warts is not superior to other therapies and it has not been specifically studied for efficacy among HIV-infected persons.

Oral warts can be located on various surfaces in the mouth. In contrast to other oral manifestations of HIV, an increased prevalence of oral warts in patients on ART has been reported from the United States and the United Kingdom (*935,936*). No randomized trials of treatment of oral warts exist. Treatments include surgical excision and cryotherapy; some topical modalities have had success (*937*).

Treatment of CIN and Cervical Cancer

HIV-infected women with CIN should be managed by a specialist. Women having undergone satisfactory colposcopy with biopsy-confirmed CIN 1 preceded by ASC-US, ASC-H, or LSIL cytology can be followed with repeat cytological assessment at 6 and 12 months **(BII)**. Referral to colposcopy is indicated if follow-up shows ASC or greater **(AII).** After two consecutive negative cytology tests, annual cytologic screening can be resumed **(AII)**. If CIN 1 persists for at least 2 years, either continued follow-up or treatment with excision or ablation is acceptable **(AI)**. ASCCP guidelines should be followed if the colposcopy is unsatisfactory, the endocervical sampling contains CIN, or the patient has been previously treated **(AIII)** (*938*). A diagnostic excisional procedure or observation with colposcopy and cytology at 6- month intervals for 1 year is acceptable for CIN 1, preceded by HSIL or AGC-NOS **(BIII).** Women with satisfactory colposcopy and biopsy-confirmed high-grade CIN can be treated with either ablation (cryotherapy, laser vaporization, electrocautery, diathermy, and cold coagulation) or excisional methods (loop electrosurgical excision procedure [LEEP], laser conization, cold knife conization) **(AI)**. In patients with recurrent high-grade CIN, diagnostic excisional methods are recommended **(AII)**. Hysterectomy is acceptable for treatment of recurrent/persistent biopsy-confirmed high-grade CIN **(BII)**. ASCCP guidelines should be followed if colposcopy is unsatisfactory (*938*).

After treatment of high-grade CIN, follow-up with cervical cytology or combination of cervical cytology and colposcopy at 6-month intervals with at least two cytologic results of "negative for squamous intraepithelial lesion or malignancy" is

acceptable **(AI).** Annual cytology can be done thereafter. Any ASC or greater requires colposcopy **(AII).**

Invasive cervical cancer is usually treated by radical hysterectomy with lymph node dissection or by radiation therapy for advanced disease. If cone biopsy or loop excision reveals microinvasive cervical cancer with clear margins, a simple hysterectomy can be done. An alternative for women with microinvasive lesions who want to preserve their fertility is local surgical procedure such as LEEP or cone biopsy with careful follow-up.

Treatment of VIN and Vulvar Cancer and of VAIN and Vaginal Cancer

Various treatment modalities for VIN are available, including local excision, laser vaporization, or ablation. Management of vulvar cancer must be individualized in consultation with a specialist. The cornerstone of the treatment of vulvar cancer is surgery. There is no standard operation and the emphasis is on the most conservative operation consistent with curing the disease. Radical vulvectomy with "en bloc" inguinofemoral lymphadenectomy has led to a favorable prognosis but with substantial morbidity (*939,940*). Further studies are needed to determine the optimal combined modality treatments. Radiation is also an option for some patients. The optimal treatment recommendations for HIV-seropositive women with advanced vulvar cancer remain unclear.

Similarly, treatment of VAIN is individualized in consultation with a specialist and depends on the patient's medical condition and the location and extent of the disease. Various methods of local tissue ablation to more extensive surgery have been used to treat VAIN. Treatment options include topical 5-fluorouracil, 5% imiquimod cream, laser vaporization with CO_2 laser, and excisional procedures with electrosurgical loops or a scalpel excision. On occasion, total vaginectomy may be necessary. Radiation therapy is the treatment of choice for vaginal cancer.

Treatment of AIN and Anal Cancer

For AIN, no randomized, controlled therapeutic trials have been reported and data are insufficient to recommend a specific treatment approach. Treatment decisions are based on assessment of the size and location of the lesion and the grade of histology. The least aggressive approaches should be tried first whenever possible (**CIII**): for example, several different treatments, including topical 5-fluorouracil, photodynamic therapy, infrared coagulation, cryotherapy, laser therapy, and surgical excision, have been described in small open-label studies (*881,922,941–944*). In retrospective analysis, infrared coagulation has been proven to have moderate efficacy to treat AIN 2 or 3 in HIV-seropositive patients **(CIII)** (*943*) and was safe and well tolerated in this population in a recent AIDS Malignancy Consortium study. No indications exist for radiation therapy for patients with AIN in the absence of evidence of invasive cancer **(EIII).**

The results of studies do not indicate that treatment for AIN should be modified for patients receiving ART. Conversely, no evidence indicates that ART should be instituted or modified for the purpose of treating AIN **(CIII)**.

Treatment of anal cancer must be individualized in consultation with a specialist.

Treatment of HPV-Associated Disease at Other Sites, Including the Penis and Mouth

Penile and some oral cancers are associated with HPV infection. Treatment options do not differ between HIV-seropositive and HIV-seronegative men and women. Data suggest a more favorable prognosis among HPV-associated oropharyngeal cancers compared with non-HPV associated oropharyngeal cancers (*945*).

Monitoring and Adverse Events, Including Immune Reconstitution Inflammatory Syndrome (IRIS)

Monitoring is required during and after treatment of genital warts because each of the treatments has associated toxicity and recurrences are common after treatment. Patients can be monitored by physical examination for evidence of recurrence. The major toxicity of podophylloxotin and topical podophyllin resin is local skin irritation. Also, if podophyllin is applied to a large treatment area, systemic absorption can cause nausea, vomiting, and CNS effects. The major toxicity of imiquimod is inflammation at the application site. The major toxicity of cryotherapy is local pain. The major side effects of surgical treatment for genital warts are local pain, bleeding, and secondary infection. The major adverse events associated with acid cauterization are local pain and irritation or ulceration of adjacent normal skin. Intralesional interferon can be associated with systemic toxicities of interferon, including fever, fatigue, myalgia, malaise, depression, and other influenza-like symptoms. Infrared coagulation might lead to bleeding and abscess formation.

Because risk for recurrence of CIN and cervical cancer after conventional therapy is increased among HIV-seropositive persons, patients should be followed after treatment with frequent cytologic screening and colposcopic examination according to published guidelines **(AII)** (*853,946*). Treatment of CIN with ablative and excisional modalities can be associated with several adverse events such as pain and discomfort, intraoperative hemorrhage, postoperative hemorrhage, infection, and cervical stenosis.

Each of the treatment modalities for AIN described above is associated with adverse events, primarily pain, bleeding, ulceration, and, rarely, development of abscesses, fissures, or fistulas. Patients may be monitored for adverse events using the methods described above. Treatment of anal cancer is associated with a high rate of morbidity, even when the treatment is successful. Adverse events associated with anal cancer treatment include short-term side effects commonly associated with chemotherapy, such as neutropenia, and longer-term toxicities associated with radiation therapy, such as radiation proctitis.

IRIS has not been described in association with HPV infections.

Management of Treatment Failure

Treatment failure is defined as the persistence or recurrence of lesions after appropriate therapy. For persistent or recurrent genital warts, retreatment with any of the modalities previously described should be considered, preferably with an alternative modality to the one that previously failed **(AIII)**. Genital warts often require more than one course of treatment. A repeat diagnostic excision or hysterectomy is acceptable for women with histological diagnosis or recurrent or persistent CIN 2 or 3 **(BII)** (*853*). Lesion persistence and recurrences after treatment of AIN are common. No data exist to guide the choice of treatment for recurrence of AIN, but either the original therapeutic modality or a different one may be used. Treatment of anal cancer that recurs after standard chemoradiation therapy often consists of abdominoperineal resection of the tumor.

Preventing Recurrence

HIV-seropositive women are at high risk for recurrent CIN after therapy, and HIV-seropositive men and women are at high risk for recurrent AIN. Preventing recurrence requires careful follow-up of patients after treatment. Patients should be monitored with cytologic screening according to published guidelines and, when indicated, colposcopic examination for recurrent lesions **(AI)** (*923,947*)**.** In one study of HIV-seropositive women treated for high-grade CIN, low-dose intravaginal 5-fluorouracil (i.e., 2 grams twice weekly for 6 months) reduced the short-term risk for recurrence (*948*). However, clinical experience with this therapy is too limited to provide a recommendation for use and no follow-up study to confirm these observations has been reported. One study documented that women receiving ART are less likely to have recurrence of CIN compared with women who are not receiving treatment (*949*), but treatment for CIN should not be considered an indication for ART.

No guidelines exist regarding frequency of monitoring after therapy and the monitoring intervals will vary depending on the treatment approach, extent of disease, and other factors. Patients with AIN can be monitored by anal cytology, standard anoscopy, HRA, and biopsy as indicated. Patients with perianal intraepithelial neoplasia can be monitored by visual inspection and biopsy as indicated. Recommendations for monitoring patients for recurrence of anal cancer after completion of therapy are the same for HIV-seropositive and HIV-seronegative persons.

No indication exists for secondary prophylaxis (chronic maintenance therapy) with any of the conventional modalities to prevent recurrence of genital warts, CIN, or AIN.

Special Considerations During Pregnancy

HIV-infected pregnant women with genital warts or anogenital HPV-related neoplasia are best managed by an interdisciplinary team of specialists (e.g.,OB/GYN, infectious disease physician). Pregnancy might be associated with an increased frequency and rate of growth of genital warts (*950–952*). Podophyllin and podofilox should not be used during pregnancy **(EIII)**. Use of podophyllin has been associated with an increased risk for fetal death in several animal models and case reports in humans, but not with congenital anomalies. No experience with imiquimod in human pregnancy has been reported; therefore, its use in pregnancy is not recommended **(DIII)**. No anomalies have been observed among animals with use during pregnancy.

Other topical treatments (e.g., bichloroacetic and trichloroacetic acid) and ablative therapies (i.e., laser, cryotherapy, and excision) can be used during pregnancy.

Transmission of genital HPV6 and 11 from vaginal secretions at delivery is the presumed mechanism of early onset recurrent laryngeal papillomatosis in infants. This condition is rare but is more common among women who have genital warts at delivery (*953*). Cesarean delivery is not known to prevent this condition in infants and children (*950–952*) *(954*). No change in obstetrical management is indicated for women with HPV infection unless extensive condylomata are present that might impede vaginal delivery or cause extensive bleeding (*955–958*).

For evaluation of CIN, all pregnant women should have a Pap test at their initial prenatal visit unless a normal cervical cytology result has been obtained within the past year (*80*). Cytobrush sampling can be done during pregnancy (*959*). Pregnant women with abnormal cervical cytology results should undergo colposcopy and cervical biopsy of lesions suspicious for high-grade disease or cancer **(BIII)**. Endocervical curettage is unacceptable in pregnant women **(EIII)**. Increased bleeding might occur with cervical biopsy during pregnancy.

Pregnant women with ASC-US can be managed the same as nonpregnant women, with the exception that it is acceptable

to defer colposcopy until at least 6 weeks postpartum **(CIII)**. In the absence of invasive disease, treatment of CIN is not recommended during pregnancy. Re-evaluation with cytology and colposcopy is recommended after 6 weeks postpartum. Women with CIN can deliver vaginally.

Pregnant women with suspected cervical cancer should be referred to a gynecologic oncologist for definitive diagnosis, treatment, and delivery planning. Vaginal delivery is not recommended for women with invasive cervical cancer.

The effects of treatment of AIN on pregnancy are not known. Most experts recommend deferral of diagnosis and treatment of AIN until after delivery unless a strong clinical suspicion of anal cancer exists.

Hepatitis B Virus Infection

Epidemiology

Hepatitis B virus (HBV) is the leading cause of chronic liver disease worldwide (*960,961*). In countries with a low prevalence of endemic chronic HBV infection, HBV is transmitted primarily through sexual contact and injection-drug use, whereas perinatal and early childhood exposures are responsible for the majority of HBV transmission in high-prevalence countries. Although risk factors are similar, HBV is transmitted more efficiently than HIV (*960–962*). Up to 90% of HIV-infected persons have at least one serum marker of previous exposure to HBV (*963,964*), and approximately 10% have evidence of chronic hepatitis B (*965–967*). Several genotypes of HBV (A–H) have been identified and are geographically distributed. Genotype A is the most common among patients in the United States and Western Europe.

Clinical Manifestations

Most patients with acute or chronic HBV infection are asymptomatic or have nonspecific symptoms, such as fatigue. When present, symptoms of acute infection might include right upper quadrant abdominal pain, nausea, vomiting, fever, and arthralgias with or without jaundice.

Chronic HBV might lead to mild, moderate, or severe hepatitis with eventual development of cirrhosis and portal hypertension. The physical examination might be notable for signs of cirrhosis such as spider angiomata, palmar erythema, and signs of portal hypertension such as splenomegaly. Uncommon extrahepatic manifestations include polyarteritis nodosa, glomerulonephritis, and vasculitis. Without proper laboratory screening, HBV infection might not be clinically apparent until the onset of end-stage liver disease (ESLD), which is manifested as portal hypertension with ascites, variceal bleeding, coagulopathy, jaundice, or hepatic encephalopathy.

Hepatocellular carcinoma (HCC), which might complicate HBV infection before the onset of cirrhosis, is usually asymptomatic in its early stages. Patients with advanced HCC might experience abdominal pain, symptoms of liver failure, or ESLD, as previously described, or paraneoplastic syndromes (e.g., diarrhea, hypoglycemia, fever).

Diagnosis

Diagnosis of Infection and Disease with Serologic Testing

HIV-infected persons should be tested for HBV infection (*789*). Initial testing for hepatitis B surface antigen (HBsAg), hepatitis B core antibody (anti-HBc total), and hepatitis B surface antibody (anti-HBs) should be performed because these will identify the majority of patients with chronic hepatitis B or who need vaccination to prevent infection. Certain specialists would test for HBsAg and anti-HBs only, excluding anti-HBc, as its presence or absence does not usually affect clinical practice. Chronic HBV infection is defined as a positive HBsAg and anti-HBc or a positive HBsAg, HBV DNA level, or hepatitis B e antigen (HBeAg) on two occasions at least 6 months apart.

Patients with chronic HBV infection should be tested for HBeAg, antibody to HBeAg (anti-HBe), and HBV DNA. Several tests for HBV DNA detection are available; however, the results are not interchangeable. Laboratories report either copies/mL or International Units (IU/mL). The latter is based upon a WHO standard and has greater interlaboratory reproducibility. HBV DNA levels are usually high in chronic infection. Patients with chronic HBeAg-positive infection tend to have higher levels of replicating virus than those with HBeAg-negative infection (10^8–10^{10} copies/mL of blood compared with 10^5–10^6copies/mL). Among HIV-uninfected adults with HBV monoinfection, high HBV DNA levels predict progression of liver disease, development of HCC, and lower responses to therapy. Data characterizing the predictive value in those with HIV/HBV coinfection are lacking.

Some patients test positive for anti-HBc alone, which might signify a false-positive result; exposure in the past with subsequent loss of anti-HBs; or "occult" HBV infection, which can be confirmed by detection of HBV DNA (*968,969*). The clinical significance of isolated anti-HBc is unknown (*968–971*). HIV-infected patients have a higher frequency of isolated anti-HBc, particularly those patients with underlying hepatitis C virus (HCV) infection (*972*). The prevalence of HBV DNA in HIV-infected patients with isolated anti-HBc ranges from 1% to 45% (*973,974*), with most having low levels. Certain specialists recommend that HIV-infected persons with anti-HBc alone should be tested for HBV DNA before vaccination for HBV or before initiating ART because of the risk for reactivation of HBV and the occurrence of IRIS.

Diagnosis of Disease Progression and the Role of Liver Biopsy

Impairment of cellular immunity caused by HIV infection is associated with higher levels of hepatitis B viremia and lower viral clearance rates following acute HBV infection. Limited data indicate that HIV patients with chronic HBV infection are more likely to have detectable HBeAg (*975,976*), lower rates of seroconversion, and an increased risk for liver-related mortality and morbidity (*977*). Despite these differences, the pattern of disease progression is similar to that in monoinfected persons.

Liver biopsy with histologic examination remains a valuable tool for characterizing the activity and severity of chronic hepatitis B and might provide important information in monitoring disease progression and guiding treatment. However, the decision to perform a liver biopsy should be individualized based on the phase of chronic HBV as described below. Liver biopsies might result in major complications, such as excessive bleeding (<0.5%), bile peritonitis (0.09%), and, rarely, internal organ injury, although the overall mortality rate is fewer than 1 in 10,000 (*978,979*).

Patients with a diagnosis of chronic HBV infection who are not treated with antiviral agents should have a complete blood count, platelet count, alanine aminotransferase (ALT), albumin, prothrombin time, and bilirubin monitored at baseline and every 6 months to assess severity and progression of liver disease. Persistent low-level serum aminotransferase abnormalities might be associated with significant liver disease, although normal aminotransferases might also be seen in the setting of cirrhosis. Transient or persistent elevations in serum aminotransferase levels might occur before loss of HBeAg, on discontinuation of anti-HBV therapy, and in association with emergence of HBV drug resistance.

Patients who are HBe-Ag seropositive usually have high HBV DNA levels (>20,000 IU/mL) and abnormal levels of ALT. In some instances, increased levels of ALT might precede a decline in HBV DNA that is accompanied by the loss of HBeAg and development of anti-HBe. Seroconversion marks a transition from active disease to an inactive carrier state (*980*). This transition can be spontaneous or associated with effective HBV treatment. Approximately 8%–12% of monoinfected patients spontaneously convert from a positive to a negative HBeAg and a positive anti-HBe per year (*981*). Spontaneous conversion rates in HIV-infected patients appear to be lower.

Although seroconversion usually implies transition to an inactive carrier state, the re-emergence of abnormal liver enzyme tests might reflect HBeAg-negative chronic hepatitis B disease. Although levels of HBV DNA are usually lower than in HBeAg-positive patients, HBeAg-negative patients experience an unrelenting but fluctuating course of disease progression, with viral loads usually ranging from 10^5 to 10^6 copies/mL (2×10^4–2×10^5 IU/mL), but they can be higher. Thus, in a patient without HBeAg, HBV DNA levels should still be measured. Liver biopsy is recommended in HBeAg-seronegative patients with detectable HBV DNA primarily for persons aged >40 years with "borderline" indications for treatment, such as those with minimally elevated ALT but high HBV DNA level (*982,983*).

Persons who acquire HBV infection perinatally have a high chance of becoming "immune tolerant," with normal aminotransferase levels despite the presence of high levels of HBV DNA. Such patients tend to have minimal disease and liver biopsy is usually not indicated; however, they tend to have HBeAg-positive chronic hepatitis B with elevated ALT levels later in life and remain at risk for the development of HCC, cirrhosis, and flares of hepatitis B (*980*).

The inactive HBsAg carrier state is characterized by a negative HBeAg, normal ALT levels, and an HBV DNA level of <2,000–20,000 IU/mL (or 10,000–100,000 copies/mL). Liver biopsy is not recommended in patients who have cleared the virus (undetectable HBV DNA by PCR assay). However, although their prognosis is usually good, patients in the inactive carrier state remain at risk for reactivation of HBV and development of HCC, but the risk is lower than for those with active HBV replication. This is particularly true for those carriers who are older or who have cirrhosis or coinfection with HCV (*984–987*).

Reactivation of HBV, spontaneous or related to chemotherapy or immunosuppression, can lead to substantial hepatic flares and necroinflammatory liver disease (*988–991*). Although reactivation of HBV can be associated with flares in serum aminotransferases, other etiologies for increased aminotransferase levels, such as hepatotoxicity from ARVs or other drugs or acquisition of another hepatitis virus infection such as hepatitis A, C, or hepatitis delta virus (HDV), must be ruled out (*992–995*).

Patients with chronic hepatitis B are at increased risk for HCC. Among HIV-coinfected persons, who might have an even higher risk for HBV-related HCC than HBV monoinfected patients, monitoring alpha fetoprotein (AFP) level and ultrasound of the liver every 6 months (*996*) might be recommended; however, the effectiveness of this screening strategy has not been studied in this population, and the optimal HCC screening method and interval are not known (*997–999*).

Preventing Exposure

HIV-infected persons should be counseled about the risk for household, sexual, and needle-sharing transmission of HBV; the avoidance of behaviors associated with such transmission;

and the need for any such susceptible contacts to receive hepatitis A and B vaccine as described below. As drug injection via contaminated syringes previously used by infected persons is the primary route of HBV transmission among IDUs, they should be encouraged to stop using injection drugs, preferably by entering a substance abuse treatment program **(AII).** If IDUs are unwilling or unable to discontinue the use of injection drugs, they should be advised not to share needles or drug preparation equipment to reduce the risk for transmission of HBV infection **(BII).** Access to sterile injection equipment may be facilitated through enrollment of IDUs in needle exchange programs (NEPs) (*1000–1002*).

Persons considering tattooing or body-piercing should be informed of potential risks of acquiring HBV, which could be transmitted if equipment is not sterile or if proper infection control procedures are not followed **(AIII)**.

Safe-sex practices should be encouraged for all HIV-infected persons; barrier precautions (e.g., latex condoms) are recommended to reduce the risk for exposure to sexually transmitted pathogens, including HBV **(AII)**.

Preventing Disease

HIV-infected patients who do not have evidence of previous exposure to HBV should be vaccinated with hepatitis B vaccine **(AII)**. Given the decreased response rate to the vaccine in the setting of HIV infection, all HIV-infected patients should have anti-HBs titers obtained 1 month after completion of the vaccine series to document response **(BIII)**. If no response is observed, revaccination should be considered **(BIII)**. HBV vaccination is safe in HIV-infected patients. Transient increases in HIV RNA have been reported after HBV vaccination but do not appear to have clinical relevance (*1003–1005*).

A patient who is seropositive for anti-HBc and anti-HBs has resolved infection and does not need vaccination. However, reactivation of HBV has been observed in immunosuppressed patients. The presence of anti-HBs alone at levels of >10 IU/mL is consistent with seroprotection, usually from vaccination (*1006*), and no further vaccinations are required.

Determining whether hepatitis B vaccine should be administered to patients with "isolated" anti-HBc is not clear because, in addition to a false-positive result, this pattern might signify exposure in the distant past with subsequent loss of anti-HBs or more rarely, occult HBV (*1007*). One approach in this setting is to administer one dose of hepatitis B vaccine followed in 2 weeks by anti-HBs testing to determine if an anamnestic response occurs, although the overall response rate described in previous studies is low (16%) (*973,1008,1009*). Larger studies in HIV-uninfected persons with isolated anti-HBc demonstrate that most persons mount a slow, or primary, rather than a rapid, or anamnestic, response after vaccination (*1007*). The majority of HIV-infected patients with isolated anti-HBc are not immune to HBV infection and should be vaccinated with a complete primary series of hepatitis B vaccine **(BII)** (*973,1009*)**.** Certain specialists would test for HBV DNA to rule out occult chronic HBV infection before administering a complete primary series of hepatitis B vaccine.

The immunogenicity of hepatitis B vaccination in HIV-infected adults is 18%–72% (*974*) and is lower than in HIV-seronegative healthy adults, in whom seroconversion rates are >90% (*1010*). Compared with HIV-seronegative healthy adults, HIV-seropositive patients also have lower mean antibody titers and have faster declines of protective antibody over time (*1004,1011,1012*). The negative impact of low $CD4^+$ counts on hepatitis B vaccine responses has been a consistent finding across several studies (*1003–1005,1013–1016*). Other factors associated with lower seroconversion rates include the presence of detectable HIV RNA (*1005,1016,1017*), coinfection with HCV, occult hepatitis B infection, and the general health status of the host (*973,1018–1023*).

Several novel approaches have been investigated to improve primary vaccine responses and those among vaccine nonresponders. These have included increasing the dosage of vaccine (*1003,1005*), the number of doses (*1004*), or use of adjuvant immunostimulatory molecules (*1024*). One double-blind, randomized controlled trial that compared the use of a standard dose (20 mcg) with a double dose (40 mcg) of recombinant hepatitis B vaccine in 210 previously unvaccinated HIV-infected patients demonstrated a substantially higher seroconversion rate with use of the double dose of vaccine, but only in the subgroup of patients with $CD4^+$ counts >350 cells/μL (*1003*). In one study of 32 HIV-infected patients, administration of 1 additional vaccine dose increased the proportion of responders only marginally; however, a sixfold increase in geometric mean titers was demonstrated among those who did respond (*1014*). Doubling the number of vaccine doses in nine HIV-infected patients who did not initially respond to a hepatitis B vaccination series led to protective surface antibody levels in seven persons (*1004*).

On the basis of these data, early vaccination is recommended in HIV-infected patients before the $CD4^+$ count declines to <350 cells/μL **(AII)** (*1014,1025*). However, vaccination should not be deferred for those with negative or indeterminate serologies while awaiting a rise in $CD4^+$ count to >350 cells/μL. Because some HIV-infected patients with $CD4^+$ counts <200 cells/μL do respond to vaccination, vaccination should be performed as previously recommended **(AII)**, with testing for anti-HBs 1 month after completion of the series **(BIII)**. If no response occurs, revaccination should be considered **(BIII).** Certain specialists might delay revaccination until after a sustained increase in $CD4^+$ count is achieved on ART.

One study has suggested that HIV-infected persons with a CD4+ count >350 cells/μL had improved responses when vaccinated with 40 mcg of HBV vaccine on a 0-, 1-, and 6-month schedule (*1003*). Thus, certain specialists recommend initial hepatitis B vaccination in any HIV-infected person with 40 mcg doses of either vaccine at the recommended intervals **(CIII)**. Additional studies are needed to determine optimal vaccination strategies in patients with advanced immunosuppression. ART should be optimized to attain complete suppression of HIV replication and increased CD4+ count, as these factors have been associated with better antibody responses to HBV vaccination **(CIII).** Trials of immunomodulatory agents to improve HBV vaccine responses have led to mixed results, and data are currently insufficient to warrant a recommendation favoring their use **(CIII).**

No vaccination strategy has been consistently effective or adequately studied in vaccine nonresponders. For patients who have not attained an anti-HBs level >10 IU/mL after completion of a primary vaccine series, a second vaccine series is recommended **(BIII).** Certain specialists recommend that in such cases, revaccination with 40 mcg doses of either of the available vaccines be considered, regardless of which dose was used initially **(CIII)**. Anti-HBs should be obtained approximately 1 month after completion of the vaccine series to assess vaccine response **(BIII)** (*1025*). Certain specialists suggest once yearly evaluations for patients who have an ongoing risk for HBV acquisition **(CIII)**, as recommended for dialysis patients (*1026*). This is particularly important in patients who have a low level of protective antibody, because loss of antibody over time is related to the maximal antibody response after vaccination, and loss of antibody among dialysis patients has translated into loss of protection against HBV infection (*1006,1027,1028*). Immune-competent hepatitis B vaccine responders, however, remain protected against the development of clinical disease and chronic HBV infection despite subsequent declines in anti-HBs to <10 IU/mL (*1027,1029*).

Hepatitis A vaccination is recommended in persons with chronic liver disease, MSM, and IDUs (*529,1030*). HAV-susceptible, HIV-infected persons with risk factors for HAV infection should receive hepatitis A vaccination (**AII**). As with hepatitis B vaccination, the response to hepatitis A vaccination is reduced in those with CD4+ counts <200 cells/μL. Certain specialists might delay hepatitis A vaccination until the CD4+ count is >200 cells/μL on ART (**CIII**). Antibody response should be assessed 1 month after vaccination; nonresponders should be revaccinated **(BIII)**.

Treatment of Disease

Patients with chronic hepatitis B disease should be advised to avoid or limit alcohol consumption because of its effects on the liver **(AIII)**. In addition, they should be counseled about the risk for household, sexual, and needle-sharing transmission and the need for any such susceptible contacts to receive hepatitis A and B vaccine as described above.

The goals of anti-HBV therapy are to prevent disease progression and reduce HBV-related morbidity and mortality. Treated patients rarely become HBsAg negative because HBV reservoirs generally are not sufficiently reduced by available anti-HBV therapy. HBV might persist in the liver, in the absence of circulating virus, as closed circular DNA (ccDNA), which can lead to reactivation after chemotherapy, steroid use, or immunosuppression, including HIV-associated immunosuppression. Nevertheless, studies in HBV-monoinfected patients suggest suppression of HBV DNA to a "nonreplicative" state, HBeAg seroconversion from positive to negative, seroconversion to anti-HBe, loss of HBsAg, and acquisition of anti-HBs are all associated with decreased incidence of HCC and improved survival; thus, these surrogates also are goals of anti-HBV treatment for HIV-infected persons. For HBeAg-negative patients with increased ALT and HBV DNA levels, long-term antiviral suppression might be indicated because treatment discontinuation has been associated with virologic relapse.

In HIV/HBV-coinfected patients, the imperative to treat depends not only on the level of HBV viremia and degree of biochemical and/or histologic disease, but also on whether the patient is initiating ART. HIV/HBV-coinfected patients initiating ART should be treated for HBV, regardless of the level of HBV DNA, either with antiviral agents active against both HIV and HBV or with antiviral agents with independent activity against each virus (**CIII**). This approach might reduce the risk for IRIS, particularly in those who have advanced immunodeficiency. If ART is not required, then initiation of treatment for HBV is the same as for HBV-monoinfected patients. Anti-HBV therapy is indicated for persons with abnormal ALT levels and HBV DNA levels >20,000 IU/mL (>10^5 copies per mL) for HBeAg-positive patients, and abnormal ALT levels with HBV DNA levels >2,000 IU/mL (>10^4 copies per mL) for HBeAg-negative patients **(CIII)**. However, because of the increased rate of liver disease progression in the setting of HIV infection, certain specialists recommend treatment at any level of detectable HBV DNA, especially in the setting of elevated ALT levels **(CIII)**. In addition, anti-HBV treatment should be considered for HIV-infected patients with low but detectable HBV DNA levels who have substantial histologic inflammatory activity or fibrosis on liver biopsy **(CIII).** Certain specialists recommend treatment of those with advanced fibrosis or cirrhosis on liver biopsy with any detectable HBV DNA level, provided other causes for chronic liver disease have been eliminated (*1031*).

Treatment options for HBV in the setting of HIV infection must consider the goals of therapy and the effect treatment might have on both HIV and HBV replication. FDA-approved antiviral drugs available for treatment of HBV infection include lamivudine, adefovir, entecavir, tenofovir, standard interferon-alfa, pegylated interferon (pegIFN)-alfa, and telbivudine. FDA-approved HIV antiretroviral medications, such as emtricitabine (and its single-pill combination with tenofovir), also have substantial activity against HBV, although they are not approved for this indication.

IFN-alfa-2a and -2b, administered in subcutaneous doses of 5 MU daily or 10 MU three times per week, are approved for the treatment of chronic hepatitis B disease among HIV-uninfected persons, but not among HIV-infected patients. Approximately one-third of HIV-seronegative patients will clear HBeAg with either of these IFN regimens (*996,1032*), and the response is sustained among 80%–90% of persons followed for 4–8 years (*1033*). PegIFN alfa-2a is also approved for treatment of HBV among HIV-seronegative patients and in clinical trials was proven to be superior to standard IFN for both HBeAg-positive and HBeAg-negative patients when used for 48 weeks (*1034,1035*). No published data exist regarding efficacy of either formulation of pegIFN in the setting of HIV/HBV coinfection. Although HIV replication can be suppressed by pegIFN alfa (*1036*), no evidence indicates that IFN selects for resistance mutations that will influence future therapeutic options for HIV infection. On the basis of this information, pegIFN alfa-2a might be considered for treatment of HBV infection in HIV-coinfected patients irrespective of the need for ART for treatment of their HIV infection **(CIII)**.

Among HIV-uninfected persons, the response rates to lamivudine-containing regimens are >50% in patients with ALT levels >5 times the ULN and 20%–35% among patients with ALT levels 2–5 times the ULN. Lamivudine is active against hepatitis B and HIV at the 150 mg twice-daily dose used for treatment of HIV infection. HBeAg seroconversion rates appear to be low in HIV-infected patients treated with this agent. Resistance to lamivudine occurs in the majority of patients on chronic therapy; the rates of resistance appear to be even higher in patients with HIV infection (*1037*). Because lamivudine is active against both HBV and HIV and monotherapy for HBV will select for HIV resistance mutations, lamivudine should not be used for treatment of HBV in HIV-infected patients who are not also being treated with combination ART for their HIV infection **(EIII)**.

Emtricitabine is active against HBV and HIV. Because of its structural similarities to lamivudine, emtricitabine also is associated with a relatively rapid onset of HBV and HIV drug resistance, and cross resistance of HIV and HBVto lamivudine also should be assumed in patients with suspected lamivudine resistance. As with lamivudine, emtricitabine should not be used for treatment of HBV in coinfected patients who are not being treated with combination ART for their HIV infection **(EIII)**.

Adefovir is effective in both HBeAg-positive and HBeAg-negative patients with chronic HBV infection, although viral suppression occurs at a slower rate than with other agents and rates of seroconversion are low. Despite the slower viral load decline, the onset of drug resistance to adefovir is delayed compared with lamivudine or emtricitabine. The addition of adefovir to lamivudine in HIV/HBV-coinfected patients with HBV lamivudine resistance has been associated with an approximately 4-$\log_{10}$ decline in HBV viremia (*1038*). During 4 years of treatment, 25% of patients in one study attained complete virologic suppression. In those with detectable HBV viremia, no adefovir-associated mutations were observed. In coinfected patients, initial reports suggested that adefovir dipivoxil might be associated with selection of HIV-associated mutations (K65R and K70E) (*1039*). However, additional studies have not demonstrated selection of these mutations after up to 4 years of therapy, although minority variants could have been missed (*1040*). On the basis of these data, adefovir might be considered for treatment of HBV in HIV-coinfected patients, irrespective of the need for their HIV infection. (**CIII**).

Tenofovir, 300 mg daily, is more potent in vitro than adefovir, 10 mg daily, against HBV and data from human clinical trials and clinical experience indicate it is also active against lamivudine-resistant and wild-type HBV. A prospective, randomized, double-blind, placebo-controlled, noninferiority trial comparing tenofovir to adefovir in HIV-infected patients demonstrated benefit of tenofovir in the setting of lamivudine-resistant HBV (*1041*). Two recent randomized, double-blind studies, one with HBeAg-negative and another with HBeAg-positive patients, demonstrated the superiority of tenofovir over adefovir related to HBV DNA suppression in HBV-monoinfected patients (*1042,1043*). As with lamivudine and emtricitabine, tenofovir should not be used for treatment of HBV in HIV-coinfected patients who are not receiving combination ART for treatment of their HIV infection because of the risk for acquiring HIV-associated resistance mutations **(EII)**.

Entecavir is approved for treatment of HBV and in clinical trials was proven to be more effective than lamivudine with regard to the rate of HBV DNA decline and viral suppression at 48 weeks of treatment. Of the available agents for treatment of HBV other than interferon, entecavir is associated with the slowest onset of resistance, which usually requires a background of mutations at M204V/I and L180M to emerge. Literature in HIV/HBV coinfection is limited, but in a trial of 68 coinfected, lamivudine-experienced patients who were randomly assigned

to receive either entecavir or continue on lamivudine monotherapy, a >3-$\log_{10}$ decline in HBV DNA was noted in the entecavir arm versus the lamivudine arm. No change in HIV RNA levels occurred although these patients were on effective HIV therapy. However, a recent report described three patients who experienced an approximately 1-$\log_{10}$ drop in HIV RNA with initiation of entecavir monotherapy (*1044*). In addition, one patient who had received lamivudine in the past developed an HIV-associated mutation (M184V) during monotherapy with entecavir. A case report of the M184V emerging in a treatment-naïve patient on entecavir monotherapy also has been reported (*1045*). An FDA warning is available at http://www.fda.gov/medwatch/safety/2007/Baraclude_DHCP_02-2007.pdf. On the basis of this information, entecavir should not be used as monotherapy for treatment of HBV in HIV-coinfected patients who are not also receiving combination ART for treatment of their HIV infection because of the risk for developing HIV-associated resistance mutations **(EII).**

Telbivudine has demonstrated efficacy in patients with HBeAg-positive and HBeAg-negative infection and is FDA approved for treatment of chronic HBV infection *(1046,1047)*. It is well tolerated, but like lamivudine, emergence of HBV resistance over time is common. Telbivudine is not active against lamivudine-resistant HBV. Therefore, telbivudine monotherapy is not recommended **(DII).** No clinical data are currently available in HIV/HBV-coinfected patients, but studies are in progress.

Famciclovir is less active than lamivudine against HBV and is not active in lamivudine-resistant HBV; therefore, its use is not recommended **(DII)** (*1048–1050*).

Treatment of HBV in HIV-Infected Patients Who Are Receiving ART

Current guidelines recommend ART for HIV-infected patients who require treatment for HBV infection, regardless of $CD4^+$ count. In such patients, simplifying the treatment regimen can be achieved by offering at least two agents with dual activity against HIV and HBV, considering that a third agent is also required for effective treatment of HIV. Chronic administration of lamivudine as the only active drug against HBV leads to a high rate of HBV drug resistance because of key mutations in the YMDD (M204V/I) motif. One retrospective study suggested that the combination of tenofovir and lamivudine was associated with improved viral suppression compared with either agent alone (*1051*). Other studies also suggested that combination therapy reduces development of drug-resistant mutations (*1034,1052*). For HIV-infected persons, certain specialists recommend combination therapy with two agents active against HBV to reduce the risk for HBV drug resistance, although no results from controlled trials exist to support this strategy **(CII)**. Certain specialists recommend combination therapy with emtricitabine and tenofovir as part of an ART regimen because of ease of administration, tolerability, and dual HBV and HIV activity (**CIII**). Initiation of combination therapy also avoids the administration of sequential monotherapy, which can lead to multi-drug HBV resistance over time (*1053,1054*). The combination of lamivudine and pegIFN is not superior to pegIFN alone and is usually not recommended (*1055,1056*). The strategy of combination therapy versus monotherapy for treatment of HBV is being evaluated in a comparative clinical trial (*1045*).

Entecavir also can be considered in patients with complete HIV suppression who do not demonstrate YMDD motif (M204V/I) mutations in HBV DNA **(CIII)**. If entecavir is used in the presence of the M204V/I mutation, then careful monitoring of HBV DNA levels is indicated because of the increased risk for entecavir resistance in the presence of these pre-existing mutations.

Dual HBV and HCV infections are seen in 3%–5% of HIV-infected persons (*1057*). The replication of one virus usually predominates over another; this phenomenon is referred to as "viral interference." A thorough laboratory evaluation to detect dual HBV and HCV coinfection should include HBV DNA and HCV RNA assays. Among patients infected with HBV, HCV, and HIV, consideration of ART should be the first priority. If ART is administered, then anti-HBV therapy must be included as part of the regimen (as above) and anti-HCV therapy can be introduced as needed. If ART is not desired, IFN-based therapy, which suppresses both HCV and HBV, should be considered **(CIII)**. If IFN-based therapy for HCV has failed, treatment of chronic hepatitis B with nucleoside or nucleotide analogs is recommended **(CIII)**.

Treatment of HBV in HIV-Infected Patients Who Are Not Receiving ART

For patients deferring therapy for HIV infection, agents with sole activity against HBV must be selected for treatment of chronic HBV infection **(BIII)**. The lack of data regarding many of these agents in HIV/HBV-coinfected persons impedes firm treatment recommendations in this population. No data exist regarding the efficacy of pegIFN or the safety or efficacy of telbivudine in HIV-infected persons; adefovir has been evaluated in this population only in those with lamivudine-resistant HBV; and the clinical implications of entecavir-associated HIV resistance mutations prevent its use in this situation. Individualized therapy is necessary; however, certain guiding principles should be followed. The criteria for initiation of treatment for chronic HBV are the same for HIV-infected persons as for those with HBV monoinfection **(CIII)**. Factors that might influence the choice of agent include the immune status

of the patient, the level of hepatitis B viremia, and the patient's HBeAg status. For patients with $CD4^+$ counts >350 cells/μL, adefovir or pegIFN alfa-2a monotherapy for 48 weeks might be considered, with close monitoring of HBV DNA levels and follow-up to evaluate for HBeAg seroconversion **(CIII)**.

Duration of Anti-HBV Therapy

In HIV-seronegative patients, HBeAg seroconversions are sustained among approximately 80% of patients if lamivudine is continued 6–12 months after seroconversion. On the basis of data in HIV-uninfected persons, HIV/HBV-coinfected persons who are HBeAg positive and who become HBeAg negative and anti-HBe positive on lamivudine therapy should be treated for a minimum of 6–12 months beyond HBeAg seroconversion **(BIII)**. All patients receiving ART should continue HBV therapy, even if they have seroconverted to anti-HBe **(CIII)**.

Similar guidance on the duration of therapy can be applied to the use of other HBV active agents, with the exception of peg-IFN-based therapy, which is administered for a standard 48-week course. If HBeAg seroconversion does not occur but viral suppression has been achieved, treatment with anti-HBV agents, if tolerated, should be continued indefinitely **(CIII)**.

Among HIV-seronegative, HBeAg-negative patients with chronic hepatitis B who are treated with lamivudine, ALT and HBV DNA levels might decline, but high rates of relapse have been reported when therapy is stopped (*1058*). Considering these findings, a majority of specialists would continue therapy indefinitely to achieve long-term HBV viral suppression **(CIII)**.

Monitoring and Adverse Events, Including Immune Reconstitution Inflammatory Syndrome (IRIS)

Treatment response should be monitored by testing for HBV DNA and HBeAg at 3-month intervals and at 6–12-month intervals after stopping treatment. A virologic response is defined as a ≥2-log10 decrease in HBV DNA after 6 months of therapy. Ideally, the HBV DNA level after 6–12 months is <20–100 IU/mL based on a real-time PCR assay (*1059*). A maintained virological response is a response that continues while on therapy, and a sustained virological response is one that is still present 6 months after stopping therapy. For patients who are HBeAg positive, loss of HBeAg is also a measure of virological response. Other markers that should be monitored and indicate treatment success include improvement in liver histology based on biopsy; normalization of serum aminotransferases; and, in those with loss of HBeAg, the development of anti-HBe. Sustained loss of HBsAg is considered by some to be a complete response; however, this desirable serologic response is uncommon (**1060**).

Major toxicities of IFN-alfa (pegylated or standard) include influenza-like symptoms (e.g., fever, myalgia, headache, and fatigue), neuropsychiatric abnormalities (e.g., depression, irritability, and cognitive dysfunction), cytopenias (e.g., thrombocytopenia, neutropenia, and reversible reduction in $CD4^+$ count), retinopathy, neuropathy, and exacerbation of autoimmune disease. Depression might be severe enough to trigger suicide. Certain specialists recommend psychiatric evaluation before initiation of IFN-alfa for patients with a prior history of depression and frequent (monthly) monitoring for signs and symptoms of depression during treatment. Hypo- or hyperthyroidism, which is often irreversible, might occur 3–6 months after initiation of therapy with IFN-alfa. As a result, serum thyroid stimulating hormone (TSH) level should be monitored at baseline and periodically (e.g., every 3 months) for the duration of treatment. Depending on the severity of these toxicities and individual patient tolerance, side effects might be dose limiting or interfere with the ability to complete a course of treatment. IFN-alfa is contraindicated in patients with decompensated liver disease.

Adefovir causes renal tubular disease at doses of 30 mg/day or higher, but this toxicity is uncommon at the recommended 10 mg/day dose. Renal toxicity with tenofovir used solely for treatment of HBV has been reported rarely, although isolated cases of increased serum creatinine or renal tubular dysfunction have been observed, and might be more frequent in HIV-infected persons with underlying renal insufficiency or those treated for prolonged periods. Patients on either drug should have baseline urinalysis and creatinine monitoring. Periodic monitoring of serum creatinine and phosphate also should be done in patients receiving adefovir or tenofovir, especially those with underlying diabetes or taking other nephrotoxic agents, because they might be at increased risk for renal toxicity (*1061*).

When anti-HBV therapy with lamivudine, adefovir, or tenofovir is initiated, discontinuation is associated with a flare of liver disease in approximately 15% of cases, with loss of the benefit accrued from previous anti-HBV treatment (*1062*) and possible decompensation of liver disease. Even for patients not receiving ART, certain specialists recommend that when anti-HBV therapies are initiated, they should be continued unless contraindicated or unless the patient has been treated for 6–12 months beyond loss of HBeAg positivity **(CIII)**. However, the risks and benefits of this practice are unknown. If anti-HBV therapy is discontinued and a flare occurs, anti-HBV therapy should be reinstituted because it can be potentially life saving **(BIII)**.

Return of immune competence after ART (or after steroid withdrawal or chemotherapy) can lead to reactivation of HBV-associated liver disease. Any immune reconstitution can lead to a rise in serum aminotransferases, so called "hepatitis

flare" (*1063*), which constitutes IRIS in HIV/HBV-coinfected persons. IRIS might be manifested by dramatic increases in serum aminotransferases as $CD4^+$ counts rise within the first 6–12 weeks after starting ART, with signs and symptoms characteristic of acute hepatitis. After introduction of ART, serum aminotransferases should be monitored closely; some experts recommend monthly for the first 3–6 months and then every 3 months thereafter **(CIII)**. Any association between abnormal aminotransferases and clinical jaundice or synthetic dysfunction (elevated INR and low serum albumin) should prompt consultation with a hepatologist.

All patients with HBV and HIV must receive concomitant anti-HBV therapy when ART is used because these flares can be life threatening. Flares are worse in patients with more severe liver disease, especially cirrhosis. Distinguishing hepatotoxicity or other causes of hepatitis (acute HAV or acute HCV) from IRIS in this setting is difficult. When changing antiretroviral regimens, continuing agents with anti-HBV activity is important because of the risk for IRIS.

All classes of ARVs have been associated with hepatotoxicity as evidenced by substantial elevations in serum aminotransferases (*1064*). ARV-associated hepatotoxicity might be dose dependent or idiosyncratic. The risk for hepatotoxicity has been consistently associated with elevated pre-ART aminotransferases and the presence of HBV or HCV coinfection (*1065–1073*). Despite the increased risk for hepatotoxicity in the setting of HCV or HBV coinfection, the majority of (80%–90%) coinfected patients do not have hepatotoxicity (*1067*), and clinically significant hepatotoxicity is rare; aminotransferases return to baseline in the majority of cases, even if the offending medication is continued (*1066,1074*). Therefore, discontinuing ART is probably not necessary in the presence of hepatotoxicity unless the patient has symptoms of hypersensitivity (fever, lymphadenopathy, rash), symptomatic hepatitis (nausea, vomiting, abdominal pain, or jaundice), or elevations of serum aminotransferase levels >10 times the ULN. However, the development of jaundice is associated with severe morbidity and mortality and should trigger discontinuation of the offending drug(s) (*1075*).

The major problem in managing adverse effects and drug-induced liver injury is determining which medication is the offending culprit and distinguishing drug toxicity from hepatic flares associated with IRIS. Close interaction of HIV clinicians and hepatologists is needed because liver histology might help to differentiate drug toxicity (e.g., eosinophils) from viral hepatitis (e.g., portal inflammation). Spontaneous HBV clearance can be associated with a flare, but occurs rarely in HIV-infected patients. Initiation of ART without anti-HBV therapy might lead to reactivation of HBV. A hepatic flare might also occur when patients must discontinue their ART. Although this should be discouraged, if ART must be discontinued for some reason, patients need to be counseled about the urgent need to continue HBV therapy but without any agents active against HIV to prevent inadvertent mono or dual anti-HIV drug selection pressure favoring development of HIV drug resistance. Elevated aminotransferases might also occur after the onset of drug resistance, which is common and increases over time with medications such as lamivudine (*1037*). Serum HBV DNA testing will help determine if a flare of HBV has occurred. In this situation, HBV resistance testing should be undertaken in consultation with a specialist. Other causes of abnormal liver tests should be sought, including drugs, alcohol, viral hepatitis, and nonalcoholic fatty liver disease.

Management of Treatment Failure

Treatment failure is defined as the presence of HBV DNA greater than 1 $\log_{10}$ above nadir in a patient who is consistently adherent to therapy. Laboratory findings associated with treatment failure include persistent ALT elevations and persistently positive HBeAg for those who had detectable HBeAg at treatment onset.

In HIV-infected persons with lamivudine-resistant HBV, data from a case series of 35 HIV-HBV coinfected patients indicated that treatment with the combination of adefovir and continuation of lamivudine has substantial antiviral effect against lamivudine –resistant HBV (*1076*). Addition of either adefovir or tenofovir appears to lead to greater declines in HBV DNA in lamivudine-resistant coinfected patients (*1041*). Flares of liver disease have been reported with development of resistance to lamivudine. The rate of development of lamivudine resistance is approximately 20% per year among HIV/HBV-coinfected persons treated with lamivudine (*1037*). If lamivudine resistance is suspected or documented, tenofovir or adefovir should be added to lamivudine therapy **(CIII)**. HBV DNA testing might be useful in this setting because increasing levels are associated with emergence of lamivudine resistance or relapse, and stable levels should suggest an alternative cause of acute deterioration. Patients receiving lamivudine who have no detectable HIV RNA, but do have detectable plasma HBV DNA, can be assumed to be lamivudine resistant. Treatment options for patients on ART who have lamivudine-resistant HBV, but fully suppressed HIV, include the addition of adefovir or pegIFN to lamivudine, or tenofovir can be exchanged for one of the nucleoside agents in the ART regimen **(CIII)**. Persons with lamivudine-resistant HBV will have cross resistance to emtricitabine and telbivudine. In the setting of lamivudine-resistant HBV disease, either lamivudine or emtricitabine should be continued because this might decrease development of mutations to other anti-HBV drugs **(CIII)**.

Treatment for ESLD among HIV/HBV-coinfected patients should be managed as it is in HIV-seronegative patients **(BI)**. IFN-alfa is contraindicated in ESLD, but limited data indicate that lamivudine, adefovir, or tenofovir can be used safely (*1037*,*1077*,*1078*). All patients with ascites should undergo paracentesis for analysis to verify that portal hypertension is the etiology and to exclude spontaneous bacterial peritonitis (SBP) (1079). Assessment of the serum-ascites albumin gradient (SAAG) is advisable; SAAG ≥1.1 mg/dL strongly suggests ascites secondary to portal hypertension. Management includes sodium restriction (>2 g/day) to alleviate fluid retention and diuretics. The recommended diuretic regimen is spironolactone alone or combined with furosemide (ratio of 40 mg furosemide: 100 mg spironolactone). Consideration should be given to primary prophylaxis against SBP with the administration of oral antibiotics such as norfloxacin (400 mg/day) or TMP-SMX (1 double-strength tablet/day) in those with an ascites total protein <1 g/dL (*1080*). Secondary antibiotic prophylaxis is recommended for all persons with a history of SBP **(AI)**.

Esophagogastroduodenoscopy (EGD or upper endoscopy) should be performed in all persons who progress to cirrhosis, particularly those with thrombocytopenia, at the time of diagnosis and then every 1–2 years to identify substantial gastroesophageal varices. For persons with varices, nonselective beta blockers (e.g., nadolol or propranolol) are the mainstay of both primary and secondary prevention of variceal hemorrhage; esophageal variceal ligation or banding is another preventive option, particularly for persons who cannot tolerate beta blockers. Hepatic encephalopathy, due to the accumulation of unmetabolized ammonia and other false neurotransmitters absorbed from the gut in the setting of liver dysfunction, might be subtle in early stages (*916*). Preventive measures include restriction of animal dietary protein consumption and the use of nonabsorbable disaccharides (e.g., lactulose) and/or antibiotics (e.g., neomycin, rifaximin).

Patients with HBV-related cirrhosis are at increased risk for HCC (*1081*). Whether additional risk occurs in the setting of HIV infection is unclear (998). Although the optimal screening strategy to detect HCC is unknown, screening for HCC is recommended in patients with documented cirrhosis using hepatic ultrasound imaging performed at 6–12-month intervals **(BIII)** (*1082*). The utility of serum AFP for HCC screening in persons with HIV is unknown, and, because of poor specificity and sensitivity, results of AFP testing should be confirmed with liver imaging studies. In the absence of contraindications, HIV/HBV-coinfected persons with decompensated liver disease and/or early HCC are candidates for orthotopic liver transplantation because HIV infection is not a contraindication to organ transplantation with the use of effective ART (*1083*). Persons with cirrhosis should undergo periodic assessment of their liver disease status through the application of validated prognostic models (Child-Pugh-Turcotte [CPT] Score and Model for End-stage Liver Disease [MELD]) that predict mortality risk and are used to determine the medical need for liver transplantation (*1084*). Where feasible, coinfected persons with well-controlled HIV infection found to have liver decompensation (defined as CPT score ≥7 and/or MELD score >10) or evidence of early HCC should be referred for orthotopic liver transplantation **(BIII)**. Because transplantation does not cure HBV infection, post-transplant HBV treatment is required **(BIII)**.

Special Considerations During Pregnancy

Pregnant women, including HIV-infected women, should be screened for HBsAg. Those who are HBsAg negative and without antibody to hepatitis B should be offered vaccination against hepatitis B. This vaccination can be administered during pregnancy, preferably after the woman is on a stable ART regimen, to prevent the theoretical risk for HIV RNA rebound with vaccination. Treatment of symptomatic acute HBV infection during pregnancy should be supportive, with special attention given to maintaining blood glucose levels and normal clotting status. Risk for preterm labor and delivery might be increased with acute HBV infection.

Treatment of chronic HBV infection is usually not indicated in pregnancy **(DIII),** but HBV positivity must be taken into account when considering therapy options for the HIV-infected pregnant woman.

For women having indications for ART for their own health and expected to continue antiretrovirals postpartum, a regimen including two agents with activity against hepatitis B should be used **(AIII)** (*1085*). Of the antiretroviral agents with activity against hepatitis B, the one most used in pregnancy is lamivudine. Approximately 1,800 cases of pregnancy outcomes after first-trimester exposure to lamivudine have been reported to the Antiretroviral Pregnancy Registry (APR) with no indication of an increased risk for birth defects after exposure (*1086*). Lamivudine has been well tolerated by pregnant women. Tenofovir was not teratogenic in animals, but reversible bone changes at high doses were seen in multiple animal species. A total of 266 cases of first-trimester exposure have been reported to the APR with no increase in birth defects noted (*1086*). Although tenofovir is not usually recommended as a first-line agent in pregnancy, in the setting of maternal chronic HBV infection, it can be included as the second agent with anti-HBV activity, in addition to lamivudine **(BIII)**. Several other antiretroviral agents with activity against HBV, including emtricitabine, adefovir, and telbivudine, have been evaluated and not found to be teratogenic in animals, but experience with these agents in human pregnancy is limited. These agents could

be included in a regimen during pregnancy if other options are not appropriate. Entecavir was associated with skeletal anomalies in rats and rabbits but only at high, maternally toxic doses. Data on use of entecavir in human pregnancy are not available. Cases of exposure during pregnancy to any of the antiretrovirals and HBV drugs listed should be reported to the Antiretroviral Pregnancy Registry (800-258-4263; http://www.apregistry.com). Interferons are not recommended for use in pregnancy, and ribavirin (RBV) is contraindicated in pregnancy. Although IFNs are not teratogenic, they are abortifacient at high doses in monkeys and should not be used in pregnant women because of the direct antigrowth and antiproliferative effects of these agents (*1087*).

The choice of antiretroviral regimen for the pregnant woman with chronic HBV infection who requires antiretrovirals during pregnancy only for prevention of mother-to-child transmission (MTCT) and plans to discontinue therapy after delivery is more complex. Options include starting a triple therapy regimen including two agents with activity against HBV (as discussed above) but stopping therapy after delivery and monitoring closely for a flare of HBV activity, or using a regimen not including drugs active against HBV to avoid a potential flare when discontinued. As an alternative, if only short-term therapy is planned (e.g., starting in the third trimester), consideration should be given to using a combination antiretroviral regimen using lamivudine as the sole agent with activity against HBV **(CIII)**. Certain specialists recommend the first option, using a regimen with dual HBV activity. This recommendation is made even when planning to discontinue postpartum because of the concern about potential IRIS-related flare of HBV activity during pregnancy, even among women with relatively high CD4$^+$ counts, if ARV without anti-HBV activity is used. They believe that treating a potential flare in the postpartum period after discontinuing ARV is associated with less risk than treating an immune-mediated flare during pregnancy. In addition, using drugs with anti-HBV activity during pregnancy will lower HBV levels and potentially decrease the risk for failure of hepatitis B immune globulin (HBIG) and hepatitis B vaccine to prevent perinatal transmission of HBV, which is increased among women with high HBV DNA levels. Certain specialists would use an antiretroviral regimen without anti-HBV activity to avoid the possibility of flare when discontinued postpartum and to avoid the use of tenofovir, a drug with limited experience with long-term use in pregnancy. Certain specialists would use a highly active regimen that includes lamivudine as the only antiretroviral agent with activity against HBV, especially if starting the regimen later in pregnancy because of late care or delayed HIV diagnosis, to avoid use of tenofovir while still treating HBV. Decisions regarding choice of ARV regimen should be made taking into account CD4$^+$ count, HIV RNA levels, time needed for chronic HIV therapy, HBV levels and indications for HBV therapy, gestational age when starting therapy, and patient preference.

Infants born to HBsAg-positive women should receive HBIG and hepatitis B vaccine within 12 hours of birth (**AI**). The second and third doses of vaccine should be administered at 1 and 6 months of age, respectively. This regimen is >95% effective in preventing HBV infection in these infants. Postvaccination testing for anti-HBs and HBsAg should be performed at age 9–15 months because of the infant's ongoing exposure to HBV.

Hepatitis C Virus Infection

Epidemiology

Hepatitis C virus (HCV) is a single-stranded RNA virus that is most efficiently spread through direct blood exposure to contaminated blood or blood products. Both HIV and HCV can be transmitted by percutaneous exposure to blood, through sexual intercourse, and from a mother to her infant. However, the relative efficiency of transmission by these routes varies. HCV is approximately 10 times more infectious than HIV through percutaneous blood exposures, but sexual transmission of HCV is inefficient compared with HIV. Transmission of HIV and HCV through contaminated blood products is now rare because of effective screening of blood and blood-derived products in the United States.

Heterosexual transmission of HCV is uncommon but more likely occurs in persons with partners who are coinfected with HIV and HCV. Likewise, existing data suggest that sexual contact is a relatively inefficient mode of HCV transmission between MSM, but sexual HCV transmission has been increasingly reported among sex networks of HIV-infected men, particularly those engaged in high-risk sex practices. Cases of acute HCV infection are increasingly recognized and reported in this patient population (*1088*).

HCV infection occurs in approximately 2%–5% of infants born to HCV-seropositive mothers. In a majority of studies, the incidence of HCV transmission from mother to infant increases if the mother is coinfected with HIV (*1089–1091*). Overall, rates of HCV vertical and perinatal transmission are relatively low, although increased in the setting of HIV coinfection (*1029,1092*).

In the United States, HIV/HCV coinfection is most prevalent in persons who have a history of hemophilia or injection-drug use, in whom HCV infection rates approach 70%–95% compared with 1%–20% in those who acquired HIV through sex (*1092,1093*). Although studies have suggested that sexual transmission of HCV is inefficient, the exact risk related to dif-

ferent types of sexual activity is unknown. Risk factors for the sexual transmission of HCV include anal-receptive intercourse and concurrent sexually transmitted infection.

Cirrhosis develops in approximately 20% of persons with chronic HCV infection within 20 years after acute infection, although the range and time to development of cirrhosis varies widely. Risk factors for the development of substantial liver disease are older age at the time of infection, male sex, concomitant alcohol use (>20–50 g/day), and advanced immunosupression ($CD4^+$ count of ≤200 cells/μL) (*1094–1096*). Compared with HCV monoinfection, the natural history of HCV infection is accelerated in the setting of HIV (*1097*), with more rapid progression to cirrhosis, decompensated liver disease, hepatocellular carcinoma (HCC), and death (*1098*). Because of its high prevalence and rapid progression, liver disease caused by chronic HCV is a leading cause of death among persons with HIV (*997,999*). Reports of the effect of immune restoration with ART on liver-related mortality are conflicting, with some studies reporting decreases and others little change in the rate of liver-related mortality (*1099,1100*). In addition to liver disease, HCV infection might be associated with changes in cognitive and psychiatric function (*1101*), decreased quality of life (*1102*), and increased prevalence of diabetes mellitus (*1103*), all of which potentially affect HIV management.

The effect of HCV infection on HIV disease progression and immune reconstitution is uncertain (*1093,1104,1105*), although not likely to be clinically relevant based on current observations (*1106*). Patients with underlying viral hepatitis are at increased risk for progression to ARV-related hepatotoxicity (*1068*), although most coinfected patients (approximately 90%) do not have severe hepatotoxicity. The risk for ART-associated hepatotoxicity might be related to the underlying degree of liver fibrosis (*1107*).

Clinical Manifestations

Both acute and chronic HCV infections are typically minimally symptomatic or asymptomatic. Fewer than 20% of patients with acute infection have symptoms characteristic of acute hepatitis, including low-grade fever, mild right upper quadrant pain, nausea, vomiting, anorexia, dark urine, and jaundice. Unexplained elevations of serum ALT or AST levels might be the only laboratory finding during acute infection. Recognition of acute HCV infection is important because antiviral treatment targeting HCV initiated during this period is associated with higher response rates (*1108,1109*).

Chronic hepatitis C infection is often asymptomatic, although complaints of fatigue are common. Serum cryoglobulins might be present but rarely (<5%) cause symptomatic skin (vasculitis), renal (membranoproliferative glomerulonephritis), or neurologic manifestations. HCV-infected patients might experience cutaneous manifestations, including porphyria cutanea tarda. The rate of these manifestations in the setting of HIV is unknown. With progression of liver disease, patients might experience stigmata of cirrhosis with portal hypertension and ESLD, including spider angiomata, palmar erythema, splenomegaly, caput medusa, ascites, jaundice, pruritus, asterixis, and encephalopathy.

Diagnosis

HIV-infected patients should be tested routinely for evidence of chronic HCV infection. Initial testing for HCV should be performed using the most sensitive immunoassays licensed for detection of antibody to HCV (anti-HCV) in blood (*1110*).

False-negative anti-HCV immunoassay results might occur among HIV-infected persons with advanced immunosuppression, but this is uncommon with the most sensitive immunoassays (third-generation assays) (*1090,1111*). If serologic test results are negative or indeterminate and HCV infection is suspected based on elevations of serum aminotransferases or risk factors such as injection-drug use, testing for HCV RNA should be performed (*1112*). True-negative antibody tests might also occur early in the course of acute HCV, in which elevations in serum aminotransferases and detectable viremia are evident before seroconversion; therefore, HCV RNA testing also should be performed when acute HCV infection is suspected.

To confirm the presence of chronic infection, all HCV-seropositive persons should be tested for plasma HCV RNA using a qualitative or quantitative assay. Quantitative HCV RNA level (i.e., viral load) does not correlate with degree of liver damage and does not serve as a surrogate for measuring disease severity, but it does provide important prognostic information about the response to antiviral therapy. Serial quantitative HCV RNA testing should be limited to persons receiving HCV treatment. Diagnostic assays using reverse transcriptase-polymerase chain reaction (RT-PCR) or transcription-mediated amplification (TMA) have been approved by the FDA for qualitative detection of HCV RNA. A single positive HCV RNA result is sufficient to confirm the diagnosis of active HCV infection, but a single negative result cannot exclude viremia because RNA levels might transiently decline below the limit of detection in persons with active infection, especially during the acute phase of infection. A repeat qualitative assay can be performed to confirm the absence of active infection.

Quantitative tests for HCV RNA include quantitative RT-PCR or branched DNA (bDNA) signal amplification assays. Newer real-time PCR assays have excellent sensitivity with lower limits of detection similar to qualitative assays and

a broad dynamic range (e.g., COBAS TaqMan HCV Test; Roche Molecular Systems Inc., Branchburg, NJ). An HCV RNA standard has been established that permits normalization of viral titers in international units (IUs); nonetheless, substantial variability exists among available assays, and if serial values are required to monitor antiviral therapy, continued use of the same quantitative assay for all assessments is strongly recommended.

Six distinct HCV genotypes have been described (*1113*). Genotype 1 infection accounts for approximately 75% of all HCV infections in the United States and approximately 90% of infections among blacks (*1114*). In HCV-monoinfected patients, genotype information is used to guide both the duration of treatment and the dosing of RBV. In contrast, in persons with coinfection, only the dosing of RBV is genotype specific. HCV genotyping should be performed in all HIV-infected persons considering HCV treatment to guide RBV dosing and because it is the best predictor of response to IFN-based treatment and might, therefore, influence the decision to treat and/or perform liver biopsy. Repeat HCV genotype testing is not indicated.

Baseline and periodic monitoring of serum ALT and AST levels should be performed. Levels often fluctuate among patients with chronic HCV infection, regardless of HIV infection, and long periods during which these values are normal might be observed. Although higher serum ALT and AST levels are, to some degree, predictive of more rapid disease progression, (*1091*) substantial liver disease might be present even in the presence of persistently normal ALT levels.

Computed tomography (CT), MRI, and ultrasonography have limited utility in staging liver disease because they are often abnormal only in advanced disease. Ultrasonography is recommended as the initial test for evaluation of persons with liver cirrhosis for the detection of hepatic mass lesions suspicious for HCC. Because of cost, the use of bi- or triphasic CT with contrast or MRI scanning should typically be limited to evaluation of hepatic mass lesions in patients with cirrhosis.

Liver biopsy remains the preferred test for evaluation of HCV-related disease (fibrosis) stage and is useful to assess prognosis and guide treatment decisions. Although ultrasound guidance reduces the risk (*1115*), liver biopsies might result in major complications, including excessive bleeding (<0.5%), bile peritonitis (0.09%), and, rarely, internal organ injury, although the overall mortality rate is <1 in 10,000 (*978,979*). Further, disease staging by biopsy is expensive and subject to sampling error because of the heterogeneity of hepatic fibrosis. In some studies, disease progression has been observed during short periods in persons with minimal fibrosis. Therefore, although liver biopsy is helpful in the evaluation of coinfected persons, it is not required before the initiation of therapy for HCV infection, particularly in patients with a high probability of responding to treatment.

Noninvasive testing strategies to evaluate liver fibrosis are an area of active research. Several tests are available that can reliably separate patients with minimal fibrosis from those with cirrhosis, but these tests fail to distinguish intermediate stages of fibrotic disease (*1116–1119*). Although some tests are proprietary commercial assays (e.g., HCV FibroSURE, Laboratory Corporation of America Holdings), others are based on laboratory tests that are routinely obtained in most HIV-infected persons (FIB-4: age, ALT, AST, and platelet count; APRI: AST-Platelet Ratio Index). Additional studies are evaluating liver stiffness using transient elastography as a surrogate for liver fibrosis (*1120*). Prospective studies are ongoing to determine the test(s) with the best predictive value for disease progression.

Preventing Exposure

The primary route of HCV transmission among IDUs is drug injection via a syringe previously used by an infected person. An increased frequency of injection, a longer duration of injection-drug use, and cocaine use are additional factors that increase the potential for HCV transmission (*1121*). Strategies should be pursued to encourage IDUs to stop using injection drugs, preferably by entering a substance abuse treatment program **(AII).**

In addition to sharing syringes, other factors associated with injection, such as sharing drug solution containers, "cookers," filters, "cottons," and mixing water, also increase the likelihood of HCV transmission (*1122*). If IDUs are unwilling or unable to discontinue the use of injection drugs, they should be advised not to share needles or drug preparation equipment to reduce the risk for transmission of HCV infection **(BII)**. Access to sterile injection equipment can be facilitated through enrollment of IDUs in NEPs (*1000–1002*).

Persons considering tattooing or body piercing should be informed of potential risks for acquiring HCV infection, which could be transmitted if equipment is not sterile or if proper infection-control procedures are not followed **(AIII)**.

Although efficiency of sexual transmission of HCV is relatively low, safe-sex practices should be encouraged for all HIV-infected persons; barrier precautions (e.g., latex condoms) are recommended to reduce the risk for exposure to sexually transmitted pathogens, including HCV **(AII)**.

Preventing Disease

All HIV-infected persons should be screened for active HCV infection. HCV-seronegative persons with elevations in serum aminotransferase levels should be screened for acute infection with assays to detect HCV RNA.

Higher rates of viral clearance have been reported in HIV-infected and -uninfected persons treated with IFN-based therapy for acute HCV infection (*1108,1109*). On the basis of this information and in the absence of contraindications, acutely infected persons (<6 months from the time of HCV exposure) should be routinely offered treatment for HCV infection to prevent the development of chronic HCV infection **(BII).** The optimal time to initiate therapy for acute HCV is unknown but it might be as soon as 8–12 weeks after acquisition of the infection (*1109*) (see Treatment Recommendations).

Chronically infected persons should be counseled about methods to prevent liver damage and HCV transmission, evaluated for chronic liver disease, and considered for treatment of HCV infection. All HIV/HCV-coinfected patients should be offered antiviral treatment to prevent development of HCV-related liver disease complications **(AI)**. All HIV-infected patients with HCV coinfection should be advised to avoid or limit alcohol consumption **(AII)** because alcohol ingestion, particularly in quantities greater than 20–50 grams (approximately 2–5 drinks) per day, might accelerate the progression of liver disease (*1123*). Enrollment of active substance abusers into drug and/or alcohol treatment programs is strongly recommended. Persons with liver disease should limit ingestion of potentially hepatotoxic medications (e.g., acetaminophen <2 grams/day). Because iron overload might worsen liver disease, patients should avoid iron supplementation in the absence of documented iron deficiency.

Because of its increased morbidity, HIV-infected persons who are coinfected with HCV should be tested for previous or concurrent HBV infection. Despite evidence of decreased response to hepatitis B vaccine in immunosuppressed persons, those without previous HBV infection should be vaccinated. Likewise, because acute HAV infection is more likely to be fulminant in persons with underlying hepatitis, HAV-susceptible HIV-infected persons with risk factors for HAV infection should receive hepatitis A vaccination **(AII)**. As with hepatitis B vaccination, the response to hepatitis A vaccination is reduced in those with $CD4^+$ counts <200 cells/μL. Certain specialists recommend delaying hepatitis A vaccination until the $CD4^+$ count is >200 cells/μL on ART **(BIII)**. Antibody response should be assessed 1 month after vaccination; nonresponders should be revaccinated **(BIII)**.

Among coinfected persons with cirrhosis, measures to identify and prevent complications of advanced liver disease are identical to those established in persons without HIV and should be performed routinely **(BI)**. All patients with ascites should undergo paracentesis for analysis to verify that portal hypertension is the etiology and to exclude infection (ascites polymorphonuclear cell count >250 cells/mL) (*1079*). Assessment of the serum-ascites albumin gradient (SAAG) is advisable; SAAG ≥1.1 mg/dL strongly suggests ascites secondary to portal hypertension. Management includes sodium restriction (>2 g/day) and diuretics to alleviate fluid retention. The recommended diuretic regimen is spironolactone alone or combined with furosemide (ratio of 40 mg furosemide: 100 mg spironolactone). Consideration should be given to primary prophylaxis against spontaneous bacterial peritonitis (SBP) through the administration of oral antibiotics such as norfloxacin (400 mg/day) or TMP-SMX (1 double-strength tablet/day) in those with an ascites total protein <1 grams/dL (*1080*). Secondary antibiotic prophylaxis is recommended for all persons with a history of SBP **(AI)**. Upper endoscopy should be performed in all persons with cirrhosis, particularly those with thrombocytopenia, at the time of diagnosis and then every 1–2 years to identify substantial varices (*1124*). For persons with varices, nonselective beta blockers (e.g., nadolol or propranolol) are the mainstay of both primary and secondary prevention of variceal hemorrhage; esophageal variceal ligation or banding is another preventive option, particularly for persons who cannot tolerate beta blockers. Hepatic encephalopathy, caused by the accumulation of unmetabolized ammonia and other false neurotransmitters absorbed from the gut in the setting of liver dysfunction, might be subtle in early stages (*916*). Preventive measures include restriction of animal dietary protein consumption and the use of nonabsorbable disaccharides (e.g., lactulose) and/or antibiotics (e.g., neomycin, rifaximin).

Patients with HCV-related cirrhosis are at increased risk for HCC (*1081*). Whether there is additional risk in the setting of HIV infection is unclear (*998*). Although the optimal screening strategy to detect HCC is unknown, screening is recommended in patients with documented cirrhosis using hepatic ultrasound imaging performed at 6–12-month intervals **(BIII)** (*1082*). The utility of serum AFP for HCC screening in persons with HIV is unknown. Because of relatively poor specificity and sensitivity, results of AFP testing should be confirmed with liver imaging studies. In the absence of contraindications, HIV/HCV-coinfected persons with decompensated liver disease and/or early HCC might be candidates for orthotopic liver transplantation because HIV infection is not a contraindication to organ transplantation with the use of effective ART (*1083*). Persons with cirrhosis should undergo periodic assessment of their liver disease status through the application of validated prognostic models (e.g., Model for End-Stage Liver Disease [MELD] score) that predict mortality risk and are used to determine the medical need for liver transplantation (*1084*). Where feasible, HIV/HCV-coinfected persons with well-controlled HIV infection found to have liver decompensation (defined as Child-Pugh-Turcotte score ≥7 and/or MELD

score >10) or evidence of early HCC should be referred for orthotopic liver transplantation **(BIII)**.

Treatment of Disease

Antiviral treatment for HCV infection should be considered for all HIV-infected persons with acute or chronic HCV infection (**AI**). In the absence of contraindications to pegIFN or RBV, treatment for HCV infection should be offered routinely to persons in whom the potential benefits of therapy are judged to outweigh the potential risks, including (but not limited to) persons with the following conditions **(BII)**:

- HCV genotype 2 or 3 infection
- HCV genotype 1 infection with a low HCV RNA level (<800,000 IU/mL) (although certain specialists might not recommend treatment of patients with HCV genotype 1 infection and low or intermittently undetectable HCV RNA, response to pegIFN plus RBV is improved in those with HCV RNA levels <800,000 IU/mL compared with those with levels above this threshold, which might favor treatment in this group)
- Significant hepatic fibrosis (bridging fibrosis or cirrhosis)
- Stable HIV infection not requiring ART
- Acute HCV infection (<6 months' duration)
- Cryoglobulinemic vasculitis
- Cryoglobulinemic membranoproliferative glomerulonephritis
- Strong motivation to treat their HCV infection

The goals of therapy include eradication of HCV infection; prevention of hepatic fibrosis progression; and, among persons with HCV-related cirrhosis, prevention of ESLD, HCC, and death. Although viral eradication is not anticipated in most treated persons, histologic and clinical benefits of therapy have been observed in the absence of virologic response (*1125*).

On the basis of well-designed, randomized, controlled trials, pegIFN plus RBV is the recommended treatment for hepatitis C in HIV-infected persons **(AI)**. Sustained virologic response (SVR) rates range from 14%–29% for HCV genotype 1 infection and 43%–73% for HCV genotypes 2 and 3 infection (*1036*,*1125*–*1127*). Whereas fixed-dose RBV (800 mg/day) is recommended for HIV-infected persons with genotype 2 or 3 disease, the appropriate RBV dose for persons with genotype 1 disease has not been determined because the pivotal trials studied only fixed-dose RBV. Among HIV seronegative persons with genotype 1, pegIFN plus weight-based RBV (1,000 mg/day for persons weighing <75 kg; 1,200 mg for persons weighing ≥75 kg) was more effective than fixed-dose RBV (*1128*). Although the efficacy of weight-based RBV has not yet been established in coinfected persons, several studies indicate that this strategy is not associated with increased risk for adverse effects (e.g., anemia). Accordingly, certain specialists recommend the use of weight-based RBV combined with pegIFN in HIV-infected persons with HCV genotype 1 disease **(AII)**.

For HCV genotypes 1,4,5, or 6, the recommended treatment regimen is either pegIFN alfa-2a (180 mcg) or pegIFN alfa-2b (1.5 mcg/kg) administered by subcutaneous injection weekly plus oral RBV twice daily (<75 kg or 165 lbs body weight, 600 mg each morning and 400 mg each evening; ≥75 kg or 165 lbs body weight, 600 mg twice daily) for a total duration of 48 weeks **(AI)**. For HCV genotype 2 or 3, the recommended treatment is either pegIFN alfa-2a (180 mcg) or pegIFN alfa-2b (1.5 mg/kg) administered by subcutaneous injection weekly plus oral RBV in a fixed dose of 400 mg twice daily for a total duration of 48 weeks **(AI)**.

The optimal treatment regimen and duration of treatment for acute HCV in coinfected patients has not been determined. Among HIV-seronegative persons, regimens including pegIFN with or without RBV in dosing schedules described above have been administered for 24 weeks' duration with good results. Therefore, in the absence of better information, HIV-infected persons with acute HCV infection should be treated with one of the previously recommended regimens for ≥24 weeks' duration **(BIII)**. Because the efficacy of shorter treatment duration has not been adequately evaluated in HIV-infected persons with acute or chronic HCV infection, the recommended duration of treatment is 48 weeks for chronic infection with all HCV genotypes, including 2 and 3 **(BII)**; on the basis of this information, certain specialists would also treat HIV-infected patients with acute HCV infection for a total duration of 48 weeks.

Treatment for HCV infection with pegIFN plus RBV should NOT be routinely administered to persons in whom the potential risks of therapy are judged to outweigh the potential benefits including (but not limited to) persons with the following conditions **(DII)**:

- Pregnancy, or who are not willing to use birth control;
- Advanced HIV-associated immunosuppression uncontrolled on ART;
- Hepatic decompensation (e.g., coagulopathy, hyperbilirubinemia, encephalopathy, ascites) because liver transplantation, where feasible, should be the primary treatment option for such patients **(CIII)**;
- Severe, uncontrolled comorbid medical conditions (e.g., cancer or cardiopulmonary disease);
- Severe, active depression with suicidal ideation, although HCV treatment may be considered after the successful implementation of psychiatric care and treatment for depression;
- Significant hematologic abnormality (e.g., hemoglobin <10.5 g/dL, absolute neutrophil count <1,000/μL, platelet count <50,000/μL), although HCV treatment

may be considered after the correction of hematologic abnormalities (e.g., treatment of underlying causative conditions and/or use of hematopoietic growth factors);
- Renal insufficiency (creatinine >1.5 or creatinine clearance <50 cc/min), although in such persons, treatment with pegIFN alone may be considered;
- Sarcoidosis because of increased risk for severe disease exacerbation with IFN therapy;
- Active, uncontrolled autoimmune conditions (e.g., systemic lupus erythematosus [SLE] or rheumatoid arthritis) because of increased risk for severe disease exacerbation with IFN therapy.

Patients with contraindications to the use of RBV (e.g., unstable cardiopulmonary disease, pre-existing anemia unresponsive to erythropoietin, renal failure, or hemoglobinopathy) can be treated with pegIFN alfa (2a or 2b) monotherapy **(AII)**. However, substantially lower SVR rates are expected in persons not receiving RBV. Additionally, persons with modifiable contraindications to treatment should be reassessed at regular intervals to evaluate their candidacy for therapy. Active injection-drug use does not represent an absolute contraindication to treatment of HCV infection; treatment of active IDUs should be considered on a case-by-case basis, considering comorbid conditions, adherence to medical care, and risk for reinfection. Management of HCV-infected IDUs is enhanced by linking IDUs to drug treatment programs. Alcohol use negatively affects HCV disease progression and treatment; therefore, alcohol abstinence is strongly recommended before and during antiviral therapy. A history of alcohol abuse is not a contraindication to therapy.

Management of HCV in the Context of ART

The optimal timing of initiation of ART relative to treatment for HCV infection has not been established. Although control of HIV replication and higher $CD4^+$ count as a result of successful ART might be associated with improved response to treatment for HCV infection, this theoretical possibility has not been demonstrated in clinical trials. In addition, data from randomized controlled trials indicate that no substantial relationship exists between pretreatment $CD4^+$ count and higher SVR rates. Also, because persons with $CD4^+$ counts <200 cells/μL have usually been excluded from clinical trials, the efficacy and safety of pegIFN plus RBV has not been established in this population. Therefore, the majority of experts recommend initiation of ART and control of HIV viral replication before initiating treatment for HCV infection for HIV-coinfected patients with $CD4^+$ counts <200 cells/μL **(CIII)**. However, limited evidence suggests that for persons unable to tolerate ART because of hepatotoxicity or who have persistently elevated serum aminotransferase levels (>2 times the ULN), treatment of HCV infection before initiating ART might reduce the risk for recurrent hepatotoxicity or progression of liver disease (*1129*) and should be considered in this situation, regardless of $CD4^+$ count **(CIII)**.

Monitoring and Adverse Events, Including Immune Reconstitution Inflammatory Syndrome (IRIS)

The most appropriate intervals with which to monitor patients for whom treatment for HCV infection is deferred (e.g., those with no or minimal fibrosis or inflammatory changes on liver biopsy) have not been determined, but because of unpredictable progression of fibrosis, even among those with limited fibrosis on initial liver biopsy, serial liver biopsies should be performed every 2–3 years (*1130*).

Assessment of HCV RNA level is the best measure of treatment response and should be performed at baseline and after completion of the first 12 weeks of therapy for HCV infection (*1131*). An early virologic response (EVR) is defined as either an undetectable HCV RNA level or a decrease of ≥2 log10, as measured by quantitative HCV RNA assays, at the end of 12 weeks of treatment. Patients who do not achieve an EVR by week 12 have a limited chance (<3%) of achieving SVR regardless of duration of therapy, and most specialists recommend that treatment should be discontinued after 12 weeks **(AI)**. If an EVR is documented, treatment should be continued **(AI)** and a quantitative or qualitative HCV RNA assay should be performed at the end of 24 weeks of treatment. If HCV RNA levels are undetectable at the end of 24 weeks of treatment, therapy should be continued for a total duration of 48 weeks. If HCV RNA levels remain detectable after 24 weeks of treatment, therapy should be stopped **(AI)**. An HCV RNA assay should be repeated both at the completion of 48 weeks of treatment and 24 weeks after completion of treatment **(AI)**. An SVR is defined as the absence of detectable HCV RNA, using an HCV RNA assay with a lower limit of detection of at least 50 IU/mL, measured at 24 weeks after completion of treatment.

In the context of treatment monitoring, relapse is defined as the absence of detectable HCV RNA at the end of treatment that is not sustained after the discontinuation of therapy. Breakthrough is the re-emergence of detectable HCV RNA following suppression below the limit of detection despite the continuation of therapy. Virologic failure or nonresponse is defined as the failure to suppress HCV RNA below detection at any time during treatment. Certain specialists recommend the continuation of treatment despite virologic failure in persons with advanced liver fibrosis based on the observation that approximately one third of coinfected patients who underwent liver biopsy had histologic improvement in fibrosis, despite the absence of a virologic response in one trial (*1125,1132*).

However, more recent data suggest this approach is ineffective and it is not recommended.

HIV-infected patients who achieve an SVR should be monitored with serial HCV RNA testing at 6–12 month intervals for an additional 1–5 years to exclude late relapse or reinfection with HCV, especially those at risk for continued exposure **(CIII)** (*1133*).

The major toxicities of IFN-alfa (pegylated or standard) include influenza-like symptoms (e.g., fever, myalgia, headache, and fatigue), neuropsychiatric abnormalities (e.g., depression, irritability, and cognitive dysfunction), cytopenias (e.g., thrombocytopenia and neutropenia, including a reversible reduction in $CD4^+$ count), retinopathy, neuropathy, and exacerbation of autoimmune disease. Depression might be severe enough to trigger suicide. Depending on the severity of these toxicities and individual patient tolerance, side effects might be dose limiting or interfere with the ability to complete a course of treatment.

The major toxicities of RBV include dose-dependent hemolytic anemia, cough, and dyspepsia. RBV potentiates the intracellular activity of didanosine through inhibition of inosine monophosphate dehydrogenase. Because the interaction of RBV and didanosine might lead to clinically significant inhibition of mitochondrial DNA polymerase gamma, resulting in severe pancreatitis, lactic acidosis and, in some patients, death, the combination of RBV and didanosine is strictly contraindicated **(EI)** (*1134*). Zidovudine can potentiate RBV-related anemia, and if other ARVs are available, modification of the ART regimen to remove zidovudine is recommended before treatment for HCV infection **(BII)** (*1135*). Persons in whom the discontinuation of zidovudine is not feasible should be monitored closely (every 2 weeks) for the new onset of severe anemia during the first 8 weeks of treatment. Studies support the use of erythropoietin for the management of clinically significant anemia during HCV treatment. The use of epoetin alfa might permit RBV doses to be optimized and has been associated with improved quality of life (*1136*).

Mental health should be evaluated before initiation of therapy for HCV infection and should be monitored at regular intervals during treatment. Certain specialists recommend the use of standardized depression screening tools such as the Center for Epidemiologic Studies Depression Scale (CES-D). Adverse neuropsychiatric effects of pegIFN-alfa and RBV might be modified by the use of adjunctive agents such as antidepressants.

As with HBV coinfection, in HCV-coinfected persons, IRIS might be manifested by dramatic increases in serum aminotransferases as $CD4^+$ counts rise within the first 6–12 weeks after starting ART. The signs and symptoms are characteristic of hepatitis flares. After introduction of ART, serum aminotransferases should be monitored closely; some experts recommend monthly for the first 3–6 months and then every 3 months thereafter. Any association between abnormal aminotransferases and clinical jaundice or synthetic dysfunction (elevated INR) should prompt consultation with a hepatologist.

In this setting, distinguishing hepatotoxicity or other causes of hepatitis (acute HAV or acute HBV infections) from IRIS is difficult. All classes of ARVs have been associated with hepatotoxicity, which might be dose-dependent or idiosyncratic. The risk for hepatotoxicity has been consistently associated with elevated pre-ART aminotransferases and the presence of HBV or HCV coinfection (*1065-1067,1069–1073,1137*). Despite the increased risk for hepatotoxicity in the setting of HCV or HBV coinfection, the majority of (80%–90%) coinfected patients do not develop hepatotoxicity (*1067*), and clinically significant hepatotoxicity is rare; aminotransferases return to baseline in the majority of cases, even if the offending medication is continued (*1066,1074*). Therefore, discontinuing treatment in the presence of hepatotoxicity is probably not necessary unless the patient has symptoms of hypersensitivity (fever, lymphadenopathy, rash), symptomatic hepatitis (nausea, vomiting, abdominal pain, or jaundice), or elevations of serum aminotransferase levels >10 times the ULN. The development of jaundice is associated with severe morbidity and mortality and should trigger discontinuation of the offending drug(s) (*1075*). No reliable clinical or laboratory parameter is available that will distinguish hepatotoxicity from IRIS. Similarly, liver biopsy might not be diagnostic and are not recommended except in the presence of hepatotoxicity grade 4 or fulminant hepatitis. Prospective studies are evaluating the incidence of presumptive IRIS within the first 12 months of ART initiation. No studies exist to inform the optimal management of persons who experience IRIS in this setting.

Management of Treatment Failure

No data are available on which to base recommendations for treatment of HIV/HCV coinfected patients who fail to respond to initial treatment for HCV infection. Certain patients might benefit from retreatment with interferon-based regimens depending on their previous response, tolerance, and adherence to and the type of previous therapy, the potential potency of the new treatment regimen, the severity of liver disease, viral genotype, and other underlying factors that influence response. On the basis of limited data in persons with HCV monoinfection, extension of the duration of treatment with pegIFN plus RBV might enhance SVR rates in coinfected persons who experience a virologic response to HCV treatment followed by relapse after adequate therapy. For persons with advanced fibrosis (e.g., bridging fibrosis or cirrhosis) and for HIV/HCV-coinfected persons who fail to demonstrate an EVR

on a pegIFN and weight-based RBV regimen, clinical trials indicate that maintenance pegIFN therapy is not associated with decreased risk for hepatic events or with slowing of liver fibrosis progression in HIV-infected and -uninfected persons (*1138*). Therefore, maintenance pegIFN therapy is not recommended **(AI)**.

Preventing Recurrence

For HIV/HCV coinfected patients, treatment-induced SVR appears to be durable and low rates of recurrent viremia have been observed in persons with undetectable HCV RNA >1 year after completion of therapy (*1133*). Persons with HIV infection who achieve SVR should be counseled to stop using injection drugs, and those who continue to inject drugs should be counseled to use safe injection practices to prevent reinfection. Use of barrier precautions and other methods to prevent sexual transmission of HIV should be adequate to prevent reinfection with HCV via sexual practices.

Special Considerations During Pregnancy

Pregnant HIV-infected women should be tested for HCV infection to allow appropriate management during pregnancy and following delivery, and for their infants after birth (*1139*). The treatment of chronic hepatitis C during pregnancy is contraindicated **(EIII)**. Both peginterferon and RBV are contraindicated in pregnancy. Although interferons are not teratogenic, they are abortifacient at high doses in monkeys and should not be used in pregnant women because of the direct antigrowth and antiproliferative effects of these agents (*1087*).

RBV is an FDA category X drug because of its teratogenicity at low doses in multiple animal species. Defects noted in animals include limb abnormalities, craniofacial defects, exencephaly, and anophthalmia. RBV should not be used during pregnancy **(EIII)**. Women of childbearing potential and men receiving RBV should be counseled about the risks and need for consistent contraceptive use during and for 6 months after completion of RBV therapy. However, inadvertent pregnancy during paternal exposure has not been associated with adverse events (*1140*). Pregnancies that occur in women taking RBV should be reported to the Ribavirin Pregnancy Registry (800-593-2214 or http://www.ribavirinpregnancyregistry.com).

Evaluation of HCV-infected pregnant women, including liver biopsy, can be delayed until >3 months after delivery to allow potential pregnancy-related changes in disease activity to resolve. Hepatitis A and hepatitis B vaccination can be administered during pregnancy.

Elective Cesarean delivery does not appear to reduce the risk for HCV transmission from mother to child in HIV-uninfected women, but might be protective against transmission of HCV among HIV-infected women (*1089,1141*). The adjusted odds for perinatal transmission of HCV with scheduled Cesarean delivery among HIV-infected, HCV-seropositive women was 0.36 (0.2–0.8) compared with other modes of delivery. However, another study was unable to confirm the protective effect of Cesarean delivery, possibly because two thirds of the women with HIV/HCV coinfection received an elective Cesarean delivery (*1142*). Although elective Cesarean delivery in HIV/HCV-coinfected women might be considered based on HIV-related indications, data are insufficient to support its routine use for prevention of HCV transmission **(DIII)**.

Infants born to HIV/HCV-coinfected women should be tested for HCV RNA at 2 and 6 months and for HCV antibody after 15 months of age **(CIII)**.

Progressive Multifocal Leukoencephalopathy/JC Virus Infection

Epidemiology

Progressive multifocal leukoencephalopathy (PML) is an OI of the CNS, caused by the polyoma virus JC virus (JCV) and characterized by focal demyelination (*1143*). The virus has worldwide distribution and approximately 85% of adults are seropositive for JCV (*1144*). Primary JCV infection usually occurs in childhood but is not accompanied by any identified symptoms. However, infection likely results in a chronic asymptomatic carrier state in most persons, explaining frequent virus detection in urine (30%) and tonsils (40%) of immunologically normal adults (*1145–1150*). Outside of the context of HIV infection, PML is rare and usually manifests as a complication of other diseases or therapies accompanied by compromised immunity (*1151,1152*). Interest in PML has increased outside of the HIV context as a result of three cases that developed in patients with multiple sclerosis and regional enteritis after treatment with natalizumab, a therapeutic antibody directed against alpha-4 integrins (*1153–1156*). More recently, two patients with SLE receiving rituximab, a therapeutic antibody directed at the B-cell antigen CD20, acquired PML (http://www.fda.gov/cder/drug/advisory/rituximab.htm). This event raises a cautionary note regarding monitoring PML risk when treating non-Hodgkin's lymphoma with rituximab in HIV-infected patients (*1157,1158*). However, no reports have documented PML associated with use of rituximab in HIV infection.

Before the advent of potent combination ART, PML eventually occurred in 3%–7% of AIDS patients (*1159–1161*) and was almost invariably fatal, with only rare spontaneous remission (*1162*). After the widespread use of combination ART in the developed world, the incidence of PML has decreased substantially (*1163*). However, morbidity and mortality associated with PML in HIV-infected patients remains high

(*1164*). Unlike some of the other CNS OIs that are almost wholly prevented when $CD4^+$ counts are maintained above 100–200 cells/μL, PML might still appear in such patients and in those on ART (*1165,1166*). Moreover, PML might develop in the setting of initiating ART and immune reconstitution (*1166,1167*).

Clinical Manifestations

PML manifests as focal neurological deficits, usually with insidious onset and steady progression. Because the demyelinating lesions might involve different brain regions, the specific deficits vary from patient to patient. Any region of the CNS might be involved, but some areas seem to be more favored, including the occipital lobes (with hemianopia), frontal and parietal lobes (hemiparesis and hemisensory deficits), and cerebellar peduncles and deep white matter (dysmetria and ataxia). Spinal cord involvement appears rare (*1168*). Although lesions can be multiple, often one predominates clinically. Additionally, because the individual lesions expand concentrically or along white matter tracts, initial symptoms and signs often begin as "partial" deficits (e.g., weakness of one leg) that worsen and involve a larger territory (e.g., evolution to hemiparesis). The focal or multifocal nature of the pathology is responsible for the consistency of clinical presentations with distinct focal symptoms and signs rather than as a more diffuse encephalopathy or dementia, which is rare (*1169*).

The time course of this evolving demyelination, with clinical progression during several weeks, often provides a clue to diagnosis, because the other major opportunistic focal brain disorders (cerebral toxoplasmosis and primary CNS lymphoma) characteristically progress more rapidly in hours or a few days, and cerebral infarcts begin even more abruptly. Headache and fever are not part of the disease, but seizures develop in nearly 20% of PML patients and are associated with PML lesions immediately adjacent to the cortex (*1170*).

Diagnosis

The initial recognition of PML relies on a combination of clinical and neuroimaging findings. The first step is usually identifying the clinical picture of steady progression of focal neurological deficits. The MRI almost always confirms distinct white matter lesions in areas of the brain corresponding to the clinical deficits. The lesions are usually hyperintense (white) on T2-weighted and fluid attenuated inversion recovery sequences, and also characteristically hypointense (dark) on T1-weighted sequences. The latter might be subtle but helps to distinguish the PML lesion from other pathologies, including the white matter lesions of HIV encephalitis. In contrast to cerebral toxoplasmosis and primary CNS lymphoma, no mass effect or displacement of normal structures is usually evident. Although contrast enhancement is present in 10%–15% of cases, it is usually sparse, with a thin or reticulated appearance adjacent to the edge of the lesions. Exceptions to these characteristic imaging findings might be noted when the inflammatory form of PML develops in the setting of immune reconstitution after initiation of ART.

In most cases, clinical picture and imaging findings support a confident presumptive diagnosis of PML. However, confirming the presence of JCV as the cause is often an advantage. This is invaluable in atypical cases, and even in the more typical setting, helps physicians to proceed rapidly and with certainty in therapy, preventing the need to revisit diagnosis when disease progression continues. The first approach to etiological diagnosis uses PCR to identify JCV DNA in CSF obtained by lumbar puncture. This is positive in approximately 70%–90% of patients not taking ART, and a positive result can be taken as diagnostic in this clinical context (*197,1148*). In patients not on ART, the number of JCV DNA copies can add additional information for prognosis, although this does not seem to hold for those on ART (*1171,1172*). CSF analysis may be repeated if JCV PCR is negative but suspicion remains high, and alternative diagnoses (e.g., focal VZV or primary CNS lymphoma) also are not supported by negative VZV and EBV PCR analysis. When these practices fail, brain biopsy may be undertaken unless otherwise contraindicated. PML can usually be identified by the characteristic tissue cytopathology, including oligodendrocytes with intranuclear inclusions, bizarre astrocytes, and lipid-laden macrophages, whereas JCV infection is confirmed by immunohistochemistry, in situ nucleic acid hybridization, or electron microscopy (*1151,1173,1174*). Because PML develops as a result of endogenous infection and high seroprevalence of JCV infection, blood serology is not useful in diagnosis.

PML developing in the setting of immune reconstitution related to ART warrants special consideration and presents some differences from classical PML. PML has been reported to occur within the first weeks to months after initiating ART in certain patients (*1166,1167*). Additionally, some patients exhibit atypical features that include mass effect of the PML lesions with surrounding edema and on occasion, striking contrast enhancement on MRI. This presentation has been referred to as inflammatory PML or IRIS PML. Histopathology might demonstrate perivascular mononuclear inflammatory infiltration (*1175–1178*). In addition, the likelihood of detecting JCV in CSF might be reduced in these patients compared with classic PML, although this needs further study (*1179,1180*). These cases are presumed to represent the confluence of subclinical CNS JCV infection and restoration of immune responses to JCV by ART with resultant local immune and inflammatory

responses, but other undefined factors might affect PML development in this setting.

Preventing Exposure

JCV has a worldwide distribution and most persons exhibit serologic evidence of exposure by their late teens. No known way exists to prevent exposure to the virus.

Preventing Disease

JCV likely continues as a silent productive infection in the kidney in many persons, and this might increase in the presence of immunosuppression. Whether JCV is latent in the CNS or whether PML results from temporally more proximate hematogenous dissemination in those who have this disease is unknown. Protection is presumably conferred by active, effective immunosurveillance. Therefore, the only effective way to prevent disease is to prevent progressive HIV-related immunosuppression with ART **(AIII)**.

Treatment of Disease

No established specific therapy exists for JCV infection or PML, and the main approach to treatment involves ART to reverse the immunosuppression that interferes with the normal host response to this virus. Treatment strategies depend on the patient's antiretroviral treatment status and its effect. Thus, in patients who have PML and who are not on therapy, ART should be started immediately **(AII)**. For patients with PML who remain HIV-viremic because of antiretroviral resistance, their ART regimen should be optimized for virologic suppression **(AIII)**. More problematic are patients who have PML despite successful virologic suppression while taking HAART. A recent report of patients who were treated intensively with four classes of ART (including enfuvirtide) suggested that this strategy might offer higher than anticipated survival (*1181*). The effectiveness of an ART-intensification strategy in patients with undetectable plasma HIV requires further study **(CIII)**. Approximately half of patients with PML in the setting of HIV infection experience a remission after initiating effective ART (*1179,1182–1189*). Although their neurological deficits frequently persist, disease progression in these patients remits. Some also will experience a degree of functional improvement. In one retrospective study, including 118 consecutive patients with PML, 75 patients (63.6%) remained alive for a median of 114 weeks (2.2 years) after diagnosis of PML (*1189*). Neurological function of the survivors was categorized as cure or improvement in 33, stabilization or worsening in 40, and unknown in 2. In this study the $CD4^+$ count at presentation was the only variable that predicted survival; the odds ratio for death among patients with $CD4^+$ counts <100 cells/μL compared with patients who had higher $CD4^+$ counts was 2.71. According to some case series, prognosis also depends on whether patients are not on therapy at the time of presentation (and thus whether treatment can be improved), plasma HIV RNA levels, and virologic responses to treatment (*1166,1179,1185,1188–1190*). Contrast enhancement on imaging also might predict better outcome (*1165*).

Several agents have been proposed or reported anecdotally as more specific treatments for PML, but none of these has proven effective after more intensive scrutiny or more extensive study. On the basis of earlier case reports and drug inhibition of JCV in cell culture, IV and intrathecal cytaribine (cytosine arabinoside) were tested in a clinical trial, but neither exhibited clinical benefit (*1191*). Therefore, treatment with cytarabine is not recommended **(DI)**. Although cidofovir is not effective against JCV in cell culture (*1192*), initial case reports and retrospective series described efficacy in HIV-infected and uninfected patients with PML (*1186*). However, subsequent reports, including retrospective case-control studies (*1187,1189,1193*), an open-label study of cidofovir in HIV-infected PML patients (*1188*) and, eventually, a meta-analysis including the patients from the four above studies (*1194*) demonstrated no neurological benefit. Thus, treatment with cidofovir is not recommended **(DII)**.

Immunomodulatory approaches for treatment of PML also have been tried, but none has yet been studied in a prospective, controlled clinical trial. Although an initial retrospective analysis suggested that interferon-alpha might improve survival of HIV-infected patients with PML (*1195*), a subsequent retrospective analysis did not demonstrate benefit beyond that afforded by ART; therefore, interferon-alpha cannot be recommended **(DIII)** (*1196*)**.** A single report described failure of interferon-beta treatment of HIV-associated PML (*1197*). Case reports describe improvement in PML-related neurological dysfunction or recovery in three non-HIV-infected patients who underwent transplantation for lymphoma and in one patient with myelodysplastic syndrome treated with interleukin-2 (*1198–1200*). After a cell-culture study that indicated JCV replication could be inhibited by a topoisomerase inhibitor (*1201*), an analogue, topotecan, was studied in a small trial. Results suggested a salutary effect in some, although likely little different from the natural course in other AIDS patients; therefore, topotecan is not recommended **(DIII)** (*1202*).

On the basis of a report indicating that the serotonergic 5HT2a receptor can serve as the cellular receptor for JCV in a glial cell culture system (*1203*), drugs that block the 5HT2a receptor, including olanzapine, zisprasidone, mirtazapine, cyproheptadine, and risperidone, have been suggested as treatment for PML (*1204*), although the rationale for this practice has been questioned (*1205*). Although anecdotal reports of using 5HT2a receptor inhibitors are available

(*1143,1206–1208*), previous disappointments after case reports of "successful" treatment emphasize the need to test this strategy by formal trial. Therefore, routine use of these agents is not justified **(CIII)**.

Because ART-induced immune reconstitution is associated with both onset and paradoxical worsening of PML, corticosteroids have also been advocated and sometimes empirically used—at varying dosages and durations—in the treatment of PML. This approach has been extended by some to include all cases of PML, including those with little or no demonstrable inflammatory component. However, no evidence supports the routine use of corticosteroids in HIV-related PML without an inflammatory response on neuroimaging **(DIII)**. In patients with inflammatory PML, corticosteroid treatment might have a more rational basis.

Monitoring and Adverse Events, Including Immune Reconstitution Inflammatory Syndrome (IRIS)

Because the main approach to PML treatment is to reverse immunosuppression, patients might experience an exuberant response that can be classified as an IRIS or immune restoration disease (IRD) (*298*). Because restoration of anti-JCV defenses is the objective of ART treatment in PML patients, the salutary therapeutic response and the immunopathology of IRIS might intersect and overlap in the same patient. The concern in these patients is to determine when the immune or inflammatory response is helpful and when harmful by virtue of local bystander cytotoxicity and edema that cause further injury and threaten brain displacement and herniation. The cellular immune response against JCV, mediated by $CD8^+$ T-lymphocytes, is critical to the containment of PML progression and has been associated with a favorable clinical outcome (*1209*).

However, an "excessive" response related to IRIS might be lethal as a consequence of the inflammatory reaction or, rarely, brain swelling and herniation (*1210*). This inflammatory PML might be the disease phenotype on initial examination in patients who have recently begun ART or might evolve after ART has been initiated in the context of PML treatment. Corticosteroids have been used to control the local inflammatory reaction and reduce associated cerebral edema in this setting. Little published information exists to support their efficacy or, more specifically, to guide dosage and duration of this treatment. Corticosteroid treatment should be as short as possible and not overused. Mild swelling, edema, or contrast enhancement might be noted in some patients who respond favorably to ART, but most often these complications require no additional treatment if the patient is clinically stable and has no sign of impending brain herniation. However, in those with progressing clinical deficits and neuoroimaging features suggesting inflammatory disease (edema, swelling, and contrast enhancement), corticosteroid treatment is justified **(BIII)**. Although some have suggested stopping ART in the face of PML-IRIS, this is likely counterproductive and is not recommended **(DIII)**.

Management of Treatment Failure

Because PML remission might take several weeks, no strict criteria define disease progression. However, a working definition might be continued clinical worsening and continued detection of CSF JCV at 3 months. In the case of ART treatment, the plasma HIV RNA and blood $CD4^+$ count responses might provide ancillary predictive information. When the suppression of HIV RNA or the boost of $CD4^+$ count fails, attention might focus on modifying ART. Augmenting ART even when plasma HIV RNA is below detection is under study. However, when HIV responds well to ART but PML continues to worsen, attempting one of the unproven and not routinely recommended therapies described above is reasonable, after all are informed of their rationale and unproven efficacy. Better treatments and their rigorous assessment are needed.

Preventing Recurrence

Patients experiencing remission of PML after ART rarely suffer a subsequent recrudescence (*1187*), although no formal study of this has been undertaken. The main preventive measure, based on its role in reversing the disease, is an effective ART regimen that suppresses viremia and maintains $CD4^+$ counts **(AII)**.

Special Considerations During Pregnancy

Diagnostic evaluation for PML should be the same in pregnant women as in nonpregnant women. Therapy during pregnancy should consist of optimizing the antiretroviral regimen.

Geographic OIs of Specific Consideration

Malaria

Plasmodium falciparum malaria and HIV both cause substantial morbidity and mortality, particularly in sub-Saharan Africa. Given this substantial overlap, even modest interactions between them have public health importance. Early studies failed to identify important interactions between malaria and HIV (*1211,1212*). However, more recent evidence supports the presence of the effect of each infection on the other (*1213*).

Epidemiology

P. falciparum, *P. vivax*, *P. ovale*, and *P. malariae*, and a recently described species in humans, *P. knowlesi*, differ in geographic distribution, microscopic appearance, and clinical features. Although *P. vivax* infections are more common, worldwide, *P. falciparum* malaria represents the most serious public health problem because of its tendency toward severe or fatal infections.

Malaria is typically transmitted by the bite of an infected female *Anopheles sp*. mosquito. Nonmosquito-borne routes of infection (congenital, transfusion) occur less frequently (*1214–1216*).

Malaria transmission has occurred in 107 countries and territories worldwide (*1217*). Thirty-six percent of the global population lives in areas in which a risk for malaria transmission occurs (*1218*). Each year an estimated 300–500 million clinical cases of malaria occur, making it one of the most prevalent infectious diseases (*1219*). Approximately 80% of the approximately 1 million deaths attributed to malaria each year occur among African children (*1217*).

The clinical syndromes caused by malaria depend on whether a patient comes from an area with stable endemic malaria transmission or unstable (infrequent or very low) transmission (*1220*). In stable endemic areas, young children (<5 years) might experience chronic infections with recurrent parasitemia, resulting in severe anemia and often death. Those who survive repeated infections acquire partial immunity by age 5 years and, if they remain in the area where malaria is endemic, maintain this immunity into adulthood. Adults in stable endemic areas usually experience asymptomatic or milder infections. In unstable transmission areas, immunity is not acquired. In these areas, the overwhelming clinical manifestation is acute febrile disease that can be accompanied by cerebral malaria, affecting persons of all ages.

Pregnant women in areas of unstable transmission might experience acute malaria, spontaneous abortion, and stillbirth. In more stable transmission areas, pregnant women might lose some acquired immunity. Although infections might be asymptomatic, women acquire placental malaria that contributes to intrauterine growth retardation, low birthweight, and the concomitant risk for increased infant mortality.

HIV impact on malaria

Parasitemia and clinical severity. HIV disease impairs the acquired immunity to malaria evident in older children and adults in endemic areas. Large cohort studies have demonstrated evidence of increased frequency (with rates one- to twofold higher) of both parasitemia and clinical malaria in HIV-infected adults, with increasing risk and higher density parasitemia associated with more advanced immunosuppression (*1221,1222*). The rates of increased malaria among persons with HIV are not as great as observed with classic OIs like TB and PCP (*1223*).

In a prospective cohort study in an area with unstable malaria transmission, HIV-infected nonimmune adults were at increased risk for severe malaria, and the risk was associated with a low $CD4^+$ count (*1224*). Nonimmune HIV-infected patients were substantially more likely to have severe clinical malaria than were nonimmune patients without HIV. In another area of unstable malaria transmission, HIV-infected adults hospitalized for malaria were substantially more likely to die or require an ICU admission than those without HIV (*1225*). In contrast, HIV infection did not confer an increased risk for these severity measures among partially immune adults from areas with more stable transmission (*1221*).

The situation is more complex in children. Early studies among HIV-infected infants did not suggest an increase in frequency or density of parasitemia associated with HIV infection (*1226,1227*). More recent data suggest increased rates of parasitemia and higher densities among somewhat older HIV-infected children (up to age 5 years) compared with those without HIV (*1228*). As with adults, older children with HIV might be at increased risk for clinical malaria because of HIV-induced impairment of acquired anti-malarial immunity. HIV-infected infants in Kenya were at increased risk for severe anemia and for hospitalization because of malaria (*1229*). Limited data from areas in which malaria is not endemic also suggest HIV is associated with more severe malaria in older children (*1230*).

Malaria treatment outcomes. Prospective clinical trial data from Kenya indicated that among adults with uncomplicated malaria treated with sulfadoxine-pyrimethamine (SP), the risk for failure 28 days post treatment was substantially higher among HIV-infected adults with low $CD4^+$ counts (<200 cells/uL) than in the HIV-uninfected group (*1231*). In multivariable analysis, the combination of HIV infection with $CD4^+$ count <200 cells/uL and anemia was the only substantial risk factor for treatment failure at 28 days. Similar results were observed in Zambian adults with uncomplicated malaria (*1232*). Widespread resistance to SP has prompted certain countries to adopt policies calling for use of artemisinin-containing combination therapies (ACTs) for first-line treatment for malaria. Assessing whether HIV-related immunosuppression adversely affects efficacy of ACTs in malaria treatment is important.

Malaria Effect on HIV

Viral load and transmission. As occurs with TB and other major OIs, malarial episodes are associated with increased HIV viral load (*24*). Modeling studies have suggested that this increase could affect HIV transmission (*25*). In preg-

nant women, recent studies have also confirmed that malaria parasitemia was associated with increased HIV concentrations, with a magnitude similar to that observed in asymptomatically infected nonpregnant adults (*1233*).

Mother-to-child HIV transmission. Placental malaria also has been associated with increased expression of CCR5 receptors in placental macrophages (*1234*) and increased viral load (*1235*), raising the possibility of placental malaria leading to increased MTCT of HIV. However, data concerning the effect of malaria during pregnancy on the risk for MTCT of HIV are conflicting. One study in Uganda demonstrated increased MTCT in women with placental malaria (*1236*), but studies from Kenya did not demonstrate this association (*1237,1238*).

Blood transfusion transmission. Because anemia caused by *P. falciparum* remains a frequent indication for blood transfusions, malarial anemia can have an important indirect effect on the risk for HIV transmission (*1239*). Improved blood collection and testing practices are leading to improved transfusion safety in Africa (*1240,1241*), but few countries conduct universal screening of blood.

Clinical Manifestations

Patients with malaria can exhibit various symptoms and a broad spectrum of severity depending upon such factors as the infecting species and level of acquired immunity in the host. As noted previously, HIV-immunosuppressed persons in endemic areas might lose acquired malarial immunity, and HIV-immunosuppressed adults with little or no previous malaria exposure such as travelers might be at increased risk for severe outcomes (*1242*).

Among nonimmune persons, typical symptoms of malaria include fever, chills, myalgias and arthralgias, headache, diarrhea, vomiting, and other nonspecific signs. Splenomegaly, anemia, thrombocytopenia, pulmonary or renal dysfunction, and neurologic findings also might be present. Classically, paroxysmal fevers occur every 48 hours for *P. falciparum*, *P. vivax*, and *P. ovale* malaria; those of *P. malariae* occur every 72 hours. However, this classic presentation is highly variable and might not be present.

Uncomplicated malaria infection can progress to severe disease or death within hours. Malaria with CNS symptoms can be particularly ominous. Cerebral malaria refers to unarousable coma not attributable to any other cause in a patient infected with *P. falciparum*; in Africa, case fatality rates with cerebral malaria might approach 40% (*1243–1245*). The risk for severe and complicated illness is increased in patients with high levels of parasitemia and without partial immunity. Metabolic acidosis appears to be an important manifestation of severe malaria and indicator of poor prognosis (*1246*). Other acute complications include renal failure, hypoglycemia, disseminated intravascular coagulation, shock, and acute pulmonary edema (*1247*). *P. falciparum* is the species responsible for severe disease and death; severe or fatal malaria rarely results from infections with the other species. A rare exception is spleen rupture, which can occur with acute nonfalciparum malaria (*1248*).

Diagnosis

The diagnosis of malaria must be considered in all febrile patients who have traveled to or lived in malaria-endemic areas or who have received blood products, tissues, or organs from persons who have been to such areas. Several diagnostic methods are available, including microscopic diagnosis, antigen detection tests, PCR-based assays, and serologic tests. Direct microscopic examination of intracellular parasites on stained blood films is the standard for definitive diagnosis in nearly all settings. In nonimmune persons, symptoms might develop before detectable levels of parasitemia are evident. For this reason, several blood smear examinations taken at 12–24-hour intervals might be needed to positively rule out a diagnosis of malaria in a symptomatic patient. Guidelines for laboratory diagnosis are summarized elsewhere and are available at CDC's malaria website (http://www.cdc.gov/malaria/).

Preventing Exposure

Infection with *P. falciparum* in HIV-infected persons with low $CD4^+$ counts and in pregnant women regardless of HIV infection status can be more severe than in other persons. Because no chemoprophylactic regimen is completely effective, HIV-infected persons with low $CD4^+$ counts and women who are pregnant or likely to become pregnant should be advised to avoid travel to areas with malaria transmission if possible **(AIII)**. If travel to a malarious area cannot be deferred, use of an effective chemoprophylaxis regimen is essential, along with careful attention to personal protective measures to prevent mosquito bites.

Preventing Disease

In areas where malaria is endemic, strategies to prevent malaria and its consequences include vector control, prophylaxis, and intermittent preventive treatment in pregnancy. For U.S. travelers (including HIV-infected persons) to malarious areas, a combination of chemoprophylaxis and personal protective measures can be highly effective in preventing malaria. One of three drugs is recommended for prophylaxis: atovaquone-proguanil, mefloquine, or doxycycline. Recommendations for prophylaxis are the same for HIV-infected persons as for noninfected persons and are available at CDC's malaria website **(AIII)** (http://www.cdc.gov/malaria). Malaria incidence has been markedly reduced in African adults with HIV who

receive cotrimoxazole (TMP-SMX) prophylaxis (*30,1249*). A recent study of HIV-infected persons in Uganda demonstrated that malaria burden was reduced by 70% with cotrimoxazole, was then reduced a further 50% when antiretroviral drugs were provided, and finally a further 50% with provision of insecticide-treated nets (*1250*). However, cotrimoxazole is not as effective an antimalarial prophylactic regimen as the antimalarials recommended (Table 2). Therefore, HIV-infected travelers on prophylaxis with cotrimoxazole should not rely on it for chemoprophylaxis against malaria **(AIII)**.

Treatment of Disease

Because *falciparum* malaria can progress within hours to severe disease or death, all HIV-infected persons with confirmed or suspected *P. falciparum* infections should be admitted to the hospital for evaluation, initiation of treatment, and observation of response to treatment. Ideally, antimalarial treatment should not be initiated until the diagnosis has been confirmed by laboratory investigations. However, treatment should not be delayed when malaria is strongly suspected but laboratory results are pending.

The choice of treatment is guided by the degree of parasitemia and the species of *Plasmodium* identified, the clinical status of the patient, and the likely drug susceptibility of the infecting species as determined by where the infection was acquired. Although impaired response has been noted in HIV-immunosuppressed persons treated with older antimalarials such as sulfadoxine pyrimethamine (*1231,1232*), no evidence indicates that response in these persons is impaired if currently recommended drugs are used. Therefore, for HIV-infected patients who do acquire *Plasmodium* infection, treatment recommendations are the same as for HIV-uninfected patients **(AIII)**. Detailed antimalarial treatment recommendations have been reviewed recently (*1251*). CDC posts current treatment recommendations on its website (http://www.cdc.gov/malaria) and has clinicians on call 24 hours to provide advice to clinicians on the diagnosis and treatment of malaria (CDC Malaria Hotline 770-488-7788 M–F 8 AM–4:30 PM ET, 770-488-7100 after hours).

Monitoring and Adverse Events, Including Immune Reconstitution Inflammatory Syndrome (IRIS)

Several potential drug interactions can occur between antimalarial and HIV drugs, and these have been reviewed recently (*1252*). Atovaquone and doxycycline interactions with antiretroviral drugs and with drugs used to prevent and treat OIs have been summarized previously (*37,1253*). Mefloquine in repeated doses has been observed to reduce area under the concentration-time curve and maximal plasma concentrations of ritonavir by 31% and 36%, respectively. Sufficient data are not available to suggest that dose adjustments are needed.

Quinine levels might be increased by ritonavir-containing regimens; conversely, nevirapine and efavirenz could reduce plasma quinine levels. Potential interactions can occur between ritonavir with chloroquine; however, the clinical significance of these interactions is unclear and until further data are available, no dose adjustments are recommended. Artemisinin-containing compounds such as artesunate, which are widely used for antimalarial treatment in other parts of the world, are not yet approved in the United States. However, artesunate might soon be available for treatment of severe malaria in the United States through a compassionate use Investigational New Drug application. PIs and NNRTIs have the potential to affect metabolism of artemisinin-containing drugs (*1254*), but the overall effect and clinical significance remain unclear. No IRIS has been described in association with malaria.

Management of Treatment Failure

Management of treatment failure for persons with HIV infection should not differ from HIV-positive patients except in terms of drug interactions and drug toxicities as noted above.

Prevention of Recurrence

Not Applicable.

Special Considerations During Pregnancy

Malaria in pregnancy affects both the mother and the fetus. Infection with *P. falciparum* during pregnancy can increase the mother's risk for having severe disease and anemia and increase the risk for stillbirth, preterm birth, and low birthweight (*1255*). The diagnosis of malaria in pregnant women is the same as in nonpregnant women.

For pregnant women with a diagnosis of uncomplicated malaria caused by *P. malariae*, *P. ovale*, chloroquine-sensitive *P. vivax*, and chloroquine-sensitive *P. falciparum*, prompt treatment with chloroquine is recommended (*1251*). For pregnant women with a diagnosis of chloroquine-resistant *P. vivax*, treatment with quinine for 7 days is recommended (**AIII**). For pregnant women with a diagnosis of uncomplicated chloroquine-resistant *P. falciparum* malaria, prompt treatment with quinine and clindamycin is recommended.

On the basis of extensive experience with its use, chloroquine is considered the drug of choice for prophylaxis and treatment of sensitive strains of malaria in pregnancy. Although quinine at high doses has been associated with an increased risk for birth defects (especially deafness) in some animal species and humans (usually during attempted abortion), use of therapeutic doses in pregnancy is considered safe (*1251,1256*). Because of the potential for hypoglycemia, pregnant women treated

with quinine and their neonates should have monitoring of glucose levels. Clindamycin use has not been associated with birth defects. Because of limited data, atovaquone-proquanil or mefloquine are not recommended for treatment in pregnancy and should be used only if quinine plus clindamycin or quinine monotherapy is not available or not tolerated (*1256*). Animal data and human data on use of prophylactic doses of mefloquine do not suggest teratogenicity. Tetracyclines are not recommended in pregnancy because of increased risk for maternal hepatotoxicity and staining of fetal teeth and bones. Primaquine use during pregnancy is not recommended because of limited experience with its use and the potential for fetal G6PD deficiency. Artesunates are not available in the United States.

After treatment, all pregnant women with *P. vivax* and *P. ovale* should be administered chloroquine prophylaxis for the duration of the pregnancy to avoid relapses. For pregnant women with *P. vivax* acquired in an area with chloroquine-resistant strains, once-weekly mefloquine can be used for prophylaxis. Women can be treated with primaquine after delivery if they have a normal G6PD screening test.

Penicilliosis marneffei

Epidemiology

Penicilliosis marneffei (penicilliosis) is caused by the dimorphic fungus *Penicillium marneffei*, which is endemic in Southeast Asia (especially Northern Thailand) and southern China (*1257–1259*). More recently, 50 indigenous cases of penicilliosis occurred in Manipur State, India, a new endemic area of this fungus (*1260,1261*). International travel requires increased awareness and recogntion of penicilliosis and its treatment.

Before the antiretroviral treatment era, penicilliosis was the presenting AIDS-defining illness in 6.8% of HIV-infected patients from the northern provinces of Thailand but less frequently elsewhere (*1262*). The majority of cases of penicilliosis are observed in patients who have $CD4^+$ counts of <100 cells/μL (*1263*). The infection is associated with a high mortality rate if timely treatment with appropriate antifungal drugs is not administered (*1264*).

Clinical Manifestations

The common clinical manifestations include fever, anemia, weight loss, and generalized skin papules with central umbilication resembling molluscum contagiosum (*1257*). Cutaneous penicilliosis lesions commonly appear on the face, ears, extremities, and occasionally the genitalia. Involvement of other organs such as bone marrow, lymph node, lung, liver, and intestine have been reported. Patients with hepatic penicilliosis have fever, abdominal pain, hepatomegaly, and a marked increase in serum alkaline phosphatase levels (*1259*).

Diagnosis

The definitive diagnosis of penicilliosis is based on isolation of organisms from blood culture or other clinical specimens or by histopathologic demonstration of organisms in biopsy material. Fungal cultures at 25ºC (77ºF) demonstrate characteristic features that include a flat green surface and underlying deep red coloring. An early presumptive diagnosis can be made several days before the results of fungal cultures are available by microscopic examination of the Wright-stained samples of skin scrapings, bone marrow aspirate, or lymph-node biopsy specimens. Many intracellular and extracellular basophilic, spherical, oval, and elliptical yeast-like organisms can be seen, some with clear central septation, which is a characteristic feature of *P. marneffei* (*1257*). In some patients, the fungus can be identified by microscopic examination of the Wright's-stained peripheral blood smear (*1265*).

Preventing Exposure

Available information does not support specific recommendations regarding exposure avoidance. However, patients with advanced HIV disease should avoid visiting the disease-endemic areas **(BIII)**.

Preventing Disease

Not applicable to residents of the United States.

Treatment of Disease

P. marneffei is highly susceptible to miconazole, itraconazole, ketoconazole, and 5-flucytosine. Amphotericin B has intermediate antifungal activity, whereas fluconazole is the least active (*1264*). The recommended treatment is amphotericin B in a dose of 0.6 mg/kg body weight/day administered intravenously for 2 weeks, followed by oral itraconazole in a dose of 400 mg/day for a subsequent duration of 10 weeks **(AII)** (*1266*). Patients with mild disease can be initially treated with oral itraconazole 400 mg/day for 8 weeks **(BII)** (*1267*), followed by 200 mg/day for prevention of recurrence. Itraconazole capsule is better absorbed when it is taken with or immediately after a meal. Itraconazole oral solution could be taken on an empty stomach. ART should be administered in accordance with standards of care in the community; consideration should be given to simultaneous administration of treatment for penicilliosis and initiation of ART to improve outcome **(CIII)**.

Monitoring and Adverse Events, Including Immune Reconstitution Inflammatory Syndrome (IRIS)

Patients treated with amphotericin B should be monitored for dose-dependent nephrotoxicity and electrolyte distur-

bances. Preinfusion administration of 500 mL of normal saline appears to reduce the risk for nephrotoxicity during treatment. Infusion-related adverse reactions might be ameliorated by pretreatment with acetaminophen and diphenhydramine; in rare cases, glucocorticosteroids administered approximately 30 minutes before the infusion might be required **(CIII)**.

Because absorption of itraconazole can be erratic, serum itraconazole levels should be obtained once in all patients to ensure adequate absorption **(AIII)**. The serum concentration should be >1 μg/mL, ideally drawn for reasons of consistency as a trough level after at least 7 days on the current regimen. Itraconazole solution is recommended over the capsule formulation because absorption is improved, but this has not been studied specifically in HIV-infected patients.

The immune restoration inflammatory syndrome has been reported uncommonly in patients with penicilliosis (*1268,1269*). It usually occurs within a few weeks or months after starting ART, suggesting a possibility of immune reconstitution unmasking active disease. ART should not be withheld because of concern for the possible development of IRIS **(AIII)**. In patients with severely symptomatic IRIS, short-course glucocorticosteroids are recommended by certain specialists **(BIII)**. Delaying the initiation of potent ART until the end of the first 2 weeks of induction therapy for penicilliosis might be prudent **(CIII)**.

Management of Treatment Failure

Alternative treatment options for penicilliosis are not established. A small case series reported good outcomes with voriconazole (*1270*). For those whose initial therapy has failed, the approach to treatment should consist of reinitiating parenteral amphotericin B followed by another course of oral itraconazole, coupled with optimizing ART, addressing obstacles to adherence, avoiding adverse drug interactions, and ensuring that adequate absorption and serum concentrations of itraconazole are achieved **(AIII)**.

Preventing Recurrence

A study from Chiang Mai University documented that approximately 50% of patients had relapse of penicilliosis marneffei within 6 months after discontinuation of antifungal therapy (*1267,1271*). A double-blind, placebo-controlled study from Chiang Mai, Thailand, demonstrated that oral itraconazole 200 mg daily for secondary prophylaxis in AIDS patients reduced the relapse rate of penicilliosis marneffei from 57% to 0% (p<0.001) (*1271*). All patients who successfully complete treatment for penicilliosis should be administered secondary prophylaxis (chronic maintenance therapy) with oral itraconazole in a dose of 200 mg/day **(AI)**.

Discontinuing Secondary Prophylaxis (Chronic Maintenance Therapy)

No randomized controlled study exists that could demonstrate the safety of discontinuation of secondary prophylaxis for penicilliosis. However, an open-label, historical-controlled trial from Chiang Mai University Hospital indicated that no relapse of penicilliosis and invasive fungal infections occurred after discontinuation of itraconazole in patients receiving ART and $CD4^+$ cell count >100 cells/μL (*1272*). Therefore, discontinuing secondary prophylaxis for penicilliosis is recommended for AIDS patients who receive combination ART and have $CD4^+$ count >100 cells/μL for ≥6 months **(BII)**. Secondary prophylaxis should be reintroduced if the $CD4^+$ count decreases to <100 cells/μL **(AIII)** or if penicilliosis recurs at a $CD4^+$ count of >100 cells/μL **(CIII)**.

Special Considerations During Pregnancy

The diagnosis and treatment of penicilliosis during pregnancy are similar to those in nonpregnant women with the following considerations regarding antifungal use in pregnancy. Because of their risk for teratogenicity, azoles should not be used during the first trimester of pregnancy **(EII)** (See mucocutaneous candidiasis). Neonates born to women on chronic amphotericin B at delivery should be evaluated for renal dysfunction and hypokalemia.

Leishmaniasis

Epidemiology

Leishmaniasis is caused by obligate intracellular protozoa that survive and replicate in intracellular vacuoles within macrophages. The *Leishmania* genus has traditionally been differentiated into multiple species that cause cutaneous, mucosal, or visceral disease *(1273, 1274)*.

Leishmaniasis occurs in 88 countries worldwide with an estimated incidence of 2 million new cases annually *(1275)*.

Leishmaniasis among persons with HIV/AIDS has been reported primarily from Spain, Italy, France, Brazil, and Ethiopia, but most coinfections in the developing world are never reported *(1275)*. The incidence has decreased substantially in developed countries with the introduction of ART *(1276, 1277)*; however, HIV-leishmaniasis coinfection poses a growing problem in Asia and Africa *(1278, 1279)*.

Most infections in immunocompetent hosts are asymptomatic; in some disease-endemic areas, approximately 30% of the population has evidence of latent infection in the form of a positive leishmanin skin test *(1280-1282)*. After primary infection, *Leishmania* remain viable in healthy persons for long periods, leading to a susceptible population if immunosuppression occurs. In HIV-infected persons without severe

immunosuppression, disease manifestations are similar to those in immunocompetent persons. Among those with advanced immunosuppression and low CD4+ counts (<200 cells/μL), manifestations of leishmaniasis might be both atypical and more severe, and relapse after treatment is common *(1283)*.

Leishmaniasis is usually spread by sand flies of the genus *Phlebotomus* or *Lutzomyia (1274)*. However, in Southern Europe, HIV and *Leishmania* coinfections have been reported in association with injection-drug use, suggesting that *Leishmania* also might be acquired by needle sharing *(1284)*. *Leishmania* parasites were demonstrated in 34%–52% of used syringes discarded by IDUs in Madrid, and based on molecular characteristics, investigators have described a new, epidemiologically significant leishmaniasis transmission cycle, relying on mechanical transfer of amastigotes via syringe *(1285, 1286)*.

Clinical Manifestations

Leishmaniasis can occur in four major syndromes: localized cutaneous, diffuse cutaneous, mucosal, and visceral disease. The most common clinical presentation of leishmaniasis in persons with AIDS is a disseminated visceral disease syndrome, but the distribution varies geographically, reflecting differences in the predominant parasite species. In Europe, visceral disease has been reported in 95% of cases (87% typical visceral, 8% atypical visceral) *(1287)*. In contrast, in Brazil, mucocutaneous (43%) and cutaneous (20%) are common *(1288)*.

Among persons with visceral disease, the most common clinical and laboratory findings are fever (65%–100%), systemic malaise (70%–90%), splenomegaly (usually moderate) (60%–90%), hepatomegaly without splenomegaly (34%–85%), hepatosplenomegaly (68%–73%), lymphadenopathy (12%–57%), and pancytopenia (50%–80%)*(1287, 1289)*. Anemia is usually marked with <10g hemoglobin/dL (49%–100%), leukopenia moderate with <2,400 leukocytes/μL (56%–95%), and thrombocytopenia is usually present (52%–93%). Splenomegaly is somewhat less common in HIV-coinfected patients than in immunocompetent patients with visceral leishmaniasis *(1289)*. Among those with more profound immunosuppression, atypical manifestations have been described, including involvement of the upper and lower gastrointestinal tract, lung, pleural and peritoneal cavities, and skin *(1276, 1287, 1289, 1290)*. Esophageal involvement can lead to dysphagia and odynophagia, and must be distinguished from other causes of esophagitis in HIV-infected patients, such as candidiasis *(1287)*. Nonulcerative cutaneous lesions that mimic KS, nodular diffuse leishmaniasis, and post-kala-azar dermal leishmaniasis have been described *(1291)*. However, the presence of *Leishmania* amastigotes in skin might occur in the absence of lesions or in combination with other pathology, such as KS, and might not indicate that the parasite is the cause of the lesions *(1292, 1293)*. Disfiguring mucosal lesions associated with anergy to *Leishmania* antigens have been observed among European persons with AIDS, in contrast to mucocutaneous disease in immunocompetent persons that is associated with strong leishmanin skin-test responses *(1290, 1294, 1295)*.

Diagnosis

Demonstration of characteristic amastigote forms of *Leishmania* by histopathology, cultures, and smears in tissue specimens (e.g., scrapings, aspirates, biopsies) is the standard for diagnosis of cutaneous leishmaniasis among HIV-coinfected patients *(1287)*. The diagnosis of visceral leishmaniasis can also be made by the demonstration of amastigote forms in blood smears (approximately 50% sensitivity in expert hands), buffy-coat smear preparations, cultures from the peripheral blood, and smears or cultures from bone marrow or splenic aspirates. Other methods useful for demonstrating *Leishmania* in the blood or tissue of coinfected patients include detection of *Leishmania* nucleic acid by PCR amplification (>95% sensitivity) *(1296)*.

Antibodies against *Leishmania* antigens are of high sensitive for the diagnostic value among immunocompetent patients with visceral disease (*1297*). However, the sensitivity of serologic tests is substantially lower in HIV-coinfected patients (*1287*, *1298*). The use of recombinant antigen (e.g., rK39) in ELISA assays might increase sensitivity, but a proportion of coinfected patients will remain seronegative (*1299*). Immunoblotting with *Leishmania infantum* soluble antigen has been successful in detecting specific antileishmanial antibodies in up to 70% of European patients (*1298*). Leishmanial skin tests are nearly always negative in active visceral leishmaniasis, with or without HIV coinfection (*1274*).

Preventing Exposure

Primary prevention of leishmanial infection relies on reservoir host control in areas with zoonotic transmission; vector control activities, such as indoor residual spraying and/or insecticide-treated nets; and measures to decrease transmission of infectious agents in IDUs, such as NEPs. For North American residents, these measures are only relevant during travel.

Preventing Disease

Not applicable

Treatment of Disease

Liposomal amphotericin B is the only agent approved by the FDA for the treatment of visceral leishmaniasis *(1300, 1301)*. Pentavalent antimony is the most widely used treatment for leishmaniasis in many parts of the world and remains the

first-line treatment for cutaneous leishmaniasis caused by most species in otherwise healthy patients *(1274, 1302)*.

For HIV-visceral leishmaniasis-coinfected patients, the efficacy of conventional and lipid-associated formulations of amphotericin B appears to be similar to that of pentavalent antimony *(1303-1306)*. However, liposomal and lipid complex preparations are substantially better tolerated than conventional amphotericin B or pentavalent antimony *(1307-1309)*. The equivalent efficacy and better toxicity profile have led most clinicians to regard liposomal amphotericin B as the drug of choice for visceral leishmaniasis in HIV-coinfected patients **(AII)** *(1300)*. The optimal amphotericin B dosage has not been determined *(1300, 1310)*. Regimens with efficacy include conventional amphotericin B 0.5–1.0 mg/kg body weight/day IV to achieve a total dose of 1.5–2.0 grams **(BII)**, or liposomal or lipid complex preparations of 2–4 mg/kg body weight administered on consecutive days or in an interrupted schedule (e.g., 4 mg/kg on Days 1–5, 10, 17, 24, 31, and 38) to achieve a total cumulative dose of 20–60 mg/kg body weight **(BII)** *(1300, 1301, 1303, 1305, 1306, 1311)*. A higher daily dosage is recommended for liposomal or lipid complex (ABLC) preparations than for conventional amphotericin B **(BII)** *(1300, 1301)*.

Few systematic data are available on the efficacy of treatment for cutaneous, mucocutaneous, or diffuse cutaneous leishmaniasis in HIV-coinfected patients. On the basis of data in HIV-negative patients with cutaneous leishmaniasis and case reports in HIV-coinfected patients, first-line treatments include liposomal amphotericin B **(BIII)**, as outlined above, and pentavalent antimony (sodium stibogluconate, which is available in the United States through CDC, and meglumine antimoniate), 20 mg/kg body weight/day, by IV or IM route for 3–4 weeks depending on the form of the disease and the clinical response **(BIII)** *(1274, 1302)*. Pentavalent antimony was recently demonstrated to increase viral transcription and HIV replication in cultures of human peripheral blood mononuclear cells, raising concerns about its use in coinfected patients *(1312)*. A first-line parenteral treatment should be used for mucocutaneous and disseminated cutaneous disease and for localized cutaneous disease caused by *L. braziliensis*, the species most likely to cause mucocutaneous disease. Potential second-line alternatives for cutaneous leishmaniasis include miltefosine, topical paromomycin, intralesional pentavalent antimony, and local heat therapy; however, the effectiveness of these modalities is dependent on the infecting species of *Leishmania (1310, 1313, 1314)*.

Second-line treatment options for visceral leishmaniasis in HIV-coinfected patients include miltefosine and paromomycin. Miltefosine is an oral antileishmanial agent currently available in Germany, India, and several Latin American countries; cure rates of visceral leishmaniasis in HIV-negative patients are reported to be approximately 95% *(1315)*. The adult dose is 100 mg daily for 4 weeks. Although data to support its use among HIV-coinfected persons are limited, it is available for the treatment of visceral leishmaniasis in Europe under a compassionate use protocol **(CIII)** *(1316)*. Gastrointestinal side effects are the most common adverse effects but rarely limit treatment. Data from an Ethiopian population with a high prevalence of HIV-coinfection suggest that use of miltefosine was associated with a somewhat lower visceral leishmaniasis cure rate, but substantially lower mortality than pentavalent antimony *(1317)*. Miltefosine is teratogenic in experimental models, and its use in women of reproductive age requires a negative pregnancy test and effective contraception during and for at least 2 months after therapy. Paromomycin, a parenteral aminoglycoside, has been shown to be effective and safe in HIV-negative visceral leishmaniasis patients in India and is now in use in several countries **(BI)** *(1310)*.

Pentamidine isethionate has been used as a second-line alternative but is no longer recommended, because of toxicity that sometimes includes irreversible insulin-dependent diabetes mellitus **(DIII)**.

ART should be initiated or optimized following standard practice for HIV-infected patients **(AII)**. Appropriate use of ART has substantially improved the survival of coinfected patients in Europe and decreases the likelihood of relapse after antileishmanial therapy *(1277, 1289, 1318)*. Immunotherapy, including interferon-gamma and recombinant human granulocyte macrophage colony stimulating factor, has been used experimentally as an adjunct to antileishmanial treatment for refractory cases *(1319, 1320)*. However, a clinical trial of pentavalent antimony plus interferon-gamma for visceral leishmaniasis in HIV-coinfected patients was suspended when an interim analysis indicated that there was no advantage over pentavalent antimony alone *(1305)*. In addition, the use of interferon-gamma was reported to be associated with acceleration of KS in two patients with visceral leishmaniasis and HIV coinfection *(1292)*.

Monitoring and Adverse Events, Including Immune Reconstitution Inflammatory Syndrome (IRIS)

Patients receiving pentavalent antimonials should be monitored closely for adverse reactions, which are frequent and vary from mild phlebitis to death *(1302)*. Overall, at a dose of 20 mg/kg body weight/day, >60% of patients have one or more of the following reactions: thrombophlebitis, anorexia, myalgia, arthralgia, abdominal pain, elevation of liver transaminases, amylase or lipase, and in some patients, clinical pancreatitis. Occasional electrocardiographic changes might be observed (e.g., prolonged QT intervals and T-wave inversion). Rarely,

arrhythmias and sudden death have occurred *(1304, 1305)*. Severe adverse reactions to pentavalent antimony, including acute pancreatitis and leukopenia, appear to be more frequent in coinfected patients than in those without HIV *(1321)*.

Patients treated with amphotericin B should be monitored for dose-dependent nephrotoxicity, electrolyte disturbances, and infusion-related adverse reactions, which might be ameliorated by pretreatment with acetaminophen, diphenhydramine, or limited doses of corticosteroids **(CIII)**. Previous fluid expansion with colloidal fluids can help reduce the risk of nephrotoxicity during treatment **(CIII)**. The frequency of nephrotoxicity is lower for liposomal or lipid-associated preparations than for conventional amphotericin B *(1308)*. Conventional amphotericin B treatment might be associated with an increased risk of anemia *(1304)*.

Cases of newly symptomatic visceral and cutaneous leishmaniasis have been reported in association with the immune reconstitution syndrome following initiation of ART *(1322, 1323)*. However, existing experience regarding IRIS-associated leishmaniasis is insufficient to provide data for specific IRIS management guidelines. Leishmaniasis that manifests after initiation of ART requires specific therapy consistent with guidelines for initial treatment or management of relapse.

Management of Treatment Failure

For patients who fail to respond to initial therapy or experience a relapse after initial treatment, a repeat course of the initial regimen, or one of the recommended alternatives for initial therapy as outlined above, should be used **(AIII)**. The response rate for retreatment appears to be similar to that for initial therapy, although certain patients might evolve to a chronic disease state with serial relapses despite aggressive acute and maintenance therapies.

Preventing Recurrence

Clinical cure is dependent on concurrent T-cell-mediated parasite killing *(1324)*. Relapses, particularly of visceral leishmaniasis and disseminated cutaneous leishmaniasis, commonly follow cessation of therapy among immunosuppressed patients with AIDS. Among patients with visceral leishmaniasis who are not receiving or responding to ART, the risk of relapse at 6 and 12 months, in the absence of secondary prophylaxis (chronic maintenance therapy), is 60% and 90%, respectively *(1287, 1325)*. Therefore, secondary prophylaxis with an effective antileishmanial drug, administered at least every 2–4 weeks, is recommended, particularly for patients with visceral leishmaniasis and CD4+ counts <200 cells/μL **(AII)** *(1287, 1289, 1325, 1326)*. However, existing data are insufficient to recommend a specific regimen. The only published, randomized trial, which evaluated several patients, compared ABLC (3 mg/kg every 21 days) with no prophylaxis; this trial reported relapse rates of 50% versus 78%, respectively, after 1 year of follow-up *(1326)*. In retrospective studies, monthly pentavalent antimony or lipid formulations of amphotericin every 2–4 weeks was also associated with decreased relapse rates *(1289, 1325)*. Daily allopurinol, in a dose of 300 mg three times daily, used for maintenance therapy is less effective than monthly pentavalent antimony and is not recommended **(DIII)** *(1325)*. Although no published data on efficacy are available, maintenance therapy might be offered in immunocompromised patients with cutaneous leishmaniasis with multiple relapses after adequate treatment.

Discontinuing Secondary Prophylaxis (Chronic Maintenance Therapy)

For some investigators, clinical experience to date suggests that discontinuation of secondary antileishmanial prophylaxis can be considered in patients whose $CD4^+$ count rises above 200–350 cells/μL in response to ART, but that prophylaxis should be continued in those with counts below 200 cells/μL *(1327)*. Others, however, observe that ART might not be sufficient to control the disease, despite increases in $CD4^+$ counts and undetectable viral loads, suggesting that secondary prophylaxis should be maintained indefinitely *(1328, 1329)*. Although data are insufficient to provide a recommendation, discontinuation of secondary prophylaxis after successful treatment of leishmaniasis might be considered after a sustained (i.e., >3–6 months) increase in the $CD4^+$ count to levels >350 cells/μL after initiation of ART **(CIII)** *(1327)*.

Special Considerations During Pregnancy

Diagnostic considerations are the same among pregnant women as in nonpregnant women. Labeling for pentavalent antimony compounds (sodium stibogluconate, available in the United States through CDC, and meglumine antimoniate) states that these drugs are contraindicated for use among pregnant women, although various antimonial compounds were not teratogenic among chickens, rats, or sheep *(1330-1332)*. Good clinical and pregnancy outcomes have been reported for three pregnant women treated with meglumine antimoniate *(1333, 1334)* and five women treated with liposomal amphotericin B *(1335)*. Because of concerns about toxicity and lack of experience with use of pentavalent antimony compounds in human pregnancy, liposomal amphotericin B is the first choice for therapy of visceral leishmaniasis in pregnancy **(AIII)** *(1335)*. Pentavalent antimony should be the second choice **(AIII)**. Miltefosine is teratogenic and is contraindicated in pregnancy *(1310)*. Perinatal transmission of *Leishmania* spp. occurs rarely; eight documented cases have been reported.

No data on the risk of transmission of *Leishmania spp*. among HIV-infected pregnant women are available.

Chagas Disease

Epidemiology

American trypanosomiasis, or Chagas disease, is caused by *Trypanosoma cruzi,* a flagellated protozoan transmitted to mammals by haematophagous reduviid insects *(1337)*.

Chagas disease vectors have been reported in the Americas from 42ºN to 46ºS. The disease is distributed from the southern United States to the southern regions of Argentina and Chile. During a blood meal, *T. cruzi* parasites are deposited with the insect's feces when it defecates shortly after feeding. Humans usually become infected through mucous membranes or breaks in skin. Humans might also acquire trypanosomiasis from blood transfusions, and occasionally transplanted organ, maternal-fetal transmission, from ingesting contaminated food or drink, or from laboratory mishaps *(1338-1340)*.

Chagas disease affects approximately 10 million persons in the Americas *(1341)*. An estimated 50,000–100,000 persons in the United States have acquired *T. cruzi*; a majority are immigrants from disease-endemic areas. In the United States, vectorborne transmission of *T. cruzi* is rare, and the risk of transfusion-associated disease has been reduced recently. Screening of blood donations for anti-*T. cruzi* antibodies was introduced in 2007 by the American Red Cross and Blood Systems Laboratories *(1342)*.

In humans, acute *T. cruzi* infection is accompanied by moderate to high levels of parasitemia. After a few months, if untreated, the acute stage is followed by a lifelong chronic infection, characterized by low-grade and intermittent parasitemia in which tissue parasites are scarce and difficult to demonstrate. All patients with chronic infection are potentially able to transmit Chagas disease through triatomid insect bites, pregnancy, blood transfusion, or organ donation.

Among patients with HIV infection, symptomatic reactivation of chronic, latent *T. cruzi* infection can be triggered by profound immunosuppression *(1343-1346)*.

Clinical Manifestations

Chagas disease can be divided into two stages: acute and chronic. The acute stage of Chagas disease, usually observed among children, begins shortly after infection and lasts 1–2 months. This stage of the disease is often asymptomatic, although fever, malaise, anorexia, induration around the inoculation site (chagoma), or periocular edema (Romaña's sign) might be observed. Generalized lymphadenopathy, splenomegaly, cardiac failure, or meningoencephalitis can also occur during acute disease.

The relatively high parasitemia and symptoms (if present) in acute Chagas disease subside, and the patient enters an asymptomatic phase of the illness with low and intermittent parasitemia. After one or two decades, 10%–30% of infected patients experience chronic cardiac and/or digestive tract disease.

Persons with chronic Chagas disease who are HIV infected usually have higher levels of *T. cruzi* parasitemias than their counterparts who are HIV negative *(1345, 1347)*. Clinical reactivation occurs in HIV-infected patients, as it does with patients who are immunosuppressed by other processes *(1343-1346)*. One prospective study found reactivation in 11 (21%) of 53 patients during a median follow-up interval of 58 months *(1345)*. The majority of cases occur in patients with $CD4^+$ counts <200 cells/μL or prior OIs.

The clinical features of reactivated Chagas disease among patients with HIV infection differ from those observed in persons who are immunosuppressed from other causes. Approximately 75% of HIV-infected patients with reactivation experience an acute meningoencephalitis that is indistinguishable clinically from toxoplasmosis *(1343-1346)*. About 25%–50% of patients also have myocarditis at autopsy**,** but it is not usually the primary manifestation of reactivation.

Diagnosis

T. cruzi infection should be considered in the differential diagnosis of CNS mass lesions and cardiac disease (arrhythmias or heart failure) among patients with HIV infection who have epidemiologic risk factors for Chagas disease. The imaging pattern of brain chagoma is similar to that of cerebral toxoplasmosis, although chagomas tend to be larger than *Toxoplasma* lesions. CT and MRI show subcortical hypodense lesions that enhance with contrast or gadolinium. These lesions most often involve brain white matter. Histopathology shows inflammation and the presence of *T. cruzi* amastigotes in glial cells and, less often, in neurons. CSF shows a mild pleocytosis (lymphocyte predominance), increased protein, and *T. cruzi* trypomastigotes *(1343-1346)*.

A definitive diagnosis is established by brain biopsy or identification of the parasite (or its products) in tissue or blood. Direct tests for identifying *T. cruzi* microscopically are useful during the acute stage and in reactivation of chronic infection (e.g., in the setting of HIV infection). Circulating parasites are rarely detected microscopically in chronic Chagas disease in immunocompetent patients or in HIV-infected patients in the absence of reactivation. If observed in an immunocompromised HIV-positive patient, circulating parasites suggest reactivation and the need for treatment. Blood concentration techniques, such as capillary centrifugation (microhematocrit test), can improve sensitivity *(1348)*. In centrifuged blood,

T. cruzi trypomastigotes are found just above the buffy coat. Centrifugation of CSF also can be employed among patients with suspected CNS Chagas disease. Parasites also might be observed in lymph nodes, bone marrow, skin, pericardial fluid, and CNS mass lesions. Hemoculture is somewhat more sensitive than direct methods, but it might take 2–8 weeks to become positive. PCR of peripheral blood is not helpful for diagnosis of reactivation, because PCR is often positive in the absence of reactivation; however, PCR of CSF has been used to monitor reactivation in the CNS.

Serologic tests to detect the antibody responses to *T. cruzi* infection are useful for diagnosis of disease in chronically infected patients, to screen blood donors, and for seroepidemiologic studies. The techniques used include indirect hemagglutination, direct agglutination, complement fixation, indirect immunofluorescence, ELISA, and radioimmunoprecipitation assays. In the United States, multiple serologic tests are licensed for diagnosis. In late 2006, an ELISA assay for screening blood donors was licensed *(1342)*. As of December 2008, approximately 700 confirmed-positive donations have been reported *(1349)*. Detection of IgM antibodies is not sensitive, even during the acute stage of infection. Diagnosis based on serologic tests requires two positive tests performed with different techniques *(1350)*.

Although the serologic tests for *T. cruzi* infection are reasonably sensitive and specific, both false-positive and false-negative reactions have been reported. Therefore, the diagnosis of Chagas disease should not be excluded based on negative serologic tests if the patient has epidemiologic risk factors and clinical findings compatible with Chagas disease. In this instance, parasitologic testing directly (e.g., microscopic examination of brain tissue and/or demonstration of parasitemia) or with PCR are the best diagnostic strategies. Neonates born to mothers with chronic *T. cruzi* infection will have positive antibody tests, yet might not be infected; parasitologic tests and repeat antibody testing at 6 and 12 months are recommended in this instance *(1351)*.

Preventing Exposure

The reduviid insect vector of Chagas disease typically infests cracks and roofing of poor quality buildings constructed of adobe brick, mud, or thatch. The insects feed at night, and therefore HIV-infected persons living or visiting in areas where Chagas is endemic should avoid overnight stays in such dwellings or sleeping outdoors. They also should be aware that blood products in the United States or abroad might not always be screened routinely for *T. cruzi.* Transfusion, organ transplantation, and MTCT are the more likely infection routes in the United States. Better housing conditions and less efficient vectors might explain the lower risk of vectorial transmission in this country *(1352)*.

No drugs or vaccines for preventing *T. cruzi* infection are available. Preventive measures include spraying infested dwellings with residual-action insecticide and if sleeping outdoors or in suspect dwellings cannot be avoided then sleeping under insecticide-treated bednets,

Preventing Disease

The clinical manifestations of Chagas disease in HIV-positive persons usually represent reactivation and not acute infection with *T. cruzi*. All HIV-infected persons with epidemiologic risk factors for Chagas disease should be tested for antibody to *T. cruzi* to detect latent infection *(1353)*. Antibody-positive patients who have not been previously treated, who are likely to have been infected for less than two decades, and who are without signs or symptoms of Chagas disease might benefit from a single course of medication with benznidazole or nifurtimox **(CIII)**. Limited data and a lack of consensus exist regarding the benefit of chemotherapy in patients with longer-standing infection or chronic disease manifestations.

Optimization of ART might help prevent Chagas reactivation. The majority of cases have occurred in patients who were not taking ART.

Treatment of Disease

Chemotherapy of Chagas disease with benznidazole or nifurtimox is effective in reducing parasitemia and preventing clinical manifestations for patients with acute, early chronic, and reactivated disease. However, these drugs are limited in achieving parasitological cure. Consultation with a specialist should be sought. Benznidazole, 5–8 mg/kg body weight/day for 30–60 days, is the initial treatment most commonly recommended **(BIII)**. Nifurtimox, 8–10 mg/kg body weight/day, administered for 90–120 days is an alternative **(CIII).** However, the duration of therapy with either of these agents has not been studied for persons coinfected with HIV. Mortality is high, even in patients who receive chemotherapy. Limited data suggest that early recognition and treatment of reactivation might improve prognosis *(1345).* Neither anti-trypanosomal drug is licensed in the United States; however, the drugs are available from the CDC Drug Service (404-639-3670) for use under investigational protocols.

ART is likely to reduce or prevent initial reactivation of *T. cruzi* or its recurrence. ART should be initiated or optimized once a patient with acute disease is clinically stable **(AIII).**

Monitoring and Adverse Events, Including Immune Reconstitution Inflammatory Syndrome (IRIS)

Patients undergoing treatment should be monitored closely because both benznidazole and nifurtimox are toxic *(1354)*. Benznidazole causes peripheral neuropathy, rash, and granulocytopenia. Nifurtimox causes anorexia, nausea, vomiting, abdominal pain and weight loss, restlessness, tremors, and peripheral neuropathy. The adverse effects of both drugs wane when the drugs are discontinued.

No reports are available regarding *T. cruzi* infection and IRIS.

Management of Treatment Failure

Although no data are available, retreatment with benznidazole or nifurtimox is recommended for HIV-infected patients who fail to respond or who relapse following initial therapy **(AIII)**.

Preventing Recurrence

Patients with HIV infection are potentially at risk for recurrent or relapsing clinical manifestations because of intermittent reactivation of chronic infection. The drugs are only partially effective in the chronic stage of disease, are suppressive rather than curative, and might require lifelong administration to prevent relapse in the setting of continued immunosuppression. Because the drugs are toxic and experience with their use in HIV-infected patients is limited, expert advice about indicators and regimens should be sought. Whether secondary prophylaxis or chronic maintenance therapy should be used in HIV-infected patients with latent Chagas disease is unclear, particularly when modern ART is used.

Special Considerations During Pregnancy

The seroprevalence of *T. cruzi* infection among pregnant women in areas where the disease is endemic in Latin America can be as high as 50% in urban areas and 81% in rural areas. In the United States, one study of 3,765 pregnant women in Houston, Texas, confirmed antibody to *T. cruzi* in 0.4% of Hispanic women and 0.1% of non-Hispanic women *(1355)*.

Perinatal transmission rates among general populations of pregnant women seropositive for antibodies to *T. cruzi* range from 2% to 10% *(1356)*. The effect of concurrent HIV infection in the mother on risk of perinatal transmission of *T. cruzi* is not known; however, limited data available at present suggest that rates of perinatal transmission might be higher for HIV-infected women than the rates previously documented for immunocompetent mothers *(1345)*. Infants coinfected with HIV and *T. cruzi* might be more likely to have symptoms, especially neurologic symptoms *(1351, 1357)*.

Congenital infection with *T. cruzi* might increase the risk of spontaneous abortion, stillbirth, and low birthweight *(1356)*. Congenital Chagas disease in newborn infants ranges from subclinical to life threatening with severe neurologic and cardiac disease.

Minimal data are available on potential reproductive toxicity of benznidazole and nifurtimox, although both drugs have been associated with increased detection of chromosomal aberrations in children being treated for Chagas disease *(1358, 1359)*. Benznidazole crosses the placenta in rats and covalently binds to fetal proteins *(1360)*. Because of the toxicity and limited experience with use of these drugs in pregnancy, treatment of acute *T. cruzi* infection among pregnant women should only be undertaken in consultation with a specialist in this area, and treatment of chronic disease should be considered only after completion of the pregnancy. For HIV-infected pregnant women with symptomatic reactivation of *T. cruzi* infection, the immune response should be maximized with ART **(AIII).**

Isosporiasis

Epidemiology

Isosporiasis occurs worldwide but predominantly in tropical and subtropical regions. Immunocompromised persons, including those with AIDS, are at increased risk for chronic, debilitating illness *(30, 1361-1366)*. Although *Isospora belli* completes its life cycle in humans, the oocysts shed in the feces of infected persons must mature (sporulate) outside the host, in the environment, to become infective. On the basis of limited data, the maturation process is completed in approximately 1–2 days but might occur in <24 hours *(1361)*. Infection results from ingestion of sporulated oocysts (e.g., in contaminated food or water). After ingestion, the parasite invades enterocytes in the small intestine. Ultimately, immature oocysts are produced and shed in stool.

Clinical Manifestations

The most common manifestation is watery, nonbloody diarrhea, which may be associated with abdominal pain, cramping, anorexia, nausea, vomiting, and low-grade fever. The diarrhea can be profuse and prolonged, particularly in immunocompromised patients, resulting in severe dehydration, weight loss, and malabsorption *(1365-1370)*. Acalculous cholecystitis *(1361, 1371)* and reactive arthritis *(1372)* have also been reported.

Diagnosis

Typically, infection is diagnosed by detecting *Isospora* oocysts (dimensions, 23–36 μm by 12–17 μm) in fecal specimens *(1361)*. Oocysts might be shed intermittently and at low levels, even by persons with profuse diarrhea. Diagnosis might be facilitated by repeated stool examinations with sensitive methods (e.g., oocysts stain bright red with modified acid-

fast techniques and they autofluoresce when viewed by UV fluorescence microscopy) *(1361, 1373)*. Infection also can be diagnosed by detecting oocysts in duodenal aspirates/mucus or developmental stages of the parasite in intestinal biopsy specimens *(1361, 1369)*. Extraintestinal infection (e.g., in the biliary tract, lymph nodes, spleen, and liver) has been documented in postmortem examinations of patients with AIDS *(1361, 1374-1376)*.

Preventing Exposure

Not applicable to residents of the United States.

Preventing Disease

In some settings, chemoprophylaxis with TMP-SMX has been associated with a lower incidence or prevalence of isosporiasis *(30, 1362, 1363)*. In a randomized, placebo-controlled trial, daily TMP-SMX (160/800 mg) was protective against isosporiasis in persons with early-stage HIV infection (WHO clinical stage 2 or 3 at enrollment) *(30)*. In an observational study, the incidence of isosporiasis decreased after widespread introduction of ART, except among persons with $CD4^+$ counts <50 cells/μL *(1362)*. After adjustment for the $CD4^+$ count, the risk of isosporiasis was substantially lower among persons receiving prophylaxis with TMP-SMX, sulfadiazine, or pyrimethamine (unspecified regimens). In analyses of data from a county AIDS surveillance registry during the pre-ART era, the prevalence of isosporiasis was lower in persons with (vs. without) a history of PCP—indirect evidence of a protective effect from use of TMP-SMX for PCP *(1363)*. However, insufficient evidence is available to support a general recommendation for primary prophylaxis for isosporiasis per se **(DIII)**.

Treatment of Disease

Clinical management includes fluid and electrolyte support for dehydrated patients and nutritional supplementation for malnourished patients **(AIII)**. TMP-SMX is the antimicrobial agent of choice for treatment of isosporiasis **(AI).** It is the only agent whose use is supported by substantial published data and clinical experience. Therefore, potential alternative therapies should be reserved for patients with documented sulfa intolerance or treatment failure **(AIII).**

Three studies among HIV-infected patients in Haiti have demonstrated the effectiveness of various treatment regimens of TMP-SMX and the need for and effectiveness of secondary prophylaxis *(1365, 1366, 1377)*. The patients were not receiving ART, and laboratory indicators of immunodeficiency (e.g., $CD4^+$ counts) were not specified. On the basis of the initial studies *(1365, 1366)*, the traditional treatment regimen has been a 10-day course of TMP-SMX (160/800 mg) administered four times a day **(AII)** *(505)*. In a more recent study, TMP-SMX (160/800 mg) administered twice a day was effective **(BI)** *(1377)*. Although experience using two versus four daily doses of TMP-SMX (160/800 mg) is limited, one approach would be to start with this regimen but to increase the daily dose and/or the duration of therapy (up to 3–4 weeks) *(1365, 1369)* if symptoms worsen or persist **(BIII).** Intravenous administration of TMP-SMX should be considered for patients with potential or documented malabsorption.

Limited data suggest that therapy with pyrimethamine–sulfadiazine and pyrimethamine–sulfadoxine might be effective *(1361, 1368, 1369, 1378-1380)*. However, the combination of pyrimethamine plus sulfadoxine is not typically recommended for use in the United States **(CIII)**; it has been associated with an increased risk of severe cutaneous reactions, including Stevens-Johnson syndrome *(125)*, and pyrimethamine and sulfadoxine are slowly cleared from the body after therapy is discontinued.

Single-agent therapy with pyrimethamine has been used with anecdotal success for treatment and prevention of isosporiasis *(1362, 1381, 1382)*. Pyrimethamine (50–75 mg/day) — plus leucovorin (10–25 mg/day) to prevent myelosuppression — might be an effective treatment alternative (e.g., it is the traditional option for sulfa-intolerant patients) **(BIII).**

Monitoring and Adverse Events, Including Immune Reconstitution Inflammatory Syndrome (IRIS)

Patients should be monitored for clinical response and adverse events. Among patients with AIDS, TMP-SMX therapy is commonly associated with side effects (e.g., rash, fever, leukopenia, thrombocytopenia, elevated transaminase levels). IRIS has not been reported in association with treatment of isosporiasis.

Management of Treatment Failure

If symptoms worsen or persist despite approximately 5–7 days of TMP-SMX therapy, the possibilities of noncompliance, malabsorption, and concurrent infections/enteropathies should be considered; the TMP-SMX regimen (i.e., daily dose, duration, and mode of administration) also should be reevaluated. For patients with documented sulfa intolerance or treatment failure, use of a potential alternative agent (e.g., pyrimethamine) should be considered. Ciprofloxacin might be considered as a second-line agent **(CI).** On the basis of limited data from a randomized, controlled trial in Haiti, ciprofloxacin (500 mg twice daily for 7 days) is less effective than TMP-SMX but might have modest activity against *I. belli (1377)*.

Unsubstantiated or mixed data are available for albendazole *(1382-1384)*, nitazoxanide *(1385, 1386)*, doxycycline *(1387)*, the macrolides roxithromycin and spiramycin *(1379, 1388, 1389)*, and the veterinary anticoccidial agent diclazuril

(1390, 1391) **(CIII)**. Limited data suggest that drugs such as metronidazole, quinacrine, iodoquinol, paromomycin, and furazolidone are ineffective **(DIII)** *(1367, 1379-1381, 1388, 1390)*. Apparent or partial responses, if noted, might be attributable to treatment of concomitant infections or to nonspecific effects.

Preventing Recurrence

Patients with $CD4^+$ counts <200 cells/μL should receive secondary prophylaxis (chronic maintenance therapy) with TMP-SMX **(AI).** In studies in Haiti, approximately 50% of patients who did not receive secondary prophylaxis had symptomatic recurrences approximately 2 months after completing a course of TMP-SMX therapy, relapses rapidly responded to retreatment, and secondary prophylaxis decreased the risk for relapse *(1365, 1366, 1377)*. In a randomized, placebo-controlled trial, no symptomatic recurrences were noted among patients who received maintenance therapy with thrice-weekly TMP-SMX (160/800 mg) **(AI)** *(1366)*. Daily TMP-SMX (160/800 mg) and thrice-weekly TMP-SMX (320/1,600 mg) have been effective **(BIII)** *(1364, 1369)*.

In sulfa-intolerant patients, pyrimethamine (25 mg/day) with leucovorin (5–10 mg/day) has been used **(BIII)** *(1381)*. Ciprofloxacin (500 mg thrice weekly) might be considered as a second-line alternative **(CI)** *(1377)*.

Discontinuing Secondary Prophylaxis

The concern of discontinuing prophylaxis has not been evaluated in a clinical trial. Chemoprophylaxis probably can be safely discontinued in patients without evidence of active *I. belli* infection who have a sustained increase in the $CD4^+$ count to levels >200 cells/μL for >6 months after initiation of ART **(BIII)**.

Special Considerations During Pregnancy

TMP-SMX is usually the agent of choice for primary treatment and secondary prophylaxis in pregnant women, as it is for nonpregnant women. Although first-trimester exposure to trimethoprim might be associated with a small increased risk of birth defects *(173-176)*, in the setting of maternal symptomatic *I. belli* infection, therapy with TMP-SMX should be provided. Because of concerns about possible teratogenicity associated with drug exposure during the first trimester, clinicians might withhold secondary prophylaxis during the first trimester and treat only symptomatic infection. Although pyrimethamine has been associated with birth defects in animals, limited human data have not suggested an increased risk of defects *(228)*. Human data about the use of ciprofloxacin during several hundred pregnancies have not suggested an increased risk of birth defects or cartilage abnormalities *(395)*.

References

1. Walensky RP, Paltiel AD, Losina E, et al. The survival benefits of AIDS treatment in the United States. J Infect Dis 2006;194:11–9.
2. Palella FJ, Jr., Delaney KM, Moorman AC, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. N Engl J Med 1998;338:853–60.
3. Detels R, Munoz A, McFarlane G, Kingsley LA, et al. Effectiveness of potent antiretroviral therapy on time to AIDS and death in men with known HIV infection duration: Multicenter AIDS Cohort Study Investigators. JAMA 1998;280:1497–503.
4. Jones JL, Hanson DL, Dworkin MS, et al. Surveillance for AIDS-defining opportunistic illnesses, 1992–1997. In: Surveillance Summaries, April 16, 1999. MMWR 1999;48:(No. SS-2).
5. Mocroft A, Vella S, Benfield TL, et al. Changing patterns of mortality across Europe in patients infected with HIV-1. EuroSIDA Study Group. Lancet 1998;352:1725–30.
6. McNaghten AD, Hanson DL, Jones JL, Dworkin MS, Ward JW: Effects of antiretroviral therapy and opportunistic illness primary chemoprophylaxis on survival after AIDS diagnosis: Adult/Adolescent Spectrum of Disease Group. AIDS 1999;13:1687–95.
7. Miller V, Mocroft A, Reiss P, et al. Relations among CD4 lymphocyte count nadir, antiretroviral therapy, and HIV-1 disease progression: results from the EuroSIDA study. Ann Intern Med 1999;130:570–7.
8. Dore GJ, Li Y, McDonald A, Ree H, Kaldor JM. Impact of highly active antiretroviral therapy on individual AIDS-defining illness incidence and survival in Australia. J Acquir Immune Defic Syndr 2002;29:388–95.
9. Perbost I, Malafronte B, Pradier C, et al. In the era of highly active antiretroviral therapy, why are HIV-infected patients still admitted to hospital for an inaugural opportunistic infection? HIV Med 2005;6:232–9.
10. Palacios R, Hidalgo A, Reina C, de la Torre M, Marquez M, Santos J. Effect of antiretroviral therapy on admissions of HIV-infected patients to an intensive care unit. HIV Med 2006;7:193–6.
11. Gebo KA, Fleishman JA, Reilly ED, Moore RD. High rates of primary *Mycobacterium avium* complex and *Pneumocystis jiroveci* prophylaxis in the United States. Med Care 2005;43(Suppl. 9):23–30.
12. Bonnet F, Lewden C, May T, et al. Opportunistic infections as causes of death in HIV-infected patients in the HAART era in France. Scand J Infect Dis 2005;37:482–7.
13. Teshale EH, Hanson DL, Wolfe MI, et al. Reasons for lack of appropriate receipt of primary *Pneumocystis jiroveci* pneumonia prophylaxis among HIV-infected persons receiving treatment in the United States: 1994–2003. Clin Infect Dis 2007;44:879–83.
14. Gebo KA, Fleishman JA, Moore RD. Hospitalizations for metabolic conditions, opportunistic infections, and injection drug use among HIV patients: trends between 1996 and 2000 in 12 states. J Acquir Immune Defic Syndr 2005;40:609–16.
15. Betz ME, Gebo KA, Barber E et al. Patterns of diagnoses in hospital admissions in a multistate cohort of HIV-positive adults in 2001. Med Care 2005;43:1113–4.
16. Buchecz K, Baker R, Moorman AC, et al. Rates of hospitalizations and associated diagnoses in a large multistate cohort of HIV patients in the United States, 1994-2005. AIDS 2008;22(11):1345-54.
17. Louie JK, Hsu LC, Osmond DH, Katz MH, Schwarcz SK. Trends in causes of death among persons with acquired immunodeficiency syndrome in the era of highly active antiretroviral therapy, San Francisco, 1994–1998. J Infect Dis 2002;186:1023–7.
18. Palella FJ, Jr., Baker RK, Moorman AC, et al. Mortality in the highly active antiretroviral therapy era: changing causes of death and disease in the HIV outpatient study. J Acquir Immune Defic Syndr 2006;43:27–34.

19. Smit C, Geskus R, Walker S. et al. Effective therapy has altered the spectrum of cause-specific mortality following HIV seroconversion. AIDS 2006;20:741–9.
20. Lawn SD, Butera ST, Folks TM. Contribution of immune activation to the pathogenesis and transmission of human immunodeficiency virus type 1 infection. Clin Microbiol Rev 2001;14:753–77.
21. Toossi Z, Mayanja-Kizza H, Hirsch CS, et al. Impact of tuberculosis (TB) on HIV-1 activity in dually infected patients. Clin Exp Immunol 2001;123:233–8.
22. Sadiq ST, McSorley J, Copas A, et al. The effects of early syphilis on CD4 counts and HIV-1 RNA viral loads in blood and semen. Sex Transm Infect 2005;81:380–5.
23. Bentwich Z. Concurrent infections that rise the HIV viral load. J HIV Ther 2003;8:72–5.
24. Kublin JG, Patnaik P, Jere CS, et al. Effect of *Plasmodium falciparum* malaria on concentration of HIV-1-RNA in the blood of adults in rural Malawi: a prospective cohort study. Lancet 2005;365:233–40.
25. Abu-Raddad LJ, Patnaik P, Kublin JG. Dual infection with HIV and malaria fuels the spread of both diseases in sub-Saharan Africa. Science 2006;314:1603–6.
26. Quinn TC, Wawer MJ, Sewankambo N, et al. Viral load and heterosexual transmission of human immunodeficiency virus type 1: Rakai Project Study Group. N Engl J Med 2000; 342:921–9.
27. DiRienzo A, van Der Horst C, Finkelstein DM, Frame P, Bozzette SA, Tashima KT. Efficacy of trimethoprim-sulfamethoxazole for the prevention of bacterial infections in a randomized prophylaxis trial of patients with advanced HIV infection. AIDS Res Hum Retroviruses 2002;18:89–94.
28. Wiktor SZ, Sassan-Morokro M, Grant AD, et al. Efficacy of trimethoprim-sulphamethoxazole prophylaxis to decrease morbidity and mortality in HIV-1-infected patients with tuberculosis in Abidjan, Côte d'Ivoire: a randomised controlled trial. Lancet 1999;353:1469–75.
29. Whalen CC, Johnson JL, Okwera A, et al. A trial of three regimens to prevent tuberculosis in Ugandan adults infected with the human immunodeficiency virus. Uganda-Case Western Reserve University Research Collaboration. N Engl J Med 1997;337:801–8.
30. Anglaret X, Chene G, Attia A, et al. Early chemoprophylaxis with trimethoprim-sulphamethoxazole for HIV-1-infected adults in Abidjan, Cote d'Ivoire: a randomised trial. Cotrimo-CI Study Group. Lancet 1999;353:1463–8.
31. Chintu C, Bhat GJ, Walker AS, et al. Co-trimoxazole as prophylaxis against opportunistic infections in HIV-infected Zambian children (CHAP): a double-blind randomised placebo-controlled trial. Lancet 2004;364:1865–71.
32. CDC. Guidelines for prophylaxis against *Pneumocystis carinii* pneumonia for persons infected with human immunodeficiency virus. MMWR 1989;38:1–9.
33. Masur H. Recommendations on prophylaxis and therapy for disseminated *Mycobacterium avium* complex disease in patients infected with the human immunodeficiency virus. Public Health Service Task Force on Prophylaxis and Therapy for *Mycobacterium avium* Complex. N Engl J Med 1993; 329:898–904.
34. CDC. USPHS/IDSA guidelines for the prevention of opportunistic infections in persons infected with human immunodeficiency virus: a summary. MMWR 1995;44(No. RR-8).
35. CDC. USPHS/IDSA guidelines for the prevention of opportunistic infections in persons infected with human immunodeficiency virus. USPHS/IDSA Prevention of Opportunistic Infections Working Group. MMWR 1997;46(No. RR-12).
36. CDC. USPHS/IDSA guidelines for the prevention of oppurtunistic infections in persons infected with human immunodeficiency virus. MMWR 1999;48(No. RR-10).
37. CDC. Guidelines for preventing opportunistic infections among HIV-infected persons–2002. Recommendations of the U.S. Public Health Service and the Infectious Diseases Society of America. MMWR 2002;51(No. RR-8).
38. U.S. Public Health Service. Guidelines for the prevention of opportunistic infections in persons infected with human immunodeficiency virus: disease-specific recommendations. Clin Infect Dis 1995;21(Suppl 1):S32-43.
39. USPHS/IDSA. Prevention of Opportunistic Infections Working Group, US Public Health Services/Infectious Diseases Society of America: 1997 USPHS/IDSA guidelines for the prevention of opportunistic infections in persons infected with human immunodeficiency virus: disease-specific recommendations. Clin Infect Dis 1997;25(Suppl 3):S313-35.
40. USPHS/IDSA. Guidelines for the prevention of opportunistic infections in persons infected with human immunodeficiency virus. Clin Infect Dis 2000;30(Suppl 1):S29-65.
41. U.S. Public Health Service. Guidelines for the prevention of opportunistic infections in persons infected with human immunodeficiency virus: a summary. Ann Intern Med 1996; 124:349–68.
42. U.S. Public Health Service. Guidelines for the prevention of opportunistic infections in persons infected with human immunodeficiency virus. Ann Intern Med 1997;127:922–46.
43. U.S. Public Health Service. Guidelines for the prevention of opportunistic infections in persons infected with HIV: part I Prevention of exposure. Am Fam Physician 1997;56:823–34.
44. U.S. Public Health Service. Guidelines for the prevention of opportunistic infections in persons infected with HIV: part I. Prevention of exposure. Am Fam Physician 2000;61:163–71.
45. US Public Health Service. Antiretroviral therapy and medical management of pediatric HIV infection and 1997 USPHS/IDSA report on the prevention of opportunistic infections in persons infected with human immunodeficiency virus. Pediatrics 1998;102:999–1085.
46. Kaplan JE, Masur H, Jaffe HW, Holmes KK. Reducing the impact of opportunistic infections in patients with HIV infection. New guidelines. JAMA 1995;274:347–8.
47. Kaplan JE, Masur H, Jaffe HW, Holmes KK. Preventing opportunistic infections in persons infected with HIV: 1997 guidelines. JAMA 1997;278:337–8.
48. CDC. Treating Opportunistic Infections Among HIV-Infected Adults and Adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association/Infectious Diseases Society of America. MMWR 2004;53(No. RR-15).
49. CDC. Treating opportunistic infections among HIV-exposed and infected children: recommendations from CDC, the National Institutes of Health, and the Infectious Diseases Society of America. MMWR 2004;53(No. RR-14).
50. Carr A, Marriott D, Field A, Vasak E, Cooper DA. Treatment of HIV-1-associated microsporidiosis and cryptosporidiosis with combination antiretroviral therapy. Lancet 1998;351:256–61.
51. Foudraine NA, Weverling GJ, van Gool T, et al. Improvement of chronic diarrhea in patients with advanced HIV-1 infection during potent antiretroviral therapy. AIDS 1998;12:35–41.
52. Tantisiriwat W, Tebas P, Clifford DB, Powderly WG, Fichtenbaum CJ. Progressive multifocal leukoencephalopathy in patients with AIDS receiving highly active antiretroviral therapy. Clin Infect Dis 1999;28:1152–4.
53. Murdaca G, Campelli A, Setti M, et al. Complete remission of AIDS/Kaposi's sarcoma after treatment with a combination of two nucleoside reverse transcriptase inhibitors and one non-nucleoside reverse transcriptase inhibitor [Letter]. AIDS 2002;16:304–5.
54. Egger M, May M, Chene, et al. Prognosis of HIV-1–infected patients starting highly active antiretroviral therapy: a collaborative analysis of prospective studies. Lancet 2002;360:119–29.

55. Phillips P, Kwiatkowski MB, Copland M, et al. Mycobacterial lymphadenitis associated with the initiation of combination ART. J Acquir Immune Defic Syndr Hum Retrovirol 1999;20:122–8.
56. Race EM, Adelson-Mitty J, Kriegel GR, et al. Focal mycobacterial lymphadenitis following initiation of protease-inhibitor therapy in patients with advanced HIV-1 disease. Lancet 1998;351:252–5.
57. Dworkin MS, Fratkin MD. *Mycobacterium avium* complex lymph node abscess after use of highly active antiretroviral therapy in a patient with AIDS [Letter]. Arch Intern Med 1998;158:1828.
58. Navas E, Martin-Davila P, Moreno L. Paradoxical reactions of tuberculosis in patients with the acquired immunodeficiency syndrome who are treated with highly active antiretroviral therapy. Arch Intern Med 2002;162:97–9.
59. Wislez M, Bergot E, Antoine M, et al. Acute respiratory failure following HAART introduction in patients treated for *Pneumocystis carinii* pneumonia. Am J Respir Crit Care Med 2001;164:847–51.
60. Lanzafame M, Trevenzoli M, Carreetta G, et al. Mediastinal lymphadenitis due to cryptococcal infection in HIV-positive patients on highly active antiretroviral therapy. Chest 1999;116:848–9.
61. Miralles P, Berenguer J, Lacruz C, et al. Inflammatory reactions in progressive multifocal leukoencephalopathy after highly active antiretroviral therapy. AIDS 2001;15:1900–2.
62. Cinque P, Pierotti C, Vigano MG, et al. The good and evil of HAART in HIV- progressive multifocal leukoencephalopathy. J Neurovirol 2001;7:358–63.
63. Giudici B, Vaz B, Bossolasco S, et al. Highly active antiretroviral therapy and progressive multifocal leukoencephalopathy: effects on cerebrospinal fluid markers of JC virus replication and immuneresponse. Clin Infect Dis 2000;30:95–9.
64. DeSimone JA, Pomerantz RJ, Babinchak TJ. Inflammatory reactions in HIV-1–infected persons after initiation of highly active antiretroviral therapy. Ann Intern Med 2000;133:447–54.
65. Lipman M, Breen R. Immune reconstitution inflammatory syndrome in HIV. Curr Opin Infect Dis 2006;19:20–5.
66. Shelburne SA, Visnegarwala F, Darcourt J, et al. Incidence and risk factors for immune reconstitution inflammatory syndrome during highly active antiretroviral therapy. AIDS 2005;19:399–406.
67. Kambugu A, Meya DB, Rhein J, et al. Outcomes of cryptococcal meningitis in Uganda before and after the availability of highly active antiretroviral therapy. Clin Infect Dis 2008;46:1694–701.
68. Zolopa A, Andersen J, Komarow L, et al. Immediate versus deferred ART in the setting of acute AIDS-related OI: final results of a randomized strategy trial, ACTG A5164. 15th CROI;2008; Boston, MA. Abstract 142.
69. Jacobson MA, Zegans M, Pavan PR, et al. Cytomegalovirus retinitis after initiation of highly active antiretroviral therapy. Lancet 1997;349:1443–5.
70. French MA, Lenzo N, John M, et al. Immune restoration disease after the treatment of immunodeficient HIV-infected patients with highly active antiretroviral therapy. HIV Med 2000;1:107–15.
71. Price P, Mathiot N, Krueger R, et al. Immune dysfunction and immune restoration disease in HIV patients given highly active antiretroviral therapy. J Clin Virol 2001; 22:279–87
72. Fox PA, Barton SE, Francis N, et al. Chronic erosive herpes simplex virus infection of the penis, a possible immune reconstitution disease. HIV Med 1999;1:10–8.
73. Currier JS, Williams PL, Koletar SL, et al. Discontinuation of *Mycobacterium avium* complex prophylaxis in patients with antiretroviral therapy–induced increases in CD4+ cell count: a randomized, double-blind, placebo-controlled trial. Ann Intern Med 2000;133:493–503.
74. Cinti SK, Kaul DR, Sax PE, et al. Recurrence of *Mycobacterium avium* infection in patients receiving highly active antiretroviral therapy and antimycobacterial agents. Clin Infect Dis 2000;30:511–4.
75. Cruickshank DP, Wigton TR, Hays PM. Maternal physiology in pregnancy. In: Gabbe SG, Neibyl JR, Simpson JL, eds. Obstetrics: Normal and Problem Pregnancies. New York, NY: Churchchill Livingstone, 1996.
76. ACOG Committee: Opinion. Number 299, September 2004 (replaces No. 158, September 1995). Guidelines for diagnostic imaging during pregnancy. Obstet Gynecol 2004;104(3):647–51.
77. Toppenberg KS, Hill DA, Miller DP. Safety of radiographic imaging during pregnancy. Am Fam Physician 1999;59:1813–8,1820.
78. Adelstein SJ. Administered radionuclides in pregnancy. Teratology 1999;59:236–9.
79. CDC. USPHS task force recommendations for the use of antiretroviral drugs in pregnant women infected with HIV-1 for maternal health and for reducing perinatal HIV-1 transmission in the United States. MMWR 1998;47(No. RR-2).
80. American College of Obstetricians and Gynecologists. Practice Bulletin: Antepartum fetal surveillance. No. 9; October 1999.
81. Pifer LL, Hughes WT, Stagno S, Woods D. *Pneumocystis carinii* infection: evidence for high prevalence in normal and immunosuppressed children. Pediatrics 1978;61:35–41.
82. Keely SP, Stringer JR, Baughman RP, et al. Genetic variation among *Pneumocystis carinii hominis* isolates in recurrent pneumocystosis. J Infect Dis 1995;172:595–8.
83. Helweg-Larsen J, Tsolaki AG, Miller RF, Lundgren B, Wakefield AE. Clusters of *Pneumocystis carinii* pneumonia: analysis of person-to-person transmission by genotyping. Qjm 1998;91:813–20.
84. Huang LM, Huang SY, Chen MY, et al. Geographical differences in human herpesvirus 8 seroepidemiology: a survey of 1,201 individuals in Asia. J Med Virol 2000;60:290–3.
85. Phair J, Munoz A, Detels R, et al. The risk of *Pneumocystis carinii* pneumonia among men infected with human immunodeficiency virus type 1. Multicenter AIDS Cohort Study Group. N Engl J Med 1990;322:161–5.
86. Kaplan JE, Hanson DL, Navin TR, Jones JL. Risk factors for primary *Pneumocystis carinii* pneumonia in human immunodeficiency virus-infected adolescents and adults in the United States: reassessment of indications for chemoprophylaxis. J Infect Dis 1998;178:1126–32.
87. Kaplan JE, Hanson DL, Jones JL, Dworkin MS. Viral load as an independent risk factor for opportunistic infections in HIV-infected adults and adolescents. AIDS 2001;15:1831–6.
88. Furrer H, Egger M, Opravil M, et al. Discontinuation of primary prophylaxis against *Pneumocystis carinii* pneumonia in HIV-1-infected adults treated with combination antiretroviral therapy. Swiss HIV Cohort Study. N Engl J Med 1999;340:1301–6.
89. Lundberg BE, Davidson AJ, Burman WJ. Epidemiology of *Pneumocystis carinii* pneumonia in an era of effective prophylaxis: the relative contribution of non-adherence and drug failure. AIDS 2000;14:2559–66.
90. Wolff AJ, O'Donnell AE. Pulmonary manifestations of HIV infection in the era of highly active antiretroviral therapy. Chest 2001;120:1888–93.
91. Kovacs JA, Hiemenz JW, Macher AM, et al. *Pneumocystis carinii* pneumonia: a comparison between patients with the acquired immunodeficiency syndrome and patients with other immunodeficiencies. Ann Intern Med 1984;100:663–71.
92. Selwyn PA, Pumerantz AS, Durante A, et al. Clinical predictors of *Pneumocystis carinii* pneumonia, bacterial pneumonia and tuberculosis in HIV-infected patients. AIDS 1998;12:885–93.
93. Smith DE, McLuckie A, Wyatt J, Gazzard B. Severe exercise hypoxaemia with normal or near normal X-rays: a feature of *Pneumocystis carinii* infection. Lancet 1988; 2:1049–51.
94. Zaman MK, White DA. Serum lactate dehydrogenase levels and *Pneumocystis carinii* pneumonia: diagnostic and prognostic significance. Am Rev Respir Dis 1988;137:796–800.
95. Opravil M, Marincek B, Fuchs WA, et al. Shortcomings of chest radiography in detecting *Pneumocystis carinii* pneumonia. J Acquir Immune Defic Syndr 1994;7:39–45.

96. Metersky ML, Colt HG, Olson LK, Shanks TG. AIDS-related spontaneous pneumothorax: risk factors and treatment. Chest 1995;108:946–51.
97. Sepkowitz KA, Telzak EE, Gold JW, et al. Pneumothorax in AIDS. Ann Intern Med 1991;114:455–9.
98. Baughman RP, Dohn MN, Frame PT. The continuing utility of bronchoalveolar lavage to diagnose opportunistic infection in AIDS patients. Am J Med 1994;97:515–22.
99. Stover DE, Zaman MB, Hajdu SI, et al. Bronchoalveolar lavage in the diagnosis of diffuse pulmonary infiltrates in the immunosuppressed host. Ann Intern Med 1984;101:1–7.
100. Gruden JF, Huang L, Turner J, et al. High-resolution CT in the evaluation of clinically suspected *Pneumocystis carinii* pneumonia in AIDS patients with normal, equivocal, or nonspecific radiographic findings. Am J Roentgenol 1997;169:967–75.
101. Hidalgo A, Falco V, Mauleon S, et al. Accuracy of high-resolution CT in distinguishing between *Pneumocystis carinii* pneumonia and non-*Pneumocystis carinii* pneumonia in AIDS patients. Eur Radiol 2003;13:1179–84.
102. Rosso J, Guillon JM, Parrot A, et al. Technetium-99m-DTPA aerosol and gallium-67 scanning in pulmonary complications of human immunodeficiency virus infection. J Nucl Med 1992;33:81–7.
103. Kovacs JA, Ng VL, Masur H, et al. Diagnosis of *Pneumocystis carinii* pneumonia: improved detection in sputum with use of monoclonal antibodies. N Engl J Med 1988;318:589–93.
104. Roger PM, Vandenbos F, Pugliese P, et al. Persistence of *Pneumocystis carinii* after effective treatment of *P. carinii* pneumonia is not related to relapse or survival among patients infected with human immunodeficiency virus. Clin Infect Dis 1998;26:509–10.
105. Larsen HH, Masur H, Kovacs JA, et al. Development and evaluation of a quantitative, touch-down, real-time PCR assay for diagnosing *Pneumocystis carinii* pneumonia. J Clin Microbiol 2002;40:490–4.
106. Torres J, Goldman M, Wheat LJ, et al. Diagnosis of *Pneumocystis carinii* pneumonia in human immunodeficiency virus-infected patients with polymerase chain reaction: a blinded comparison to standard methods. Clin Infect Dis 2000;30:141–5.
107. Larsen HH, Huang L, Kovacs JA, et al. A prospective, blinded study of quantitative touch-down polymerase chain reaction using oral-wash samples for diagnosis of *Pneumocystis* pneumonia in HIV-infected patients. J Infect Dis 2004;189:1679–83.
108. Pisculli M, Sax P. Use of a Serum b-Glucan Assay for Diagnosis of HIV-related *Pneumocystis jiroveci* pneumonia in patients with negative microscopic examination results. Clin Infect Dis 2008 (in press).
109. Bozzette SA, Finkelstein DM, Spector SA, et al. A randomized trial of three antipneumocystis agents in patients with advanced human immunodeficiency virus infection. N Engl J Med 1995;332:693–9.
110. Schneider MM, Hoepelman AI, Eeftinck Schattenkerk JK, et al. A controlled trial of aerosolized pentamidine or trimethoprim-sulfamethoxazole as primary prophylaxis against *Pneumocystis carinii* pneumonia in patients with human immunodeficiency virus infection. N Engl J Med 1992;327:1836–41.
111. Schneider MM, Nielsen TL, Nelsing S, et al. Efficacy and toxicity of two doses of trimethoprim-sulfamethoxazole as primary prophylaxis against *Pneumocystis carinii* pneumonia in patients with human immunodeficiency virus. J Infect Dis 1995;171:1632–6.
112. El-Sadr WM, Luskin-Hawk R, Yurik TM, et al. A randomized trial of daily and thrice-weekly trimethoprim-sulfamethoxazole for the prevention of *Pneumocystis carinii* pneumonia in human immunodeficiency virus-infected persons. Clin Infect Dis 1999;29:775–83.
113. Carr A, Tindall B, Brew BJ, et al. Low-dose trimethoprim-sulfamethoxazole prophylaxis for toxoplasmic encephalitis in patients with AIDS. Ann Intern Med 1992; 117:106–11.
114. Hardy WD, Feinberg J, Finkelstein DM, et al. A controlled trial of trimethoprim-sulfamethoxazole or aerosolized pentamidine for secondary prophylaxis of *Pneumocystis carinii* pneumonia in patients with the acquired immunodeficiency syndrome. N Engl J Med 1992;327:1842–8.
115. Para MF, Finkelstein D, Becker S, et al. Reduced toxicity with gradual initiation of trimethoprim-sulfamethoxazole as primary prophylaxis for *Pneumocystis carinii* pneumonia. J Acquir Immune Defic Syndr 2000;24:337–43.
116. Leoung GS, Stanford JF, Giordano MF, et al. Trimethoprim-sulfamethoxazole (TMP-SMZ) dose escalation versus direct rechallenge for *Pneumocystis carinii* pneumonia prophylaxis in human immunodeficiency virus-infected patients with previous adverse reaction to TMP-SMZ. J Infect Dis 2001;184:992–7.
117. Podzamczer D, Salazar A, Jimenez J, et al. Intermittent trimethoprim-sulfamethoxazole compared with dapsone-pyrimethamine for the simultaneous primary prophylaxis of *Pneumocystis* pneumonia and toxoplasmosis in patients infected with HIV. Ann Intern Med 1995;122:755–61.
118. Opravil M, Hirschel B, Lazzarin A, et al. Once-weekly administration of dapsone/pyrimethamine vs. aerosolized pentamidine as combined prophylaxis for *Pneumocystis carinii* pneumonia and toxoplasmic encephalitis in human immunodeficiency virus-infected patients. Clin Infect Dis 1995;20:531–41.
119. Girard PM, Landman R, Gaudebout C, et al. Dapsone-pyrimethamine compared with aerosolized pentamidine as primary prophylaxis against *Pneumocystis carinii* pneumonia and toxoplasmosis in HIV infection. N Engl J Med 1993;328:1514–20.
120. Chan C, Montaner J, Lefebvre EA, et al. Atovaquone suspension compared with aerosolized pentamidine for prevention of *Pneumocystis carinii* pneumonia in human immunodeficiency virus-infected subjects intolerant of trimethoprim or sulfonamides. J Infect Dis 1999;180:369–76.
121. El-Sadr WM, Murphy RL, Yurik TM, et al. Atovaquone compared with dapsone for the prevention of *Pneumocystis carinii* pneumonia in patients with HIV infection who cannot tolerate trimethoprim, sulfonamides, or both. N Engl J Med 1998;339:1889–95.
122. Payen MC, De Wit S, Sommereijns B, Clumeck N. A controlled trial of dapsone versus pyrimethamine-sulfadoxine for primary prophylaxis of *Pneumocystis carinii* pneumonia and toxoplasmosis in patients with AIDS. Biomed Pharmacother 1997;51:439–45.
123. Schurmann D, Bergmann F, Albrecht H, et al. Twice-weekly pyrimethamine-sulfadoxine effectively prevents *Pneumocystis carinii* pneumonia relapse and toxoplasmic encephalitis in patients with AIDS. J Infect Dis 2001;42:8–15.
124. Schurmann D, Bergmann F, Albrecht H, et al. Effectiveness of twice-weekly pyrimethamine-sulfadoxine as primary prophylaxis of *Pneumocystis carinii* pneumonia and toxoplasmic encephalitis in patients with advanced HIV infection. Eur J Clin Microbiol Infect Dis 2002;21:353–61.
125. Navin TR, Miller KD, Satriale RF, Lobel HO. Adverse reactions associated with pyrimethamine-sulfadoxine prophylaxis for *Pneumocystis carinii* infections in AIDS. Lancet 1985;1:1332.
126. Dworkin MS, Hanson DL, Kaplan JE, Jones JL, Ward JW. Risk for preventable opportunistic infections in persons with AIDS after antiretroviral therapy increases $CD4^+$ T lymphocyte counts above prophylaxis thresholds. J Infect Dis 2000;182:611–5.

127. Mussini C, Pezzotti P, Govoni A, et al. Discontinuation of primary prophylaxis for *Pneumocystis carinii* pneumonia and toxoplasmic encephalitis in human immunodeficiency virus type I-infected patients: the changes in opportunistic prophylaxis study. J Infect Dis 2000;181:1635–42.
128. Schneider MM, Borleffs JC, Stolk RP, Jaspers CA, Hoepelman AI. Discontinuation of prophylaxis for *Pneumocystis carinii* pneumonia in HIV-1-infected patients treated with highly active antiretroviral therapy. Lancet 1999;353:201–3.
129. Weverling GJ, Mocroft A, Ledergerber B, et al. Discontinuation of *Pneumocystis carinii* pneumonia prophylaxis after start of highly active antiretroviral therapy in HIV-1 infection. Lancet 1999;353:1293–8.
130. Yangco BG, Von Bargen JC, Moorman AC, Holmberg SD. Discontinuation of chemoprophylaxis against *Pneumocystis carinii* pneumonia in patients with HIV infection. Ann Intern Med 2000;132:201–5.
131. Furrer H, Opravil M, Rossi M, et al. Discontinuation of primary prophylaxis in HIV-infected patients at high risk of *Pneumocystis carinii* pneumonia: prospective multicentre study. AIDS 2001;15:501–7.
132. Kirk O, Lundgren JD, Pedersen C, Nielsen H, Gerstoft J. Can chemoprophylaxis against opportunistic infections be discontinued after an increase in CD4 cells induced by highly active antiretroviral therapy? AIDS 1999;13:1647–51.
133. Lopez Bernaldo de Quiros JC, Miro JM, et al. A randomized trial of the discontinuation of primary and secondary prophylaxis against *Pneumocystis carinii* pneumonia after highly active antiretroviral therapy in patients with HIV infection. N Engl J Med 2001;344:159–67.
134. Green H, Hay P, Dunn DT, McCormack S. A prospective multicentre study of discontinuing prophylaxis for opportunistic infections after effective antiretroviral therapy. HIV Med 2004;5:278–83.
135. Hughes W, Leoung G, Kramer F, et al. Comparison of atovaquone (566C80) with trimethoprim-sulfamethoxazole to treat *Pneumocystis carinii* pneumonia in patients with AIDS. N Engl J Med 1993;328:1521–7.
136. Safrin S, Finkelstein DM, Feinberg J, et al. Comparison of three regimens for treatment of mild to moderate *Pneumocystis carinii* pneumonia in patients with AIDS: a double-blind, randomized, trial of oral trimethoprim-sulfamethoxazole, dapsone-trimethoprim, and clindamycin-primaquine. Ann Intern Med 1996;124:792–802.
137. Safrin S, Lee BL, Sande MA. Adjunctive folinic acid with trimethoprim-sulfamethoxazole for *Pneumocystis carinii* pneumonia in AIDS patients is associated with an increased risk of therapeutic failure and death. J Infect Dis 1994;170:912–7.
138. Crothers K, Beard CB, Turner J, et al. Severity and outcome of HIV-associated *Pneumocystis* pneumonia containing *Pneumocystis jirovecii* dihydropteroate synthase gene mutations. AIDS 2005;19:801–5.
139. Huang L, Crothers K, Atzori C, et al. Dihydropteroate synthase gene mutations in *Pneumocystis* and sulfa resistance. Emerg Infect Dis 2004;10:1721–8.
140. Stein CR, Poole C, Kazanjian P, Meshnick SR. Sulfa use, dihydropteroate synthase mutations, and *Pneumocystis jirovecii* pneumonia. Emerg Infect Dis 2004;10:1760–5.
141. Nielsen TL, Eeftinck Schattenkerk JK, Jensen BN, et al. Adjunctive corticosteroid therapy for *Pneumocystis carinii* pneumonia in AIDS: a randomized European multicenter open label study. J Acquir Immune Defic Syndr 1992;5:726–31.
142. Bozzette SA, Sattler FR, Chiu J, et al. A controlled trial of early adjunctive treatment with corticosteroids for *Pneumocystis carinii* pneumonia in the acquired immunodeficiency syndrome. N Engl J Med 1990;323:1451–7.
143. National Institutes of Health. Consensus statement on the use of corticosteroids as adjunctive therapy for *Pneumocystis* pneumonia in the acquired immunodeficiency syndrome. N Engl J Med 1990;323:1500–4.
144. Montaner JS, Lawson LM, Levitt N, et al. Corticosteroids prevent early deterioration in patients with moderately severe *Pneumocystis carinii* pneumonia and the acquired immunodeficiency syndrome (AIDS). Ann Intern Med 1990;113:14–20.
145. Gallant JE, Chaisson RE, Moore RD. The effect of adjunctive corticosteroids for the treatment of *Pneumocystis carinii* pneumonia on mortality and subsequent complications. Chest 1998;114:1258–63.
146. Briel M, Bucher HC, Boscacci R, Furrer H. Adjunctive corticosteroids for *Pneumocystis jiroveci* pneumonia in patients with HIV-infection. Cochrane Database Syst Rev 2006:3:CD006150.
147. Medina I, Mills J, Leoung G, et al. Oral therapy for *Pneumocystis carinii* pneumonia in the acquired immunodeficiency syndrome: a controlled trial of trimethoprim–sulfamethoxazole versus trimethoprim-dapsone. N Engl J Med 1990;323:776–82.
148. Black JR, Feinberg J, Murphy RL, et al. Clindamycin and primaquine therapy for mild-to-moderate episodes of *Pneumocystis carinii* pneumonia in patients with AIDS. Clin Infect Dis 1994;18:905–13.
149. Toma E, Thorne A, Singer J, et al. Clindamycin with primaquine vs. Trimethoprim-sulfamethoxazole therapy for mild and moderately severe *Pneumocystis carinii* pneumonia in patients with AIDS: a multicenter, double-blind, randomized trial. Clin Infect Dis 1998;27:524–30.
150. Smego RA, Jr., Nagar S, Maloba B, Popara M. A meta-analysis of salvage therapy for *Pneumocystis carinii* pneumonia. Arch Intern Med 2001;161:1529–33.
151. Dohn MN, Weinberg WG, Torres RA, et al. Oral atovaquone compared with intravenous pentamidine for *Pneumocystis carinii* pneumonia in patients with AIDS. Ann Intern Med 1994;121:174–80.
152. Conte JE, Jr., Chernoff D, Feigal DW, Jr., et al. Intravenous or inhaled pentamidine for treating *Pneumocystis carinii* pneumonia in AIDS: a randomized trial. Ann Intern Med 1990;113:203–9.
153. Wharton JM, Coleman DL, Wofsy CB, et al. Trimethoprim-sulfamethoxazole or pentamidine for *Pneumocystis carinii* pneumonia in the acquired immunodeficiency syndrome: a prospective randomized trial. Ann Intern Med 1986;105:37–44.
154. Soo Hoo GW, Mohsenifar Z, Meyer RD. Inhaled or intravenous pentamidine therapy for *Pneumocystis carinii* pneumonia in AIDS: a randomized trial. Ann Intern Med 1990;113:195–202.
155. Montgomery AB, Feigal DW, Jr., Sattler F, et al. Pentamidine aerosol versus trimethoprim-sulfamethoxazole for *Pneumocystis carinii* in acquired immune deficiency syndrome. Am J Respir Crit Care Med 1995;151:1068–74.
156. Randall Curtis J, Yarnold PR, Schwartz DN, Weinstein RA, Bennett CL. Improvements in outcomes of acute respiratory failure for patients with human immunodeficiency virus-related *Pneumocystis carinii* pneumonia. Am J Respir Crit Care Med 2000;162:393–8.
157. Dworkin MS, Hanson DL, Navin TR. Survival of patients with AIDS, after diagnosis of *Pneumocystis carinii* pneumonia, in the United States. J Infect Dis 2001;183:1409–12.
158. Morris A, Wachter RM, Luce J, Turner J, Huang L. Improved survival with highly active antiretroviral therapy in HIV-infected patients with severe *Pneumocystis carinii* pneumonia. AIDS 2003;17:73–80.

159. Huang L, Quartin A, Jones D, Havlir DV. Intensive care of patients with HIV infection. N Engl J Med 2006; 355:173–81.
160. Wislez M, Bergot E, Antoine M, et al. Acute respiratory failure following HAART introduction in patients treated for *Pneumocystis carinii* pneumonia. Am J Respir Crit Care Med 2001;164:847–51.
161. Eeftinck Schattenkerk JK, Lange JM, van Steenwijk RP, Danner SA. Can the course of high dose cotrimoxazole for *Pneumocystis carinii* pneumonia in AIDS be shorter? A possible solution to the problem of cotrimoxazole toxicity. J Intern Med 1990;227:359–62.
162. Gordin FM, Simon GL, Wofsy CB, Mills J. Adverse reactions to trimethoprim-sulfamethoxazole in patients with the acquired immunodeficiency syndrome. Ann Intern Med 1984;100:495–9.
163. Hughes WT, LaFon SW, Scott JD, Masur H. Adverse events associated with trimethoprim-sulfamethoxazole and atovaquone during the treatment of AIDS-related *Pneumocystis carinii* pneumonia. J Infect Dis 1995;171:1295–301.
164. Klein NC, Duncanson FP, Lenox TH, et al. Trimethoprim-sulfamethoxazole versus pentamidine for *Pneumocystis carinii* pneumonia in AIDS patients: results of a large prospective randomized treatment trial. AIDS 1992;6:301–5.
165. Sattler FR, Frame P, Davis R, et al. Trimetrexate with leucovorin versus trimethoprim-sulfamethoxazole for moderate to severe episodes of *Pneumocystis carinii* pneumonia in patients with AIDS: a prospective, controlled multicenter investigation of the AIDS Clinical Trials Group Protocol 029/031. J Infect Dis 1994;170:165–72.
166. Koval C, Gigliotti FN, Demeter, LM. Immune reconstitution syndrome after successful treatment of *Pneumocystis carinii* pneumonia in a man with human immunodeficiency virus type 1 infection. Clin Infect Dis 2002;35:491–3.
167. Masur H, Kaplan JE, Holmes KK. Guidelines for preventing opportunistic infections among HIV-infected persons—2002: Recommendations of the U.S. Public Health Service and the Infectious Diseases Society of America. Ann Intern Med 2002;137:435–78.
168. Soriano V, Dona C, Rodriguez-Rosado R, Barreiro P, Gonzalez-Lahoz J. Discontinuation of secondary prophylaxis for opportunistic infections in HIV-infected patients receiving highly active antiretroviral therapy. AIDS 2000;14:383–6.
169. Zellweger C, Opravil M, Bernasconi E, et al. Long-term safety of discontinuation of secondary prophylaxis against *Pneumocystis pneumonia*: prospective multicentre study. AIDS 2004;18:2047–53.
170. Mussini C, Pezzotti P, Antinori A, et al. Discontinuation of secondary prophylaxis for *Pneumocystis carinii* pneumonia in human immunodeficiency virus-infected patients: a randomized trial by the CIOP Study Group. Clin Infect Dis 2003;36:645–51.
171. Ledergerber B, Mocroft A, Reiss P, et al. Discontinuation of secondary prophylaxis against *Pneumocystis carinii* pneumonia in patients with HIV infection who have a response to antiretroviral therapy. N Engl J Med 2001;344:168–74.
172. Connelly RT, Lourwood DL. *Pneumocystis carinii* pneumonia prophylaxis during pregnancy. Pharmacotherapy 1994;14:424–9.
173. Czeizel AE, Rockenbauer M, Sorensen HT, Olsen J. The teratogenic risk of trimethoprim-sulfonamides: a population based case-control study. Reprod Toxicol 2001;15:637–46.
174. Hernandez-Diaz S, Werler MM, Walker AM, Mitchell AA. Folic acid antagonists during pregnancy and the risk of birth defects. N Engl J Med 2000;343:1608–14.
175. Hernandez-Diaz S, Werler MM, Walker AM. Neural tube defects in relation to use of folic acid antagonists during pregnancy. Am J Epidemiol 2001;153:961–8.
176. Jungmann EM, Mercey D, DeRuiter A, et al. Is first trimester exposure to the combination of antiretroviral therapy and folate antagonists a risk factor for congenital abnormalities? Sex Transm Infect 2001;77:441–3.
177. CDC. Recommendations for the use of folic acid to reduce the number of cases of spina bifida and other neural tube defects. MMWR 1992;41(No. RR-14).
178. Andersen DH, Blanc WA, Crozier DN, Silverman WA. A difference in mortality rate and incidence of kernicterus among premature infants allotted to two prophylactic antibacterial regimens. Pediatrics 1956;18:614–25.
179. Harstad TW, Little BB, Bawdon RE, et al. Embryofetal effects of pentamidine isethionate administered to pregnant Sprague-Dawley rats. Am J Obstet Gynecol 1990;163:912–6.
180. Albino JA, Shapiro JM. Respiratory failure in pregnancy due to *Pneumocystis carinii*: report a successful outcome. Obstet Gynecol 1994;83:823–4.
181. Madinger NE, Greenspoon JS, Ellrodt AG. Pneumonia during pregnancy: has modern technology improved maternal and fetal outcome? Am J Obstet Gynecol 1989;161:657–62.
182. Koonin LM, Ellerbrock TV, Atrash HK, et al. Pregnancy-associated deaths due to AIDS in the United States. JAMA 1989;261:1306–9.
183. Benedetti TJ, Valle R, Ledger WJ. Antepartum pneumonia in pregnancy. Am J Obstet Gynecol 1982;144:413–7.
184. Luft BJ, Conley F, Remington JS, et al. Outbreak of central-nervous-system toxoplasmosis in Western Europe and North America. Lancet 1983;1:781–4.
185. Luft BJ, Brooks RG, Conley FK. Toxoplasmic encephalitis in patients with acquired immune deficiency syndrome. JAMA 1984;252:913–7.
186. Wong B, Gold JW, Brown AE, et al. Central-nervous-system toxoplasmosis in homosexual men and parenteral drug abusers. Ann Intern Med 1984;100:36–42.
187. Israelski DM, Chmiel JS, Poggensee L, Phair JP, Remington JS. Prevalence of Toxoplasma infection in a cohort of homosexual men at risk of AIDS and toxoplasmic encephalitis. J Acquir Immune Defic Syndr 1993;6:414–8.
188. Mathews WC, Fullerton SC. Use of a clinical laboratory database to estimate Toxoplasma seroprevalence among human immunodeficiency virus-infected patients. Overcoming bias in secondary analysis of clinical records. Arch Pathol Lab Med 1994;118:807–10.
189. Abgrall S, Rabaud C, Costagliola D. Incidence and risk factors for toxoplasmic encephalitis in human immunodeficiency virus-infected patients before and during the highly active antiretroviral therapy era. Clin Infect Dis 2001;33:1747–55.
190. Leport C, Chene G, Morlat P, et al. Pyrimethamine for primary prophylaxis of toxoplasmic encephalitis in patients with human immunodeficiency virus infection: a double-blind, randomized trial. J Infect Dis 1996;173:91–7.
191. Kupfer MC, Zee CS, Colletti PM, Boswell WD, Rhodes R. MRI evaluation of AIDS-related encephalopathy: toxoplasmosis vs. lymphoma. Magn Reson Imaging 1990;8:51–7.
192. Pierce MA, Johnson MD, Maciunas RJ, et al. Evaluating contrast-enhancing brain lesions in patients with AIDS by using positron emission tomography. Ann Intern Med 1995;123:594–8.
193. Ruiz A, Ganz WI, Post MJ, et al. Use of thallium-201 brain SPECT to differentiate cerebral lymphoma from toxoplasma encephalitis in AIDS patients. Am J Neuroradiol 1994;15:1885–94.
194. Derouin F, Leport C, Pueyo S, et al. Predictive value of *Toxoplasma gondii* antibody titres on the occurrence of toxoplasmic encephalitis in HIV-infected patients. AIDS 1996;10:1521–7.

195. Conley FK, Jenkins KA, Remington JS. *Toxoplasma gondii* infection of the central nervous system: use of the peroxidase-antiperoxidase method to demonstrate toxoplasma in formalin fixed, paraffin embedded tissue sections. Hum Pathol 1981;12:690–8.
196. Novati R, Castagna A, Morsica G, et al. Polymerase chain reaction for *Toxoplasma gondii* DNA in the cerebrospinal fluid of AIDS patients with focal brain lesions. AIDS 1994;8:1691–4.
197. Cinque P, Scarpellini P, Vago L, Linde A, Lazzarin A. Diagnosis of central nervous system complications in HIV-infected patients: cerebrospinal fluid analysis by the polymerase chain reaction. AIDS 1997;11:1–17.
198. Antinori A, Ammassari A, De Luca A, et al. Diagnosis of AIDS-related focal brain lesions: a decision-making analysis based on clinical and neuroradiologic characteristics combined with polymerase chain reaction assays in CSF. Neurology 1997;48:687–94.
199. Antinori A, De Rossi G, Ammassari A. Value of combined approach with thallium-201 single-photon emission computed tomography and Epstein-Barr virus DNA polymerase chain reaction in CSF for the diagnosis of AIDS-related primary CNS lymphoma. J Clin Oncol 1999;17:554–60.
200. Department of Agriculture. FoodSafety.gov: gateway to government food safety information. www.foodsafety.gov. Last accessed December 22, 2008.
201. Furrer H, Opravil M, Bernasconi E, Telenti A, Egger M. Stopping primary prophylaxis in HIV-1-infected patients at high risk of toxoplasma encephalitis. Lancet 2000;355:2217–8.
202. Miro JM, Lopez JC, Podzamczer D, et al. Discontinuation of primary and secondary *Toxoplasma gondii* prophylaxis is safe in HIV-infected patients after immunological restoration with highly active antiretroviral therapy: results of an open, randomized, multicenter clinical trial. Clin Infect Dis 2006;43:79–89.
203. Katlama C, De Wit S, O'Doherty E, Van Glabeke M, Clumeck N. Pyrimethamine-clindamycin vs. pyrimethamine-sulfadiazine as acute and long-term therapy for toxoplasmic encephalitis in patients with AIDS. Clin Infect Dis 1996; 22:268–75.
204. Dannemann B, McCutchan JA, Israelski D, et al. Treatment of toxoplasmic encephalitis in patients with AIDS. a randomized trial comparing pyrimethamine plus clindamycin to pyrimethamine plus sulfadiazine. Ann Intern Med 1992;116:33–43.
205. Leport C, Raffi F, Matheron S, et al. Treatment of central nervous system toxoplasmosis with pyrimethamine/sulfadiazine combination in 35 patients with the acquired immunodeficiency syndrome: efficacy of long-term continuous therapy. Am J Med 1988;84:94–100.
206. Luft BJ, Hafner R, Korzun AH, et al. Toxoplasmic encephalitis in patients with the acquired immunodeficiency syndrome. N Engl J Med 1993;329:995–1000.
207. Leport C, Meulemans A, Robine D, Dameron G, Vilde JL. Levels of pyrimethamine in serum and penetration into brain tissue in humans. AIDS 1992;6:1040–1.
208. Van Delden C, Hirschel B. Folinic acid supplements to pyrimethamine-sulfadiazine for *Toxoplasma* encephalitis are associated with better outcome. J Infect Dis 1996;173:1294–5.
209. Frenkel JK, Hitchings GH. Relative reversal by vitamins (p-aminobenzoic, folic, and folinic acids) of the effects of sulfadiazine and pyrimethamine on *Toxoplasma*, mouse and man. Antibiotic Chemotherapy 1957:7:630–8.
210. Torre D, Casari S, Speranza F, et al. Randomized trial of trimethoprim-sulfamethoxazole versus pyrimethamine-sulfadiazine for therapy of toxoplasmic encephalitis in patients with AIDS. Antimicrob Agents Chemother 1998;42:1346–9.
211. Chirgwin K, Hafner R, Leport C, et al. Randomized phase II trial of atovaquone with pyrimethamine or sulfadiazine for treatment of toxoplasmic encephalitis in patients with acquired immunodeficiency syndrome. Clin Infect Dis 2002;34:1243–50.
212. Kovacs JA. Efficacy of atovaquone in treatment of toxoplasmosis in patients with AIDS. Lancet 1992;340:637–8.
213. Torres RA, Weinberg W, Stansell J, et al. Atovaquone for salvage treatment and suppression of toxoplasmic encephalitis in patients with AIDS. Clin Infect Dis 1997;24:422–9.
214. Katlama C, Mouthon B, Gourdon D, Lapierre D, Rousseau F. Atovaquone as long-term suppressive therapy for toxoplasmic encephalitis in patients with AIDS and multiple drug intolerance. AIDS 1996;10:1107–12.
215. Saba J, Morlat P, Raffi F, et al. Pyrimethamine plus azithromycin for treatment of acute toxoplasmic encephalitis in patients with AIDS. Eur J Clin Microbiol Infect Dis 1993;12:853–6.
216. Jacobsen J, Hafner R, Remington J, et al. Dose-escalation, phase I/II study of azithromycin and pyrimethamine for the treatment of toxoplasmic encephalitis in AIDS. AIDS 2001;15:583–9.
217. Fernandez-Martin J, Leport C, Morlat P, Meyohas MC, Chauvin JP, Vilde JL. Pyrimethamine-clarithromycin combination for therapy of acute *Toxoplasma* encephalitis in patients with AIDS. Antimicrob Agents Chemother 1991;35:2049–52.
218. Dhiver C, Milandre C, Poizot-Martin I, et al. 5-Fluoro-uracil-clindamycin for treatment of cerebral toxoplasmosis. AIDS 1993;7:143–4.
219. Derouin F, Piketty C, Chastang C, Chau et al. Anti-*Toxoplasma* effects of dapsone alone and combined with pyrimethamine. Antimicrob Agents Chemother 1991;35:252–5.
220. Lacassin F, Schaffo D, Perronne C, et al. Clarithromycin-minocycline combination as salvage therapy for toxoplasmosis in patients infected with human immunodeficiency virus. Antimicrob Agents Chemother 1995;39:276–7.
221. Hagberg L, Palmertz B, Lindberg J. Doxycycline and pyrimethamine for toxoplasmic encephalitis. Scand J Infect Dis 1993;25:157–60.
222. Lawn SD, Myer L, Bekker LG, Wood R. Tuberculosis-associated immune reconstitution disease: incidence, risk factors and impact in an antiretroviral treatment service in South Africa. AIDS 2007;21:335–41.
223. Jordan MK, Burstein AH, Rock-Kress D, et al. Plasma pharmacokinetics of sulfadiazine administered twice daily versus four times daily are similar in human immunodeficiency virus-infected patients. Antimicrob Agents Chemother 2004;48:635–7.
224. Podzamczer D, Miro JM, Ferrer E, et al. Thrice-weekly sulfadiazine-pyrimethamine for maintenance therapy of toxoplasmic encephalitis in HIV-infected patients. Eur J Clin Microbiol Infect Dis 2000;19:89–95.
225. Duval X, Pajot O, Le Moing V, et al. Maintenance therapy with cotrimoxazole for toxoplasmic encephalitis in the era of highly active antiretroviral therapy. AIDS 2004; 18:1342–4.
226. Bertschy S, Opravil M, Cavassini M, et al. Discontinuation of maintenance therapy against *Toxoplasma* encephalitis in AIDS patients with sustained response to anti-retroviral therapy. Clin Microbiol Infect 2006;12:666–71.
227. Mitchell CD, Erlich SS, Mastrucci MT, Hutto SC, Parks WP, Scott GB. Congenital toxoplasmosis occurring in infants perinatally infected with human immunodeficiency virus 1. Pediatr Infect Dis J 1990;9:512–8.

228. Deen JL, von Seidlein L, Pinder M, Walraven GE, Greenwood BM. The safety of the combination artesunate and pyrimethamine-sulfadoxine given during pregnancy. Trans R Soc Trop Med Hyg 2001;95:424–8.
229. Dunn CS, Beyer C, Kieny MP, et al. High viral load and CD4 lymphopenia in rhesus and cynomolgus macaques infected by a chimeric primate lentivirus constructed using the env, rev, tat, and vpu genes from HIV-1 Lai. Virology 1996;223:351–61.
230. Wong SY, Remington JS: Toxoplasmosis in pregnancy. Clin Infect Dis 1994;18:853–61.
231. Dunn DT, Newell ML, Gilbert R, et al. Low incidence of congenital toxoplasmosis in children born to women infected with human immunodeficiency virus. Eur J Obstet Gynecol Reprod Biol 1996;68:93–6.
232. Flanigan T, Whalen C, Turner J, et al. *Cryptosporidium* infection and CD4 counts. Ann Intern Med 1992;116:840–2.
233. Cama V, Gilman RH, Vivar A, et al. Mixed *Cryptosporidium* infections and HIV. Emerg Infect Dis 2006;12:1025–8.
234. Goodgame RW. Understanding intestinal spore-forming protozoa: cryptosporidia, microsporidia, isospora, and cyclospora. Ann Intern Med 1996;124:429–41.
235. de Souza Ldo R, Rodrigues MA, Morceli J, Kemp R, Mendes RP. Cryptosporidiosis of the biliary tract mimicking pancreatic cancer in an AIDS patient. Rev Soc Bras Med Trop 2004;37:182–5.
236. Chen XM, LaRusso NF. Cryptosporidiosis and the pathogenesis of AIDS-cholangiopathy. Semin Liver Dis 2002;22:277–89.
237. Chen C, Gulati P, French SW. Pathologic quiz case: a patient with acquired immunodeficiency syndrome and an unusual biliary infection. Arch Pathol Lab Med 2003;127:243–4.
238. Ducreux M, Buffet C, Lamy P, et al. Diagnosis and prognosis of AIDS-related cholangitis. AIDS 1995;9:875–80.
239. Moore JA, Frenkel JK. Respiratory and enteric cryptosporidiosis in humans. Arch Pathol Lab Med 1991;115:1160–2.
240. Mercado R, Buck GA, Manque PA, Ozaki LS. *Cryptosporidium hominis* infection of the human respiratory tract. Emerg Infect Dis 2007;13:462–4.
241. Weber R, Bryan RT, Bishop HS, et al. Threshold of detection of *Cryptosporidium* oocysts in human stool specimens: evidence for low sensitivity of current diagnostic methods. J Clin Microbiol 1991;29:1323–7.
242. Huang DB, Zhou J. Effect of intensive handwashing in the prevention of diarrhoeal illness among patients with AIDS: a randomized controlled study. J Med Microbiol 2007;56:659–63.
243. Holmberg SD, Moorman AC, Von Bargen JC, et al. Possible effectiveness of clarithromycin and rifabutin for cryptosporidiosis chemoprophylaxis in HIV disease. JAMA 1998;279:384–6.
244. Fichtenbaum CJ, Zackin R, Feinberg J, Benson C, Griffiths JK. Rifabutin but not clarithromycin prevents cryptosporidiosis in persons with advanced HIV infection. AIDS 2000;14:2889–93.
245. Miao YM, Awad-El-Kariem FM, Franzen C, et al. Eradication of cryptosporidia and microsporidia following successful antiretroviral therapy. J Acquir Immune Defic Syndr 2000;25:124–9.
246. Abubakar I, Aliyu SH, Arumugam C, Hunter PR, Usman NK. Prevention and treatment of cryptosporidiosis in immunocompromised patients. Cochrane Databse Syst Rev 2007;24:4932.
247. Abubakar I, Aliyu SH, Arumugam C, Usman NK, Hunter PR. Treatment of cryptosporidiosis in immunocompromised individuals: systematic review and meta–analysis. Br J Clin Pharmacol 2007;63:387–93.
248. Rossignol JF, Ayoub A, Ayers MS. Treatment of diarrhea caused by *Cryptosporidium parvum*: a prospective randomized, double-blind, placebo-controlled study of Nitazoxanide. J Infect Dis 2001;184:103–6.
249. Rossignol JF, Hidalgo H, Feregrino M, et al. A double-blind placebo-controlled study of nitazoxanide in the treatment of cryptosporidial diarrhoea in AIDS patients in Mexico. Trans R Soc Trop Med Hyg 1998;92:663–6.
250. Simon DM, Cello JP, Valenzuela J, et al. Multicenter trial of octreotide in patients with refractory acquired immunodeficiency syndrome-associated diarrhea. Gastroenterology 1995;108:1753–60.
251. Rossignol JF. Nitazoxanide in the treatment of acquired immune deficiency syndrome-related cryptosporidiosis: results of the United States compassionate use program in 365 patients. Aliment Pharmacol Ther 2006;24:887–94.
252. Tzipori S, Rand W, Griffiths J, Widmer G, Crabb J. Evaluation of an animal model system for cryptosporidiosis: therapeutic efficacy of paromomycin and hyperimmune bovine colostrum-immunoglobulin. Clin Diagn Lab Immunol 1994;1:450–63.
253. Hewitt RG, Yiannoutsos CT, Higgs ES, et al. Paromomycin: no more effective than placebo for treatment of cryptosporidiosis in patients with advanced human immunodeficiency virus infection. Clin Infect Dis 2000;31:1084–92.
254. White AC, Chappell CL, Hayat CS, et al. Paromomycin for cryptosporidiosis in AIDS: a prospective, double-blind trial. J Infect Dis 1994;170:419–24.
255. Wittner M, Weiss L. The microsporidia and microsporidiosis. Washington DC: ASM Press, 1999.
256. Mathis A. Microsporidia: emerging advances in understanding the basic biology of these unique organisms. Int J Parasitol 2000;30:795–804.
257. Deplazes P, Mathis A, Weber R. Epidemiology and zoonotic aspects of microsporidia of mammals and birds. Contrib Microbiol 2000:6:236–60.
258. Didier ES, Weiss LM. Microsporidiosis: current status. Curr Opin Infect Dis 2006;19:485–92.
259. Kotler DP, Orenstein JM. Clinical syndromes associated with microsporidiosis. Adv Parasitol 1998:40:321–49.
260. Weber R, Bryan RT, Owen RL, et al. Improved light-microscopical detection of microsporidia spores in stool and duodenal aspirates. N Engl J Med 1992;326:161–6.
261. Beauvais B, Sarfati C, Molina JM, et al. Comparative evaluation of five diagnostic methods for demonstrating microsporidia in stool and intestinal biopsy specimens. Ann Trop Med Parasitol 1993;87:99–102.
262. Weiss LM, Vossbrinck CR. Microsporidiosis: molecular and diagnostic aspects. Adv Parasitol 1998:40:351–95.
263. Maggi P, Larocca AM, Quarto M, et al. Effect of antiretroviral therapy on cryptosporidiosis and microsporidiosis in patients infected with human immunodeficiency virus type 1. Eur J Clin Microbiol Infect Dis 2000;19:213–7.
264. Goguel J, Katlama C, Sarfati C,et al. Remission of AIDS-associated intestinal microsporidiosis with highly active antiretroviral therapy. AIDS 1997;11:1658–9.
265. Conteas CN, Berlin OG, Speck CE, et al. Modification of the clinical course of intestinal microsporidiosis in acquired immunodeficiency syndrome patients by immune status and anti-human immunodeficiency virus therapy. Am J Trop Med Hyg 1998;58:555–8.
266. Molina JM, Goguel J, Sarfati C, et al. Trial of oral fumagillin for the treatment of intestinal microsporidiosis in patients with HIV infection. AIDS 2000;14:1341–48.
267. Molina JM, Tourneur M, Sarfati C, et al. Fumagillin treatment of intestinal microsporidiosis. N Engl J Med 2002;346:1963–9.

268. Didier PJ, Phillips JN, Kuebler DJ, et al. Antimicrosporidial activities of fumagillin, TNP-470, ovalicin, and ovalicin derivatives in vitro and in vivo. Antimicrob Agents Chemother 2006;50:2146–55.
269. Bicart-See A, Massip P, Linas MD, Datry A. Successful treatment with nitazoxanide of *Enterocytozoon bieneusi* microsporidiosis in a patient with AIDS. Antimicrob Agents Chemother 2000;44:167–8.
270. Akiyoshi DE, Weiss LM, Feng X, et al. Analysis of the beta-tubulin genes from *Enterocytozoon bieneusi* isolates from a human and rhesus macaque. J Eukaryot Microbiol 2007;54:38–41.
271. Franzen C, Salzberger B. Analysis of the beta-tubulin gene from *Vittaforma corneae* suggests benzimidazole resistance. Antimicrob Agents Chemother 2007;52:790–3.
272. Molina JM, Chastang C, Goguel J, et al. Albendazole for treatment and prophylaxis of microsporidiosis due to *Encephalitozoon intestinalis* in patients with AIDS: a randomized double-blind controlled trial. J Infect Dis 1998;177:1373–7.
273. Diesenhouse MC, Wilson LA, Correnti GF, et al. Treatment of microsporidial keratoconjunctivitis with topical fumagillin. Am J Ophthalmol 1993;115:293–8.
274. Dieterich DT, Lew EA, Kotler DP, Poles MA, Orenstein JM. Treatment with albendazole for intestinal disease due to *Enterocytozoon bieneusi* in patients with AIDS. J Infect Dis 1994;169:178–83.
275. World Health Organization. Global tuberculosis control—surveillance, planning, financing. Geneva, Switzerland: WHO Report 2007.
276. CDC. Guidelines for the investigation of contacts of persons with infectious tuberculosis: recommendations from the National Tuberculosis Controllers Association and CDC. MMWR 2005;54(No. RR-15).
277. CDC. Treatment of tuberculosis. MMWR 2003;52(No. RR-11).
278. CDC: Trends in tuberculosis incidence—United States, 2007. MMWR 2008;57(11):281–5.
279. Bennett D, Couval JM, Onorato MD, et al. Prevalence of TB infection in the US population 1999-2000. San Francisco, CA: Program and abstracts of the American Public Health Association 131st Annual Meeting; November 15-19, 2003.
280. CDC. Guidelines for preventing the transmission of *Mycobacterium tuberculosis* in health-care settings, 2005. MMWR 2005;54(No. RR-17).
281. CDC. Revised recommendations for HIV testing of adults, adolescents, and pregnant women in health-care settings. MMWR 2006;55(No. RR-14).
282. CDC. Targeted tuberculin testing and treatment of latent tuberculosis infection. MMWR 2000;49(No. RR-6).
283. CDC. Targeted tuberculin testing and treatment of latent tuberculosis infection. MMWR 2000;49(No. RR-6).
284. Horsburgh CR, Jr. Priorities for the treatment of latent tuberculosis infection in the United States. N Engl J Med 2004;350:2060–7.
285. Batungwanayo J, Taelman H, Dhote R, et al. Pulmonary tuberculosis in Kigali, Rwanda: impact of human immunodeficiency virus infection on clinical and radiographic presentation. Am Rev Respir Dis 1992;146:53–6.
286. Jones BE, Young SM, Antoniskis D, Davidson PT, Kramer F, Barnes PF. Relationship of the manifestations of tuberculosis to CD4 cell counts in patients with human immunodeficiency virus infection. Am Rev Respir Dis 1993;148:1292–7.
287. Hirsch HH, Kaufmann G, Sendi P, Battegay M. Immune reconstitution in HIV-infected patients. Clin Infect Dis 2004;38:1159–66.
288. Breen RA, Smith CJ, Cropley I, et al. Does immune reconstitution syndrome promote active tuberculosis in patients receiving highly active antiretroviral therapy? AIDS 2005;19:1201–6.
289. Perlman DC, El-Sadr WM, Nelson ET, et al. Variation of chest radiographic patterns in pulmonary tuberculosis by degree of human immunodeficiency virus-related immunosuppression. Clin Infect Dis 1997;25:242–6.
290. Shafer RW, Kim DS, Weiss JP, Quale JM. Extrapulmonary tuberculosis in patients with human immunodeficiency virus infection. Medicine 1991;70:384–97.
291. Whalen C, Horsburgh CR, Hom D, et al. Site of disease and opportunistic infection predict survival in HIV-associated tuberculosis. AIDS 1997;11:455–60.
292. Kourbatova EV, Leonard MK, Jr., Romero J, et al. Risk factors for mortality among patients with extrapulmonary tuberculosis at an academic inner-city hospital in the US. Eur J Epidemiol 2006;21:715–21.
293. Post FA, Wood R, Pillay GP. Pulmonary tuberculosis in HIV infection: radiographic appearance is related to $CD4^+$ T-lymphocyte count. Tuber Lung Dis 1995;76:518–21.
294. Shelburne SA, 3rd, Hamill RJ, Rodriguez-Barradas MC, et al. Immune reconstitution inflammatory syndrome: emergence of a unique syndrome during highly active antiretroviral therapy. Medicine 2002;81:213–7.
295. Colebunders R, John L, Huyst V, et al. Tuberculosis immune reconstitution inflammatory syndrome in countries with limited resources. Int J Tuberc Lung Dis 2006;10:946–53.
296. Manosuthi W, Kiertiburanakul S, Phoorisri T, Sangkanuparph S. Immune reconstitution inflammatory syndrome of tuberculosis among HIV-infected patients receiving antituberculosis and antiretroviral therapy. J Infect Dis 2006;53:357–63.
297. Michailidis C, Pozniak AL, Mandalia S, Basnayake S, M.R. N, Gazzard BG. Clinical characteristics of IRIS syndrome in patients with HIV and tuberculosis. Antivir Ther 2005;10:417–22.
298. French MA, Price P, Stone SF. Immune restoration disease after antiretroviral therapy. AIDS 2004;18:1615–27.
299. Nahid P, Pai M, Hopewell PC. Advances in the diagnosis and treatment of tuberculosis. Proc Am Thorac Soc 2006;3:103–10.
300. Jasmer RM, Nahid P, Hopewell PC. Clinical practice: latent tuberculosis infection. N Engl J Med 2002;347:1860–6.
301. Menzies D, Pai M, Comstock G. New tests for the diagnosis of latent tuberculosis infection: areas of uncertainty and recommendations for research. Ann Intern Med 2007;146:340–54.
302. Mazurek GH, Jereb J, Lobue P, et al. Guidelines for using the QuantiFERON-TB Gold test for detecting *Mycobacterium tuberculosis* infection, United States. MMWR 2005;54(No. RR-15).
303. Brock I, Ruhwald M, Lundgren B, et al. Latent tuberculosis in HIV positive, diagnosed by the *M. tuberculosis* specific interferon-gamma test. Respir Res 2006:1;7:56.
304. Pai M, Lewinsohn DM. Interferon–gamma assays for tuberculosis: is anergy the Achilles' heel? Am J Respir Crit Care Med 2005;172:519–21.
305. Luetkemeyer AF, Charlebois ED, Flores LL, et al. Comparison of an interferon-gamma release assay with tuberculin skin testing in HIV-infected individuals. Am J Respir Crit Care Med 2007;175:737–42.
306. Chapman AL, Munkanta M, Wilkinson KA, et al. Rapid detection of active and latent tuberculosis infection in HIV-positive individuals by enumeration of *Mycobacterium tuberculosis*-specific T cells. AIDS 2002;16:2285–93.
307. Greenberg SD, Frager D, Suster B, et al. Active pulmonary tuberculosis in patients with AIDS: spectrum of radiographic findings (including a normal appearance). Radiology 1994;193:115–9.

308. American Thoracic Society. Diagnostic standards and classification of tuberculosis in adults and children. Am J Respir Crit Care Med 2000;161:1376–95.
309. Steingart KR, Ng V, Henry M, et al. Sputum processing methods to improve the sensitivity of smear microscopy for tuberculosis: a systematic review. Lancet Infect Dis 2006;6:64–74.
310. Artenstein AW, Kim JH, Williams WJ, Chung RC. Isolated peripheral tuberculous lymphadenitis in adults: current clinical and diagnostic issues. Clin Infect Dis 1995;20:876–82.
311. Golden MP. Vikram HR. Extrapulmonary tuberculosis: an overview. Am Fam Physician 2005;72:1761–8.
312. Shriner KA, Mathisen GE, Goetz MB. Comparison of mycobacterial lymphadenitis among persons infected with human immunodeficiency virus and seronegative controls. Clin Infect Dis 1992;15:601–5.
313. Rich ML, Socci AR, Mitnick CD, et al. Representative drug susceptibility patterns for guiding design of retreatment regimens for MDR-TB. Int J Tuberc Lung Dis 2006;10:290–6.
314. Geng E, Kreiswirth B, Burzynski J, Schluger NW. Clinical and radiographic correlates of primary and reactivation tuberculosis: a molecular epidemiology study. JAMA 2005;293:2740–5.
315. Hopewell PC, Pai M, Maher D, et al. International standards for tuberculosis care. Lancet 2006;6:710–25.
316. Elzi L, Schlegel M, Weber R, et al. Reducing tuberculosis incidence by tuberculin skin testing, preventive treatment, and antiretroviral therapy in an area of low tuberculosis transmission. Clin Infect Dis 2007;44:94–102.
317. Day JH, Charalambous S, Fielding KL, et al. Screening for tuberculosis prior to isoniazid preventive therapy among HIV-infected gold miners in South Africa. Int J Tuberc Lung Dis 2006;10:523–9.
318. Sterling T, Bethel J, Goldberg S, Weinfurter P, Yun L. The scope and impact of treatment of latent tuberculosis infection in the United States and Canada. Am J Respir Crit Care Med 2006;173:927–31.
319. CDC, Taylor Z, Nolan CM, Blumberg HM. Controlling tuberculosis in the United States: recommendations from the American Thoracic Society, CDC, and the Infectious Diseases Society of America. MMWR 2005;54(No. RR-12).
320. Kaplan J, Masur H, Holmes K, et al. Guidelines for preventing opportunistic infections among HIV-infected persons–2002: recommendations of the U.S. Public Health Service and the Infectious Diseases Society of America. MMWR 2002;51(No. RR-8).
321. CDC. Prevention and treatment of tuberculosis among patients infected with human immunodeficiency virus: principles of therapy and revised recommendations. MMWR 1998;47(No. RR-20).
322. CDC. Updated guidelines for the use of rifamycins for the treatment of tuberculosis among HIV-infected patients taking protease inhibitors or nonnucleoside reverse transcriptase inhibitors. MMWR 2000;49(No. RR-4).
323. Sterling TR, Hackman J, Horsburgh CR. Design of Tuberculosis Trials Consortium Study 26: once-weekly rifapentine (RPT) + isoniazid (INH) for 3 months vs. daily INH for 9 months for the treatment of latent TB infection (Abstract). Washington, DC: 4th World Congress on Tuberculosis; June 3-5, 2002.
324. Thwaites GE, Nguyen DB, Nguyen HD, et al. Dexamethasone for the treatment of tuberculous meningitis in adolescents and adults. N Engl J Med 2004;351:1741–51.
325. Nahid P, Gonzalez LC, Rudoy I, et al. Treatment outcomes of patients with HIV and tuberculosis. Am J Respir Crit Care Med 2007;175:1199–206.
326. Lopez-Cortes LF, Marin-Neibla A, Lopez-Cortez LE, Villanego I, Rodriguez-Diez M P-CR. Influence of treatment and immunological recovery on tuberculosis relapses in HIV-infected patients. Int J Tuberc Lung Dis 2005;9:1385–90.
327. de Jong BC, Israelski DM, Corbett EL, Small PM. Clinical management of tuberculosis in the context of HIV infection. Annu Reb Med 2004:55:283–301.
328. CDC. Acquired rifamycin resistance in persons with advanced HIV disease being treated for active tuberculosis with intermittent rifamycin-based regimens. MMWR 2002;51:214–5.
329. Vernon A, Burman W, Benator D, Khan A, Bozeman L. Acquired rifamycin monoresistance in patients with HIV-related tuberculosis treated with once-weekly rifapentine and isoniazid. Lancet 1999;353:1843–7.
330. Burman W, Benator D, Vernon A, et al. Acquired rifamycin resistance with twice-weekly treatment of HIV-related tuberculosis. Am J Respir Crit Care Med 2006; 173:350–6.
331. CDC. Update: adverse event data and revised American Thoracic Society/CDC recommendations against the use of rifampin and pyrazinamide for treatment of latent tuberculosis infection–United States, 2003. MMWR 2003;52:735–9.
332. Nolan CM, Goldberg SV, Buskin SE. Hepatotoxicity associated with isoniazid preventive therapy: a 7-year survey from a public health tuberculosis clinic. JAMA 1999; 281:1014–8.
333. Saukkonen JJ, Cohn DL, Jasmer RM, et al. Hepatotoxicity of antituberculosis therapy. Am J Respir Crit Care Med 2006;174:935–52.
334. Chideya SR, Jappero J, Peloquin C, et al. Sub-therapeutic serum concentrations of anti-tuberculosis medications and treatment—Botswana, 1997-1999. In: 56th Annual Epidemic Intelligence Service (EIS) Conference. Atlanta, Georgia: US Department of Health and Human Services, Public Health Service, April 2007.
335. Peloquin CA. Therapeutic drug monitoring in the treatment of tuberculosis. Drugs 2002;62:2169–83.
336. Yew WW, Leung CC. Antituberculosis drugs and hepatotoxicity. Am J Respir Crit Care Med 2007;175:858.
337. Breen RA, Miller RF, Gorsuch T, et al. Adverse events and treatment interruption in tuberculosis patients with and without HIV co–infection. Thorax 2006;61:791–4.
338. Yee D, Valiquette C, Pelletier M, et al. Incidence of serious side effects from first-line antituberculosis drugs among patients treated for active tuberculosis. Am J Respir Crit Care Med 2003;167:1472–7.
339. Dean GL, Edwards SG, Ives NJ, et al. Treatment of tuberculosis in HIV-infected persons in the era of highly active antiretroviral therapy. AIDS 2002;16:75–83.
340. CDC. Core curriculum on tuberculosis: what the clinician should know, Atlanta, GA: US Department of Health and Human Services, CDC. Available at http://www.cdc.gov/nchstp/tb.
341. Mehta YS, Jijina FF, Badakere SS, Pathare AV, Mohanty D. Rifampicin-induced immune thrombocytopenia. Tuber Lung Dis 1996;77:558–62.
342. Chien JW, Johnson JL. Paradoxical reactions in HIV and pulmonary TB. Chest 1998;114:933–6.
343. Steele MA, Burk RF, DesPrez RM. Toxic hepatitis with isoniazid and rifampin: a meta-analysis. Chest 1991;99:465–71.
344. Ormerod LP. Hepatotoxicity of antituberculosis drugs. Thorax 1996;51:111–3.
345. Burman WJ, Gallicano K, Peloquin C. Therapeutic implications of drug interactions in the treatment of human immunodeficiency virus-related tuberculosis. Clin Infect Dis 1999;28:419–29.

346. CDC. Updated guidelines for the use of rifamycins for the treatment of tuberculosis among HIV-infected patients taking protease inhibitors or nonnucleoside reverse transcriptase inhibitors. Available at http://www.cdc.gov/nchstp/tb/tb_hiv_drugs/toc.html. 2004.
347. Roche pharmaceuticals. Dear Health-care provider letter 7 February 2005 http://www.fda.gov/medwatch/SAFETY/2005/safety05.htm#Invirase.
348. Pedral-Sampaio DB, Alves CR, Netto EM, et al. Efficacy and safety of efavirenz in HIV patients on Rifampin for tuberculosis. Braz J Infect Dis 2004;8:211–6.
349. World Health Organization. Antiretroviral therapy for HIV infection in adults and adolescents in resource-limited settings: towards universal access: recommendations for a public health approach 2006. Available at http://www.who.int/hiv/pub/guidelines/adult/en/index.html.2006.
350. Borin MT, Chambers JH, Carel BJ, et al. Pharmacokinetic study of the interaction between rifabutin and delavirdine mesylate in HIV-1 infected patients. Antiviral Res 1997;35:53–63.
351. Nelson M, Lipman M. Management of advanced HIV disease in patients with tuberculosis or hepatitis co-infection. Int J Clin Pract 2006;60:976–83.
352. Pozniak AL, Miller RF, Lipman MC, et al. Treatment guidelines for tuberculosis (TB)/HIV infection. HIV Med 2005;6(Suppl 2):62-83.
353. Dheda K, Lampe FC, Johnson MA, Lipman MC. Outcome of HIV-associated tuberculosis in the era of highly active antiretroviral therapy. J Infect Dis 2004;190:1670–6.
354. Lawn SD, Bekker LG, Miller RF. Immune reconstitution disease associated with mycobacterial infections in HIV-infected individuals receiving antiretrovirals. Lancet Infect Dis 2005;5:361–73.
355. World Health Organization. Guidelines for the programmatic management of drug-resistant tuberculosis. Geneva, Switzerland: WHO/HTM/TB/2006.361; 2006.
356. CDC. Transmission of multidrug-resistant tuberculosis among immunocompromised persons in a correctional system—New York, 1991. MMWR 1992;41:507–9.
357. Jereb JA, Klevens RM, Privett TD, Smith PJ, Crawford JT. Tuberculosis in health care workers at a hospital with an outbreak of multidrug-resistant *Mycobacterium tuberculosis*. Arch Intern Med 1995;155:854–9.
358. Frieden TR, Sherman LF, Maw KL, et al. A multi-institutional outbreak of highly drug-resistant tuberculosis: epidemiology and clinical outcomes. JAMA 1996;276:1229–35.
359. Agerton TB, Valway SE, Blinkhorn RJ, et al. Spread of strain W, a highly drug-resistant strain of *Mycobacterium tuberculosis*, across the United States. Clin Infect Dis 1999;29:85–92.
360. Bifani PJ. Plikaytis BB, Kapur V, et al. Origin and interstate spread of a New York City multidrug-resistant *Mycobacterium tuberculosis* clone family. JAMA 1996;275: 452-7.
361. CDC. Emergence of *Mycobacterium tuberculosis* with extensive resistance to second-line drugs—worldwide, 2000-2004. MMWR 2006;55:301–5.
362. CDC. Revised definition of extensively drug-resistant tuberculosis. MMWR 2006;55:1176.
363. Wells CD, Cegielski JP, Nelson L, et al. HIV infection and multidrug resistant tuberculosis—the perfect storm. J Infect Dis 2007;196 (Suppl 1):S86–107.
364. Samper S, Martín C. Spread of extensively drug-resistant tuberculosis. Emerg Infect Dis 2007;13:647–8.
365. CDC. Extensively drug-resistant tuberculosis—United States, 1993-2006. MMWR 2007;56:250–3.
366. Gandhi NR, Moll A, Sturm AW, et al. Extensively drug-resistant tuberculosis as a cause of death in patients co-infected with tuberculosis and HIV in a rural area of South Africa. Lancet 2006;368:1575–80.
367. Ahuja SD, Munsiff SS, Nilsen D. Clinical outcomes of extensively drug resistant tuberculosis patients in New York City. Union World Conference on Lung Health. Capetown, South Africa, 2007. Int J Tuberc Lung Dis 2007. (Suppl 1):S1-S320.
368. CDC. Guidelines for the investigation of contracts or persons with infectious tuberculosis: recommendations from the National Tuberculosis Controllers Association and CDC. MMWR 2005;54(No. RR-15).
369. Banda H, Kang'ombe C, Harries AD, et al. Mortality rates and recurrent rates of tuberculosis in patients with smear-negative pulmonary tuberculosis and tuberculous pleural effusion who have completed treatment. Int J Tuberc Lung Dis 2000;4:968–74.
370. Mallory KF, Churchyard GJ, Kleinschmidt I, De Cock KM, Corbett EL. The impact of HIV infection on recurrence of tuberculosis in South African gold miners. Int J Tuberc Lung Dis 2000;4:455–62.
371. Fitzgerald DW, Desvarieux M, Severe P, et al. Effect of post-treatment isoniazid on prevention of recurrent tuberculosis in HIV-1-infected individuals: a randomised trial. Lancet 2000;356:1470–4.
372. Sonnenberg P, Murray J, Glynn JR, Shearer S, Kambashi B, Godfrey-Faussett P. HIV-1 and recurrence, relapse, and reinfection of tuberculosis after cure: a cohort study in South African mineworkers. Lancet 2001;358:1687–93.
373. Churchyard GJ, Fielding K, Charalambous S, et al. Efficacy of secondary isoniazid preventive therapy among HIV-infected Southern Africans: time to change policy? AIDS 2003;17:2063–70.
374. Glynn JR, Yates MD, Crampin AC, et al. DNA fingerprint changes in Tuberculosis: reinfection, evolution, or laboratory error? J Infect Dis 2003;190:1158–66.
375. Seyler C, Toure S, Messou E, et al. Risk factors for active tuberculosis after antiretroviral treatment initiation in Abidjan. Am J Respir Crit Care Med 2005; 172:123–7.
376. Haller L, Sossouhounto R, Coulibaly IM, et al. Isoniazid plus sulphadoxine-pyrimethamine can reduce morbidity of HIV-positive patients treated for tuberculosis in Africa: a controlled clinical trial. Chemotherapy 1999;45:452–65.
377. Cain KP, Haley CA, Armstrong LR, et al. Tuberculosis among foreign-born persons in the United States: achieving tuberculosis elimination. Am J Respir Crit Care Med 2007;175:75–9.
378. Chin DP, DeRiemer K, Small PM, et al. Differences in contributing factors to tuberculosis incidence in U.S.-born and foreign-born persons. Am J Respir Crit Care Med 1998;158:1797–803.
379. Geng E, Kreiswirth B, Driver C, et al. Changes in the transmission of tuberculosis in New York City from 1990 to 1999. N Engl J Med 2002;346:1453–8.
380. Jasmer RM, Hahn JA, Small PM, et al. A molecular epidemiologic analysis of tuberculosis trends in San Francisco, 1991-1997. Ann Intern Med 1999;130:971–8.
381. Torineporth NG, Ptachewich Y, Poltoraskaia N, et al. Tuberculosis among foreign-born persons in New York City, 1992-1994: implications for tuberculosis control. Int J Tuberc Lung Dis 1997;1:528–35.
382. Mofenson LM, Rodriguez EM, Hershow R, et al. *Mycobacterium tuberculosis* infection in pregnant and nonpregnant women infected with HIV in the Women and Infants Transmission Study. Arch Intern Med 1995;155:1066–72.
383. Eriksen NL, Helfgott AW. Cutaneous anergy in pregnant and nonpregnant women with human immunodeficiency virus. Infect Dis Obstet Gynecol 1998;6:13–7.

384. Jana N, Vasishta K, Jindal SK, Khunnu B, Ghosh K. Perinatal outcome in pregnancies complicated by pulmonary tuberculosis. Int J Gynaecol Obstet 1994;44:119–24.
385. Jana N, Vasishta K, Saha SC, Ghosh K. Obstetrical outcomes among women with extrapulmonary tuberculosis. N Engl J Med 1999;341:645–9.
386. Brost BC, Newman RB. The maternal and fetal effects of tuberculosis therapy. Obstet Gynecol Clin North Am 1997;24:659–73.
387. Bothamley G. Drug treatment for tuberculosis during pregnancy: safety considerations. Drug Saf 2001;24:553–65.
388. Czeizel AE, Rockenbauer M, Olsen J, Sorensen HT. A population-based case-control study of the safety of oral anti-tuberculosis drug treatment during pregnancy. Int J Tuberc Lung Dis 2001;5:564–8.
389. Efferen LS. Tuberculosis and pregnancy. Curr Opin Infect Dis 2007;13:205–11.
390. Vilarinho LC. Congenital tuberculosis: a case report. Braz J Infect Dis 2006;10:368–70.
391. Franks AL, Binkin NJ, Snider DE, Jr., Rokaw WM, Becker S. Isoniazid hepatitis among pregnant and postpartum Hispanic patients. Public Health Rep 1989;104:151–5.
392. World Health Organizations. Treatment of tuberculosis:guidelines for national programs. Geneva, Switzerland: WHO/TB/97.220; 1997.
393. Enarson D, Rieder H, Arnodottir T, Trebucq A. Management of tuberculosis: a guide for low income countries, 4th ed. Paris, France: International Union Against Tuberculosis and Lung Disease, 1996.
394. Dluzniewski A, Gastol-Lewinska L. The search for teratogenic activity of some tuberlostatic drugs. Diss Pharm Pharmacol 1971:23:383–92.
395. Nahum GG, Uhl K, Kennedy DL. Antibiotic use in pregnancy and lactation: what is and is not known about teratogenic and toxic risks. Obstet Gynecol 2006;107:1120–38.
396. Varpela E. On the effect exerted by first line tuberculosis medicines on the foetus. Acta Tuberc Scand 1964:45:53–69.
397. CDC. USPHS task force recommendations for the use of antiretroviral drugs in pregnant women infected with HIV-1 for maternal health and for reducing perinatal HIV-1 transmission in the United States. MMWR 1998;47(No. RR-2).
398. Inderlied CB: Microbiology and minimum inhibitory concentration testing for *Mycobacterium avium* complex prophylaxis. Am J Med 1997;102:2–10.
399. Benson CA, Williams PL, Cohn DL, et al. Clarithromycin or rifabutin alone or in combination for primary prophylaxis of *Mycobacterium avium* complex disease in patients with AIDS: a randomized, double-blind, placebo-controlled trial. J Infect Dis 2000;181:1289–97.
400. Benson CA, Williams PL, Currier JS, et al. A prospective, randomized trial examining the efficacy and safety of clarithromycin in combination with ethambutol, rifabutin, or both for the treatment of disseminated *Mycobacterium avium* complex disease in persons with acquired immunodeficiency syndrome. Clin Infect Dis 2003;37:1234–43.
401. Kemper CA, Havlir D, Bartok AE, et al. Transient bacteremia due to *Mycobacterium avium* complex in patients with AIDS. J Infect Dis 1994;170:488–93.
402. Gordin FM, Cohn DL, Sullam PM, et al. Early manifestations of disseminated *Mycobacterium avium* complex disease: a prospective evaluation. J Infect Dis 1997;176:126–32.
403. Benson CA, Ellner JJ. *Mycobacterium avium* complex infection and AIDS: advances in theory and practice. Clin Infect Dis 1993;17:7–20.
404. Havlik JA, Jr., Horsburgh CR, Jr., Metchock B, et al. Disseminated *Mycobacterium avium* complex infection: clinical identification and epidemiologic trends. J Infect Dis 1992;165:577–80.
405. Benson CA. Treatment of disseminated disease due to the *Mycobacterium avium* complex in patients with AIDS. Clin Infect Dis 1994;18(Suppl 3):S237-42.
406. Benson CA. Disease due to the *Mycobacterium avium* complex in patients with AIDS: epidemiology and clinical syndrome. Clin Infect Dis 1994;18(Suppl 3):S218-22.
407. Nightingale SD, Byrd LT, Southern PM, Jockusch JD, Cal SX, Wynne BA. Incidence of *Mycobacterium avium*-intracellulare complex bacteremia in human immunodeficiency virus-positive patients. J Infect Dis 1992;165:1082–5.
408. Chaisson RE, Moore RD, Richman DD, Keruly J, Creagh T. Incidence and natural history of *Mycobacterium avium*-complex infections in patients with advanced human immunodeficiency virus disease treated with zidovudine. Am Rev Respir Dis 1992;146:285–9.
409. Barbaro DJ, Orcutt VL, Coldiron BM. *Mycobacterium avium-Mycobacterium intracellulare* infection limited to the skin and lymph nodes in patients with AIDS. Rev Infect Dis 1989;11:625–8.
410. Hellyer TJ, Brown IN, Taylor MB, Allen BW, Easmon CS. Gastrointestinal involvement in *Mycobacterium avium-intracellulare* infection of patients with HIV. J Infect 1993;26:55–66.
411. Owen RL, Roth RI, St. Hilaire RJ, Keren DF. Pseudo Whipple's disease: intestinal infection with *Mycobacterium avium-intracellulare* (M.avium) in acquired immune deficiency syndrome (AIDS). Gastroenterology 1984;84:1267.
412. Torriani FJ, McCutchan JA, Bozzette SA, Grafe MR, Havlir DV. Autopsy findings in AIDS patients with *Mycobacterium avium* complex bacteremia. J Infect Dis 1994; 170:1601–5.
413. Inderlied CB, Kemper CA, Bermudez LE. The *Mycobacterium avium* complex. Clin Microbiol Rev 1993;6:266–310.
414. Packer SJ, Cesario T, Williams JH, Jr. *Mycobacterium avium* complex infection presenting as endobronchial lesions in immunosuppressed patients. Ann Intern Med 1988;109:389–93.
415. Phillips P, Kwiatkowski MB, Copland M, Craib K, Montaner J. Mycobacterial lymphadenitis associated with the initiation of combination antiretroviral therapy. J Acquir Immune Defic Syndr Hum Retrovirol 1999;20:122–8.
416. Phillips P, Bonner S, Gataric N, et al. Nontuberculous mycobacterial immune reconstitution syndrome in HIV-infected patients: spectrum of disease and long-term follow-up. Clin Infect Dis 2005;41:1483–97.
417. Race EM, Adelson-Mitty J, Kriegel GR, et al. Focal mycobacterial lymphadenitis following initiation of protease-inhibitor therapy in patients with advanced HIV-1 disease. Lancet 1998;9098:252–5.
418. Cabie A, Abel S, Brebion A, et al. Mycobacterial lymphadenitis after initiation of highly active antiretroviral therapy. Eur J Clin Microbiol Infect Dis 1998;17:812–3.
419. Shanson DC, Dryden MS. Comparison of methods for isolating *Mycobacterium avium*-intracellulare from blood of patients with AIDS. J Clin Pathol 1988;41:687–90.
420. Hafner R, Inderlied CB, Peterson DM, et al. Correlation of quantitative bone marrow and blood cultures in AIDS patients with disseminated *Mycobacterium avium* complex infection. J Infect Dis 1999;180:438–47.
421. Havlir DV, Dube MP, Sattler FR, et al. Prophylaxis against disseminated *Mycobacterium avium* complex with weekly azithromycin, daily rifabutin, or both. N Engl J Med 1996;335:392–8.
422. Pierce M, Crampton S, Henry D, et al. A randomized trial of clarithromycin as prophylaxis against disseminated *Mycobacterium avium* complex infection in patients with advanced acquired immunodeficiency syndrome. N Engl J Med 1996;335:384–91.

423. CDC. TB/HIV Drug Interactions. www.cdc.gov/tb/tb_hiv_Drugs/rifabutin.htm. Last accessed December 22, 2008.
424. US Department of Health and Human Services. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Available at http://AIDSinfo.nih.gov.
425. El-Sadr WM, Burman WJ, Grant LB, et al. Discontinuation of prophylaxis for *Mycobacterium avium* complex disease in HIV-infected patients who have a response to antiretroviral therapy. N Engl J Med 2000; 342:1085–92.
426. Currier JS, Williams PL, Koletar SL, et al. Discontinuation of *Mycobacterium avium* complex prophylaxis in patients with antiretroviral therapy-induced increases in $CD4^+$ cell count: a randomized, double-blind, placebo-controlled trial. Ann Intern Med 2000;133:493–503.
427. Furrer H, Telenti A, Rossi M, Ledergerber B. Discontinuing or withholding primary prophylaxis against *Mycobacterium avium* in patients on successful antiretroviral combination therapy: the Swiss HIV Cohort Study. AIDS 2000;14:1409–12.
428. Brooks JT, Song R, Hanson DL, et al. Discontinuation of primary prophylaxis against *Mycobacterium avium* complex infection in HIV-infected persons receiving antiretroviral therapy: observations from a large national cohort in the United States, 1992-2002. Clin Infect Dis 2005;41:549–53.
429. Chaisson RE, Benson CA, Dube MP, et al. Clarithromycin therapy for bacteremic *Mycobacterium avium* complex disease: a randomized, double-blind, dose-ranging study in patients with AIDS. Ann Intern Med 1994;121:905–11.
430. May T, Brel F, Beuscart C, et al. Comparison of combination therapy regimens for treatment of human immunodeficiency virus-infected patients with disseminated bacteremia due to *Mycobacterium avium*. Clin Infect Dis 1997;25:621–9.
431. Gordin FM, Sullam PM, Shafran SD, et al. A randomized, placebo-controlled study of rifabutin added to a regimen of clarithromycin and ethambutol for treatment of disseminated infection with *Mycobacterium avium* complex (MAC). Clin Infect Dis 1999;28:1080–5.
432. Dube MP, Sattler FR, Torriani FJ, et al. A randomized evaluation of ethambutol for prevention of relapse and drug resistance during treatment of *Mycobacterium avium* complex bacteremia with clarithromycin-based combination therapy. J Infect Dis 1997;176:1225–32.
433. Cohn DL, Fisher EJ, Peng GT, et al. A prospective randomized trial of four three-drug regimens in the treatment of disseminated *Mycobacterium avium* complex disease in AIDS patients: excess mortality associated with high-dose clarithromycin. Clin Infect Dis 1999;29:125–33.
434. Aberg JA, Yajko DM, Jacobson MA. Eradication of AIDS-related disseminated *Mycobacterium avium* complex infection after 12 months of antimycobacterial therapy combined with highly active antiretroviral therapy. J Infect Dis 1998;178:1446–9.
435. Ward TT, Rimland D, Kauffman C, et al. Randomized, open-label trial of azithromycin plus ethambutol vs. clarithromycin plus ethambutol as therapy for *Mycobacterium avium* complex bacteremia in patients with human immunodeficiency virus infection. Clin Infect Dis 1998;27:1278–85.
436. Dunne M, Fessel J, Kumar P, et al. A randomized, double-blind trial comparing azithromycin and clarithromycin in the treatment of disseminated *Mycobacterium avium* infection in patients with human immunodeficiency virus. Clin Infect Dis 2000;31:1245–52.
437. Shafran SD, Singer J, Zarowny DP, et al. A comparison of two regimens for the treatment of *Mycobacterium avium* complex bacteremia in AIDS: rifabutin, ethambutol, and clarithromycin versus rifampin, ethambutol, clofazimine, and ciprofloxacin. N Engl J Med 1996;335:377–83.
438. Griffith DE, Aksamit T, Brown-Elliott BA, et al. Diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. Am J Respir Crit Care Med 2007;175:367–416.
439. Gardner EM, Burman WJ, DeGroote MA, et al. Conventional and molecular epidemiology of macrolide resistance among new *Mycobacterium avium* complex isolates recovered from HIV-infected patients. Clin Infect Dis 2005;41:1041–4.
440. Abbot Laboratories: Clarithromycin (biaxin) (package insert). Abbot Park, IL: Abbot Laboratories, 1995.
441. Shafran SD, Deschenes J, Miller M, Phillips P, Toma E. Uveitis and pseudojaundice during a regimen of clarithromycin, rifabutin, and ethambutol. N Engl J Med 1994;330:438–9.
442. Hafner R, Bethel J, Power M, et al. Tolerance and pharmacokinetic interactions of rifabutin and clarithromycin in human immunodeficiency virus-infected volunteers. Antimicrob Agents Chemother 1998;42:631–9.
443. Graves M, Salvato P, Thompson C. MAIC and the effect of prednisone on disease progression in AIDS patients. Presented at the 11th International Conference on AIDS, Vancouver, Canada: July 7-12, 1996.
444. Wormser GP, Horowitz H, Dworkin B. Low-dose dexamethasone as adjunctive therapy for disseminated *Mycobacterium avium* complex infections in AIDS patients. Antimicrob Agents Chemother 1994;38:2215–7.
445. Heifets L, Lindholm LP, Libonati J. Radiometric broth macrodilution method for determination of minimal inhibitory concentrations (MIC) with *Mycobacterium avium* complex isolates: proposed guidelines. Denver, CO:National Jewish Center for Immunology and Respiratory Medicine, 1993.
446. Heifets L, Mor N, Vanderkolk J. *Mycobacterium avium* strains resistant to clarithromycin and azithromycin. Antimicrob Agents Chemother 1993;37:2364–70.
447. Kemper CA, Meng TC, Nussbaum J, et al. Treatment of *Mycobacterium avium* complex bacteremia in AIDS with a four-drug oral regimen: rifampin, ethambutol, clofazimine, and ciprofloxacin. Ann Intern Med 1992;116:466–72.
448. Chaisson RE, Keiser P, Pierce M, et al. Clarithromycin and ethambutol with or without clofazimine for the treatment of bacteremic *Mycobacterium avium* complex disease in patients with HIV infection. AIDS 1997;11:311–7.
449. Chiu J, Nussbaum J, Bozzette S, et al. Treatment of disseminated *Mycobacterium avium* complex infection in AIDS with amikacin, ethambutol, rifampin, and ciprofloxacin. Ann Intern Med 1990;113:358–61.
450. Rodriguez Diaz JC, López M, Ruiz M, Royo G. In vitro activity of new fluoroquinolones and linezolid against non-tuberculous mycobacteria. Int J Antimicrobial Agents 2003;21:585–8.
451. Aberg JA, Williams PL, Liu T, et al. A study of discontinuing maintenance therapy in human immunodeficiency virus-infected subjects with disseminated *Mycobacterium avium* complex. J Infect Dis 2003;187:1046–52.
452. Einarson A, Phillips E, Mawji F, et al. A prospective controlled multicentre study of clarithromycin in pregnancy. Am J Perinatol 1998;15:523–5.

453. Drinkard CR, Shatin D, Clouse J. Postmarketing surveillance of medications and pregnancy outcomes: clarithromycin and birth malformations. Pharmacoepidemiol Drug Saf 2000;9:549–56.
454. Hirschtick R, Glassroth J, Jordan MC, et al. Bacterial pneumonia in persons infected with the human immunodeficiency virus. N Engl J Med 1995;333:845–51.
455. Wallace JM, Hansen NI, Lavange L, et al. Respiratory disease trends in the Pulmonary Complications of HIV Infection Study cohort. Am J Respir Crit Care Med 1997;72-80.
456. Sullivan JH, Moore RD, Keruly JC, Chaisson RE. Effect of antiretroviral therapy on the incidence of bacterial pneumonial in patients with advanced HIV infection. Am J Respir Crit Care Med 2000;162:64–7.
457. Serraino D, Puro V, Boumis E, et al. Epidemiological aspects of major opportunistic infections of the respiratory tract in persons with AIDS: Europe, 1993-2000. AIDS 2003;17:2109–16.
458. Polsky B, Gold JW, Whimbey E, et al. Bacterial pneumonia in patients with the acquired immunodeficiency syndrome. Ann Intern Med 1986;104:38–41.
459. Burack JH, Hahn JA, Saint-Maurice D, Jacobson MA. Microbiology of community-acquired bacterial pneumonia in persons with and at risk for human immunodeficiency virus type 1 infection: implications for rational empiric antibiotic therapy. Arch Intern Med 1994;154:2589–96.
460. Miller RF, Foley NM, Kessel D, Jeffrey AA. Community acquired lobar pneumonia in patients with HIV infection and AIDS. Thorax 1994;49:367–8.
461. Mundy LM, Auwaerter PG, Oldach D, et al. Community-acquired pneumonia: impact of immune status. Am J Respir Crit Care Med 1995;152:1309–15.
462. Afessa B, Green B. Bacterial pneumonia in hospitalized patients with HIV infection: the Pulmonary Complications, ICU Support, and Prognostic Factors of Hospitalized Patients with HIV (PIP) Study. Chest 2000; 117:1017–22.
463. Park DR, Sherbin VL, Goodman MS, et al. The etiology of community-acquired pneumonia at an urban public hospital: influence of human immunodeficiency virus infection and initial severity of illness. J Infect Dis 2001;184:268–77.
464. Rimland D, Navin TR, Lennox JL, et al. Prospective study of etiologic agents of community-acquired pneumonia in patients with HIV infection. AIDS 2002;16:85–95.
465. Turett GS, Blum S, Fazal BA, Justman JE, Telzak EE. Penicillin resistance and other predictors of mortality in pneumococcal bacteremia in a population with high human immunodeficiency virus seroprevalence. Clin Infect Dis 1999;29:321–7.
466. Tarp B, Jensen JS, Ostergaard L, Andersen PL. Search for agents causing atypical pneumonia in HIV-positive patients by inhibitor-controlled PCR assays. Eur Respir J 1999;13:175–9.
467. Levine SJ, White DA, Fels AO. The incidence and significance of *Staphylococcus aureus* in respiratory cultures from patients infected with the human immunodeficiency virus. Am Rev Respir Dis 1990;141:89–93.
468. Redd SC, Rutherford GW, 3rd, Sande MA, et al. The role of human immunodeficiency virus infection in pneumococcal bacteremia in San Francisco residents. J Infect Dis 1990;162:1012–7.
469. Falco V, Fernandez de Sevilla T, Alegre J, et al. Bacterial pneumonia in HIV-infected patients: a prospective study of 68 episodes. Eur Respir J 1994;7:235–9.
470. Feldman C, Glatthaar M, Morar R, et al. Bacteremic pneumococcal pneumonia in HIV-seropositive and HIV-seronegative adults. Chest 1999;116:107–14.
471. Osmond DH, Chin DP, Glassroth J, et al. Impact of bacterial pneumonia and *Pneumocystis carinii* pneumonia on human immunodeficiency virus disease progression. Clin Infect Dis 1999;29:536–43.
472. Kohli R, Lo Y, Homel P, et al. Bacterial pneumonia, HIV therapy, and disease progression among HIV-infected women in the HIV epidemiologic research (HER) study. Clin Infect Dis 2006;43:90–8.
473. Cordero E, Pachon J, Rivero A, et al. Community-acquired bacterial pneumonia in human immunodeficiency virus-infected patients: validation of severity criteria. Am J Respir Crit Care Med 2000;162:2063–8.
474. Gil Suay V, Cordero PJ, Martinez E, et al. Parapneumonic effusions secondary to community-acquired bacterial pneumonia in human immunodeficiency virus-infected patients. Eur Respir J 1995;8:1934–9.
475. Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis 2007;44(Suppl 2):S27-72.
476. Gebo KA, Moore RD, Keruly JC, Chaisson RE. Risk factors for pneumococcal disease in human immunodeficiency virus-infected patients. J Infect Dis 1996;173:857–62.
477. Guerrero M, Kruger S, Saitoh A, et al. Pneumonia in HIV-infected patients: a case-control survey of factors involved in risk and prevention. AIDS 1999;13:1971–5.
478. Breiman RF, Keller DW, Phelan MA, et al. Evaluation of effectiveness of the 23-valent pneumococcal capsular polysaccharide vaccine for HIV-infected patients. Arch Intern Med 2000;160:2633–8.
479. CDC. Recommended adult immunization schedule—United States, October 2007–September 2008. MMWR 2007; 56(41):2–4.
480. French N, Nakiyingi J, Carpenter LM, et al. 23-valent pneumococcal polysaccharide vaccine in HIV-1-infected Ugandan adults: double-blind, randomised and placebo controlled trial. Lancet 2000;355:2106–11.
481. Watera C, Nakiyingi J, Miiro G, et al. 23-Valent pneumococcal polysaccharide vaccine in HIV-infected Ugandan adults: 6-year follow-up of a clinical trial cohort. AIDS 2004;18:1210–3.
482. Hung CC, Chen MY, Hsieh SM, Hsiao CF, Sheng WH. Clinical experience of the 23-valent capsular polysaccharide pneumococcal vaccination in HIV-1-infected patients receiving highly active antiretroviral therapy: a prospective observational study. Vaccine 2004;22:2006–12.
483. Grau I, Pallares R, Tubau F, Schulze MH, et al. Epidemiologic changes in bacteremic pneumococcal disease in patients with human immunodeficiency virus in the era of highly active antiretroviral therapy. Arch Intern Med 2005; 165:1533–40.
484. Oldfield EC, Fessel WJ, Dunne MW, et al. Once weekly azithromycin therapy for prevention of *Mycobacterium avium* complex infection in patients with AIDS: a randomized, double-blind, placebo-controlled multicenter trial. Clin Infect Dis 1998;26:611–9.
485. Navin TR, Rimland D, Lennox JL, et al. Risk factors for community-acquired pneumonia among persons infected with human immunodeficiency virus. J Infect Dis 2000; 181:158–64.
486. Justice AC, Lasky E, McGinnis KA, et al. Medical disease and alcohol use among veterans with human immunodeficiency infection: a comparison of disease measurement strategies. Med Care 2006;44(Suppl 2):S52-60.
487. Christensen D, Feldman C, Rossi P, et al. HIV infection does not influence clinical outcomes in hospitalized patients with bacterial community-acquired pneumonia: results from the CAPO international cohort study. Clin Infect Dis 2005;41:554–6.
488. Celum CL, Chaisson RE, Rutherford GW, et al. Incidence of salmonellosis in patients with AIDS. J Infect Dis 1987;156:998–1002.

489. Sorvillo FJ, Lieb L, Waterman SH. Incidence of campylobacteriosis among patients with AIDS in Los Angeles County. J Acquir Immune Defic Syndr 1991;4:598–602.
490. Angulo FJ, Swerdlow DL. Bacterial enteric infections in persons infected with human immunodeficiency virus. Clin Infect Dis 1995;21(Suppl 1):S84-93.
491. Nelson MR, Shanson DC, Hawkins DA, Gazzard BG. *Salmonella*, *campylobacter* and *shigella* in HIV-seropositive patients. AIDS 1992;6:1495–8.
492. Sanchez TH, Brooks JT, Sullivan PS, et al. Bacterial diarrhea in persons with HIV infection, United States, 1992-2002. Clin Infect Dis 2005;41:1621–7.
493. Aragon TJ, Vugia DJ, Shallow S, et al. Case-control study of shigellosis in San Francisco: the role of sexual transmission and HIV infection. Clin Infect Dis 2007;44:327–34.
494. Quinn TC, Goodell SE, Fennell C, et al. Infections with *Campylobacter jejuni* and *Campylobacter*-like organisms in homosexual men. Ann Intern Med 1984;101:187–92.
495. Huang DB, Mohanty A, DuPont HL, Okhuysen PC, Chiang T. A review of an emerging enteric pathogen: enteroaggregative *Escherichia coli*. J Med Microbiol 2006; 55:1303–11.
496. Baer JT, Vugia DJ, Reingold AL, et al. HIV infection as a risk factor for shigellosis. Emerg Infect Dis 1999;5:820–3.
497. Kristjansson M, Viner B, Maslow JN. Polymicrobial and recurrent bacteremia with *Shigella* in a patient with AIDS. Scand J Infect Dis 1994;26:411–6.
498. Snijders F, Kuijper EJ, de Wever B, et al. Prevalence of *Campylobacter*-associated diarrhea among patients infected with human immunodeficiency virus. Clin Infect Dis 1997;24:1107–13.
499. Tee W, Mijch A. *Campylobacter jejuni* bacteremia in human immunodeficiency virus (HIV)-infected and non-HIV-infected patients: comparison of clinical features and review. Clin Infect Dis 1998;26:91–6.
500. Tee W, Mijch A, Wright E, Yung A. Emergence of multidrug resistance in *Campylobacter jejuni* isolates from three patients infected with human immunodeficiency virus. Clin Infect Dis 1995;21:634–8.
501. Meier PA, Dooley DP, Jorgensen JH,et al. Development of quinolone-resistant *Campylobacter* fetus bacteremia in human immunodeficiency virus-infected patients. J Infect Dis 1998;177:951–4.
502. Casado JL, Valdezate S, Calderon C, et al. Zidovudine therapy protects against *Salmonella* bacteremia recurrence in human immunodeficiency virus-infected patients. J Infect Dis 1999;179:1553–6.
503. Mayer KH, Hanson E. Recurrent *Salmonella* infection with a single strain in the acquired immunodeficiency syndrome: confirmation by plasmid fingerprinting. Diagn Microbiol Infect Dis 1986;4:71–6.
504. Rubino S, Spanu L, Mannazzu M, et al. Molecular typing of non-typhoid *Salmonella* strains isolated from HIV-infected patients with recurrent salmonellosis. AIDS 1999;13:137–9.
505. Guerrant RL, Van Gilder T, Steiner TS, et al. Practice guidelines for the management of infectious diarrhea. Clin Infect Dis 2001;32:331–51.
506. Spach DH, Koehler JE. *Bartonella*-associated infections. Infect Dis Clin North Am 1998;12:137–55.
507. Koehler JE, Sanchez MA, Garrido CS, et al. Molecular epidemiology of *Bartonella* infections in patients with bacillary angiomatosis-peliosis. N Engl J Med 1997;337:1876–83.
508. Koehler JE, Glaser CA, Tappero JW. *Rochalimaea henselae* infection. A new zoonosis with the domestic cat as reservoir. JAMA 1994;271:531–5.
509. Koehler J, Sanchez M, Tye S, et al. Prevalence of *Bartonella* infection among human immunodeficiency virus-infected patients with fever. Clin Infect Dis 2003;37:559–66.
510. LeBoit PE, Berger TG, Egbert BM, et al. Bacillary angiomatosis: the histopathology and differential diagnosis of a pseudoneoplastic infection in patients with human immunodeficiency virus disease. Am J Surg Pathol 1989;13:909–20.
511. Regnery RL, Olson JG, Perkins BA, Bibb W. Serological response to "*Rochalimaea henselae*" antigen in suspected cat-scratch disease. Lancet 1992;339:1443–5.
512. Rolain JM, Brouqui P, Koehler JE, et al. Recommendations for treatment of human infections caused by *Bartonella* species. Antimicrob Agents Chemother 2004;48:1921–33.
513. Kikendall JW, Friedman AC, Oyewole MA, Fleischer D, Johnson LF. Pill-induced esophageal injury: case reports and review of the medical literature. Dig Dis Sci 1983;28:174–82.
514. Maguina C, Garcia PJ, Gotuzzo E, Cordero L, Spach DH. Bartonellosis (Carrión's disease) in the modern era. Clin Infect Dis 2001;33:772–9.
515. Riley LE, Tuomala RE. Bacillary angiomatosis in a pregnant patient with acquired immunodeficiency syndrome. Obstet Gynecol 1992;79:818–9.
516. Fleming DT, Wasserheit JN. From epidemiological synergy to public health policy and practice: the contribution of other sexually transmitted diseases to sexual transmission of HIV infection. Sex Transm Infect 1999;75:3–17.
517. Rottingen JA, Cameron DW, Garnett GP. A systematic review of the epidemiologic interactions between classic sexually transmitted diseases and HIV: how much really is known? Sex Transm Dis 2001;28:579–97.
518. Blocker ME, Levine WC, St Louis ME. HIV prevalence in patients with syphilis, United States. Sex Transm Dis 2000;7:53–9.
519. Torian LV, Makki HA, Menzies IB, Murrill CS, Weisfuse IB. HIV infection in men who have sex with men, New York City Department of Health sexually transmitted disease clinics, 1990-1999: a decade of serosurveillance finds that racial disparities and associations between HIV and gonorrhea persist. Sex Transm Dis 2002;29:73–8.
520. CDC. Outbreak of syphilis among men who have sex with men--Southern California, 2000. MMWR 2001;50:117–20.
521. Stolte IG, Dukers NH, de Wit JB, Fennema JS, Coutinho RA. Increase in sexually transmitted infections among homosexual men in Amsterdam in relation to HAART. Sex Transm Infect 2001;77:184–6.
522. Peterman TA, Heffelfinger JD, Swint EB, Groseclose SL. The changing epidemiology of syphilis. Sex Transm Dis 2005;32(10 Suppl):S4-10.
523. Golden MR, Marra CM, Holmes KK. Update on syphilis: resurgence of an old problem. JAMA 2003;290:1510–4.
524. Paz-Bailey G, Meyers A, Blank S, et al. A case-control study of syphilis among men who have sex with men in New York City: association With HIV infection. Sex Transm Dis 2004;31:581–7.
525. Calza L, Manfredi R, Marinacci G, et al. Efficacy of penicillin G benzathine as antimicrobial treatment of cutaneous secondary syphilis in patients with HIV infection. J Chemother 2002;14:533–4.
526. Rompalo AM, Lawlor J, Seaman P, et al. Modification of syphilitic genital ulcer manifestations by coexistent HIV infection. Sex Transm Dis 2001;28:448–54.
527. Musher DM, Hamill RJ, Baughn RE. Effect of human immunodeficiency virus (HIV) infection on the course of syphilis and on the response to treatment. Ann Intern Med 1990;113:872–81.
528. Radolf JD, Kaplan RP. Unusual manifestations of secondary syphilis and abnormal humoral immune response to *Treponema pallidum* antigens in a homosexual man with asymptomatic human immunodeficiency virus infection. J Am Acad Dermatol 1988;18:423–8.

529. CDC. Workowski KA, Berman SM: Sexually transmitted diseases treatment guidelines. MMWR 2006;55(No. RR-11).
530. Stoner B: Current controversies in the management of adult syphilis. Clin Infect Dis 2007;44(Suppl 3):S130-46.
531. Buchacz K, Patel P, Taylor M, et al. Syphilis increases HIV viral load and decreases CD4 cell counts in HIV-infected patients with new syphilis infections. AIDS 2004;18:2075–9.
532. Koefoed K, Gerstoft J, Mathiesen LR, Benfield T. Syphilis and human immunodeficiency virus (HIV)-1 coinfection: influence on CD4 T-cell count, HIV-1 viral load, and treatment response. Sex Transm Dis 2006;33:143–8.
533. Palacios R, Jiménez-Oñate F, Aguilar M, et al. Impact of syphilis infection on HIV viral load and CD4 cell counts in HIV-infected patients. J Acquir Immune Defic Syndr 2007;44:356–9.
534. Rompalo AM, Joesoef MR, O'Donnell JA, et al. Clinical manifestations of early syphilis by HIV status and gender: results of the syphilis and HIV study. Sex Transm Dis 2001;28:158–65.
535. Bayne LL, Schmidley JW, Goodin DS. Acute syphilitic meningitis: its occurrence after clinical and serologic cure of secondary syphilis with penicillin G. Arch Neurol 1986;43:137–8.
536. Berry CD, Hooton TM, Collier AC, Lukehart SA, Lukehart SA. Neurologic relapse after benzathine penicillin therapy for secondary syphilis in a patient with HIV infection. N Engl J Med 1987;316:1587–9.
537. Marra CM, Maxwell CL, Smith SL, et al. Cerebrospinal fluid abnormalities in patients with syphilis: association with clinical and laboratory features. J Infect Dis 2004;189:369–76.
538. CDC: Symptomatic early neurosyphilis among HIV-positive men who have sex with men—four cities, United States, January 2002–June 2004. MMWR 2007;56:625–8.
539. Marra CM, Maxwell CL, Tantalo L, et al. Normalization of cerebrospinal fluid abnormalities after neurosyphilis therapy: does HIV status matter? Clin Infect Dis 2004;38:1001–6.
540. Wicher K, Horowitz HW, Wicher V. Laboratory methods of diagnosis of syphilis for the beginning of the third millennium. Microbes Infect 1999;1:1035–49.
541. Pope V. Use of treponemal tests to screen for syphilis. Infect Med 2004;21:399–404.
542. Rompalo AM, Cannon RO, Quinn TC. Association of biologic false-positive reactions for syphilis with human immunodeficiency virus infection. J Infect Dis 1992;165:1124–6.
543. Augenbraun MH, DeHovitz JA, Feldman J, et al. Biological false-positive syphilis test results for women infected with human immunodeficiency virus. Clin Infect Dis 1994;19:1040–4.
544. Rolfs RT, Joesoef MR, Hendershot EF, et al. A randomized trial of enhanced therapy for early syphilis in patients with and without human immunodeficiency virus infection. N Engl J Med 1997;337:307–14.
545. Augenbraun M, Rolfs R, Johnson R, Joesoef R, Pope V. Treponemal specific tests for the serodiagnosis of syphilis. Sex Transm Dis 1998;25:549–52.
546. Kingston A, Vujevich J, Shapiro M, et al. Seronegative secondary syphilis in 2 patients coinfected with human immunodeficiency virus. Arch Dermatol 2005;141:431–3.
547. Hicks CB, Benson PM, Lupton GP, Tramont EC. Seronegative secondary syphilis in a patient infected with the human immunodeficiency virus (HIV) with Kaposi sarcoma: a diagnostic dilemma. Ann Intern Med 1987;107:492–5.
548. Kamb ML, Fishbein M, Douglas JM, Jr. et al. Efficacy of risk-reduction counseling to prevent human immunodeficiency virus and sexually transmitted diseases: a randomized controlled trial. JAMA 1998;280:1161–7.
549. Fisher JD, Cornman DH, Osborn CY, et al. Clinician-initiated HIV risk reduction intervention for HIV-positive persons: formative research, acceptability, and fidelity of the Options Project. J Acquir Immune Defic Syndr 2004;37(Suppl 2):S78-87.
550. Richardson JL, Milam J, Stoyanoff S, et al. Using patient risk indicators to plan prevention strategies in the clinical care setting. J Acquir Immune Defic Syndr 2004;37(Suppl 2):S88-94.
551. CDC, HRSA NIH, HIVMA/IDSA, and the HIV Prevention in Clinical Care Working Group. Recommendations for incorporating human immunodeficiency virus (HIV) prevention into the medical care of persons living with HIV. Clin Infect Dis 2004;38:104–21.
552. Kiddugavu MG, Kiwanuka N, Wawer MJ, et al. Effectiveness of syphilis treatment using azithromycin and/or benzathine penicillin in Rakai, Uganda. Sex Transm Dis 2005;32:1–6.
553. Riedner G, Rusizoka M, Todd J, et al. Single-dose azithromycin versus penicillin G benzathine for the treatment of early syphilis. N Engl J Med 2005;353:1236–44.
554. CDC. Azithromycin treatment failures in syphilis infections—San Francisco, California, 2002-2003. MMWR 2004;53:197–8.
555. Lukehart SA, Godornes C, Molini BJ, et al. Macrolide resistance in *Treponema pallidum* in the United States and Ireland. N Engl J Med 2004;351:154–8.
556. Mitchell SJ, Engelman J, Kent CK, et al. Azithromycin-resistant syphilis infection: San Francisco, California, 2000-2004. Clin Infect Dis 2006;42:337–45.
557. Smith NH, Musher DM, Huang DB, et al. Response of HIV-infected patients with asymptomatic syphilis to intensive intramuscular therapy with ceftriaxone or procaine penicillin. Int J STD AIDS 2004;15:328–32.
558. Long CM, Klausner JD, Leon S, et al. Syphilis treatment and HIV infection in a population-based study of persons at high risk for sexually transmitted disease/HIV infection in Lima, Peru. Sex Transm Dis 2006;33:151–5.
559. Marra CM, Longstreth WT, Jr., Maxwell CL, Lukehart SA. Resolution of serum and cerebrospinal fluid abnormalities after treatment of neurosyphilis: influence of concomitant human immunodeficiency virus infection. Sex Transm Dis 1996;23:184–9.
560. Gordon SM, Eaton ME, George R, et al. The response of symptomatic neurosyphilis to high-dose intravenous penicillin G in patients with human immunodeficiency virus infection. N Engl J Med 1994;331:1469–73.
561. Walter T, Lebouche B, Mialhes P, et al. Symptomatic relapse of neurologic syphilis after benzathine penicillin G therapy for primary or secondary syphilis in HIV-infected patients. Clin Infect Dis 2006;43:787–90.
562. Genc M, Ledger WJ. Syphilis in pregnancy. Sex Transm Infect 2000;76:73–9.
563. Berman SM. Maternal syphilis: pathophysiology and treatment. Bull World Health Organ 2004;82:433–8.
564. Tess BH, Rodrigues LC, Newell ML, et al. Breastfeeding, genetic, obstetric and other risk factors associated with mother-to-child transmission of HIV-1 in Sao Paulo State, Brazil: Sao Paulo Collaborative Study for Vertical Transmission of HIV-1. AIDS 1998;12:513–20.
565. Lee MJ, Hallmark RJ, Frenkel LM, Del Priore G. Maternal syphilis and vertical perinatal transmission of human immunodeficiency virus type-1 infection. Int J Gynaecol Obstet 1998;63:247–52.
566. Wendel GD, Sheffield JS, Hollier LM, et al. Treatment of syphilis in pregnancy and prevention of congenital syphilis. Clin Infect Dis 2002;35(Suppl 2):S200-9.

567. Mwapasa V, Rogerson SJ, Kwiek JJ, et al. Maternal syphilis infection is associated with increased risk of mother-to-child transmission of HIV in Malawi. AIDS 2006;20:1869–77.
568. Kreitchmann R, Fuchs SC, Suffert T, Preussler G. Perinatal HIV-1 transmission among low income women participants in the HIV/AIDS Control Program in Southern Brazil: a cohort study. BJOG 2004;111:579–84.
569. Donders GG, Desmyter J, Hooft P, Dewet GH. Apparent failure of one injection of benzathine penicillin G for syphilis during pregnancy in human immunodeficiency virus-seronegative African women. Sex Transm Dis 1997;24:94–101.
570. Sheffield JS, Sanchez PJ, Morris G, et al. Congenital syphilis after maternal treatment for syphilis during pregnancy. Am J Obstet Gynecol 2002;186:569–73.
571. Ramsey PS, Vaules MB, Vasdev GM, Andrews WW, Ramin KD. Maternal and transplacental pharmacokinetics of azithromycin. Am J Obstet Gynecol 2003;188:714–8.
572. Zhou P, Gu Z, Xu J, Wang X, Liao K. A study evaluating ceftriaxone as a treatment agent for primary and secondary syphilis in pregnancy. Sex Transm Dis 2005; 32:495–8.
573. Klein VR, Cox SM, Mitchell MD, Wendel GD, Jr. The Jarisch-Herxheimer reaction complicating syphilotherapy in pregnancy. Obstet Gynecol 1990;75:375–80.
574. Klein RS, Harris CA, Small CB, et al. Oral candidiasis in high-risk patients as the initial manifestation of the acquired immunodeficiency syndrome. N Engl J Med 1984;311:354–8.
575. Rex JH, Rinaldi MG, Pfaller MA. Resistance of *Candida* species to fluconazole. Antimicrob Agents Chemother 1995;39:1–8.
576. Fichtenbaum CJ, Koletar S, Yiannoutsos C, et al. Refractory mucosal candidiasis in advanced human immunodeficiency virus infection. Clin Infect Dis 2000; 30:749–56.
577. Maenza JR, Merz WG, Romagnoli MJ, et al. Infection due to fluconazole-resistant *Candida* in patients with AIDS: prevalence and microbiology. Clin Infect Dis 1997;24:28–34.
578. Martins MD, Lozano-Chiu M, Rex JH. Point prevalence of oropharyngeal carriage of fluconazole-resistant *Candida* in human immunodeficiency virus-infected patients. Clin Infect Dis 1997;25:843–6.
579. Powderly WG, Finkelstein D, Feinberg J, et al. A randomized trial comparing fluconazole with clotrimazole troches for the prevention of fungal infections in patients with advanced human immunodeficiency virus infection. N Engl J Med 1995;332:700–5.
580. Schuman P, Capps L, Peng G, et al. Weekly fluconazole for the prevention of mucosal candidiasis in women with HIV infection: a randomized, double-blind, placebo-controlled trial. Ann Intern Med 1997;126:689–96.
581. Havlir DV, Dube MP, McCutchan JA, et al. Prophylaxis with weekly versus daily fluconazole for fungal infections in patients with AIDS. Clin Infect Dis 1998;27:1369–75.
582. Goldman M, Cloud GA, Wade KD, et al. A randomized study of the use of fluconazole in continuous versus episodic therapy in patients with advanced HIV infection and a history of oropharyngeal candidiasis. Clin Infect Dis 2005;41:1473–80.
583. Pappas PG, Rex JH, Sobel JD, et al. Guidelines for treatment of candidiasis. Clin Infect Dis 2004;38:161–89.
584. Van Roey J, Haxaire M, Kamya M, Lwanga I, Katabira E. Comparative efficacy of topical therapy with a slow-release mucoadhesive buccal tablet containing miconazole nitrate versus systemic therapy with ketoconazole in HIV-positive patients with oropharyngeal candidiasis. J Acquir Immune Defic Syndr 2004;35:144–50.
585. Vazquez JA, Skiest DJ, Nieto L, et al. A multicenter randomized trial evaluating posaconazole versus fluconazole for the treatment of oropharyngeal candidiasis in subjects with HIV/AIDS. Clin Infect Dis 2006;42:1179–86.
586. de Wet N, Llanos-Cuentas A, Suleiman J, et al. A randomized, double-blind, parallel-group, dose-response study of micafungin compared with fluconazole for the treatment of esophageal candidiasis in HIV-positive patients. Clin Infect Dis 2004;39:842–9.
587. Krause DS, Simjee AE, van Rensburg C, et al. A randomized, double-blind trial of anidulafungin versus fluconazole for the treatment of esophageal candidiasis. Clin Infect Dis 2004;39:770–5.
588. Skiest D, Vazquez J, Anstead G, et al. Posaconazole for the treatment of azole-refractory oropharyngeal and esophageal candidiasis in subjects with HIV infection. Clin Infect Dis 2007;44:607–14.
589. Marty F, Mylonakis E. Antifungal use in HIV infection. Expert Opin Pharmacother 2002;3:91–102.
590. Lopez-Rangel E, Van Allen MI. Prenatal exposure to fluconazole: an identifiable dysmorphic phenotype. Birth Defects Res A Clin Mol Teratol 2005;73:919–23.
591. Aberg JA, Powderly WG. Cryptococcosis. In: Dolin R, Masur H, Saag MS, eds. AIDS Therapy. New York, NY: Churcill Livingstone 2002:498–510.
592. Mirza S, Phelan M, Rimland D, et al. The changing epidemiology of cryptococcosis: an update from population-based active surveillance in 2 large metropolitan areas, 1992-2000. Clin Infect Dis 2003;36:789–94.
593. Powderly WG, Cloud GA, Dismukes WE, Saag MS. Measurement of cryptococcal antigen in serum and cerebrospinal fluid: value in the management of AIDS-associated cryptococcal meningitis. Clin Infect Dis 1994;18:789–92.
594. McKinsey DS, Wheat LJ, Cloud GA, et al. Itraconazole prophylaxis for fungal infections in patients with advanced human immunodeficiency virus infection: randomized, placebo-controlled, double-blind study. Clin Infect Dis 1999;28:1049–56.
595. Saag MS, Graybill RJ, Larsen RA, et al. Practice guidelines for the management of cryptococcal disease. Clin Infect Dis 2000;30:710–8.
596. van der Horst CM, Saag MS, Cloud GA, et al. Treatment of cryptococcal meningitis associated with the acquired immunodeficiency syndrome. N Engl J Med 1997;337:15–21.
597. Brouwer AE, Rajanuwong A, Chierakul W, et al. Combination antifungal therapies for HIV-associated cryptococcal meningitis: a randomised trial. Lancet 2004;363:1764–7.
598. Larsen RA, Bozzette SA, Jones BE, et al. Fluconazole combined with flucytosine for treatment of cryptococcal meningitis in patients with AIDS. Clin Infect Dis 1994; 19:741–5.
599. Baddour LM, Perfect JR, Ostrosky-Zeichner L. Successful use of amphotericin B lipid complex in the treatment of cryptococcosis. Clin Infect Dis 2005;40(Suppl 6):S409-13.
600. Leenders AC, Reiss P, Portegies P, et al. Liposomal amphotericin B (AmBisome) compared with amphotericin B both followed by oral fluconazole in the treatment of AIDS-associated cryptococcal meningitis. AIDS 1997;11:1463–71.
601. Bicanic T, Meintjes G, Wood R, et al. Fungal burden, early fungicidal activity, and outcome in cryptococcal meningitis in antiretroviral-naive or antiretroviral-experienced patients treated with amphotericin B or fluconazole. Clin Infect Dis 2007;45:76–80.
602. Saag MS, Cloud GA, Graybill JR, et al. A comparison of itraconazole versus fluconazole as maintenance therapy for AIDS-associated cryptococcal meningitis. Clin Infect Dis 1999;28:291–6.

603. Graybill JR, Sobel J, Saag M, et al. Diagnosis and management of increased intracranial pressure in patients with AIDS and cryptococcal meningitis. Clin Infect Dis 2000;30:47–54.
604. Fessler RD, Sobel J, Guyot L, et al. Management of elevated intracranial pressure in patients with cryptococcal meningitis. J Acquir Immune Defic Syndr Hum Retrovirol 1998;17:137–42.
605. Shelburne SA, Darcourt J, White AC, et al. The role of immune reconstitution inflammatory syndrome in AIDS-related *Cryptococcus neoformans* disease in the era of highly active antiretroviral therapy. Clin Infect Dis 2005; 40:1049–52.
606. Brandt ME, Pfaller M, Hajjeh R, et al. Trends in antifungal drug susceptibility of *Cryptococcus neoformans* isolates in the United States: 1992 to 1994 and 1996 to 1998. Antimicrob Agents Chemother 2001;45:3065–9.
607. Chen SC. Cryptococcosis in Australasia and the treatment of cryptococcal and other fungal infections with liposomal amphotericin B. J Antimicrob Chemother 2002;49(Suppl 1):57-61.
608. Larsen RA. A comparison of itraconazole versus fluconazole as maintenance therapy for AIDS-associated cryptococcal meningitis. Clin Infect Dis 1999;28:297–8.
609. Powderly WG, Saag MS, Cloud GA, et al. A controlled trial of fluconazole or amphotericin B to prevent relapse of cryptococcal meningitis in patients with the acquired immunodeficiency syndrome. N Engl J Med 1992;326:793–8.
610. Kirk O, Reiss P, Uberti-Foppa C, et al. Safe interruption of maintenance therapy against previous infection with four common HIV-associated opportunistic pathogens during potent antiretroviral therapy. Ann Intern Med 2002;137:239–50.
611. Vibhagool A, Sungkanuparph S, Mootsikapun P, et al. Discontinuation of secondary prophylaxis for cryptococcal meningitis in human immunodeficiency virus-infected patients treated with highly active antiretroviral therapy: a prospective, multicenter, randomized study. Clin Infect Dis 2003;36:1329–31.
612. Mussini C, Pezzotti P, Miro JM, et al. Discontinuation of maintenance therapy for cryptococcal meningitis in patients with AIDS treated with highly active antiretroviral therapy: an international observational study. Clin Infect Dis 2004;38:565–71.
613. McKinsey DS, Spiegel RA, Hutwagner L, et al. Prospective study of histoplasmosis in patients infected with human immunodeficiency virus: incidence, risk factors, and pathophysiology. Clin Infect Dis 1997;24:1195–203.
614. Wheat LJ, Connolly-Stringfield PA, Baker RL, et al. Disseminated histoplasmosis in the acquired immune deficiency syndrome: clinical findings, diagnosis and treatment, and review of the literature. Medicine (Baltimore) 1990;69:361–74.
615. Sarosi GA, Johnson PC. Disseminated histoplasmosis in patients infected with human immunodeficiency virus. Clin Infect Dis 1992;14(Suppl 1):S60-7.
616. Wheat LJ, Musial CE, Jenny-Avital E. Diagnosis and management of central nervous system histoplasmosis. Clin Infect Dis 2005;40:844–52.
617. Assi M, McKinsey DS, Driks MR, et al. Gastrointestinal histoplasmosis in the acquired immunodeficiency syndrome: report of 18 cases and literature review. Diagn Microbiol Infect Dis 2006;55:195–201.
618. Williams B, Fojtasek M, Connolly-Stringfield P, Wheat J. Diagnosis of histoplasmosis by antigen detection during an outbreak in Indianapolis, Ind. Arch Pathol Lab Med 1994;118:1205–8.
619. Wheat J. Current diagnosis of histoplasmosis. Trends Microbiol 2003;11:488–94.
620. Johnson PC, Wheat LJ, Cloud GA, et al. Safety and efficacy of liposomal amphotericin B compared with conventional amphotericin B for induction therapy of histoplasmosis in patients with AIDS. Ann Intern Med 2002;137:105–9.
621. Wheat J, Sarosi G, McKinsey D, et al. Practice guidelines for the management of patients with histoplasmosis. Clin Infect Dis 2000;30:688–95.
622. Wheat J, Hafner R, Korzun AH, et al. Itraconazole treatment of disseminated histoplasmosis in patients with the acquired immunodeficiency syndrome. Am J Med 1995;98:336–42.
623. Restrepo A, Tobon A, Clark B, et al. Salvage treatment of histoplasmosis with posaconazole. J Infect 2007;54:319–27.
624. Tobon AM, Agudelo CA, Rosero DS, et al. Disseminated histoplasmosis: a comparative study between patients with acquired immunodeficiency syndrome and non-human immunodeficiency virus-infected individuals. Am J Trop Med Hyg 2005;73:576–82.
625. Nacher M, Sarazin F, El Guedj M, et al. Increased incidence of disseminated histoplasmosis following highly active antiretroviral therapy initiation. J Acquir Immune Defic Syndr 2006;41:468–70.
626. Al-Agha OM, Mooty M, Salarieh A. A 43-year-old woman with acquired immunodeficiency syndrome and fever of undetermined origin: disseminated histoplasmosis. Arch Pathol Lab Med 2006;130:120–3.
627. Freifeld AG, Iwen PC, Lesiak BL, et al. Histoplasmosis in solid organ transplant recipients at a large Midwestern university transplant center. Transpl Infect Dis 2005;7:109–15.
628. Wheat LJ, Connolly P, Smedema M, et al. Activity of newer triazoles against *Histoplasma capsulatum* from patients with AIDS who failed fluconazole. J Antimicrob Chemother 2006;57:1235–9.
629. Hecht FM, Wheat J, Korzun AH, et al. Itraconazole maintenance treatment for histoplasmosis in AIDS: a prospective, multicenter trial. J Acquir Immune Defic Syndr Hum Retrovirol 1997;16:100–7.
630. Goldman M, Zackin R, Fichtenbaum CJ, et al. Safety of discontinuation of maintenance therapy for disseminated histoplasmosis after immunologic response to antiretroviral therapy. Clin Infect Dis 2004;38:1485–9.
631. Jones JL, Fleming PL, Ciesielski CA, et al. Coccidioidomycosis among persons with AIDS in the United States. J Infect Dis 1995;171:961–6.
632. Ampel NM, Dols CL, Galgiani JN. Coccidioidomycosis during human immunodeficiency virus infection: results of a prospective study in a coccidioidal endemic area. Am J Med 1993;94:235–40.
633. Woods CW, McRill C, Plikaytis BD, et al. Coccidioidomycosis in human immunodeficiency virus-infected persons in Arizona, 1994-1997: incidence, risk factors, and prevention. J Infect Dis 2000;181:1428–34.
634. Fish DG, Ampel NM, Galgiani JN, et al. Coccidioidomycosis during human immunodeficiency virus infection: a review of 77 patients. Medicine (Baltimore) 1990;69:384–91.
635. Arguinchona HL, Arguinchona HL, Ampel NM, et al. Persistent coccidioidal seropositivity without clinical evidence of active coccidioidomycosis in patients infected with human immunodeficiency virus. Clin Infect Dis 1995;20:1281–5.
636. Galgiani JN, Ampel NM, Blair JE, et al. Coccidioidomycosis. Clin Infect Dis 2005;41:1217–23.
637. Galgiani JN, Ampel NM, Catanzaro A, et al. Practice guideline for the treatment of coccidioidomycosis. Clin Infect Dis 2000;30:658–61.
638. Galgiani JN, Catanzaro A, Cloud GA, et al. Fluconazole therapy for coccidioidal meningitis. Ann Intern Med 1993;119:28–35.
639. Tucker RM, Denning DW, Dupont B, Stevens DA. Itraconazole therapy for chronic coccidioidal meningitis. Ann Intern Med 1990;112:108–12.

640. Cortez KJ, Walsh TJ, Bennett JE. Successful treatment of coccidioidal meningitis with voriconazole. Clin Infect Dis 2003;36:1619–22.
641. Proia LA, Tenorio AR. Successful use of voriconazole for treatment of *Coccidioides* meningitis. Antimicrob Agents Chemother 2004;48:2341.
642. Anstead GM, Corcoran G, Lewis J, Berg D, Graybill JR. Refractory coccidioidomycosis treated with posaconazole. Clin Infect Dis 2005;40:1770–6.
643. Catanzaro A, Galgiani JN, Levine BE, et al. Fluconazole in the treatment of chronic pulmonary and nonmeningeal disseminated coccidioidomycosis. Am J Med 1995;98:249–56.
644. Graybill JR, Stevens DA, Galgiani JN, Dismukes WE, Cloud GA. Itraconazole treatment of coccidioidomycosis. Am J Med 1990;89:282–90.
645. Dewsnup DH, Galgiani JN, Graybill JR, et al. Is it ever safe to stop azole therapy for *Coccidioides immitis* meningitis? Ann Intern Med 1996;124:305–10.
646. Peterson CM, Schuppert K, Kelly PC, Pappagianis D. Coccidioidomycosis and pregnancy. Obstet Gynecol Surv 1993;48:149–56.
647. Mylonakis E, Barlam TF, Flanigan T, Rich JD. Pulmonary aspergillosis and invasive disease in AIDS: review of 342 cases. Chest 1998;114:251–62.
648. Holding KJ, Dworkin MS, Wan PC, et al. Aspergillosis among people infected with human immunodeficiency virus: incidence and survival. Clin Infect Dis 2000;31:1253–7.
649. Wallace JM, Lim R, Browdy BL, et al. Risk factors and outcomes associated with identification of *Aspergillus* in respiratory specimens from persons with HIV disease: Pulmonary Complications of HIV Infection Study Group. Chest 1998;114:131–7.
650. Lortholary O, Meyohas MC, Dupont B, et al. Invasive aspergillosis in patients with acquired immunodeficiency syndrome: report of 33 cases. Am J Med 1993;95:177–87.
651. Kemper CA, Hostetler JS, Follansbee SE, et al. Ulcerative and plaque-like tracheobronchitis due to infection with *Aspergillus* in patients with AIDS. Clin Infect Dis 1993;17:344–52.
652. Mylonakis E, Paliou M, Sax PE, et al. Central nervous system aspergillosis in patients with human immunodeficiency virus infection: report of 6 cases and review. Medicine (Baltimore) 2000;79:269–80.
653. Maertens J, Verhaegen J, Lagrou K, Van Eldere J, Boogaerts M. Screening for circulating galactomannan as a noninvasive diagnostic tool for invasive aspergillosis in prolonged neutropenic patients and stem cell transplantation recipients: a prospective validation. Blood 2001;97:1604–10.
654. Cornely OA, Maertens J, Winston DJ, et al. Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with neutropenia. N Engl J Med 2007;356:348–59.
655. Segal BH, Walsh TJ. Current approaches to diagnosis and treatment of invasive aspergillosis. Am J Respir Crit Care Med 2006;173:707–17.
656. Walsh TJ, Raad I, Patterson TF, et al. Treatment of invasive aspergillosis with posaconazole in patients who are refractory to or intolerant of conventional therapy: an externally controlled trial. Clin Infect Dis 2007;44:2–12.
657. Sambatakou H, Denning DW. Invasive pulmonary aspergillosis transformed into fatal mucous impaction by immune reconstitution in an AIDS patient. Eur J Clin Microbiol Infect Dis 2005;24:628–33.
658. Jabs DA, Van Natta ML, Kempen JH, et al. Characteristics of patients with cytomegalovirus retinitis in the era of highly active antiretroviral therapy. Am J Ophthalmol 2000;133:48–61.
659. Dieterich DT, Rahmin M. Cytomegalovirus colitis in AIDS: presentation in 44 patients and a review of the literature. J Acquir Immune Defic Syndr 1991;4:29–35.
660. Arribas JR, Storch GA, Clifford DB, Tselis AC. Cytomegalovirus encephalitis. Ann Intern Med 1996;125:577–87.
661. Jabs DA, Van Natta ML, Holbrook JT, et al. Longitudinal study of the ocular complications of AIDS: 1. Ocular diagnoses at enrollment. Ophthalmology 2007;114:780–6.
662. Jabs DA, Van Natta M, Thorne JE, et al. Course of cytomegalovirus retinitis in the era of highly active antiretroviral therapy: retinitis progression. Ophthalmology 2004;111:12.
663. Jabs DA, Van Natta ML, Thorne JE, et al. Course of cytomegalovirus retinitis in the era of highly active antiretroviral therapy: 2. Second eye involvement and retinal detachment. Ophthalmology 2004;111:2232–9.
664. Arribas JR, Clifford DB, Fichtenbaum CJ, et al. Level of cytomegalovirus (CMV) DNA in cerebrospinal fluid of subjects with AIDS and CMV infection of the central nervous system. J Infect Dis 1995;172:527–31.
665. Dodt KK, Jacobsen PH, Hofmann B, et al. Development of cytomegalovirus (CMV) disease may be predicted in HIV-infected patients by CMV polymerase chain reaction and the antigenemia test. AIDS 1997;11:21–8.
666. Zurlo JJ, O'Neill D, Polis MA, et al. Lack of clinical utility of cytomegalovirus blood and urine cultures in patients with HIV infection. Ann Intern Med 1993;118:12–7.
667. Rodriguez-Barradas MC, Stool E, Musher DM, et al. Diagnosing and treating cytomegalovirus pneumonia in patients with AIDS. Clin Infect Dis 1996;23:76–81.
668. Wolf DG, Spector SA. Diagnosis of human cytomegalovirus central nervous system disease in AIDS patients by DNA amplification from cerebrospinal fluid. J Infect Dis 1992;166:1412–5.
669. Deayton JR, Prof Sabin CA, Johnson MA, et al. Importance of cytomegalovirus viraemia in risk of disease progression and death in HIV-infected patients receiving highly active antiretroviral therapy. Lancet 2004;363:2116–21.
670. Karimi K, Wheat LJ, Connolly P, et al. Differences in histoplasmosis in patients with acquired immunodeficiency syndrome in the United States and Brazil. J Infect Dis 2002;186:1655–60.
671. Kempen JH, Jabs DA, Wilson LA, et al. Mortality risk for patients with cytomegalovirus retinitis and acquired immune deficiency syndrome. Clin Infect Dis 2003;37:1365–73.
672. Holland GN. AIDS and ophthalmology: the first quarter century. Am J Ophthalmol 2008;145(3):397–408.
673. Studies of Ocular Complications of AIDS Research, Group in collaboration with the AIDS Clinical Trials Group: Foscarnet-Ganciclovir Cytomegalovirus Retinitis Trial. 4. Visual outcomes. Ophthalmology 1994;101:1250–61.
674. Musch DC, Martin DF, Gordon JF, Davis MD, Kuppermann BD. Treatment of cytomegalovirus retinitis with a sustained-release ganciclovir implant. N Engl J Med 1997;337:83–90.
675. Martin DF, Sierra-Madero J, Walmsley S, et al. A controlled trial of valganciclovir as induction therapy for cytomegalovirus retinitis. N Engl J Med 2002;346:1119–26.
676. Kempen JH, Jabs DA, Wilson LA, et al. Risk of vision loss in patients with cytomegalovirus retinitis and the acquired immunodeficiency syndrome. Arch Ophthalmol 2003; 121:466–76.
677. Studies of Ocular Complications of AIDS Research Group. The ganciclovir implant plus oral ganciclovir versus parenteral cidofovir for the treatment of cytomegalovirus retinitis in patients with acquired immunodeficiency syndrome: The Ganciclovir Cidofovir Cytomegalovirus Retinitis Trial. Am J Ophthalmol 2001;131:457–67.

678. Bowen EF, Wilson P, Cope A, et al. Cytomegalovirus retinitis in AIDS patients: influence of cytomegaloviral load on response to ganciclovir, time to recurrence and survival. AIDS 1996;10:1515–20.
679. Spector SA, Wong R, Hsia K, Pilcher M, Stempien MJ. Plasma cytomegalovirus (CMV) DNA load predicts CMV disease and survival in AIDS patients. J Clin Invest 1998;101:497–502.
680. Jabs DA. AIDS and ophthalmology in 2004. Arch Ophthalmol 2004;122:1040–2.
681. Nguyen QD, Kempen JH, Bolton SG, Dunn JP, Jabs DA. Immune recovery uveitis in patients with AIDS and cytomegalovirus retinitis after highly active antiretroviral therapy. Am J Ophthalmol 2000;129:634–9.
682. Karavellas MP, Plummer DJ, Macdonald JC, et al. Incidence of immune recovery vitritis in cytomegalovirus retinitis patients following institution of successful highly active antiretroviral therapy. J Infect Dis 1999;179:697–700.
683. Robinson MR, Reed G, Csaky KG, Polis MA, Whitcup SM. Immune-recovery uveitis in patients with cytomegalovirus retinitis taking highly active antiretroviral therapy. Am J Ophthalmol 2000;130:49–56.
684. Karavellas MP, Song M, Macdonald JC, Freeman WR. Long-term posterior and anterior segment complications of immune recovery uveitis associated with cytomegalovirus retinitis. Am J Ophthalmol 2000;130:57–64.
685. Kempen JH, Min YI, Freeman WR, Holland GN. Friedberg DN, Dieterich DT . Risk of immune recovery uveitis in patients with AIDS and cytomegalovirus retinitis. Ophthalmology 2006;113:684–94.
686. Kosobucki BR, Goldberg DE, Bessho K, et al. Valganciclovir therapy for immune recovery uveitis complicated by macular edema. Am J Ophthalmol 2004;137:636–8.
687. Jabs DA, Wingard JR, de Bustros S, et al. Cytomegalovirus retinitis: intraocular drug penetration. Arch Ophthalmol 1986;104:1436–7.
688. Kuppermann BD, Quiceno JI, Flores-Aguilar M, et al. Intravitreal ganciclovir concentration after intravenous administration in AIDS patients with cytomegalovirus retinitis: implications for therapy. J Infect Dis 1993;168:1506–9.
689. Arevalo JF, Gonzales C, Capparelli EV, et al. Intravitreous and plasma concentrations of ganciclovir and foscarnet after intravenous therapy in patients with AIDS and cytomegalovirus retinitis. J Infect Dis 1995;172:951–6.
690. Marx JL, Kapusta MA, Patel SS, et al. Use of the ganciclovir implant in the treatment of recurrent cytomegalovirus retinitis. Arch Ophthalmol 1996;114:815–20.
691. Hatton MP, Duker JS, Reichel E, Morley MG, Puliafito CA. Treatment of relapsed cytomegalovirus retinitis with the sustained-release ganciclovir implant. Retina 1998;18:50–5.
692. Ocular Complications of AIDS Research Group. Combination foscarnet and ganciclovir therapy vs. monotherapy for the treatment of relapsed cytomegalovirus retinitis in patients with AIDS. Arch Ophthalmol 1996;114:23–33.
693. Jabs DA, Enger C, Dunn JP, Forman M. Cytomegalovirus retinitis and viral resistance: ganciclovir resistance. J Infect Dis 1998;177:770–3.
694. Jabs DA, Enger C, Forman M, Dunn JP. Incidence of foscarnet resistance and cidofovir resistance in patients treated for cytomegalovirus retinitis. Antimicrob Agents Chemother 1998;42:2240–4.
695. Jabs DA, Martin BK, Forman MS, et al. Longitudinal observations on mutations conferring ganciclovir resistance in a cohort of patients with acquired immunodeficiency syndrome and cytomegalovirus retinitis. J Infect Dis 2001;132:700–10.
696. Emery VC, Griffiths PD. Prediction of cytomegalovirus load and resistance patterns after antiviral chemotherapy. Proc Natl Acad Sci U.S.A 2000; 97:8039–44.
697. Jabs DA, Enger C, Dunn JP, Forman M, Hubbard L. Cytomegalovirus retinitis and viral resistance: 3. Culture results. Am J Ophthalmol 1998;126:543–9.
698. Weinberg A, Jabs DA, Chou S, et al. Mutations conferring foscarnet resistance in a cohort of patients with acquired immunodeficiency syndrome and cytomegalovirus retinitis. J Infect Dis 2003;187:777–84.
699. Chou S, Erice A, Jordan MC, et al. Analysis of the UL97 phosphotransferase coding sequence in clinical cytomegalovirus isolates and identification of mutations conferring ganciclovir resistance. J Infect Dis 1995;171:576–83.
700. Chou S, Guentzel S, Michels KR, Miner RC, Drew WL. Frequency of UL97 phosphotransferase mutations related to ganciclovir resistance in clinical cytomegalovirus isolates. J Infect Dis 1995;172:239–42.
701. Smith IL, Cherrington JM, Jiles RE, Fuller MD, Freeman WR, Spector SA. High-level resistance of cytomegalovirus to ganciclovir is associated with alterations in both the UL97 and DNA polymerase genes. J Infect Dis 1997;176:69–77.
702. Jabs DA, Martin BK, Forman MS, Dunn JP. Mutations conferring ganciclovir resistance in a cohort of patients with acquired immunodeficiency syndrome and cytomegalovirus retinitis. J Infect Dis 2001;183:333–7.
703. Chou S, Lurain NS, Thompson KD, Miner RC, Drew WL. Viral DNA polymerase mutations associated with drug resistance in human cytomegalovirus. J Infect Dis 2003;188:32–9.
704. Chou S, Van Wechel LC, Lichy HM, Marousek GI. Phenotyping of cytomegalovirus drug resistance mutations by using recombinant viruses incorporating a reporter gene. Antimicrob Agents Chemother 2005;49:2710–5.
705. Wolf DG, Smith IL, Lee DJ, et al. Mutations in human cytomegalovirus UL97 gene confer clinical resistance to ganciclovir and can be detected directly in patient plasma. J Clin Invest 1995;95:257–63.
706. The Vitravene Study Group. A randomized controlled clinical trial of intravitreous fomivirsen for treatment of newly diagnosed peripheral cytomegalovirus retinitis in patients with AIDS. Am J Ophthalmol 2002;133:467–74.
707. Jabs DA, Martin BK, Ricks MO, Forman MS, Group. Detection of ganciclovir resistance in patients with AIDS and cytomegalovirus retinitis: correlation of genotypic methods with viral phenotype and clinical outcome. J Infect Dis 2006;193:1728–37.
708. Hu H, Jabs DA, Forman MS, et al. Comparison of cytomegalovirus (CMV) UL97 gene sequences in the blood and vitreous of patients with acquired immunodeficiency syndrome and CMV retinitis. J Infect Dis 2002;185:861–7.
709. Jabs DA, Martin BK, Forman MS, et al. Cytomegalovirus resistance to ganciclovir and clinical outcomes of patients with cytomegalovirus retinitis. Am J Ophthalmol 2003;135:26–34.
710. Martin DF, Kuppermann BD, Wolitz RA, Palestine AG, Li H, Robinson CA. Oral ganciclovir for patients with cytomegalovirus retinitis treated with a ganciclovir implant. N Engl J Med 1999;340:1063–70.
711. Tural C, Romeu J, Sirera G, et al. Long-lasting remission of cytomegalovirus retinitis without maintenance therapy in human immunodeficiency virus-infected patients. J Infect Dis 1998;177:1080–3.
712. Vrabec TR, Baldassano VF, Whitcup SM. Discontinuation of maintenance therapy in patients with quiescent cytomegalovirus retinitis and elevated CD4+ counts. Ophthalmology 1998;105:1259–64.

713. Macdonald JC, Torriani FJ, Morse LS, et al. Lack of reactivation of cytomegalovirus (CMV) retinitis after stopping CMV maintenance therapy in AIDS patients with sustained elevations in CD4 T cells in response to highly active antiretroviral therapy. J Infect Dis 1998;177:1182–7.
714. Whitcup SM, Fortin E, Lindblad AS, et al. Discontinuation of anticytomegalovirus therapy in patients with HIV infection and cytomegalovirus retinitis. JAMA 1999;282:1633–7.
715. Jabs DA, Bolton SG, Dunn JP, Palestine AG. Discontinuing anticytomegalovirus therapy in patients with immune reconstitution after combination antiretroviral therapy. Am J Ophthalmol 1998;126:817–22.
716. Jouan M, Saves M, Tubiana R, et al. Discontinuation of maintenance therapy for cytomegalovirus retinitis in HIV-infected patients receiving highly active antiretroviral therapy. AIDS 2001;15:23–31.
717. Torriani FJ, Freeman WR, Macdonald JC, et al. CMV retinitis recurs after stopping treatment in virological and immunological failures of potent antiretroviral therapy. AIDS 2000;14:173–80.
718. Walmsley SL, Raboud J, Angel JB, et al. Long-term follow-up of a cohort of HIV-infected patients who discontinued maintenance therapy for cytomegalovirus retinitis. HIV Clin Trials 2006;7:1–9.
719. Faqi AS, Klug A, Merker HJ, Chahoud I. Ganciclovir induces reproductive hazards in male rats after short-term exposure. Hum Exp Toxicol 1997;16:505–11.
720. Miller BW, Howard TK, Goss JA, et al. Renal transplantation one week after conception. Transplantation 1995;60:1353–4.
721. Pescovitz MD. Absence of teratogenicity of oral ganciclovir used during early pregnancy in a liver transplant recipient. Transplantation 1999;67:758–9.
722. Adler SP, Nigro G, Pereira L. Recent advances in the prevention and treatment of congenital cytomegalovirus infections. Semin Perinatol 2007;31:10–8.
723. Alvarez-McLeod A, Havlik J, Drew KE. Foscarnet treatment of genital infection due to acyclovir-resistant herpes simplex virus type 2 in a pregnant patient with AIDS: case report. Clin Infect Dis 1999;29:937–8.
724. Gerber S, Hohlfeld P: Screening for infectious diseases. Childs Nerv Syst 2003;19:429–32.
725. Lipitz S, Achiron R, Zalel Y, et al. Outcome of pregnancies with vertical transmission of primary cytomegalovirus infection. Obstet Gynecol 2002;100:428–33.
726. Stagno S, Pass RF, Cloud G, et al. Primary cytomegalovirus infection in pregnancy: incidence, transmission to fetus, and clinical outcome. JAMA 1986; 256:1904–8.
727. Yow MD, Williamson DW, Leeds LJ, et al. Epidemiologic characteristics of cytomegalovirus infection in mothers and their infants. Am J Obstet Gynecol 1998;158:1189–95.
728. Kovacs A, Schluchter M, Easley K, et al. Cytomegalovirus infection and HIV-1 disease progression in infants born to HIV-1-infected women. N Engl J Med 1999;341:77–84.
729. Quinn TC, Piot P, McCormick JB, et al. Serologic and immunologic studies in patients with AIDS in North America and Africa: the potential role of infectious agents as cofactors in human immunodeficiency virus infection. JAMA 1987;257:2617–21.
730. Mussi-Pinhata MM, Yamamoto AY, Figueiredo LT, Cervi MC, Duarte G. Congenital and perinatal cytomegalovirus infection in infants born to mothers infected with human immunodeficiency virus. J Pediatr 1998;132:285–90.
731. Xu F, Sternberg MR, Kottiri BJ, et al. Trends in herpes simplex virus type 1 and type 2 seroprevalence in the United States. JAMA 2006;296:964–73.
732. Corey L, Wald A, Celum CL, Quinn TC. The effects of herpes simplex virus-2 on HIV-1 acquisition and transmission: a review of two overlapping epidemics. J Acquir Immune Defic Syndr 2004;35:435–45.
733. Corey L, Adams HG, Brown ZA, Holmes KK. Genital herpes simplex virus infections: clinical manifestations, course, and complications. Ann Intern Med 1983;98:958–72.
734. Safrin S, Elbeik T, Phan L, et al. Correlation between response to acyclovir and foscarnet therapy and in vitro susceptibility result for isolates of herpes simplex virus from human immunodeficiency virus-infected patients. Antimicrob Agents Chemother 1994;38:1246–50.
735. Wald A, Krantz E, Selke S, Lairson E, Morrow RA. Zeh J: Knowledge of partners' genital herpes protects against herpes simplex virus type 2 acquisition. J Infect Dis 2006;194:42–52.
736. Wald A, Langenberg AG, Krantz E, et al. The relationship between condom use and herpes simplex virus acquisition. Ann Intern Med 2005;143:707–13.
737. Corey L, Wald A, Patel R, et al. Once-daily valacyclovir to reduce the risk of transmission of genital herpes. N Engl J Med 2004;350:11–20.
738. Meyers JD, Wade JC, Mitchell CD, et al. Multicenter collaborative trial of intravenous acyclovir for treatment of mucocutaneous herpes simplex virus infection in the immunocompromised host. Am J Med 1982;73:229–35.
739. DeJesus E, Wald A, Schacker TW, et al. Valacyclovir for the suppression of recurrent genital herpes in human immunodeficiency virus-infected subjects. J Infect Dis 2003;188:1009–16.
740. Schacker T, Hu HL, Koelle DM, et al. Famciclovir for the suppression of symptomatic and asymptomatic herpes simplex virus reactivation in HIV-infected persons: a double-blind, placebo-controlled trial. Ann Intern Med 1998;128:21–8.
741. Conant MA, Schacker TW, Murphy RL, Gold J, Crutchfield LT. Valaciclovir versus aciclovir for herpes simplex virus infection in HIV-infected individuals: two randomized trials. Int J STD AIDS 2002;13:12–21.
742. Bell WR, Chulay JD, J.E. F. Manifestations resembling thrombotic microangiopathy in patients with advanced human immunodeficiency virus (HIV) disease in a cytomegalovirus prophylaxis trial (ACTG 204). Medicine (Baltimore) 1997;76:369–80.
743. Balfour HH, Jr. Antiviral drugs. N Engl J Med 1999;340:1255–68.
744. Safrin S, Crumpacker C, Chatis P, et al. A controlled trial comparing foscarnet with vidarabine for acyclovir-resistant mucocutaneous herpes simplex in the acquired immunodeficiency syndrome. N Engl J Med 1991;325:551–5.
745. Levin MJ, Bacon TH, Leary JJ. Resistance of herpes simplex virus infections to nucleoside analogues in HIV-infected patients. Clin Infect Dis 2004;39(Suppl 5):S248-57.
746. Stone KM, Reiff-Eldridge R, White AD, et al. Pregnancy outcomes following systemic prenatal acyclovir exposure: conclusions from the international acyclovir pregnancy registry, 1984-1999. Birth Defects Res A Clin Mol Teratol 2004;70:201–7.
747. Chen KT, Segú M, Lumey LH, et al. Genital herpes simplex virus infection and perinatal transmission of human immunodeficiency virus. Obstet Gynecol 2005;106:1341–8.
748. Sheffield JS, Hollier LM, Hill JB, Stuart GS, Wendel GD. Acyclovir prophylaxis to prevent herpes simplex virus recurrence at delivery: a systematic review. Obstet Gynecol 2003;102:1396–403.
749. Yoshikawa T, Suga S, Asano Y, et al. Distribution of antibodies to a causative agent of exanthem subitum (human herpesvirus-6) in healthy individuals. Pediatrics 1989;84:675–7.

750. Brown NA, Sumaya CV, Liu CR, et al. Fall in human herpesvirus 6 seropositivity with age. Lancet 1988;2:396.
751. Leach CT, Sumaya CV, Brown NA. Human herpesvirus–6: clinical implications of a recently discovered, ubiquitous agent. J Pediatr 1992;121:173–81.
752. Levy JA, Ferro F, Greenspan D, Lennette ET. Frequent isolation of HHV-6 from saliva and high seroprevalence of the virus in the population. Lancet 1990;335:1047–50.
753. Di Luca D, Mirandola P, Ravaioli T, et al. Human herpesviruses 6 and 7 in salivary glands and shedding in saliva of healthy and human immunodeficiency virus positive individuals. J Med Virol 1995;45:462–8.
754. Ueda K, Kusuhara K, Hirose M, et al. Exanthem subitum and antibody to human herpesvirus-6. J Infect Dis 1989;159:750–2.
755. Hall CB, Long CE, Schnabel KC CM et al. Human herpesvirus-6 infection in children: a prospective study of complications and reactivation. N Engl J Med;331:432–8. 1994.
756. Kimberlin DW, Whitley RJ. Human herpesvirus-6: neurologic implications of a newly-described viral pathogen. J Neurovirol 1998;4:474–85.
757. Lusso P, Ensoli B, Markham PD, et al. Productive dual infection of human CD4+ T lymphocytes by HIV-1 and HHV-6. Nature 1989;337:370–3.
758. Asada H, Klaus-Kovtun V, Golding H, Katz SI, Blauvelt A. Human herpesvirus 6 infects dendritic cells and suppresses human immunodeficiency virus type 1 replication in coinfected cultures. J Virol 1999;73:4019–28.
759. Chen H, Pesce AM, Carbonari M, et al. Absence of antibodies to human herpesvirus-6 in patients with slowly-progressive human immunodeficiency virus type 1 infection. Eur J Epidemiol 1992;8:217–21.
760. Iuliano R, Trovato R, Lico S, et al. Human herpesvirus-6 reactivation in a longitudinal study of two HIV-1 infected patients. J Med Virol 1997;51:259–64.
761. Boutolleau D, Bonduelle O, Sabard A, Devers L, Agut H. Detection of human herpesvirus 7 DNA in peripheral blood reflects mainly CD4+ cell count in patients infected with HIV. J Med Virol 2005;76:223–8.
762. Secchiero P, Carrigan DR, Asano Y, et al. Detection of human herpesvirus 6 in plasma of children with primary infection and immunosuppressed patients by polymerase chain reaction. J Infect Dis 1995;171:273–80.
763. De Bolle L, Manichanh C, Agut H, De Clercq E, Naesens L. Human herpesvirus 6 DNA polymerase: enzymatic parameters, sensitivity to ganciclovir and determination of the role of the A961V mutation in HHV-6 ganciclovir resistance. Antiviral Res 2004;64:17–25.
764. Buchbinder SP, Katz MH, Hessol N, et al. Herpes zoster and human immunodeficiency virus infection. J Infect Dis 1992;166:1153–6.
765. Engels EA, Rosenberg PS, Biggar RJ. Zoster incidence in human immunodeficiency virus-infected hemophiliacs and homosexual men, 1984-1997. J Infect Dis 1999;180:1784–9.
766. Vanhems P, Voisin L, Gayet-Ageron A, et al. The incidence of herpes zoster is less likely than other opportunistic infections to be reduced by highly active antiretroviral therapy. J Acquir Immune Def Syndr 2005;38:111–3.
767. Gebo KA, Kalyani R, Moore RD, Polydefkis MJ. The incidence of, risk factors for, and sequelae of herpes zoster among HIV patients in the highly active antiretroviral therapy era. J Acquir Immune Defic Syndr 2005;40:169–74.
768. Wallace MR, Hooper DG, Pyne JM, et al. Varicella immunity and clinical disease in HIV-infected adults. South Med J 1994;87:74–6.
769. Gnann JW, Crumpacker CS, Lalezari JP. Sorivudine versus acyclovir for treatment of dermatomal herpes zoster in human immunodeficiency virus-infected patients: results from a randomized, controlled clinical trial. Antimicrob Agents Chemother 1998;42:1139–45.
770. Harrison RA, Soong S, Weiss HL, Gnann JWJ, Whitley RJ. A mixed model for factors predictive of pain in AIDS patients with herpes zoster. J Pain Symptom Manage 1999;17:410–7.
771. Veenstra J, van Praag RM, Krol A, et al. Complications of varicella zoster virus reactivation in HIV-infected homosexual men. AIDS 1996;10:393–9.
772. Engstrom RE, Jr., Holland GN, Margolis TP, et al. The progressive outer retinal necrosis syndrome: a variant of necrotizing herpetic retinopathy in patients with AIDS. Ophthalmology 1994;101:1488–502.
773. Ormerod LD, Larkin JA, Margo CA, et al. Rapidly progressive herpetic retinal necrosis: a blinding disease characteristic of advanced AIDS. Clin Infect Dis 1998;26:34–45.
774. Yin PD, Kurup SK, Fischer SH, et al. Progressive outer retinal necrosis in the era of highly active antiretroviral therapy: successful management with intravitreal injections and monitoring with quantitative PCR. J Clin Virol 2007;38:254–9.
775. Levin MJ, Gershon AA, Weinberg A, Song LY, Fentin T, Team. Administration of live varicella vaccine to HIV-infected children with current or past significant depression of CD4+ T cells. J Infect Dis 2006;194:247–55.
776. CDC. Prevention of varicella: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2007;56(No. RR-4).
777. Prober CG, Kirk LE, Keeney RE. Acyclovir therapy of chickenpox in immunosuppressed children–a collaborative study. J Pediatr 1982;101:622–5.
778. Arvin AM. Antiviral therapy for varicella and herpes zoster. Semin Pediatr Infect Dis 2002;13:12–21.
779. Carcao MD, Lau RC, Gupta A, et al. Sequential use of intravenous and oral acyclovir in the therapy of varicella in immunocompromised children. Pediatr Infect Dis J 1998;17:626–31.
780. Balfour HH, Jr., Bean B, Laskin OL, et al. Acyclovir halts progression of herpes zoster in immunocompromised patients. N Engl J Med 1983;308:1448–53.
781. Austin RB. Progressive outer retinal necrosis syndrome: a comprehensive review of its clinical presentation, relationship to immune system status, and management. Clin Eye Vis Care 2007;12:119–29.
782. Martinez E, Gatell J, Morán Y, et al. High incidence of herpes zoster in patients with AIDS soon after therapy with protease inhibitors. Clin Infect Dis 1998;27:1510–3.
783. Domingo P, Torres OH, Ris J, Vazquez G. Herpes zoster as an immune reconstitution disease after initiation of combination antiretroviral therapy in patients with human immunodeficiency virus type-1 infection. Am J Med 2001;110:605–9.
784. Breton G, Fillet AM, Katlama C, Bricaire F, Caumes E. Acyclovir-resistant herpes zoster in human immunodeficiency virus-infected patients: results of foscarnet therapy. Clin Infect Dis 1998;27:1525–7.
785. Pastuszak AL, Levy M, Schick B, et al. Outcome after maternal varicella infection in the first 20 weeks of pregnancy. N Engl J Med 1994;330:901–5.
786. Gao SJ, Kingsley L, Hoover DR, et al. Seroconversion to antibodies against Kaposi's sarcoma-associated herpesvirus-related latent nuclear antigens before the development of Kaposi's sarcoma. N Engl J Med 1996;335:233–41.

787. Lennette ET, Blackbourn DJ, Levy JA. Antibodies to human herpesvirus type 8 in the general population and in Kaposi's sarcoma patients. Lancet 1996;348:858–61.
788. Oksenhendler E, Carcelain G, Aoki Y, et al. High levels of human herpesvirus 8 viral load, human interleukin-6, interleukin-10, and C reactive protein correlate with exacerbation of multicentric castleman disease in HIV-infected patients. Blood 2000;96:2069–73.
789. Cannon JS, Hamzeh F, Moore S, Nicholas J, Ambinder RF. Human herpesvirus 8-encoded thymidine kinase and phosphotransferase homologues confer sensitivity to ganciclovir. J Virol 1999;73:4786–93.
790. Neyts J, De Clercq E. Antiviral drug susceptibility of human herpesvirus 8. Antimicrob Agents Chemother 1997;41:2754–6.
791. Ioannidis JP, Collier AC, Cooper DA, et al. Clinical efficacy of high-dose acyclovir in patients with human immunodeficiency virus infection: a meta-analysis of randomized individual patient data. J Infect Dis 1998; 178:349–59.
792. Mocroft A, Youle M, Gazzard B, et al. Anti-herpesvirus treatment and risk of Kaposi's sarcoma in HIV infection. AIDS 1996;10:1101–5.
793. Glesby MJ, Hoover DR, Weng S, et al. Use of antiherpes drugs and the risk of Kaposi's sarcoma: data from the Multicenter AIDS Cohort Study. J Infect Dis 1996; 173:1477–80.
794. Eltom MA, Jemal A, Mbulaiteye SM, Devesa SS, Biggar RJ. Trends in Kaposi's sarcoma and non-Hodgkin's lymphoma incidence in the United States from 1973 through 1998. J Natl Cancer Inst 2002;94:1204–10.
795. Casper C. The aetiology and management of Castleman disease at 50 years: translating pathophysiology to patient care. Br J Haematol 2005;129:3–17.
796. Casper C, Krantz E, Selke S, et al. Frequent and asymptomatic oropharyngeal shedding of human herpesvirus 8 among immunocompetent men. J Infect Dis 2007;195:30–6.
797. Andreoni M, Sarmati L, Nicastri E, et al. Primary human herpesvirus 8 infection in immunocompetent children. JAMA 2002;287:1295–300.
798. Luppi M. Bone marrow failure associated with human herpesvirus 8 infection after transplantation. N Engl J Med 2000;343:1378–85.
799. Casper C, Redman M, Huang ML, et al. HIV infection and human herpesvirus-8 oral shedding among men who have sex with men. J Acquir Immune Defic Syndr 2004;35:233–8.
800. Corey L, Pauk J, Wald A. Mucosal shedding of human herpesvirus 8 in men. N Engl J Med 2001;344:691–2.
801. Morfeldt L, Torssander J. Long-term remission of Kaposi's sarcoma following foscarnet treatment in HIV-infected patients. Scand J Infect Dis 1994;26:749–52.
802. Robles R, Lugo D, Gee L, Jacobson MA. Effect of antiviral drugs used to treat cytomegalovirus end-organ disease on subsequent course of previously diagnosed Kaposi's sarcoma in patients with AIDS. J Acquir Immune Defic Syndr Hum Retrovirol 1999;20:34–8.
803. Casper C, Wald A. The use of antiviral drugs in the prevention and treatment of Kaposi sarcoma, multicentric Castleman disease and primary effusion lymphoma. Curr Top Microbiol Immunol 2007;312:289–307.
804. Little RF, Merced-Galindez F, Staskus K, et al. A pilot study of cidofovir in patients with kaposi sarcoma. J Infect Dis 2003;187:149–53.
805. Casper C, Nichols WG, Huang ML, Corey L, Wald A. Remission of HHV-8 and HIV-associated multicentric Castleman disease with ganciclovir treatment. Blood 2004;103:1632–4.
806. Aboulafia DM. Interleukin-2, ganciclovir, and high-dose zidovudine for the treatment of AIDS-associated primary central nervous system lymphoma. Clin Infect Dis 2002;34:1660–2.
807. Crum-Cianflone NF, Wallace MR, Looney D. Successful secondary prophylaxis for primary effusion lymphoma with human herpesvirus 8 therapy. AIDS 2006;20:1567–9.
808. Marcelin AG, Aaron L, Mateus C, et al. Rituximab therapy for HIV-associated Castleman disease. Blood 2003;102:2786–8.
809. Goedert JJ, Kedes DH, Ganem D. Antibodies to human herpesvirus 8 in women and infants born in Haiti and the USA. Lancet 1997;349:1368.
810. Lisco A, Barbierato M, Fiore JR, et al. Pregnancy and human herpesvirus 8 reactivation in human immunodeficiency virus type 1–infected women. J Clin Microbiol 2006;44:3863–71.
811. Berger P, Dirnhofer S. Kaposi's sarcoma in pregnant women. Nature 1995;377:21–2.
812. Lunardi-Iskandar Y, Bryant JL, Zeman RA, et al. Tumorigenesis and metastasis of neoplastic Kaposi's sarcoma cell line in immunodeficient mice blocked by a human pregnancy hormone. Nature 1995;375:64–8.
813. Rabkin CS, Chibwe G, Muyunda K, Musaba E. Kaposi's sarcoma in pregnant women. Nature 1995;377:21.
814. Schulz TF, Weiss RA. Kaposi's sarcoma. A finger on the culprit. Nature 1995;373:17–8.
815. Gutierrez-Ortega P, Hierro-Orozco S, Sanchez-Cisneros R, Montaño LF. Kaposi's sarcoma in a 6-day-old infant with human immunodeficiency virus. Arch Dermatol 1989;125:432–3.
816. McCarthy GA, Kampmann B, Novelli V, et al. Vertical transmission of Kaposi's sarcoma. Arch Dis Child 1996;74:455–7.
817. Sitas F, Newton R, Boschoff C. Increasing probability of mother-to-child transmission of HHV-8 with increasing maternal antibody titer for HHV-8. N Engl J Med 1999;340:1923.
818. Mbulaiteye S, Marshall V, Bagni RK, et al. Molecular evidence for mother-to-child transmission of Kaposi sarcoma-associated herpesvirus in Uganda and K1 gene evolution within the host. J Infect Dis 2006;193:1250–7.
819. Mantina H, Kankasa C, Klaskala W, et al. Vertical transmission of Kaposi's sarcoma-associated herpesvirus. Int J Cancer 2001;94:749–52.
820. Serraino D, Locatelli M, Songini M, et al. Human herpes virus-8 infection among pregnant women and their children: results from the Sardinia-IDDM Study 2. Int J Cancer 2001;91:740–1.
821. Gessain A, Mauclere P, van Beveren M, et al. Human herpesvirus 8 primary infection occurs during childhood in Cameroon, Central Africa. Int J Cancer 1999;81:189–92.
822. Bourboulia D, Whitby D, Boshoff C, et al. Serologic evidence for mother-to-child transmission of Kaposi sarcoma-associated herpesvirus infection. JAMA 1998;280:31–2.
823. Whitby D, Smith NA, Matthews S, et al. Human herpesvirus 8: seroepidemiology among women and detection in the genital tract of seropositive women. J Infect Dis 1999;179:234–6.
824. Plancoulaine S, Abel L, van Beveren M, et al. Human herpesvirus 8 transmission from mother to child and between siblings in an endemic population. Lancet 2000;356:1062–5.
825. Hildesheim A, Gravitt P, Schiffman MH, et al. Determinants of genital human papillomavirus infection in low-income women in Washington, D.C. Sex Transm Dis 1993;20:279–85.
826. Bauer HM, Hildesheim A, Schiffman MH, et al. Determinants of genital human papillomavirus infection in low-risk women in Portland, Oregon. Sex Transm Dis 1993;20:274–8.
827. Wheeler CM, Parmenter CA, Hunt WC, et al. Determinants of genital human papillomavirus infection among cytologically normal women attending the University of New Mexico student health center. Sex Transm Dis 1993;20:286–9.

828. Ho GY, Bierman R, Beardsley L, Chang CJ, Burk RD. Natural history of cervicovaginal papillomavirus infection in young women. N Engl J Med 1998;338:423–8.
829. Burk RD, Ho GY, Beardsley L, et al. Sexual behavior and partner characteristics are the predominant risk factors for genital human papillomavirus infection in young women. J Infect Dis 1996;174:679–89.
830. Dunne EF, Nielson CM, Stone KM, Markowitz LE, Giuliano AR. Prevalence of HPV infection among men: a systematic review of the literature. J Infect Dis 2006;194:1044–57.
831. Schiffman MH, Bauer HM, Hoover RN, et al. Epidemiologic evidence showing that human papillomavirus infection causes most cervical intraepithelial neoplasia. J Natl Cancer Inst 1993;85:958–64.
832. Bosch FX, Manos MM, Muñoz N, et al. Prevalence of human papillomavirus in cervical cancer: a worldwide perspective. J Natl Cancer Inst 1995;87:796–802.
833. Lorincz AT, Reid R, Jenson AB, et al. Human papillomavirus infection of the cervix: relative risk associations of 15 common anogenital types. Obstet Gynecol 1992;79:328–37.
834. Moscicki AB, Shiboski S, Broering J, et al. The natural history of human papillomavirus infection as measured by repeated DNA testing in adolescent and young women. J Pediatr 1998;132:277–84.
835. Evander M, Edlund K, Gustafsson A, et al. Human papillomavirus infection is transient in young women: a population-based cohort study. J Infect Dis 1995;171:1026–30.
836. Cogliano V, Baan R, Straif K, et al. Carcinogenicity of human papillomaviruses. Lancet Oncol 2005;6:204.
837. Munoz N, Bosch FX, de Sanjosé S, et al. Epidemiologic classification of human papillomavirus types associated with cervical cancer. N Engl J Med 2003;348:518–27.
838. Greer CE, Wheeler CM, Ladner MB, et al. Human papillomavirus (HPV) type distribution and serological response to HPV type 6 virus-like particles in patients with genital warts. J Clin Microbiol 1995;33:2058–63.
839. Kamangar F, Dores GM, Anderson WF. Patterns of cancer incidence, mortality, and prevalence across five continents: defining priorities to reduce cancer disparities in different geographic regions of the world. J Clin Oncol 2006;24:2137–50.
840. Goedert JJ, Coté TR, Virgo P, et al. Spectrum of AIDS-associated malignant disorders. Lancet 1998;351:1833–9.
841. Frisch M, Biggar RJ, Engels EA, Goedert JJ. Association of cancer with AIDS-related immunosuppression in adults. JAMA 2001;285:1736–45.
842. Frisch M, Biggar RJ, Goedert JJ. Human papillomavirus-associated cancers in patients with human immunodeficiency virus infection and acquired immunodeficiency syndrome. J Natl Cancer Inst 2000;92:1500–10.
843. Mbulaiteye SM, Biggar RJ, Goedert JJ, Engels EA. Immune deficiency and risk for malignancy among persons with AIDS. J Acquir Immune Defic Syndr 2003;32:527–33.
844. Orem J, Otieno MW, Remick SC. AIDS-associated cancer in developing nations. Curr Opin Oncol 2004;16:468–76.
845. Mbulaiteye SM, Katabira ET, Wabinga H, et al. Spectrum of cancers among HIV-infected persons in Africa: the Uganda AIDS-Cancer Registry Match Study. Int J Cancer 2006;118:985–90.
846. Moscicki AB, Ellenberg JH, Crowley-Nowick P, et al. Risk of high-grade squamous intraepithelial lesion in HIV-infected adolescents. J Infect Dis 2004;190:1413–21.
847. Schrager LK, Friedland GH, Maude D, et al. Cervical and vaginal squamous cell abnormalities in women infected with human immunodeficiency virus. J Acquir Immune Defic Syndr 1989;2:570–5.
848. Maiman M, Fruchter RG, Serur E, et al. Human immunodeficiency virus infection and cervical neoplasia. Gynecol Oncol 1990;38:377–82.
849. Feingold AR, Vermund SH, Burk RD, et al. Cervical cytologic abnormalities and papillomavirus in women infected with human immunodeficiency virus. J Acquir Immune Defic Syndr 1990;3:896–903.
850. Vermund SH, Kelley KF, Klein RS, et al. High risk of human papillomavirus infection and cervical squamous intraepithelial lesions among women with symptomatic human immunodeficiency virus infection. Am J Obstet Gynecol 1991;165:392–400.
851. Laga M, Icenogle JP, Marsella R, et al. Genital papillomavirus infection and cervical dysplasia—opportunistic complications of HIV infection. Int J Cancer 1992;50:45–8.
852. Spinillo A, Tenti P, Zappatore R, et al. Prevalence, diagnosis and treatment of lower genital neoplasia in women with human immunodeficiency virus infection. Eur J Obstet Gynecol Reprod Biol 1992;43:235–41.
853. Wright TC, Koulos J, Schnoll F, et al. Cervical intraepithelial neoplasia in women infected with the human immunodeficiency virus: outcome after loop electrosurgical excision. Gynecol Oncol 1994;55:253–8.
854. Klein RS, Ho GY, Vermund SH, Fleming I, Burk RD. Risk factors for squamous intraepithelial lesions on Pap smear in women at risk for human immunodeficiency virus infection. J Infect Dis 1994;170:1404–9.
855. Ho GY, Burk RD, Fleming I, Klein RS. Risk of genital human papillomavirus infection in women with human immunodeficiency virus-induced immunosuppression. Int J Cancer 1994;56:788–92.
856. Cappiello G, Garbuglia AR, Salvi R, et al. HIV infection increases the risk of squamous intra-epithelial lesions in women with HPV infection: an analysis of HPV genotypes. Int J Cancer 1997;72:982–6.
857. Hankins C, Coutlee F, Lapointe N, et al. Prevalence of risk factors associated with human papillomavirus infection in women living with HIV. CMAJ 1999;160:185–91.
858. Massad LS, Riester KA, Anastos KM, et al. Prevalence and predictors of squamous cell abnormalities in Papanicolaou smears from women infected with HIV-1. J Acquir Immune Defic Syndr 1999;21:33–41.
859. Cu-Uvin S, Hogan JW, Warren D, et al. Prevalence of lower genital tract infections among human immunodeficiency virus (HIV)-seropositive and high-risk HIV-seronegative women. Clin Infect Dis 1999;29:1145–50.
860. Palefsky JM, Minkoff H, Kalish LA, et al. Cervicovaginal human papillomavirus infection in human immunodeficiency virus-1 (HIV)-positive and high-risk HIV-negative women. J Natl Cancer Inst 1999;91:226–36.
861. Branca M, Migliore G, Giuliani M, et al. Squamous intraepithelial lesions (SILs) and HPV associated changes in HIV infected women or at risk of HIV. Eur J Gynaecol Oncol 2000;21:155–9.
862. Palefsky JM. Cervical human papillomavirus infection and cervical intraepithelial neoplasia in women positive for human immunodeficiency virus in the era of highly active antiretroviral therapy. Curr Opin Oncol 2003;15:382–8.
863. Hawes SE, Critchlow CW, Faye Niang MA, et al. Increased risk of high-grade cervical squamous intraepithelial lesions and invasive cervical cancer among African women with human immunodeficiency virus type 1 and 2 infections. J Infect Dis 2003;188:555–63.
864. Taylor G, Wolff T, Khanna N, Furth P, Langenberg P. Genital dysplasia in women infected with human immunodeficiency virus. J Am Board Fam Pract 2004;17:108–13.
865. Wright TC, Ellerbrock TV, Chiasson MA, et al. Cervical intraepithelial neoplasia in women infected with human immunodeficiency virus: prevalence, risk factors, and validity of Papanicolaou smears. Obstet Gynecol 1994;84:591–7.

866. Schuman P, Ohmit SE, Klein RS, et al. Longitudinal study of cervical squamous intraepithelial lesions in human immunodeficiency virus (HIV)-seropositive and at-risk HIV-seronegative women. J Infect Dis 2003;188:128–36.
867. Sun XW, Ellerbrock TV, Lungu O, et al. Human papillomavirus infection in human immunodeficiency virus-seropositive women. Obstet Gynecol 1995;85:680–6.
868. Sun XW, Kuhn L, Ellerbrock TV, et al. Human papillomavirus infection in women infected with the human immunodeficiency virus. N Engl J Med 1997;337:1343–9.
869. Heard I, Jeannel D, Bergeron C, et al. Lack of behavioural risk factors for squamous intraepithelial lesions (SIL) in HIV-infected women. Int J STD AIDS 1997;8:388–92.
870. Luque AE, Demeter LM, Reichman RC. Association of human papillomavirus infection and disease with magnitude of human immunodeficiency virus type 1 (HIV-1) RNA plasma level among women with HIV-1 infection. J Infect Dis 1999;179:1405–9.
871. Delmas MC, Larsen C, van Benthem B, et al. Cervical squamous intraepithelial lesions in HIV-infected women: prevalence, incidence and regression. AIDS 2000;14:1775–84.
872. Vonau B, Boag F. HIV-positive women and cervical screening. Int J STD AIDS 2000;11:767–73.
873. Ahr A, Scharl A, Lütke K, Staszewski S, Kacer PZ KM. Cervical intraepithelial neoplasia in human immunodeficiency virus-positive patients. Cancer Detect Prev 2000;24:179–85.
874. Heard I, Tassie JM, Schmitz V, et al. Increased risk of cervical disease among human immunodeficiency virus-infected women with severe immunosuppression and high human papillomavirus load. Obstet Gynecol 2000;96:403–9.
875. Strickler HD, Palefsky JM, Shah KV, et al. Human papillomavirus type 16 and immune status in human immunodeficiency virus-seropositive women. J Natl Cancer Inst 2003;95:1062–71.
876. Strickler HD, Burk RD, Fazzari M, et al. Natural history and possible reactivation of human papillomavirus in human immunodeficiency virus-positive women. J Natl Cancer Inst 2005;97:577–86.
877. D'Souza G, Kreimer AR, Viscidi R, et al. Case-control study of human papillomavirus and oropharyngeal cancer. N Engl J Med 2007;356:1944–56.
878. Sitas F, Pacella-Norman R, Carrara H, et al. The spectrum of HIV-1 related cancers in South Africa. Int J Cancer 2000;88:489–92.
879. Mathews WC, Sitapati A, Caperna JC, Barber RE, Tugend A, Go U. Measurement characteristics of anal cytology, histopathology, and high-resolution anoscopic visual impression in an anal dysplasia screening program. J Acquir Immune Defic Syndr 2004;37:1610–5.
880. Wilkin TJ, Palmer S, Brudney KF, et al. Anal intraepithelial neoplasia in heterosexual and homosexual HIV-positive men with access to antiretroviral therapy. J Infect Dis 2004;190:1685–91.
881. Kreuter A, Brockmeyer NH, Hochdorfer B, et al. Clinical spectrum and virologic characteristics of anal intraepithelial neoplasia in HIV infection. J Am Acad Dermatol 2005;52:603–8.
882. Palefsky JM, Holly EA, Efirdc JT, et al. Anal intraepithelial neoplasia in the highly active antiretroviral therapy era among HIV-positive men who have sex with men. AIDS 2005;19:1407–14.
883. Chiao EY, Giordano TP, Palefsky JM, Tyring S, El Serag H. Screening HIV-infected individuals for anal cancer precursor lesions: a systematic review. Clin Infect Dis 2006;43:223–33.
884. Massad LS, Silverberg MJ, Springer G, et al. Effect of antiretroviral therapy on the incidence of genital warts and vulvar neoplasia among women with the human immunodeficiency virus. Am J Obstet Gynecol 2004;190:1241–8.
885. Conley LJ, Ellerbrock TV, Bush TJ, et al. HIV-1 infection and risk of vulvovaginal and perianal condylomata acuminata and intraepithelial neoplasia: a prospective cohort study. Lancet 2002;359:108–13.
886. Jamieson DJ, Paramsothy P, Cu-Uvin S, Duerr A. Vulvar, vaginal, and perianal intraepithelial neoplasia in women with or at risk for human immunodeficiency virus. Obstet Gynecol 2006;107:1023–8.
887. Heard I, Schmitz V, Costagliola D, Orth G, Kazatchkine MD. Early regression of cervical lesions in HIV-seropositive women receiving highly active antiretroviral therapy. AIDS 1998;12:1459–64.
888. Orlando G, Fasolo MM, Signori R, et al. Impact of highly active antiretroviral therapy on clinical evolution of genital warts in HIV-infected patients. AIDS 1999;13:291–3.
889. Dorrucci M, Suligoi B, Serraino D, Tirelli U. Incidence of invasive cervical cancer in a cohort of HIV-seropositive women before and after the introduction of highly active antiretroviral therapy. J Acquir Immune Defic Syndr 2001;26:377–80.
890. Del Mistro A, Bertorelle R, Franzetti M, et al. Antiretroviral therapy and the clinical evolution of human papillomavirus-associated genital lesions in HIV-positive women. Clin Infect Dis 2004;38:737–42.
891. Ahdieh-Grant L, Li R, Levine AM, et al. Highly active antiretroviral therapy and cervical squamous intraepithelial lesions in human immunodeficiency virus-positive women. J Natl Cancer Inst 2004;96:1070–6.
892. Heard I, Palefsky JM, Kazatchkine MD. The impact of HIV antiviral therapy on human papillomavirus (HPV) infections and HPV-related diseases. Antivir Ther 2004;9:13–22.
893. Palefsky J, Holly EA, Ralston ML, et al. Effect of highly active antiretroviral therapy on the natural history of anal squamous intraepithelial lesions and anal human papillomavirus infection. J Acquir Immune Defic Syndr 2001;28:422–8.
894. Piketty C, Darragh TM, Heard I, et al. High prevalence of anal squamous intraepithelial lesions in HIV-positive men despite the use of highly active antiretroviral therapy. Sex Transm Dis 2004;31:96–9.
895. Bower M, Powles T, Newsom-Davis T, et al. HIV-associated anal cancer: has highly active antiretroviral therapy reduced the incidence or improved the outcome? J Acquir Immune Defic Syndr 2004;37:1563–5.
896. Clarke CA, Glaser SL. Population-based surveillance of HIV-associated cancers: utility of cancer registry data. J Acquir Immune Defic Syndr 2004;36:1083–91.
897. Clifford GM, Polesel J, Rickenbach M, et al. Swiss HIV Cohort. Cancer risk in the Swiss HIV Cohort Study: associations with immunodeficiency, smoking, and highly active antiretroviral therapy. J Natl Cancer Inst 2005;97:425–32.
898. Diamond C, Taylor TH, Aboumrad T, Bringman D, Anton-Culver H. Increased incidence of squamous cell anal cancer among men with AIDS in the era of highly active antiretroviral therapy. Sex Transm Dis 2005;32:314–20.
899. Hessol NA, Pipkin S, Schwarcz S, et al. The impact of highly active antiretroviral therapy on non-AIDS-defining cancers among adults with AIDS. Am J Epidemiol 2007;165:1143–53.
900. Birnbaum W, Hodgson TA, Reichart PA, et al. Prognostic significance of HIV-associated oral lesions and their relation to therapy. Oral Dis 2002;8(Suppl 2):110-4.
901. Frisch M, Melbye M, Moller H. Trends in incidence of anal cancer in Denmark. BMJ 1993;306:419–22.

902. Judson PL, Habermann EB, Baxter NN, Durham SB, Virnig BA. Trends in the incidence of invasive and in situ vulvar carcinoma. Obstet Gynecol 2006;107:1018–22.
903. Saraiya M, Ahmed F, Krishnan S, et al. Cervical cancer incidence in a prevaccine era in the United States, 1998-2002. Obstet Gynecol 2007;109:360–70.
904. Wright TC, Cox JT, Massad LS, et al. 2001 consensus guidelines for the management of women with cervical cytological abnormalities. JAMA 2002;287:2120–9.
905. Ferris DG. The 2001 ASCCP management guidelines for cervical cytology. Am Fam Physician 2004;70:1866–1868.
906. Wright TC, Jr., Massad LS, Dunton CJ, et al. 2006 consensus guidelines for the management of women with abnormal cervical cancer screening tests. Am J Obstet Gynecol 2007;197:346–55.
907. Winer RL, Hughes JP, Feng Q, et al. Condom use and the risk of genital human papillomavirus infection in young women. N Engl J Med 2006;354:2645–54.
908. Vaccarella S, Franceschi S, Herrero R, et al. Sexual behavior, condom use, and human papillomavirus: pooled analysis of the IARC human papillomavirus prevalence surveys. Cancer Epidemiol Biomarkers Prev 2006;15:326–33.
909. Manhart LE, Koutsky LA. Do condoms prevent genital HPV infection, external genital warts, or cervical neoplasia? A meta-analysis. Sex Transm Dis 2002;29:725–35.
910. Kish LS, McMahon JT, Bergfeld WF, Pelachyk JM. An ancient method and a modern scourge: the condom as a barrier against herpes. J Am Acad Dermatol 1983;9:769–70.
911. Markowitz LE, Dunne EF, Saraiya M, et al. Quadrivalent human papillomavirus vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2007;56(No. RR-2).
912. Saslow D, Castle PE, Cox JT, et al. American Cancer Society Guideline for human papillomavirus (HPV) vaccine use to prevent cervical cancer and its precursors. CA Cancer J Clin 2007;57:7–28.
913. Koutsky LA, Koutsky LA, Ault KA, et al. Proof of principle study investigators: a controlled trial of a human papillomavirus type 16 vaccine. N Engl J Med 2002;347:1645–51.
914. Villa LL, Costa RL, Petta CA, et al. Prophylactic quadrivalent human papillomavirus (types 6, 11, 16, and 18) L1 virus-like particle vaccine in young women: a randomised double-blind placebo-controlled multicentre phase II efficacy trial. Lancet Oncol 2005;6:271–8.
915. Koutsky LA, Harper DM. Current findings from prophylactic HPV vaccine trials. Vaccine 2006;24(Suppl 3):114-21.
916. Mas A. Hepatic encephalopathy: from pathophysiology to treatment. Digestion 2006;73(Suppl 1):86-93.
917. Kalogirou D, Antoniou G, Karakitsos P, et al. Vaginal intraepithelial neoplasia (VAIN) following hysterectomy in patients treated for carcinoma in situ of the cervix. Eur J Gynaecol Oncol 1997;18:188–91.
918. Paramsothy P, Duerr A, Heilig CM, et al. Abnormal vaginal cytology in HIV-infected and at-risk women after hysterectomy. J Acquir Immune Defic Syndr 2004;35:484–91.
919. Petry KU, Köchel H, Bode U, et al. Human papillomavirus is associated with the frequent detection of warty and basaloid high-grade neoplasia of the vulva and cervical neoplasia among immunocompromised women. Gynecol Oncol 1996;60:30–4.
920. Chiasson MA, Ellerbrock TV, Bush TJ, Sun XW, Wright TC, Jr. Increased prevalence of vulvovaginal condyloma and vulvar intraepithelial neoplasia in women infected with the human immunodeficiency virus. Obstet Gynecol 1997;89:690–4.
921. Marfing TE, Abel ME, Gallagher DM. Perianal Bowen's disease and associated malignancies: results of a survey. Dis Colon Rectum 1987;30:782–5.
922. Cleary RK, Schaldenbrand JD, Fowler JJ, Schuler JM, Lampman RM. Perianal Bowen's disease and anal intraepithelial neoplasia: review of the literature. Dis Colon Rectum 1999;42:945–51.
923. Goldie SJ, Kuntz KM, Weinstein MC, et al. The clinical effectiveness and cost-effectiveness of screening for anal squamous intraepithelial lesions in homosexual and bisexual HIV-positive men. JAMA 1999;281:1822–9.
924. Chin-Hong PV, Palefsky JM. Human papillomavirus anogenital disease in HIV-infected individuals. Dermatol Ther 2005;18:67–76.
925. Herida M, Mary-Krause M, Kaphan R, et al. Incidence of non-AIDS-defining cancers before and during the highly active antiretroviral therapy era in a cohort of human immunodeficiency virus-infected patients. J Clin Oncol 2003;21:3447–53.
926. Moses S, Bailey RC, Ronald AR. Male circumcision: assessment of health benefits and risks. Sex Transm Infect 1998;74:368–73.
927. Beutner KR, Wiley DJ, Douglas JM, et al. Genital warts and their treatment. Clin Infect Dis 1999;(Suppl 1):37-56.
928. Bonnez W, Elswick RK, Jr., Bailey-Farchione A, et al. Efficacy and safety of 0.5% podofilox solution in the treatment and suppression of anogenital warts. Am J Med 1994;96:420–5.
929. Tyring S, Edwards L, Cherry LK, et al. Safety and efficacy of 0.5% podofilox gel in the treatment of anogenital warts. Arch Dermatol 1998;134:33–8.
930. Beutner KR, Tyring SK, Trofatter KF, Jr., et al. Imiquimod, a patient-applied immune-response modifier for treatment of external genital warts. Antimicrob Agents Chemother 1998;42:789–94.
931. Edwards L, Ferenczy A, Eron L, et al. Self-administered topical 5% imiquimod cream for external anogenital warts. Arch Dermatol 1998;134:25–30.
932. Gilson RJ, Shupack JL, Friedman-Kien AE, et al. A randomized, controlled, safety study using imiquimod for the topical treatment of anogenital warts in HIV-infected patients. AIDS 1999;13:2397–404.
933. Matteelli A, Beltrame A, Graifemberghi S, et al. Efficacy and tolerability of topical 1% cidofovir cream for the treatment of external anogenital warts in HIV-infected persons. Sex Transm Dis 2001;28:343–6.
934. Snoeck R, Bossens M, Parent D, et al. Phase II double-blind, placebo-controlled study of the safety and efficacy of cidofovir topical gel for the treatment of patients with human papillomavirus infection. Clin Infect Dis 2001;33:597–602.
935. King MD, Reznik DA, O'Daniels CM, et al. Human papillomavirus-associated oral warts among human immunodeficiency virus-seropositive patients in the era of highly active antiretroviral therapy: an emerging infection. Clin Infect Dis 2002;34:641–8.
936. Hodgson TA, Greenspan D, Greenspan JS. Oral lesions of HIV disease and HAART in industrialized countries. Adv Dent Res 2006;19:57–62.
937. Baccaglini L, Atkinson JC, Patton LL, et al. Management of oral lesions in HIV-positive patients. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2007;103(Suppl S50):e1-23.
938. Wright TC, Jr., Massad LS, Dunton CJ, Spitzer M, Wilkinson EJ. 2006 consensus guidelines for the management of women with cervical intraepithelial neoplasia or adenocarcinoma in situ. Am J Obstet Gynecol 2007;197:340–5.
939. Hacker NF. Vulvar Cancer. Practical Gynecologic Oncology. Edition 4, Lippincott Willimans & Wilkins 2005:543–83.
940. de Hullu JA, van der Zee AG. Surgery and radiotherapy in vulvar cancer. Crit Rev Oncol Hematol 2006;60:38–58.

941. Webber J, Fromm D. Photodynamic therapy for carcinoma in situ of the anus. Arch Surg 2004;139:259–61.
942. Scholefield JH. Treatment of grade III anal intraepithelial neoplasia with photodynamic therapy: report of a case. Dis Colon Rectum 2003;46:1555–9.
943. Goldstone SE, Kawalek AZ, Huyett JW. Infrared coagulator: a useful tool for treating anal squamous intraepithelial lesions. Dis Colon Rectum 2005;48:1042–54.
944. Graham BD, Jetmore AB, Foote JE, Arnold LK. Topical 5-fluorouracil in the management of extensive anal Bowen's disease: a preferred approach. Dis Colon Rectum 2005;48:444–50.
945. Licitra L, Perrone F, Bossi P, et al. High-risk human papillomavirus affects prognosis in patients with surgically treated oropharyngeal squamous cell carcinoma. J Clin Oncol 2006;24:5630–6.
946. Fruchter RG, Maiman M, Sedlis A, et al. Multiple recurrences of cervical intraepithelial neoplasia in women with the human immunodeficiency virus. Obstet Gynecol 1996;87:338–44.
947. Kurman RJ, Henson DE, Herbst AL, Noller KL, Schiffman MH. Interim guidelines for management of abnormal cervical cytology. JAMA 1994;271:1866–9.
948. Maiman M, Watts DH, Andersen J, et al. Vaginal 5-fluorouracil for high-grade cervical dysplasia in human immunodeficiency virus infection: a randomized trial. Obstet Gynecol 1999;94:954–61.
949. Heard I, Potard V, Foulot H, et al. High rate of recurrence of cervical intraepithelial neoplasia after surgery in HIV-positive women. J Acquir Immune Defic Syndr 2005;39:412–8.
950. Shah K, Kashima H, Polk BF, et al. Rarity of cesarean delivery in cases of juvenile-onset respiratory papillomatosis. Obstet Gynecol 1986;68:795–9.
951. Morrison EA, Gammon MD, Goldberg GL, Vermund SH, Burk RD. Pregnancy and cervical infection with human papillomaviruses. Int J Gynaecol Obstet 1996;54:125–30.
952. Kjellberg L, Hallmans G, Ahren AM, et al. Smoking, diet, pregnancy and oral contraceptive use as risk factors for cervical intra-epithelial neoplasia in relation to human papillomavirus infection. Br J Cancer 2000;82:1332–8.
953. Silverberg MJ, Thorsen P, Lindeberg H, Grant LA, Shah KV. Condyloma in pregnancy is strongly predictive of juvenile-onset recurrent respiratory papillomatosis. Obstet Gynecol 2003;101:645–52.
954. Fife KH, Katz BP, Brizendine EJ, Brown DR. Cervical human papillomavirus deoxyribonucleic acid persists throughout pregnancy and decreases in the postpartum period. Am J Obstet Gynecol 1999;180:1110–4.
955. Puranen MH, Yliskoski MH, Saarikoski SV, Syrjanen KJ, Syrjanen SM. Exposure of an infant to cervical human papillomavirus infection of the mother is common. Am J Obstet Gynecol 1997;176:1039–45.
956. Watts DH, Koutsky LA, Holmes KK, et al. Low risk of perinatal transmission of human papillomavirus: results from a prospective cohort study. Am J Obstet Gynecol 1998;178:365–73.
957. Tseng CJ, Liang CC, Soong YK, Pao CC. Perinatal transmission of human papillomavirus in infants: relationship between infection rate and mode of delivery. Obstet Gynecol 1998;91:92–6.
958. Tenti P, Zappatore R, Migliora P, et al. Perinatal transmission of human papillomavirus from gravidas with latent infections. Obstet Gynecol 1999;93:475–9.
959. Orr JW, Jr., Barrett JM, Orr PF, Holloway RW, Holimon JL. The efficacy and safety of the cytobrush during pregnancy. Gynecol Oncol 1992;44:260–2.
960. Lee WM. Hepatitis B virus infection. N Engl J Med 1997;337:1733–45.
961. Levine OS, Vlahov D, Koehler J, et al. Seroepidemiology of hepatitis B virus in a population of injecting drug users: association with drug injection patterns. Am J Epidemiol 1995;142:331–41.
962. Beasley RP, Trepo C, Stevens CE, Szmuness W. The e antigen and vertical transmission of hepatitis B surface antigen. Am J Epidemiol 1977;105:94–8.
963. Rodriguez-Mendez ML, Gonzalez-Quintela A, Aguilera A, Barrio E. Prevalence, patterns, and course of past hepatitis B virus infection in intravenous drug users with HIV-1 infection. Am J Gastroenterol 2000;95:1316–22.
964. Scharschmidt BF, Held MJ, Hollander HH, et al. Hepatitis B in patients with HIV infection: relationship to AIDS and patient survival. Ann Intern Med 1992;117:837–8.
965. Homann C, Krogsgaard K, Pedersen C, Andersson P, Nielsen JO. High incidence of hepatitis B infection and evolution of chronic hepatitis B infection in patients with advanced HIV infection. J Acquir Immune Defic Syndr 1991;4:416–20.
966. Alter HJ, Seeff LB. Recovery, persistence, and sequelae in hepatitis C virus infection: a perspective on long-term outcome. Semin Liver Dis 2000;20:17–35.
967. Bodsworth NJ, Cooper DA, Donovan B. The influence of human immunodeficiency virus type 1 infection on the development of the hepatitis B virus carrier state. J Infect Dis 1991;163:1138–40.
968. Grob P, Jilg W, Bornhak H, et al. Serological pattern "anti-HBc alone": report on a workshop. J Med Virol 2000;62:450–5.
969. Hofer M, Joller-Jemelka HI, Grob PJ, Luthy R, Opravil M. Frequent chronic hepatitis B virus infection in HIV-infected patients positive for antibody to hepatitis B core antigen only. Eur J Clin Microbiol Infect Dis 1998;17:6–13.
970. Silva AE, McMahon BJ, Parkinson AJ, et al. Hepatitis B virus DNA in persons with isolated antibody to hepatitis B core antigen who subsequently received hepatitis B vaccine. Clin Infect Dis 1998;26:895–7.
971. Lok AS, Lai CL, Wu PC. Prevalence of isolated antibody to hepatitis B core antigen in an area endemic for hepatitis B virus infection: implications in hepatitis B vaccination programs. Hepatology 1988;8:766–70.
972. Gandhi RT, Wurcel A, Lee H, et al. Response to hepatitis B vaccine in HIV-1-positive subjects who test positive for isolated antibody to hepatitis B core antigen: implications for hepatitis B vaccine strategies. J Infect Dis 2005;191:1435–41.
973. Gandhi RT, Wurcel A, McGovern B, et al. Low prevalence of ongoing hepatitis B viremia in HIV-positive individuals with isolated antibody to hepatitis B core antigen. J Acquir Immune Defic Syndr 2003 34:439–41.
974. Shire NJ, Sherman KE. Management of hepatitis B virus in HIV-positive patients. Minerva Gastroenterol Dietol 2006;52:67–87.
975. Colin JF, Cazals-Hatem D, Loriot MA, et al. Influence of human immunodeficiency virus infection on chronic hepatitis B in homosexual men. Hepatology 1999;29:1306–10.
976. Gilson RJ, Hawkins AE, Beecham MR, et al. Interactions between HIV and hepatitis B virus in homosexual men: effects on the natural history of infection. AIDS 1997;11:597–606.
977. Thio CL, Seaberg EC, Skolasky R, Jr., et al. HIV-1, hepatitis B virus, and risk of liver-related mortality in the Multicenter Cohort Study (MACS). Lancet 2002;360:1921–6.
978. Van Thiel DH, Gavaler JS, Wright H, Tzakis A. Liver biopsy: its safety and complications as seen at a liver transplant center. Transplantation 1993;55:1087–90.
979. Bravo AA, Sheth SG, Chopra S. Liver biopsy. N Engl J Med 2001;344:495–500.

980. Lok AS, McMahon BJ. Chronic hepatitis B: update of recommendations. Hepatology 2004;39:857–61.
981. Hoofnagle JH, Dusheiko GM, Seeff LB, et al. Seroconversion from hepatitis B e antigen to antibody in chronic type B hepatitis. Ann Intern Med 1981;94:744–8.
982. Keeffe EB, Dieterich DT, Han SH, et al. A treatment algorithm for the management of chronic hepatitis B virus infection in the United States: an update. Clin Gastroenterol Hepatol 2006;4:936–62.
983. Lok AS. Navigating the maze of hepatitis B treatments. Gastroenterology 2007;132:1586–94.
984. McMahon BJ. Epidemiology and natural history of hepatitis B. Semin Liver Dis 2005;25(Suppl 1):3-8.
985. Fattovich G, McIntyre G, Thursz M, et al. Hepatitis B virus precore/core variation and interferon therapy. Hepatology 1995;22:1355–62.
986. Zacharakis GH, Koskinas J, Kotsiou S, et al. Natural history of chronic HBV infection: a cohort study with up to 12 years follow-up in North Greece (part of the Interreg I-II/EC-project). J Med Virol 2005;77:173–9.
987. Yang SS, Cheng KS, Lai YC, et al. Decreasing serum alpha-fetoprotein levels in predicting poor prognosis of acute hepatic failure in patients with chronic hepatitis B. J Gastroenterol 2002;37:626–32.
988. Zöllner B, Feucht HH, Sterneck M, et al. Clinical reactivation after liver transplantation with an unusual minor strain of hepatitis B virus in an occult carrier. Liver Transpl 2006;12:1283–9.
989. Mindikoglu AL, Regev A, Schiff ER. Hepatitis B virus reactivation after cytotoxic chemotherapy: the disease and its prevention. Clin Gastroenterol Hepatol 2006;4:1076–81.
990. Dai MS, Wu PF, Shyu RY, Lu JJ, Chao TY. Hepatitis B virus reactivation in breast cancer patients undergoing cytotoxic chemotherapy and the role of preemptive lamivudine administration. Liver Int 2004;24:540–6.
991. Keeffe EB. Hepatitis B virus reactivation with chemotherapy: diagnosis and prevention with antiviral prophylaxis. Rev Gastroenterol Disord 2004;4:46–8.
992. Altfeld M, Rockstroh JK, Addo M, et al. Reactivation of hepatitis B in a long-term anti-HBs-positive patient with AIDS following lamivudine withdrawal. J Hepatol 1998;29:306–9.
993. Bessesen M, Ives D, Condreay L, Lawrence S, Sherman KE. Chronic active hepatitis B exacerbations in human immunodeficiency virus-infected patients following development of resistance to or withdrawal of lamivudine. Clin Infect Dis 1999;28:1032–5.
994. Perrillo RP. Acute flares in chronic hepatitis B: the natural and unnatural history of an immunologically mediated liver disease. Gastroenterology 2001;120:1009–22.
995. Sulkowski MS, Thomas DL, Chaisson RE, Moore RD. Elevated liver enzymes following initiation of antiretroviral therapy. JAMA 2000;283:2526–7.
996. Lok AS, McMahon BJ. Chronic hepatitis B. Hepatology 2001;34:1225–41.
997. Salmon-Ceron D, Lewden C, Morlat P, et al. Liver disease as a major cause of death among HIV infected patients: role of hepatitis C and B viruses and alcohol. J Hepatol 2005;42:799–805.
998. Bruno R, Sacchi P, Filice C, Puoti M, Filice G. Hepatocellular carcinoma in HIV-infected patients with chronic hepatitis: an emerging issue. J Acquir Immune Defic Syndr 2002;30:535–6.
999. Weber R, Sabin CA, Friis-Moller N, et al. Liver-related deaths in persons infected with the human immunodeficiency virus: the D:A:D study. Arch Intern Med 2006;166:1632–41.
1000. Vlahov D, Junge B, Brookmeyer R, et al. Reductions in high-risk drug use behaviors among participants in the Baltimore needle exchange program. J Acquir Immune Defic Syndr Hum Retrovirol 1997;16:400–6.
1001. Hagan H, Jarlais DC, Friedman SR, Purchase D, Alter MJ. Reduced risk of hepatitis B and hepatitis C among injection drug users in the Tacoma syringe exchange program. Am J Public Health 1995;85:1531–7.
1002. Hagan H, McGough JP, Thiede H, et al. Syringe exchange and risk of infection with hepatitis B and C viruses. Am J Epidemiol 1999;149:203–13.
1003. Fonseca MO, Pang LW, de Paula Cavalheiro N, Barone AA, Heloisa Lopes M. Randomized trial of recombinant hepatitis B vaccine in HIV-infected adult patients comparing a standard dose to a double dose. Vaccine 2005;23:2902–8.
1004. Rey D, Krantz V, Partisani M, et al. Increasing the number of hepatitis B vaccine injections augments anti-HBs response rate in HIV-infected patients: effects on HIV-1 viral load. Vaccine 2000;18:1161–5.
1005. Veiga AP, Casseb J, Duarte AJ. Humoral response to hepatitis B vaccination and its relationship with T CD45RA+ (naive) and CD45RO+ (memory) subsets in HIV-1-infected subjects. Vaccine 2006;24:7124–8.
1006. Hadler SC, Francis DP, Maynard JE, et al. Long-term immunogenicity and efficacy of hepatitis B vaccine in homosexual men. N Engl J Med 1986;315:209–14.
1007. McMahon D, Winkelstein A, Huang XL, et al. Acute reactions associated with the infusion of ampligen. AIDS 1992;6:235–6.
1008. Al-Mekhaizeem KA, Miriello M, Sherker AH. The frequency and significance of isolated hepatitis B core antibody and the suggested management of patients. CMAJ 2001;165:1063–4.
1009. Jongjirawisan Y, Ungulkraiwit P, Sungkanuparph S. Isolated antibody to hepatitis B core antigen in HIV-1 infected patients and a pilot study of vaccination to determine the anamnestic response. J Med Assoc Thai 2006;89:2028–34.
1010. Mast EE, Weinbaum CM, Fiore AE, et al. A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2006;55(No. RR-16).
1011. Loke RH, Murray-Lyon IM, Coleman JC, Evans BA, Zuckerman AJ. Diminished response to recombinant hepatitis B vaccine in homosexual men with HIV antibody: an indicator of poor prognosis. J Med Virol 1990;31:109–11.
1012. Tayal SC, Sankar KN. Impaired response to recombinant hepatitis B vaccine in asymptomatic HIV-infected individuals. AIDS 1994;8:558–9.
1013. Bruguera M, Cremades M, Salinas R, et al. Impaired response to recombinant hepatitis B vaccine in HIV-infected persons. J Clin Gastroenterol 1992;14:27–30.
1014. Keet IP, van Doornum G, Safary A, Coutinho RA. Insufficient response to hepatitis B vaccination in HIV-positive homosexual men. AIDS 1992;6:509–10.
1015. Ristola MA, Vuola JM, Valle M, von Reyn CF. Antibody responses to intradermal recombinant hepatitis B immunization among HIV-positive subjects. Vaccine 2004;23:205–9.
1016. Tedaldi EM, Baker RK, Moorman AC, et al. Hepatitis A and B vaccination practices for ambulatory patients infected with HIV. Clin Infect Dis 2004;38:1478–84.
1017. Overton ET, Sungkanuparph S, Powderly WG, et al. Undetectable plasma HIV RNA load predicts success after hepatitis B vaccination in HIV-infected persons. Clin Infect Dis 2005;41:1045–8.
1018. Lee SD, Chan CY, Yu MI, et al. Hepatitis B vaccination in patients with chronic hepatitis C. Med Virol 1999;59:463–8.

1019. Wiedmann M, Liebert UG, Oesen U, et al. Decreased immunogenicity of recombinant hepatitis B vaccine in chronic hepatitis C. Hepatology 2000;31:230–4.
1020. Anthony DD, Yonkers NL, Post AB, et al. Selective impairments in dendritic cell-associated function distinguish hepatitis C virus and HIV infection. J Immunol 2004;172:4907–16.
1021. Sarobe P, Lasarte JJ, Casares N, et al. Abnormal priming of $CD4^+$ T cells by dendritic cells expressing hepatitis C virus core and E1 proteins. J Virol 2002;76:5062–70.
1022. Auffermann-Gretzinger S, Keeffe EB, Levy S. Impaired dendritic cell maturation in patients with chronic, but not resolved, hepatitis C virus infection. Blood 2001;97:3171–6.
1023. Shire NJ, Rouster SD, Rajicic N, Sherman KE. Occult hepatitis B in HIV-infected patients. J Acquir Immune Defic Syndr 2004;36:869–75.
1024. Cooper CL, Davis HL, Angel JB, et al. CPG 7909 adjuvant improves hepatitis B virus vaccine seroprotection in antiretroviral-treated HIV-infected adults. AIDS 2005;19:1473–9.
1025. Collier AC, Corey L, Murphy VL, Handsfield HH. Antibody to human immunodeficiency virus (HIV) and suboptimal response to hepatitis B vaccination. Ann Intern Med 1988;109:101–5.
1026. Bailey DN. Effect of coadministered drugs and ethanol on the binding of therapeutic drugs to human serum in vitro. Ther Drug Monit 2001;23:71–4.
1027. Mannucci PM, Zanetti AR, Gringeri A, et al. Long-term immunogenicity of a plasma-derived hepatitis B vaccine in HIV seropositive and HIV seronegative hemophiliacs. Arch Intern Med 1989;149:1333–7.
1028. Ahuja TS, Abbott KC, Pack L, Kuo YF. HIV-associated nephropathy and end-stage renal disease in children in the United States. Pediatr Nephrol 2004;19:808–11.
1029. Mast EE, Hwang LY, Seto DS, et al. Risk factors for perinatal transmission of hepatitis C virus (HCV) and the natural history of HCV infection acquired in infancy. J Infect Dis 2005;192:1880–9.
1030. CDC. Prevention of hepatitis A through active or passive immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2006;55(No. RR-7).
1031. Soriano V, Puoti M, Bonacini M, et al. Care of patients with chronic hepatitis B and HIV co-infection: recommendations from an HIV-HBV International Panel. AIDS 2005;19:221–40.
1032. Wong DK, Yim C, Naylor CD, et al. Interferon alfa treatment of chronic hepatitis B: randomized trial in a predominantly homosexual male population. Gastroenterology 1995;108:165–71.
1033. Krogsgaard K. The long-term effect of treatment with interferon-alpha 2a in chronic hepatitis B. J Viral Hepat 1998;5:389–97.
1034. Marcellin P, Lau GK, Bonino F, et al. Peginterferon alfa-2a alone, lamivudine alone, and the two in combination in patients with HBeAg-negative chronic hepatitis B. N Engl J Med 2004;351:1206–17.
1035. Lau GK, Piratvisuth T, Luo KX, et al. Peginterferon alfa-2a, lamivudine, and the combination for HBeAg-positive chronic hepatitis B. N Engl J Med 2005;352:2682–95.
1036. Torriani FJ, Rodriguez-Torres M, Rockstroh JK, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection in HIV-infected patients. N Engl J Med 2004;351:438–50.
1037. Benhamou Y, Bochet M, Thibault V, et al. Long-term incidence of hepatitis B virus resistance to lamivudine in human immunodeficiency virus-infected patients. Hepatology 1999;30:1302–6.
1038. Benhamou Y, Thibault V, Vig P, et al. Safety and efficacy of adefovir dipivoxil in patients infected with lamivudine-resistant hepatitis B and HIV-1. J Hepatol 2006;44:62–7.
1039. Mulato AS, Lamy PD, Miller MD, et al. Genotypic and phenotypic characterization of human immunodeficiency virus type 1 variants isolated from AIDS patients after prolonged adefovir dipivoxil therapy. Antimicrob Agents Chemother 1998;42:1620–8.
1040. Sheldon JA, Corral A, Rodés B, et al. Risk of selecting K65R in antiretroviral-naive HIV-infected individuals with chronic hepatitis B treated with adefovir. AIDS 2005;19:2036–8.
1041. Peters MG, Andersen J, Lynch P, et al. Randomized controlled study of tenofovir and adefovir in chronic hepatitis B virus and HIV infection: ACTG A5127. Hepatology 2006;44:1110–6.
1042. Chen CH, Lee CM, Hung CH, et al. Clinical significance and evolution of core promoter and precore mutations in HBeAg-positive patients with HBV genotype B and C: a longitudinal study. Liver Int 2007;27:806–15.
1043. Keeffe EB, Marcellin P. New and emerging treatment of chronic hepatitis B. Clin Gastroenterol Hepatol 2007;5:285–94.
1044. McMahon MA, Jilek BL, Brennan TP, et al. The HBV drug entecavir—effects on HIV-1 replication and resistance. N Engl J Med 2007;356:2614–21.
1045. Matthews GV, Dore GJ. Combination of tenofovir and lamivudine versus tenofovir after lamivudine failure for therapy of hepatitis B in HIV-coinfection. AIDS 2007;21:777–8.
1046. Chan HL, Heathcote EJ, Marcellin P, et al. Treatment of hepatitis B e antigen positive chronic hepatitis with telbivudine or adefovir: a randomized trial. Ann Intern Med 2007;147:745–54.
1047. Lai CL, Leung N, Teo EK, et al. A 1-year trial of telbivudine, lamivudine, and the combination in patients with hepatitis B e antigen-positive chronic hepatitis B. Gastroenterology 2005;129:528–36.
1048. Matthews GV, Pillay D, Cane P, et al. Failure of combination therapy with lamivudine and famciclovir following lamivudine monotherapy for hepatitis B virus infection in patients coinfected with human immunodeficiency virus-1. Clin Infect Dis 2001;33:2049–54.
1049. Rayes N, Seehofer D, Hopf U, et al. Comparison of famciclovir and lamivudine in the long-term treatment of hepatitis B infection after liver transplantation. Transplantation 2001;71:96–101.
1050. de Man RA, Marcellin P, Habal F, et al. A randomized, placebo-controlled study to evaluate the efficacy of 12-month famciclovir treatment in patients with chronic hepatitis B e antigen-positive hepatitis B. Hepatology 2000;32:413–7.
1051. Jain MK, Comanor L, White C, et al. Treatment of hepatitis B with lamivudine and tenofovir in HIV/HBV-coinfected patients: factors associated with response. J Viral Hepat 2007;14:176–82.
1052. Lampertico P, Vigano M, Manenti E, et al. Low resistance to adefovir combined with lamivudine: a 3-year study of 145 lamivudine-resistant hepatitis B patients. Gastroenterology 2007;133:1445–51.
1053. Yim HJ, Hussain M, Liu Y, et al. Evolution of multi-drug resistant hepatitis B virus during sequential therapy. Hepatology 2006;44:703–12.
1054. Rapti I, Dimou E, Mitsoula P, Hadziyannis SJ. Adding-on versus switching-to adefovir therapy in lamivudine-resistant HBeAg-negative chronic hepatitis B. Hepatology 2007;45:307–13.
1055. Barbaro G, Zechini F, Pellicelli AM, et al. Long-term efficacy of interferon alpha-2b and lamivudine in combination compared to lamivudine monotherapy in patients with chronic hepatitis B: an Italian multicenter, randomized trial. J Hepatol 2001;35:406–11.
1056. Schalm SW, Heathcote J, Cianciara J, et al. Lamivudine and alpha interferon combination treatment of patients with chronic hepatitis B infection: a randomised trial. Gut 2000;46:562–8.

1057. Soriano V, Barreiro P, Martín-Carbonero L, et al. Treatment of chronic hepatitis B or C in HIV-infected patients with dual viral hepatitis. J Infect Dis 2007;195:1181–3.
1058. Tassopoulos NC, Volpes R, Pastore G, et al. Efficacy of lamivudine in patients with hepatitis B e antigen-negative/hepatitis B virus DNA-positive (precore mutant) chronic hepatitis B. Hepatology 1999;29:889–96.
1059. Hoofnagle JH, Doo E, Liang TJ, Fleischer R, Lok AS. Management of hepatitis B: summary of a clinical research workshop. Hepatology 2007;45:1056–75.
1060. Lok AS, Heathcote EJ, Hoofnagle JH. Management of hepatitis B: 2000—summary of a workshop. Gastroenterology 2001;120:1828–53.
1061. Gallant JE, Parish MA, Keruly JC, Moore RD. Changes in renal function associated with tenofovir disoproxil fumarate treatment, compared with nucleoside reverse-transcriptase inhibitor treatment. Clin Infect Dis 2005;40:1194–8.
1062. Honkoop P, de Man RA, Niesters HG, Zondervan PE, Schalm SW. Acute exacerbation of chronic hepatitis B virus infection after withdrawal of lamivudine therapy. Hepatology 2000;32:635–9.
1063. Lau GK. Does treatment with interferon-based therapy improve the natural history of chronic hepatitis B infection? J Hepatol 2007;46:6–8.
1064. Pol S, Lebray P, Vallet-Pichard A. HIV infection and hepatic enzyme abnormalities: intricacies of the pathogenic mechanisms. Clin Infect Dis 2004;38(Suppl 2):65-72.
1065. Kontorinis N, Dieterich D. Hepatotoxicity of antiretroviral therapy. AIDS Rev 2003;5:36–43.
1066. Stern JO, Robinson PA, Love J, et al. A comprehensive hepatic safety analysis of nevirapine in different populations of HIV infected patients. J Acquir Immune Defic Syndr 2003;34(Suppl 1):1-33.
1067. Sulkowski MS, Mehta SH, Chaisson RE, Thomas DL, Moore RD. Hepatotoxicity associated with protease inhibitor-based antiretroviral regimens with or without concurrent ritonavir. AIDS 2004;18:2277–84.
1068. Sulkowski MS, Thomas DL, Chaisson RE, Moore RD. Hepatotoxicity associated with antiretroviral therapy in adults infected with human immunodeficiency virus and the role of hepatitis C or B virus infection. JAMA 2000;283:74–80.
1069. Torti C, Lapadula G, Casari S, et al. Incidence and risk factors for liver enzyme elevation during highly active antiretroviral therapy in HIV-HCV co-infected patients: results from the Italian EPOKA-MASTER cohort. BMC Infect Dis 2005;14:58.
1070. Martinez E, Blanco JL, Arnaiz JA, et al. Hepatotoxicity in HIV–1-infected patients receiving nevirapine-containing antiretroviral therapy. AIDS 2001;15:1261–8.
1071. Meraviglia P, Schiavini M, Castagna A, et al. Lopinavir/ritonavir treatment in HIV antiretroviral-experienced patients: evaluation of risk factors for liver enzyme elevation. HIV Med 2004;5:334–43.
1072. Saves M, Vandentorren S, Daucourt V, et al. Severe hepatic cytolysis: incidence and risk factors in patients treated by antiretroviral combinations. AIDS 1999;13:F115-21.
1073. Monforte V, Roman A, Gavalda J, et al. Nebulized amphotericin B prophylaxis for *Aspergillus* infection in lung transplantation: study of risk factors. J Heart Lung Transplant 2001;20:1274–81.
1074. Sherman KE, Shire NJ, Cernohous P, et al. Liver injury and changes in hepatitis C Virus (HCV) RNA load associated with protease inhibitor-based antiretroviral therapy for treatment-naive HCV-HIV-coinfected patients: lopinavir-ritonavir versus nelfinavir. Clin Infect Dis 2005;41:1186–95.
1075. Reuben A. Hy's law. Hepatology 2004;39:574–8.
1076. Benhamou Y, Bochet M, Thibault V, et al. Safety and efficacy of adefovir dipivoxil in patients co-infected with HIV-1 and lamivudine-resistant hepatitis B virus: an open-label pilot study. Lancet 2001;358:718–23.
1077. Lai CL, Chien RN, Leung NW, et al. A one-year trial of lamivudine for chronic hepatitis B. N Engl J Med 1998;339:61–8.
1078. Dienstag JL, Schiff ER, Wright TL, et al. Lamivudine as initial treatment for chronic hepatitis B in the United States. N Engl J Med 1999;341:1256–63.
1079. Runyon BA. Management of adult patients with ascites due to cirrhosis. Hepatology 2004;39:841–56.
1080. Singh N, Gayowski T, Yu VL, Wagener MM. Trimethoprim-sulfamethoxazole for the prevention of spontaneous bacterial peritonitis in cirrhosis: a randomized trial. Ann Intern Med 1995;122:595–8.
1081. Di Bisceglie AM. Hepatitis C and hepatocellular carcinoma. Hepatology 1997;26(Suppl 1):34-38.
1082. Gebo KA, Chander G, Jenckes MW, et al. Screening tests for hepatocellular carcinoma in patients with chronic hepatitis C: a systematic review. Hepatology 2002;36(Suppl 1):584-92.
1083. Miro JM, Laguno M, Moreno A, Rimola A. Management of end stage liver disease (ESLD): what is the current role of orthotopic liver transplantation (OLT)? J Hepatol 2006;44(Suppl 1):140-5.
1084. Forman LM, Lucey MR. Predicting the prognosis of chronic liver disease: an evolution from child to MELD (Mayo End-stage Liver Disease). Hepatology 2001;33:473–5.
1085. CDC. Report of the NIH Panel to Define Principles of Therapy of HIV Infection and guidelines for use of antiretroviral agents in HIV infected adults and adolescents. MMWR 1998;47(No. RR-5).
1086. Committee Antiretroviral Pregnancy Registry. Antiretroviral Pregnancy Registry international interim report for 1 January 1989 through 31 July 2007. Wilmington, NC: Registry Coordinating Center, 2007.
1087. Boskovic R, Wide R, Wolpin J, Bauer DJ, Koren G. The reproductive effects of beta interferon therapy in pregnancy: a longitudinal cohort. Neurology 2005;65:807–11.
1088. Gotz HM, van Doornum G, Niesters HG, et al. A cluster of acute hepatitis C virus infection among men who have sex with men—results from contact tracing and public health implications. AIDS 2005;19:969–74.
1089. Polis CB, Shah SN, Johnson KE, Gupta A. Impact of maternal HIV coinfection on the vertical transmission of hepatitis C virus: a meta-analysis. Clin Infect Dis 2007;44:1123–31.
1090. Chamot E, Hirschel B, Wintsch J, et al. Loss of antibodies against hepatitis C virus in HIV-seropositive intravenous drug users. AIDS 1990;4:1275–7.
1091. Ghany MG, Kleiner DE, Alter H, et al. Progression of fibrosis in chronic hepatitis C. Gastroenterology 2003;124:97–104.
1092. Alter MJ. Epidemiology of viral hepatitis and HIV co-infection. J Hepatol 2006;44(Suppl 1):6-9.
1093. Sulkowski MS, Moore RD, Mehta SH, Chaisson RE, Thomas DL. Hepatitis C and progression of HIV disease. JAMA 2002;288:199–206.
1094. Brau N, Salvatore M, Ríos-Bedoya CF, et al. Slower fibrosis progression in HIV/HCV-coinfected patients with successful HIV suppression using antiretroviral therapy. J Hepatol 2006;44:47–55.
1095. Benhamou Y. Factors affecting liver fibrosis in human immunodeficiency virus-and hepatitis C virus-coinfected patients: impact of protease inhibitor therapy. Hepatology 2001;34:283–7.
1096. Poynard T, Bedossa P, Opolon P. Natural history of liver fibrosis progression in patients with chronic hepatitis C. Lancet 1997;349:825–32.

1097. Graham CS, Baden LR, Yu E, et al. Influence of human immunodeficiency virus infection on the course of hepatitis C virus infection: a meta-analysis. Clin Infect Dis 2001;33:562–9.
1098. Merchante N, Girón-González JA, González-Serrano M, et al. Survival and prognostic factors of HIV-infected patients with HCV-related end-stage liver disease. AIDS 2006;20:49–57.
1099. Mehta SH, Thomas DL, Torbenson M, et al. The effect of antiretroviral therapy on liver disease among adults with HIV and hepatitis C coinfection. Hepatology 2005;41:123–31.
1100. Qurishi N, Kreuzberg C, Lüchters G, et al. Effect of antiretroviral therapy on liver-related mortality in patients with HIV and hepatitis C virus coinfection. Lancet 2004;362:1708–13.
1101. Ryan EL, Morgello S, Isaacs K, Naseer M, Gerits P. Neuropsychiatric impact of hepatitis C on advanced HIV. Neurology 2004;62:957–62.
1102. Fleming CA, Christiansen D, Nunes D, et al. Health-related quality of life of patients with HIV disease: impact of hepatitis C coinfection. Clin Infect Dis 2004;38:572–8.
1103. Mehta SH, Moore RD, Thomas DL, Chaisson RE, Sulkowski MS. The effect of HAART and HCV infection on the development of hyperglycemia among HIV-infected persons. J Acquir Immune Defic Syndr 2003;33:577–84.
1104. Greub G, Ledergerber B, Battegay M, et al. Clinical progression, survival, and immune recovery during antiretroviral therapy in patients with HIV-1 and hepatitis C virus coinfection: the Swiss HIV Cohort Study. Lancet 2000;356:1800–5.
1105. Chung RT, Evans SR, Yang Y, et al. Immune recovery is associated with persistent rise in hepatitis C virus RNA, infrequent liver test flares, and is not impaired by hepatitis C virus in co-infected subjects. AIDS 2002;16:1915–23.
1106. Sullivan PS, Hanson DL, Teshale EH, Wotring LL, Brooks JT. Effect of hepatitis C infection on progression of HIV disease and early response to initial antiretroviral therapy. AIDS 2006;20:1171–9.
1107. Aranzabal L, Casado JL, Moya J, et al. Influence of liver fibrosis on highly active antiretroviral therapy-associated hepatotoxicity in patients with HIV and hepatitis C virus coinfection. Clin Infect Dis 2005;40:588–93.
1108. Jaeckel E, Cornberg M, Wedemayer H, et al. Treatment of acute hepatitis C with interferon alfa-2b. N Engl J Med 2001;345(2):1452–7.
1109. Kamal SM, Fouly AE, Kamel RR, et al. Peginterferon alfa-2b therapy in acute hepatitis C: impact of onset of therapy on sustained virologic response. Gastroenterology 2006;130:632–8.
1110. National Institutes of Health. Consensus development conference statement: management of hepatitis C: 2002–June 10-12, 2002. Hepatology 2002;36(Suppl 1):3-20.
1111. Thio CL, Nolt KR, Astemborski J, et al. Screening for hepatitis C virus in human immunodeficiency virus-infected individuals. J Clin Microbiol 2000;38:575–7.
1112. Sulkowski MS, Thomas DL. Hepatitis C in the HIV-infected patient. Clin Liver Dis 2003;7:179–94.
1113. Scott JD, Gretch DR. Molecular diagnostics of hepatitis C virus infection: a systematic review. JAMA 2007;297:724–32.
1114. Armstrong GL, Wasley A, Simard EP, et al. The prevalence of hepatitis C virus infection in the United States, 1999 through 2002. Ann Intern Med 2006;144:705–14.
1115. Lindor KD, Bru C, Jorgensen RA, et al. The role of ultrasonography and automatic-needle biopsy in outpatient percutaneous liver biopsy. Hepatology 1996;23:1079–83.
1116. Sterling RK, Lissen E, Clumeck N, et al. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. Hepatology 2006;43:1317–25.
1117. Wilson LE, Torbenson M, Astemborski J, et al. Progression of liver fibrosis among injection drug users with chronic hepatitis C. Hepatology 2006;43:788–95.
1118. Myers RP, Benhamou Y, Imbert-Bismut F, et al. Serum biochemical markers accurately predict liver fibrosis in HIV and hepatitis C virus co-infected patients. AIDS 2003;17:721–5.
1119. Nunes D, Fleming C, Offner G, et al. HIV infection does not affect the performance of noninvasive markers of fibrosis for the diagnosis of hepatitis C virus-related liver disease. J Acquir Immune Defic Syndr 2005;40:538–44.
1120. de Ledinghen V, Douvin C, Kettaneh A, et al. Diagnosis of hepatic fibrosis and cirrhosis by transient elastography in HIV/hepatitis C virus-coinfected patients. J Acquir Immune Defic Syndr 2006;41:175–9.
1121. Thomas DL, Vlahov D, Solomon L, et al. Correlates of hepatitis C virus infections among injection drug users. Medicine (Baltimore) 1995;74:212–20.
1122. Hagan H, Thiede H, Weiss N, et al. Sharing of drug preparation equipment as a risk factor for hepatitis C. Am J Public Health 2001;91:42–6.
1123. Wiley TE, McCarthy M, Breidi L, et al. Impact of alcohol on the histological and clinical progression of hepatitis C infection. Hepatology 1998;28:805–9.
1124. Ryan BM, Stockbrugger RW, Ryan JM. A pathophysiologic, gastroenterologic, and radiologic approach to the management of gastric varices. Gastroenterology 2004;126:1175–89.
1125. Chung RT, Andersen J, Volberding P, et al. Peginterferon alfa-2a plus ribavirin versus interferon alfa-2a plus ribavirin for chronic hepatitis C in HIV-coinfected persons. N Engl J Med 2004;351:451–9.
1126. Laguno M, Murillas J, Blanco JL, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for treatment of HIV/HCV co-infected patients. AIDS 2004;18:F27-36.
1127. Carrat F, Bani-Sadr F, Pol S, et al. Pegylated interferon alfa-2b vs standard interferon alfa-2b, plus ribavirin, for chronic hepatitis C in HIV-infected patients: a randomized controlled trial. JAMA 2004;292:2839–48.
1128. Hadziyannis SJ, Sette HJ, Morgan TR, et al. Peginterferon-alpha2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. Ann Intern Med 2004;140:346–55.
1129. Labarga P, Soriano V, Vispo ME, et al. Hepatotoxicity of antiretroviral drugs is reduced after successful treatment of chronic hepatitis C in HIV-infected patients. J Infect Dis 2007;196:670–6.
1130. Sulkowski MS, Mehta SH, Torbenson MS, et al. Rapid fibrosis progression among HIV/hepatitis C virus-co-infected adults. AIDS 2007;21:2209–16.
1131. Davis GL. Monitoring of viral levels during therapy of hepatitis C. Hepatology 2002;36(Suppl 1):145-51.
1132. Rodriguez-Torres M, Rodriguez-Orengo JF, Ríos-Bedoya CF, et al. Effect of hepatitis C virus treatment in fibrosis progression rate (FPR) and time to cirrhosis (TTC) in patients co-infected with human immunodeficiency virus: a paired liver biopsy study. J Hepatol 2007;46:613–9.
1133. Soriano V, Maida I, Núñez M, et al. Long-term follow-up of HIV-infected patients with chronic hepatitis C virus infection treated with interferon-based therapies. Antivir Ther 2004;9:987–92.

1134. Fleischer R, Boxwell D, Sherman KE. Nucleoside analogues and mitochondrial toxicity. Clin Infect Dis 2004;38:79–80.
1135. Alvarez D, Dieterich DT, Brau N, et al. Zidovudine use but not weight-based ribavirin dosing impacts anaemia during HCV treatment in HIV-infected persons. J Viral Hepat 2006;13:683–9.
1136. Sulkowski MS, Dieterich DT, Bini EJ, et al. Epoetin alfa once weekly improves anemia in HIV/hepatitis C virus-coinfected patients treated with interferon/ribavirin: a randomized controlled trial. J Acquir Immune Defic Syndr 2005;39:504–6.
1137. Sulkowski MS, Thomas DL, Chaisson RE, Moore RD. Hepatotoxicity associated with antiretroviral therapy in adults infected with human immunodeficiency virus and the role of hepatitis C or B virus infection. JAMA;283:74–80. 2000.
1138. Sherman KE, Andersen JW, Butt AA, et al. Sustained long term antiviral maintenance with pegylated interferon in HCV/HIV coinfected (SLAM-C): early virologic response and effect on fibrosis in treated and control subjects (Abstract). 15th Conference on Retroviruses and Opportunistic Infections. Boston, MA, 2008.
1139. American College of Obstetricians and Gynecologists. Viral hepatitis in pregnancy. Int J Gynaecol Obstet 1998;63:195–202.
1140. Hegenbarth K, Maurer U, Kroisel PM, et al. No evidence for mutagenic effects of ribavirin: report of two normal pregnancies. Am J Gastroenterol 2001;96:2286–7.
1141. Gibb DM, Goodall RL, Dunn DT, et al. Mother-to-child transmission of hepatitis C virus: evidence for preventable peripartum transmission. Lancet 2000;356:904–7.
1142. European Paediatric Hepatitis C Virus Network. A significant sex—but not elective cesarean section—effect on mother-to-child transmission of hepatitis C virus infection. J Infect Dis 2005;192:1872–9.
1143. Koralnik IJ. Progressive multifocal leukoencephalopathy revisited: has the disease outgrown its name? Ann Neurol 2006;60:162–73.
1144. Weber T, Trebst C, Frye S, et al. Analysis of the systemic and intrathecal humoral immune response in progressive multifocal leukoencephalopathy. J Infect Dis 1997;176:250–4.
1145. Kitamura T, Aso Y, Kuniyoshi N, Hara K, Yogo Y. High incidence of urinary JC virus excretion in nonimmunosuppressed older patients. J Infect Dis 1990; 161:1128–33.
1146. Sundsfjord A, Flaegstad T, Flo R, et al. BK and JC viruses in human immunodeficiency virus type 1-infected persons: prevalence, excretion, viremia, and viral regulatory regions. J Infect Dis 1994;169:485–90.
1147. Monaco MC, Jensen PN, Hou J, Durham LC, Major EO. Detection of JC virus DNA in human tonsil tissue: evidence for site of initial viral infection. J Virol 1998;72:9918–23.
1148. Koralnik IJ, Boden D, Mai VX, Lord CI, Letvin NL. JC virus DNA load in patients with and without progressive multifocal leukoencephalopathy. Neurology 1999;52:253–60.
1149. Lednicky JA, Vilchez RA, Keitel WA, et al. Polyomavirus JCV excretion and genotype analysis in HIV-infected patients receiving highly active antiretroviral therapy. AIDS 2003;17:801–7.
1150. Kato A, Kitamura T, Takasaka T, et al. Detection of the archetypal regulatory region of JC virus from the tonsil tissue of patients with tonsillitis and tonsilar hypertrophy. J Neurovirol 2004;10:244–9.
1151. Richardson EP, Jr., Webster HD. Progressive multifocal leukoencephalopathy: its pathological features. Prog Clin Biol Res 1983:105:191–203.
1152. Garcia-Suarez J, de Miguel D, Krsnik I, et al. Changes in the natural history of progressive multifocal leukoencephalopathy in HIV-negative lymphoproliferative disorders: impact of novel therapies. Am J Hematol 2005;80:271–8.
1153. Van Assche G, Van Ranst M, Sciot R, et al. Progressive multifocal leukoencephalopathy after natalizumab therapy for Crohn's disease. N Engl J Med 2005;353:362–8.
1154. Kleinschmidt-DeMasters BK, Tyler KL. Progressive multifocal leukoencephalopathy complicating treatment with natalizumab and interferon beta-1a for multiple sclerosis. N Engl J Med 2005;353:369–74.
1155. Langer-Gould A, Atlas SW, Green AJ, Bollen AW, Pelletier D. Progressive multifocal leukoencephalopathy in a patient treated with natalizumab. N Engl J Med 2005;353:375–81.
1156. Aksamit AJ. Review of progressive multifocal leukoencephalopathy and natalizumab. Neurologist 2006;12:293–8.
1157. Mounier N, Spina M, Gisselbrecht C. Modern management of non-Hodgkin lymphoma in HIV-infected patients. Br J Haematol 2007;136:685–98.
1158. Boue F, Gabarre J, Gisselbrecht C, et al. Phase II trial of CHOP plus rituximab in patients with HIV-associated non-Hodgkin's lymphoma. J Clin Oncol 2006;24:4123–8.
1159. Petito CK, Cho ES, Lemann W, Navia BA, Price RW. Neuropathology of acquired immunodeficiency syndrome (AIDS): an autopsy review. J Neuropathol Exp Neurol 1986;45:635–46.
1160. Anders K, Steinsapir KD, Iverson DJ, et al. Neuropathologic findings in the acquired immunodeficiency syndrome (AIDS). Clin Neuropathol 1986;5:1–20.
1161. Lang W, Miklossy J, Deruaz JP, et al. Neuropathology of the acquired immune deficiency syndrome (AIDS): a report of 135 consecutive autopsy cases from Switzerland. Acta Neuropathol 1989;77:379–90.
1162. Berger JR, Mucke L. Prolonged survival and partial recovery in AIDS-associated progressive multifocal leukoencephalopathy. Neurology 1988;38:1060–5.
1163. d'Arminio Monforte A, Cinque P, Mocroft A, et al. Changing incidence of central nervous system diseases in the EuroSIDA cohort. Ann Neurol 2004;55:320–8.
1164. Mocroft A, Collaboration AC. OIs, AIDS-defining conditions, and HIV-1 disease burden (Abstract). 14th Conference on retroviruses and opportunistic infections. Los Angeles, CA, 2007.
1165. Berger JR, Levy RM, Flomenhoft D, Dobbs M. Predictive factors for prolonged survival in acquired immunodeficiency syndrome-associated progressive multifocal leukoencephalopathy. Ann Neurol 1998;44:341–9.
1166. Cinque P, Bossolasco S, Brambilla AM, et al. The effect of highly active antiretroviral therapy-induced immune reconstitution on development and outcome of progressive multifocal leukoencephalopathy: study of 43 cases with review of the literature. J Neurovirol 2003;9(Suppl 1):73-80.
1167. Du Pasquier RA, Koralnik IJ. Inflammatory reaction in progressive multifocal leukoencephalopathy: harmful or beneficial? J Neurovirol 2003;9(Suppl 1):25-31.
1168. Bernal F, J. T. Joseph ea. Spinal cord lesions of progressive multifocal leukoencephalopathy in an AIDS patient. J Neurovirol (In press).
1169. Zunt JR, Tu RK, Anderson DM, Copass MC, Marra CM. Progressive multifocal leukoencephalopathy presenting as human immunodeficiency virus type 1 (HIV)-associated dementia. Neurology 1997;49:263–5.
1170. Lima MA, Drislane FW, Koralnik IJ. Seizures and their outcome in progressive multifocal leukoencephalopathy. Neurology 2006;66:262–4.
1171. Yiannoutsos CT, Major EO, Curfman B, et al. Relation of JC virus DNA in the cerebrospinal fluid to survival in acquired immunodeficiency syndrome patients with biopsy-proven progressive multifocal leukoencephalopathy. Ann Neurol 1999;45:816–21.

1172. Bossolasco S, Calori G, Moretti F, et al. Prognostic significance of JC virus DNA levels in cerebrospinal fluid of patients with HIV-associated progressive multifocal leukoencephalopathy. Clin Infect Dis 2005;40:738–44.
1173. Silver SA, Arthur RR, Erozan YS,et al. Diagnosis of progressive multifocal leukoencephalopathy by stereotactic brain biopsy utilizing immunohistochemistry and the polymerase chain reaction. Acta Cytol 1995;39:35–44.
1174. Jochum W, Weber T, Frye S, et al. Detection of JC virus by anti-VP1 immunohistochemistry in brains with progressive multifocal leukoencephalopathy. Acta Neuropathol 1997;94:226–31.
1175. Miralles P, Berenguer J, Lacruz C, et al. Inflammatory reactions in progressive multifocal leukoencephalopathy after highly active antiretroviral therapy. AIDS 2001;15:1900–2.
1176. Safdar A, Rubocki RJ, Horvath JA, Narayan KK, Waldron RL. Fatal immune restoration disease in human immunodeficiency virus type 1-infected patients with progressive multifocal leukoencephalopathy: impact of antiretroviral therapy-associated immune reconstitution. Clin Infect Dis 2002;35:1250–7.
1177. Hoffmann C, Horst HA, Albrecht H, Schlote W. Progressive multifocal leucoencephalopathy with unusual inflammatory response during antiretroviral treatment. J Neurol Neurosurg Psychiatry 2003;74:1142–4.
1178. Di Giambenedetto S, Vago G, Pompucci A, et al. Fatal inflammatory AIDS-associated PML with high CD4 counts on HAART: a new clinical entity? Neurology 2004;63:2452–3.
1179. Antinori A, Cingolani A, Lorenzini P, et al. Clinical epidemiology and survival of progressive multifocal leukoencephalopathy in the era of highly active antiretroviral therapy: data from the Italian Registry Investigative Neuro AIDS (IRINA). J Neurovirol 2003;9(Suppl 1):47-53.
1180. Marzocchetti A, Di Giambenedetto S, Cingolani A, et al. Reduced rate of diagnostic positive detection of JC virus DNA in cerebrospinal fluid in cases of suspected progressive multifocal leukoencephalopathy in the era of potent antiretroviral therapy. J Clin Microbiol 2005;43(8):4175–7.
1181. Gasnault J, Hendel Chavez E, et al. Acceleration of immune recovery on intensified ART improves survival in patients with AIDS-related PML: preliminary reports of the ANRS 125 Trial. 14th Conference on Retroviruses and Opportunistic Illnesses. Los Angeles, CA, 2007.
1182. Clifford DB, Yiannoutsos C, Glicksman M, et al. HAART improves prognosis in HIV-associated progressive multifocal leukoencephalopathy. Neurology 1999;52:623–5.
1183. Dworkin MS, Wan PC, Hanson DL, Jones JL. Progressive multifocal leukoencephalopathy: improved survival of human immunodeficiency virus-infected patients in the protease inhibitor era. J Infect Dis 1999;180:621–5.
1184. Gasnault J, Taoufik Y, Goujard C, et al. Prolonged survival without neurological improvement in patients with AIDS-related progressive multifocal leukoencephalopathy on potent combined antiretroviral therapy. J Neurovirol 1999;5:421–9.
1185. Tassie JM, Gasnault J, Bentata M, et al. Survival improvement of AIDS-related progressive multifocal leukoencephalopathy in the era of protease inhibitors. Clinical Epidemiology Group. AIDS 1999;13:1881–7.
1186. De Luca A, Giancola ML, Ammassari A, et al. Cidofovir added to HAART improves virological and clinical outcome in AIDS-associated progressive multifocal leukoencephalopathy. AIDS 2000;14:117–21.
1187. Cinque P, Pierotti C, Vigano MG, et al. The good and evil of HAART in HIV-related progressive multifocal leukoencephalopathy. J Neurovirol 2001;7:358–63.
1188. Marra CM, Rajicic N, Barker DE, et al. A pilot study of cidofovir for progressive multifocal leukoencephalopathy in AIDS. AIDS 2002;16:1791–7.
1189. Berenguer JP, Miralles P, Arrizabalaga J, et al. Clinical course and prognostic factors of progressive multifocal leukoencephalopathy in patients treated with highly active antiretroviral therapy. Clin Infect Dis 2003;36:1047–52.
1190. Pazzi A, Galli L, et al. The relationship between outcome of progressive multifocal leukoencephalopathy and type and response to ART in previously HAART-untreated patients. 14th Conference on Retroviruses and Opportunistic Infections. Los Angeles, CA, 2007.
1191. Hall CD, U Dafni. Failure of cytarabine in progressive multifocal leukoencephalopathy associated with human immunodeficiency virus infection. N Engl J Med 1998;338:1345–51.
1192. Hou J, Major EO. The efficacy of nucleoside analogs against JC virus multiplication in a persistently infected human fetal brain cell line. J Neurovirol 1998;4:451–6.
1193. Gasnault J, Kousignian P, Kahraman M, et al. Cidofovir in AIDS-associated progressive multifocal leukoencephalopathy: a monocenter observational study with clinical and JC virus load monitoring. J Neurovirol 2001;7:375–81.
1194. De Luca A, Pezzotti P. Meta-analysis of cidofovir in AIDS-related progressive multifocal leukoencephalopathy on HAART: survival and neurological outcome. 12th Conference on Retroviruses and Opportunistic Infections. Boston, MA, 2005.
1195. Huang SS, Skolasky RL, Dal Pan GJ, Royal WR, McArthur JC. Survival prolongation in HIV-associated progressive multifocal leukoencephalopathy treated with alpha-interferon: an observational study. J Neurovirol 1998;4:324–32.
1196. Geschwind MD, Skolasky RI, Royal WS, McArthur JC. The relative contributions of HAART and alpha-interferon for therapy of progressive multifocal leukoencephalopathy in AIDS. J Neurovirol 2001;7:353–7.
1197. Nath A, Venkataramana A, Reich DS, Cortese I, Major EO. Progression of progressive multifocal leukoencephalopathy despite treatment with beta-interferon. Neurology 2006;66:149–50.
1198. Przepiorka D, Jaeckle KA, Birdwell RR, et al. Successful treatment of progressive multifocal leukoencephalopathy with low-dose interleukin-2. Bone Marrow Transplant 1997;20:983–7.
1199. Buckanovich RJ, Liu G, Stricker C, et al. Nonmyeloablative allogeneic stem cell transplantation for refractory Hodgkin's lymphoma complicated by interleukin-2 responsive progressive multifocal leukoencephalopathy. Ann Hematol 2002;81:410–3.
1200. Kunschner L, Scott TF. Sustained recovery of progressive multifocal leukoencephalopathy after treatment with IL-2. Neurology 2005;65:1510.
1201. Kerr DA, Chang CF, Gordon J, Bjornsti MA, Khalili K. Inhibition of human neurotropic virus (JCV) DNA replication in glial cells by camptothecin. Virology 1993; 196:612–8.
1202. Royal W, 3rd, Dupont B, McGuire D, et al. Topotecan in the treatment of acquired immunodeficiency syndrome-related progressive multifocal leukoencephalopathy. J Neurovirol 2003;9:411–9.
1203. Elphick GF, Querbes W, Jordan JA, et al. The human polyomavirus, JCV, uses serotonin receptors to infect cells. Science 2004;306:1380–3.
1204. Altschuler EL, Kast RE. The atypical antipsychotic agents ziprasidone, risperdone and olanzapine as treatment for and prophylaxis against progressive multifocal leukoencephalopathy. Med Hypotheses 2005;65:585–6.

1205. Santagata S, Kinney HC. Mechanism of JCV entry into oligodendrocytes. Science 2005;309:381–2.
1206. Lima MA, Auriel E, Wüthrich C, Borenstein NM, Koralnik IJ. Progressive multifocal leukoencephalopathy as a complication of hepatitis C virus treatment in an HIV-negative patient. Clin Infect Dis 2005;41:417–9.
1207. Focosi D, Fazzi R, Montanaro D, Emdin M, Petrini M. Progressive multifocal leukoencephalopathy in a haploidentical stem cell transplant recipient: a clinical, neuroradiological and virological response after treatment with risperidone. Antiviral Res 2007;74:156–8.
1208. Vulliemoz S, Lurati-Ruiz F, Borruat FX, et al. Favourable outcome of progressive multifocal leucoencephalopathy in two patients with dermatomyositis. J Neurol Neurosurg Psychiatry 2006;77:1079–82.
1209. Du Pasquier R, Kuroda M, Zheng Y, et al. A prospective study demonstrates an association between JC virus-specific cytotoxic T lymphocytes and the early control of progressive multifocal leukoencephalopathy. Brain 2004;127:1970–8.
1210. Vendrely A, Bienvenu B, Gasnault J, et al. Fulminant inflammatory leukoencephalopathy associated with HAART-induced immune restoration in AIDS-related progressive multifocal leukoencephalopathy. Acta Neuropathol 2005;109:449–55.
1211. Chandramohan D, Greenwood BM. Is there an interaction between human immunodeficiency virus and *Plasmodium falciparum*? Int J Epidemiol 1998;27:296–301.
1212. Nguyen-Dinh P, Greenberg AE, Mann JM, et al. Absence of association between *Plasmodium falciparum* malaria and human immunodeficiency virus infection in children in Kinshasa, Zaire. Bull World Health Organ 1986;65:607–13.
1213. Slutsker L, Marston BJ. HIV and malaria: interactions and implications. Curr Opin Infect Dis 2007;20:3–10.
1214. Mungai M, Tegtmeier G, Chamberland M, Parise M. Transfusion-transmitted malaria in the United States from 1963 through 1999. N Engl J Med 2001;344:1973–8.
1215. Austin SC, Stolley PD, Lasky T. The history of malariotherapy for neurosyphilis: Modern parallels. JAMA 1992;268:516–9.
1216. CDC. Update: self-induced malaria associated with malariotherapy for Lyme disease—Texas. MMWR 1991;40:665–6.
1217. World Health Organization. World Malaria Report, 2005. Geneva: World Health Organization and UNICEF; 2005.
1218. Snow RW, Craig M, Deichmann U, Marsh K. Estimating mortality, morbidity and disability due to malaria among Africa's non-pregnant population. Bull World Health Organ 1999;77:624–40.
1219. World Health Organziation. World malaria situation in 1994: part I—Population at risk. Wkly Epidemiol Rec 1997;72:269–74.
1220. Snow RW, Marsh K. The consequences of reducing transmission of *Plasmodium falciparum* in Africa. Adv Parasitol 2002:52:235–64.
1221. Whitworth J, Morgan D, Quigley M, et al. Effect of HIV-1 and increasing immunosuppression on malaria parasitaemia and clinical episodes in adults in rural Uganda: a cohort study. Lancet 2000;356:1051–6.
1222. Patnaik P, Jere CS, Miller WC, et al. Effects of HIV-1 serostatus, HIV-1 RNA concentration, and CD4 cell count on the incidence of malaria infection in a cohort of adults in rural Malawi. J Infect Dis 2005;192:984–91.
1223. Laufer MK, van Oosterhout JJ, Thesing PC, et al. Impact of HIV-associated immunosuppression on malaria infection and disease in Malawi. J Infect Dis 2006;193:872–8.
1224. Cohen C, Karstaedt A, Frean J, et al. Increased prevalence of severe malaria in HIV-infected adults in South Africa. Clin Infect Dis 2005;41:1631–7.
1225. Grimwade K, French N, Mbatha DD, et al. HIV infection as a cofactor for severe *falciparum* malaria in adults living in a region of unstable malaria transmission in South Africa. AIDS 2004;18:547–54.
1226. Greenberg AE, Nsa W, Ryder RW, et al. *Plasmodium falciparum* malaria and perinatally acquired human immunodeficiency virus type 1 infection in Kinshasa, Zaire: a prospective, longitudinal cohort study of 587 children. N Engl J Med 1991;325:105–9.
1227. Kalyesubula I, Musoke-Mudido P, Marum L, et al. Effects of malaria infection in human immunodeficiency virus type 1-infected Ugandan children. Pediatr Infect Dis J 1997;16:876–81.
1228. Mermin J, Lule J, Ekwaru JP, et al. Effect of co-trimoxazole prophylaxis on morbidity, mortality, CD4-cell count, and viral load in HIV infection in rural Uganda. Lancet 2004;364:1428–34.
1229. van Eijk AM, Ayisi JG, Ter Kuile FO, et al. Malaria and human immunodeficiency virus infection as risk factors for anemia in infants in Kisumu, western Kenya. Am J Trop Med Hyg 2002;67:44–53.
1230. Grimwade K, French N, Mbatha DD, et al. Childhood malaria in a region of unstable transmission and high human immunodeficiency virus prevalence. Pediatr Infect Dis J 2003;22:1057–63.
1231. Shah SN, Smith EE, Obonyo CO, et al. HIV immunosuppression and antimalarial efficacy: sulfadoxine-pyrimethamine for treatment of uncomplicated malaria in HIV-infected adults in Siaya, Kenya. J Infect Dis 2006;194:1519–28.
1232. Van Geertruyden JP, Mulenga M, Mwananyanda L, et al. HIV-1 immune suppression and antimalarial treatment outcome in Zambian adults with uncomplicated malaria. J Infect Dis 2006;194:917–25.
1233. ter Kuile FO, ME P, FH V, et al. The burden of co-infection with human immunodeficiency virus type 1 and malaria in pregnant women in sub-saharan Africa. Am J Trop Med Hyg 2004;71(Suppl 2):41-54.
1234. Tkachuk AN, Moormann AM, Poore JA, et al. Malaria enhances expression of CC chemokine receptor 5 on placental macrophages. J Infect Dis 2001;183:967–72.
1235. Mwapasa V, Rogerson SJ, Molyneux ME, et al. The effect of *Plasmodium falciparum* malaria on peripheral and placental HIV-1 RNA concentrations in pregnant Malawian women. AIDS 2004;18:1051–9.
1236. Brahmbhatt H, Kigozi G, Wabwire-Mangen F, et al. The effects of placental malaria on mother-to-child HIV transmission in Rakai, Uganda. AIDS 2003;17:2539–41.
1237. Inion I, Mwanyumba F, Gaillard P, et al. Placental malaria and perinatal transmission of human immunodeficiency virus type 1. J Infect Dis 2003;188:1675–8.
1238. Ayisi JG, van Eijk AM, Newman RD, et al. Maternal malaria and perinatal HIV transmission, Western Kenya. Emerg Infect Dis 2004;10:643–52.
1239. Greenberg AE, Nguyen-Dinh P, Mann JM, et al. The association between malaria, blood transfusions, and HIV seropositivity in a pediatric population in Kinshasa, Zaire. JAMA 1988;259:545–9.
1240. Moore A, Herrera G, Nyamongo J, et al. Estimated risk of HIV transmission by blood transfusion in Kenya. Lancet 2001;358:657–60.
1241. Heyns Adu P, Benjamin RJ, Swanevelder JP, et al. Prevalence of HIV-1 in blood donations following implementation of a structured blood safety policy in South Africa. JAMA 2006;295:519–26.
1242. Matteelli A, Casalini C, Bussi G, et al. Imported malaria in an HIV-positive traveler: a case report with a fatal outcome. J Travel Med 2005;12:222–4.

1243. World Health Organization. Severe and complicated malaria. Trans R Soc Trop Med Hyg 1990;84(Suppl 2):1-65.
1244. Greenberg AE, Ntumbanzondo M, Ntula N, Mawa L, Howell J. Hospital-based surveillance of malaria-related paediatric morbidity and mortality in Kinshasa, Zaire. Bull World Health Organ 1989;67:189–96.
1245. Molyneux ME, Taylor TE, Wirima JJ, Borgstein A. Clinical features and prognostic indicators in paediatric cerebral malaria: a study of 131 comatose Malawian children. Q J Med 1989;71:441–59.
1246. English M, Sauerwein R, Waruiru C, et al. Acidosis in severe childhood malaria. Q J Med 1997;90:263–70.
1247. Marsh K, Forster D, Waruiru C, et al. Indicators of life-threatening malaria in African children. N Engl J Med 1995;332:1399–404.
1248. Zingman BS, Viner BL. Splenic complications in malaria: case report and review. Clin Infect Dis 1993;16):223-32.
1249. Hamel MJ, Greene C, Chiller T, et al. A prospective study of daily cotrimoxazole prophylaxis in Kenyan HIV-Infected Adults and the development of antimicrobial resistance. Am J Trop Med 2004;71:268.
1250. Mermin J, Ekwaru JP, Liechty CA, et al. Effect of co–trimoxazole prophylaxis, antiretroviral therapy, and insecticide-treated bednets on the frequency of malaria in HIV-1-infected adults in Uganda: a prospective cohort study. Lancet 2006;367:1256–61.
1251. Griffith KS, Lewis LS, Mali S, Parise ME. Treatment of malaria in the United States: a systematic review. JAMA 2007;297:2264–77.
1252. Khoo S, Back D, Winstanley P. The potential for interactions between antimalarial and antiretroviral drugs. AIDS 2005;19:995–1005.
1253. CDC. Treating opportunistic infections among HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association/Infectious Diseases Society of America. MMWR 2004;53(No. RR-15).
1254. Parikh S, Gut J, Istvan E, et al. Antimalarial activity of human immunodeficiency virus type 1 protease inhibitors. Antimicrob Agents Chemother 2005;49:2983–5.
1255. Desai M, ter Kuile FO, Nosten F, et al. Epidemiology and burden of malaria in pregnancy. Lancet Infect Dis 2007;7:93–104.
1256. McGready R, Thwai KL, Cho T, et al. The effects of quinine and chloroquine antimalarial treatments in the first trimester of pregnancy. Trans Royal Soc Trop Med Hyg 2002;96:180–4.
1257. Supparatpinyo K, Khamwan C, Baosoung V, Nelson KE, Sirisanthana T. Disseminated *Penicillium marneffei* infection in Southeast Asia. Lancet 1994;344:110–3.
1258. Clezy K, Sirisanthana T, Sirisanthana V, Brew B, Cooper DA. Late manifestations of HIV in Asia and the Pacific. AIDS 1994;8(Suppl 2):35-43.
1259. Kantipong P, Panich V, Pongsurachet V, Watt G. Hepatic penicilliosis in patients without skin lesions. Clin Infect Dis 1998;26:1215–7.
1260. Singh PN, Ranjana K, Singh YI, et al. Indigenous disseminated *Penicillium marneffei* infection in the state of Manipur, India: report of four autochthonous cases. J Clin Microbiol 1999;37:2699–702.
1261. Ranjana KH, Priyokumar K, Singh TJ, et al. Disseminated *Penicillium marneffei* infection among HIV-infected patients in Manipur state, India. J Infect Dis 2002;45:268–71.
1262. Chariyalertsak S, Sirisanthana T, Saengwonloey O, Nelson KE. Clinical presentation and risk behaviors of patients with acquired immunodeficiency syndrome in Thailand, 1994–1998: regional variation and temporal trends. Clin Infect Dis 2001;32:955–62.
1263. Chariyalertsak S, Supparatpinyo K, Sirisanthana T, Nelson KE. A controlled trial of itraconazole as primary prophylaxis for systemic fungal infections in patients with advanced human immunodeficiency virus infection in Thailand. Clin Infect Dis 2002;34:277–84.
1264. Supparatpinyo K, Nelson KE, Merz WG, et al. Response to antifungal therapy by human immunodeficiency virus-infected patients with disseminated *Penicillium marneffei* infections and in vitro susceptibilities of isolates from clinical specimens. Antimicrob Agents Chemother 1993;37:2407–11.
1265. Supparatpinyo K, Sirisanthana T. Disseminated *Penicillium marneffei* infection diagnosed on examination of a peripheral blood smear of a patient with human immunodeficiency virus infection. Clin Infect Dis 1994;18:246–7.
1266. Sirisanthana T, Supparatpinyo K, Perriens J, Nelson KE. Amphotericin B and itraconazole for treatment of disseminated *Penicillium marneffei* infection in human immunodeficiency virus-infected patients. Clin Infect Dis 1998;26:1107–10.
1267. Supparatpinyo K, Chiewchanvit S, Hirunsri P, et al. An efficacy study of itraconazole in the treatment of *Penicillium marneffei* infection. J Med Assoc Thai 1992;75:688–91.
1268. Manosuthi W, Chaovavanich A, Tansuphaswadikul S, et al. Incidence and risk factors of major opportunistic infections after initiation of antiretroviral therapy among advanced HIV-infected patients in a resource-limited setting. J Infect 2007;55:464–9.
1269. Gupta S, Mathur P, Maskey D, Wig N, Singh S. Immune Restoration Syndrome with disseminated *Penicillium marneffei* and Cytomegalovirus co-infections in an AIDS patient. AIDS Res Ther 2007;4:21.
1270. Supparatpinyo K, Schlamm HT. Voriconazole as therapy for systemic *Penicillium marneffei* infections in AIDS patients. Am J Trop Med Hyg 2007;77:350–3.
1271. Supparatpinyo K, Perriens J, Nelson KE, Sirisanthana T. A controlled trial of itraconazole to prevent relapse of *Penicillium marneffei* infection in patients infected with the human immunodeficiency virus. N Engl J Med 1998;339:1739–43.
1272. Chaiwarith R, Charoenyos N, Sirisanthana T, Supparatpinyo K. Discontinuation of secondary prophylaxis against penicilliosis marneffei in AIDS patients after HAART. AIDS 2007;21:365–7.
1273. Desjeux P. Leishmaniasis: current situation and new perspectives. Comp Immunol Microbiol Infect Dis 2004;27(5): 305-18.
1274. Jeronimo SMB, de Queiroz Sousa A, Pearson RD. Leishmaniasis. In: Guerrant RL, Walker DH, Weller PF, eds. Tropical infectious diseases: principles, pathogens, and practice. Edinburgh, Scotland: Churchill Livingstone Elsevier;2006:1095-1113.
1275. World Health Organization. Leishmaniasis and HIV co-infection. Available at: http://www.who.int/leishmaniasis/burden/hiv_coinfection/burden_hiv_coinfection/en/index.html. Last accessed December 22, 2008.
1276. Rosenthal E, Marty E, del Guidice P, et al. HIV and *Leishmania* coinfection: a review of 91 cases with focus on atypical locations of *Leishmania*. Clin Infect Dis 2000;31(4):1093-5.
1277. Tortajada C, Perez-Cuevas B, Asuncion M, et al. Highly active antiretroviral therapy (HAART) modifies the incidence and outcome of visceral leishmaniasis in HIV-infected patients. J Acquir Immune Defic Syndr 2002;30(3):364-6.
1278. Mathur P, Samantaray JC, Vajpayee M, et al. Visceral leishmaniasis/human immunodeficiency virus co-infection in India: the focus of two epidemics. J Med Microbiol 2006;55(Pt 7:919-22.
1279. Wolday D, Berhe N, Akuffo H, Desjeux P, Britton S. Emerging *Leishmania*/HIV co-infection in Africa. Med Microbiol Immunol 2001;190(1-2):65-7.

1280. Marty P, Le Fichoux Y, Giordana D, Brugnetti A. Leishmanin reaction in the human population of a highly endemic focus of canine leishmaniasis in Alpes-Maritimes, France. Trans R Soc Trop Med Hyg 1992;86(3):249-50.
1281. Moral L, Rubio EM, Moya M. A leishmanin skin test survey in the human population of l'Alacanti region (Spain): implications for the epidemiology of *Leishmania infantum* infection in southern Europe. Trans R Soc Trop Med Hyg 2002; 96(2):129-32.
1282. Werneck GL, Rodrigues L, Santos MV, Arujo IB, Moura L. The burden of *Leishmania chagasi* infection during an urban outbreak of visceral leishmaniasis in Brazil. Acta Trop 2002;83(1):13-8.
1283. Lopez-Velez R, Perez-Molina JA, Guerrero A. Clinicoepidemiologic characteristics, prognostic factors, and survival analysis of patients coinfected with human immunodeficiency virus and *Leishmania* in an area of Madrid, Spain. Am J Trop Med Hyg 1998;58(4):436-43.
1284. Alvar J, Jimenez M. Could infected drug-users be potential *Leishmania infantum* reservoirs? AIDS 1994;8(6):854.
1285. Chicharro C, Morales J, Serra T, Ares M, Salas A. Molecular epidemiology of *Leishmania infantum* on the island of Majorca: a comparison of phenotypic and genotypic tools. Trans R Soc Trop Med Hyg 2002;96 Suppl 1:S93-9.
1286. Cruz I, Morales M, Noguer I, Rodriguez A, Alvar J. *Leishmania* in discarded syringes from intravenous drug users. Lancet 2002;359(9312):1124-5.
1287. Alvar, J, Canavate C, Gutierrez-Solar B, Jimenez M. *Leishmania* and human immunodeficiency virus coinfection: the first 10 years. Clin Microbiol Rev 1997;10(2):298-319.
1288. Rabello A, Orsini M, Disch J. *Leishmania*/HIV co-infection in Brazil: an appraisal. Ann Trop Med Parasitol 2003;97 Suppl 1: 17-28.
1289. Pintado V, Martin-Rabadan P, Rivera ML, Moreno S, Bouza E. Visceral leishmaniasis in human immunodeficiency virus (HIV)-infected and non-HIV-infected patients. A comparative study. Medicine 2001;80(1):54-73.
1290. Mota SM, Matsumo CM, Schmitz FML, Machado MP. Cutaneous leishmaniasis coinfection in AIDS patients: case report and literature review. Braz J Infect Dis 1997;1(3):142-4.
1291. Gonzalez-Beato MJ, Moyano B, Sanchez C, et al. Kaposi's sarcoma-like lesions and other nodules as cutaneous involvement in AIDS-related visceral leishmaniasis. Br J Dermatol 2000;143(6):1316-8.
1292. Albrecht H, Stellbrink J, Gross G, et al. Treatment of atypical leishmaniasis with interferon gamma resulting in progression of Kaposi's sarcoma in an AIDS patient. Clin Investig 1994;72(12):1041-7.
1293. Bosch RJ, Rodrigo AB, Sanchez P, de Galvez MV, Herrera E. Presence of *Leishmania* organisms in specific and non-specific skin lesions in HIV-infected individuals with visceral leishmaniasis. Int J Dermatol 2002;41(10):670-5.
1294. Canovas DL, Carbonell J, Torres J, Altez J, Buades J. Laryngeal leishmaniasis as initial opportunistic disease in HIV infection. J Laryngol Otol 1994;108(12):1089-92.
1295. Miralles ES, Nunez M, Hibray Y Harto A, Moreno R, Ledo A. Mucocutaneous leishmaniasis and HIV. Dermatology 1994;(189(3): 275-7.
1296. Cruz I, Canavate C, Rubio J, Morales M, Chicharro C. A nested polymerase chain reaction (Ln-PCR) for diagnosing and monitoring *Leishmania infantum* infection in patients co-infected with human immunodeficiency virus. Trans R Soc Trop Med Hyg 2002;96 Suppl 1:S185-9.
1297. Sundar S, Rai M. Laboratory diagnosis of visceral leishmaniasis. Clin Diagn Lab Immunol 2002;9(5):951-8.
1298. Medrano FJ, Canavate C, Leal J, Rey C, Lissen E, Alvar J. The role of serology in the diagnosis and prognosis of visceral leishmaniasis in patients coinfected with human immunodeficiency virus type-1. Am J Trop Med Hyg 1998;59(1): 155-62.
1299. Houghton RL, Petrescu M, Benson DR, et al. A cloned antigen (recombinant K39) of *Leishmania chagasi* diagnostic for visceral leishmaniasis in human immunodeficiency virus type 1 patients and a prognostic indicator for monitoring patients undergoing drug therapy. J Infect Dis 1998;177(5):1339-44.
1300. Bern C, Adler-Moore J, Berenguer J, et al. Liposomal amphotericin B for the treatment of visceral leishmaniasis. Clin Infect Dis 2006;43(7):917-24.
1301. Meyerhoff A. U.S. Food and Drug Administration approval of AmBisome (liposomal amphotericin B) for treatment of visceral leishmaniasis. Clin Infect Dis 1999;28(1):42-51.
1302. Herwaldt BL, Berman JD. Recommendations for treating leishmaniasis with sodium stibogluconate (Pentostam) and review of pertinent clinical studies. Am J Trop Med Hyg 1992; 46(3):296-306.
1303. Davidson RN, Martino L, Gradoni L, Giacchino R, Russo R. Liposomal amphotericin B (AmBisome) in Mediterranean visceral leishmaniasis: a multi-centre trial. Q J Med 1994;87(2):75-81.
1304. Laguna F, Lopez-Velez R, Pulido F, et al. Treatment of visceral leishmaniasis in HIV-infected patients: a randomized trial comparing meglumine antimoniate with amphotericin B. Spanish HIV-Leishmania Study Group. Aids 1999;13(9):1063-9.
1305. Laguna F, Videla S, Jimenez-Mejias ME, et al. Amphotericin B lipid complex versus meglumine antimoniate in the treatment of visceral leishmaniasis in patients infected with HIV: a randomized pilot study. J Antimicrob Chemother 2003;52(3): 464-8.
1306. Russo R, Nigro LC, Minniti S, et al. Visceral leishmaniasis in HIV infected patients: treatment with high dose liposomal amphotericin B (AmBisome). J Infect 1996;32(2):133-7.
1307. Lazanas MC, Tsekes S, Papandreu S, Harhalakis N, Nikiforakis F. Liposomal amphotericin B for leishmaniasis treatment of AIDS patients unresponsive to antimonium compounds. Aids 1993; 7(7):1018-9.
1308. Sundar S, Mehta H, Suresh AV, Singh SP, Rai M, Murray HW. Amphotericin B treatment for Indian visceral leishmaniasis: conventional versus lipid formulations. Clin Infect Dis 2004; 38(3):377-83.
1309. Torre-Cisneros J, Vaillaneuva J, Kindelan J, Jurado R, Sanchez-Guijo P. Successful treatment of antimony-resistant visceral leishmaniasis with liposomal amphotericin B in patients infected with human immunodeficiency virus. Clin Infect Dis 1993;17(4):625-7.
1310. Alvar J, Croft S, Olliaro P. Chemotherapy in the treatment and control of leishmaniasis. Adv Parasitol 2006;61:223-74.
1311. Laguna F, Torre-Cisner J, Moreno, V, Villaneuva J, Valencia E. Efficacy of intermittent liposomal amphotericin B in the treatment of visceral leishmaniasis in patients infected with human immunodeficiency virus. Clin Infect Dis 1995;21(3):711-2.
1312. Barat C, Zhao C, Ouellette M, Tremblay MJ. HIV-1 replication is stimulated by sodium stibogluconate, the therapeutic mainstay in the treatment of leishmaniasis. J Infect Dis 2007; 195(2):236-45.
1313. Reithinger R, Mohsen J, Wahid M, et al. Efficacy of thermotherapy to treat cutaneous leishmaniasis caused by *Leishmania tropica* in Kabul, Afghanistan: a randomized, controlled trial. Clin Infect Dis 2005;40(8):1148-55.
1314. Soto J, Arana BA, Toledo J, et al. Miltefosine for new world cutaneous leishmaniasis. Clin Infect Dis 2004;38(9):1266-72.

1315. Sundar S, Jha TK, Thakur CP, Bhattacharya SM, Rai M. Oral miltefosine for the treatment of Indian visceral leishmaniasis. Trans R Soc Trop Med Hyg 2006.
1316. Sindermann H, Engel KR, Fischer C, Bommer W. Oral miltefosine for leishmaniasis in immunocompromised patients: compassionate use in 39 patients with HIV infection. Clin Infect Dis 2004; 39(10):1520-3.
1317. Ritmeijer K, Dejenie A, Assefa Y, et al. A comparison of miltefosine and sodium stibogluconate for treatment of visceral leishmaniasis in an Ethiopian population with high prevalence of HIV infection. Clin Infect Dis 2006;43(3):357-64.
1318. de la Rosa R, Pineda J, Delgado J, et al. Influence of highly active antiretroviral therapy on the outcome of subclinical visceral leishmaniasis in human immunodeficiency virus-infected patients. Clin Infect Dis 2001;32(4):633-5.
1319. Badaro R, Johnson, WD Jr. The role of interferon-gamma in the treatment of visceral and diffuse cutaneous leishmaniasis. J Infect Dis 1993;167 Suppl 1:S13-7.
1320. Badaro R, Nascimento C, Carvalho JS, et al. Granulocyte-macrophage colony-stimulating factor in combination with pentavalent antimony for the treatment of visceral leishmaniasis. Eur J Clin Microbiol Infect Dis 1994;13 Suppl 2:S23-8.
1321. Delgado J, Macias J, Pineda JA, et al. High frequency of serious side effects from meglumine antimoniate given without an upper limit dose for the treatment of visceral leishmaniasis in human immunodeficiency virus type-1-infected patients. Am J Trop Med Hyg 1999;61(5):766-9.
1322. Berry A, Abraham B, Dereure J, Pinzani V, Bastien P. Two case reports of symptomatic visceral leishmaniasis in AIDS patients concomitant with immune reconstitution due to antiretroviral therapy. Scand J Infect Dis 2004;36(3):225-7.
1323. Posada-Vergara MP, Lindoso JAL, Tolezano JE, Pereira-Chioccola VL, Silva MV, Goto H. Tegumentary leishmaniasis as a manifestation of immune reconstitution inflammatory syndrome in 2 patients with AIDS. J Infect Dis 2005;192(10):1819-22.
1324. Murray HW, Ocani J, Granger AM, Schreiber RD. Requirement for T cells and effect of lymphokines in successful chemotherapy for an intracellular infection. Experimental visceral leishmaniasis. J Clin Invest 1989;83(4):1253-7.
1325. Ribera E, Ocana I, de Otero J, Cortes E, Gasser I, Pahlissa A. Prophylaxis of visceral leishmaniasis in human immunodeficiency virus-infected patients. Am J Med 1996;100(5):496-501.
1326. Lopez-Velez R, Videla S, Marquez M, et al. Amphotericin B lipid complex versus no treatment in the secondary prophylaxis of visceral leishmaniasis in HIV-infected patients. J Antimicrob Chemother 2004;53(3):540-3.
1327. Berenguer J, Cosin J, Miralles P, Padilla B. Discontinuation of secondary anti-leishmania prophylaxis in HIV-infected patients who have responded to highly active antiretroviral therapy. Aids 2000;14(18):2946-8.
1328. Casado JL, Lopez-Velez R, Pintado V, Quereda C, Antela A, Moreno, S. Relapsing visceral leishmaniasis in HIV-infected patients undergoing successful protease inhibitor therapy. Eur J Clin Microbiol Infect Dis 2001;20(3):202-5.
1329. Mira JA, Corzo JE, Rivero A, et al. Frequency of visceral leishmaniasis relapses in human immunodeficiency virus-infected patients receiving highly active antiretroviral therapy. Am J Trop Med Hyg 2004;70(3):298-301.
1330. James LF, Lazar VA, Binns W. Effects of sublethal doses of certain minerals on pregnant ewes and fetal development. Am J Vet Res 1966;27(116):132-5.
1331. Ridgway LP, Karnofsky DA. The effects of metals on the chick embryo: toxicity and production of abnormalities in development. Ann N Y Acad Sci 1952;55:203-15.
1332. Rossi F, Acampora R, Vacca C, et al. Prenatal and postnatal antimony exposure in rats: effect on vasomotor reactivity development of pups. Teratog Carcinog Mutagen 1987;7(5):491-6.
1333. Gradoni L, Gaeta GB, Pellizzer G, Maisto A, Scalone A. Mediterranean visceral leishmaniasis in pregnancy. Scand J Infect Dis 1994;26(5):627-9.
1334. Utili R, Rambaldi A, Tripodi MF, Andreana A. Visceral leishmaniasis during pregnancy treated with meglumine antimoniate. Infection 1995;23(3):182-3.
1335. Pagliano P, Corannante N, Rossi, et al. Visceral leishmaniasis in pregnancy: a case series and a systematic review of the literature. J Antimicrob Chemother 2005;55(2):229-33.
1336. Meinecke CK, Schottelius J, Oskam L, Fleischer B. Congenital transmission of visceral leishmaniasis (Kala Azar) from an asymptomatic mother to her child. Pediatrics 1999;104(5):e65.
1337. Kirchhoff, L.V. American Trypanosomiasis (Chagas' disease). In: Guerrant RL, Walker DH, Weller PF (eds). Tropical Infectious Diseases: Principles, Pathogens, & Practice. 2nd ed. Philadelphia: Elsevier;2006:1082-94.
1338. Schmunis GA, Cruz JR. Safety of the blood supply in Latin America. Clin Microbiol Rev 2005;18(1):12-29.
1339. CDC. Chagas disease after organ transplantation—Los Angeles, California. MMWR 2006;55(29):798-800.
1340. Herwaldt BL. Protozoa and helminths. In Fleming DO, Hunt DL (eds.). Biological Safety: Principles and Practices. 4th ed. Washington, DC: American Society for Microbiology. 2006;115-61.
1341. Pan American Health Organization, Quantitative estimation of Chagas disease in the Americas. OPS/HDM/CD/425-06:6. 2005. For regional updates see www.paho.org/English/AD/DPC/CD/chagas.htm, last accessed December 22, 2008.
1342. CDC. Initiation of blood donor screening for Chagas disease 2006-2007. MMWR 2007;56:141-3.
1343. Cahn P, Belloso W, Murillo J, Prada-Trujillo G. AIDS in Latin America. Infect Dis Clin North Am 2000;14(1):185-209.
1344. Rocha A, de Meneses ACO, De Meneses O, et al. Pathology of patients with Chagas' disease and acquired immunodeficiency syndrome. Am J Trop Med Hyg 1994;50(3):261-8.
1345. Sartori AM, Ibrahim KY, Nunes Westphalen EV, et al. Manifestations of Chagas disease (American trypanosomiasis) in patients with HIV/AIDS. Ann Trop Med Parasitol 2007; 101(1):31-50.
1346. Vaidian AK, Weiss, LM, Tanowitz HB. Chagas' disease and AIDS. Kinetoplastid Biol Dis 2004;3(1):2.
1347. Sartori AMC, Neto JE, Nunes EV, et al. *Trypanosoma cruzi* parasitemia in chronic Chagas disease: comparison between human immunodeficiency virus (HIV)-positive and HIV-negative patients. J Infect Dis 2002;186(6): 872-5.
1348. Strout RG. A method for concentrating hemoflagellates. J Parasitol 1962; 48:100.
1349. AABB Chagas' Biovigilance Network, http://www.aabb.org/Content/Programs_and_Services/Data_Center/Chagas. Last accessed December 22, 2008.
1350. WHO, Control of Chagas Disease, Brasilia, Brazil. World Health Organization. WHO Technical Report Series 905, 2002.
1351. Freilij H, Altcheh J, Muchinik G. Perinatal human immunodeficiency virus infection and congenital Chagas' disease. Pediatr Infect Dis J 1995;14(2):161-2.

1352. Bern, C, Montgomery SP, Herwaldt BL, et al. Evaluation and treatment of Chagas disease in the United States: a systematic review. JAMA 2007;298(18):2171-81.
1353. Technical Report. Recommendations for diagnosis, treatment and follow-up of the *Trypanosoma cruzi*: human immunodeficiency virus co-infection. Rev Soc Bras Med Trop 2006;39(4):392-415.
1354. Castro JA, de Mecca MM, Bartel LC. Toxic side effects of drugs used to treat Chagas' disease (American trypanosomiasis). Hum Exp Toxicol 2006;25(8): 471-9.
1355. Di Pentima M, Hwang LY, Skeeter CM, Edwards MS. Prevalence of antibody to *Trypanosoma cruzi* in pregnant Hispanic women in Houston. Clin Infect Dis 1999;28(6):1281-5.
1356. Bittencourt AL. Possible risk factors for vertical transmission of Chagas' disease. Rev Inst Med Trop Sao Paulo 1992;34(5):403-8.
1357. Freilij H, Altcheh J. Congenital Chagas' disease: diagnostic and clinical aspects. Clin Infect Dis 1995;21(3):551-5.
1358. Gorla NB, Ledesma OS, Barbieri GP, Larriba IB .Assessment of cytogenetic damage in chagasic children treated with benznidazole. Mutat Res 1988;206(2):217-20.
1359. Gorla NB, Ledesma OS Barbieri GP, Larriba IB. Thirteenfold increase of chromosomal aberrations non-randomly distributed in chagasic children treated with nifurtimox. Mutat Res 1989;224(2):263-7.
1360. de Toranzo EG, Masana M, Castro JA. Administration of benznidazole, a chemotherapeutic agent against Chagas disease, to pregnant rats. Covalent binding of reactive metabolites to fetal and maternal proteins. Arch Int Pharmacodyn Ther 1984;272(1):17-23.
1361. Lindsay DS, Dubey JP, Blagburn BL. Biology of *Isospora* spp. from humans, nonhuman primates, and domestic animals. Clin Microbiol Rev 1997;10:19-34.
1362. Guiguet M, Furco A, Tattevin P, Costagliola D, Molina JM. HIV-associated *Isospora belli* infection: incidence and risk factors in the French Hospital Database on HIV. HIV Med 2007;8:124-30.
1363. Sorvillo FJ, Lieb LE, Seidel J, et al. Epidemiology of isosporiasis among persons with acquired immunodeficiency syndrome in Los Angeles County. Am J Trop Med Hyg 1995;53:656-9.
1364. Certad G, Arenas-Pinto A, Pocaterra L, et al. Isosporiasis in Venezuelan adults infected with human immunodeficiency virus: clinical characterization. Am J Trop Med Hyg 2003;69:217-22.
1365. DeHovitz JA, Pape JW, Boncy M, Johnson WD, Jr. Clinical manifestations and therapy of *Isospora belli* infection in patients with the acquired immunodeficiency syndrome. N Engl J Med 1986;315:87-90.
1366. Pape JW, Verdier RI, Johnson WD, Jr. Treatment and prophylaxis of *Isospora belli* infection in patients with the acquired immunodeficiency syndrome. N Engl J Med 1989;320:1044-7.
1367. Forthal DN, Guest SS. *Isospora belli* enteritis in three homosexual men. Am J Trop Med Hyg 1984;33:1060-4.
1368. Modigliani R, Bories C, Le Charpentier Y, et al. Diarrhoea and malabsorption in acquired immune deficiency syndrome: a study of four cases with special emphasis on opportunistic protozoan infestations. Gut 1985;26:179-87.
1369. Whiteside ME, Barkin JS, May RG, et al. Enteric coccidiosis among patients with the acquired immunodeficiency syndrome. Am J Trop Med Hyg 1984;33:1065-72.
1370. Bialek R, Overkamp D, Rettig I, Knobloch J. Case report: nitazoxanide treatment failure in chronic isosporiasis. Am J Trop Med Hyg 2001;65:94-5.
1371. Benator DA, French AL, Beaudet LM, Levy CS, Orenstein JM. *Isospora belli* infection associated with acalculous cholecystitis in a patient with AIDS. Ann Intern Med 1994;121:663-4.
1372. Gonzalez-Dominguez J, Roldán R, Villanueva JL, et al. *Isospora belli* reactive arthritis in a patient with AIDS. Ann Rheum Dis 1994;53:618-9.
1373. Bialek R, Binder N, Dietz K, Knobloch J, Zelck UE. Comparison of autofluorescence and iodine staining for detection of *Isospora belli* in feces. Am J Trop Med Hyg 2002;67:304-5.
1374. Frenkel JK, Silva MB, Saldanha J, et al. *Isospora belli* infection: observation of unicellular cysts in mesenteric lymphoid tissues of a Brazilian patient with AIDS and animal inoculation. J Eukaryot Microbiol 2003;50:682-4.
1375. Restrepo C, Macher AM, Radany EH. Disseminated extraintestinal isosporiasis in a patient with acquired immune deficiency syndrome. Am J Clin Pathol 1987;87:536-42.
1376. Bernard E, Delgiudice P, Carles M, et al. Disseminated isosporiasis in an AIDS patient. Eur J Clin Microbiol Infect Dis 1997;16:699-701.
1377. Verdier RI, Fitzgerald DW, Johnson WD, Jr., Pape JW. Trimethoprim-sulfamethoxazole compared with ciprofloxacin for treatment and prophylaxis of *Isospora belli* and *Cyclospora cayetanensis* infection in HIV-infected patients: a randomized, controlled trial. Ann Intern Med 2000;132:885-8.
1378. Mojon M, Coudert J, de Landazuri EO. Serious isosporosis by *Isospora belli*: a case report treated by Fansidar [Abstract]. Southeast Asian J Trop Med Public Health 1981;12:449-50.
1379. Ebrahimzadeh A, Bottone EJ. Persistent diarrhea caused by *Isospora belli*: therapeutic response to pyrimethamine and sulfadiazine. Diagn Microbiol Infect Dis 1996;26:87-9.
1380. Trier JS, Moxey PC, Schimmel EM, et al. Chronic intestinal coccidiosis in man: intestinal morphology and response to treatment. Gastroenterology 1974;66:923-35.
1381. Weiss LM, Perlman DC, Sherman J, et al. *Isospora belli* infection: treatment with pyrimethamine. Ann Intern Med 1988;109:474-5.
1382. Jongwutiwes S, Sampatanukul P, Putaporntip C. Recurrent isosporiasis over a decade in an immunocompetent host successfully treated with pyrimethamine. Scand J Infect Dis 2002;34:859-62.
1383. Dionisio D, Sterrantino G, Meli M, et al. Treatment of isosporiasis with combined albendazole and ornidazole in patients with AIDS. AIDS 1996;10:1301-2.
1384. Zulu I, Veitch A, Sianongo S, et al. Albendazole chemotherapy for AIDS-related diarrhoea in Zambia–clinical, parasitological and mucosal responses. Aliment Pharmacol Ther 2002;16:595-601.
1385. Romero Cabello R, Guerrero LR, Muñoz Garcia MR, et al. Nitazoxanide for the treatment of intestinal protozoan and helminthic infections in Mexico. Trans R Soc Trop Med Hyg 1997;91:701-3.
1386. Doumbo O, Rossignol JF, Pichard E, et al. Nitazoxanide in the treatment of cryptosporidial diarrhea and other intestinal parasitic infections associated with acquired immunodeficiency syndrome in tropical Africa. Am J Trop Med Hyg 1997;56:637-9.
1387. Meyohas MC, Capella F, Poirot JL, et al. Treatment with doxycycline and nifuroxazide of *Isospora belli* infection in AIDS. Pathol Biol 1990;38:589-91.
1388. Gaska JA, Tietze KJ, Cosgrove EM. Unsuccessful treatment of enteritis due to *Isospora belli* with spiramycin: a case report. J Infect Dis 1985;152:1336-8.
1389. Musey KL, Chidiac C, Beaucaire G, et al. Effectiveness of roxithromycin for treating *Isospora belli* infection. J Infect Dis 1988;158:646.
1390. Limson-Pobre RN, Merrick S, Gruen D, et al. Use of diclazuril for the treatment of isosporiasis in patients with AIDS. Clin Infect Dis 1995;20:201-2.
1391. Kayembe K, Desmet P, Henry MC, et al. Diclazuril for *Isospora belli* infection in AIDS. Lancet 1989;1:1397-8.

TABLE 1. Prophylaxis to prevent first episode of opportunistic disease

Pathogen	Indication	First choice	Alternative
Pneumocystis pneumonia (PCP)	CD4+ count <200 cells/μL **(AI)** or oropharyngeal candidiasis **(AII)** CD4+ <14% or history of AIDS-defining illness **(BII)** CD4+ count >200 but <250 cells/μL if monitoring CD4+ count every 1–3 months is not possible **(BII)**	Trimethoprim-sulfamethoxazole (TMP-SMX), 1 DS PO daily **(AI)**; or 1 SS daily **(AI)**	• TMP-SMX 1 DS PO tiw **(BI)**; or • Dapsone 100 mg PO daily or 50 mg PO bid **(BI)**; or • Dapsone 50 mg PO daily + pyrimethamine 50 mg PO weekly + leucovorin 25 mg PO weekly **(BI)**; or • Aerosolized pentamidine 300 mg via Respigard II™ nebulizer every month **(BI)**; or • Atovaquone 1,500 mg PO daily **(BI)**; or • Atovaquone 1,500 mg + pyrimethamine 25 mg + leucovorin 10 mg PO daily **(CIII)**
Toxoplasma gondii encephalitis	Toxoplasma IgG positive patients with CD4+ count <100 cells/μL **(AII)** Seronegative patients receiving PCP prophylaxis not active against toxoplasmosis should have toxoplasma serology retested if CD4+ count decline to <100 cells/μL **(CIII)** Prophylaxis should be initiated if seroconversion occurred **(AII)**	TMP-SMX, 1 DS PO daily **(AII)**	• TMP-SMX 1 DS PO tiw **(BIII)**; or • TMP-SMX 1 SS PO daily **(BIII)**; • Dapsone 50 mg PO daily + pyrimethamine 50 mg PO weekly + leucovorin 25 mg PO weekly **(BI)**; or • (Dapsone 200 mg + pyrimethamine 75 mg + leucovorin 25 mg) PO weekly **(BI)**; • (Atovaquone 1,500 mg +/- pyrimethamine 25 mg + leucovorin 10 mg) PO daily **(CIII)**
Mycobacterium tuberculosis infection (TB) (Treatment of latent TB infection or LTBI)	(+) diagnostic test for LTBI, no evidence of active TB, and no prior history of treatment for active or latent TB **(AI)**; (-) diagnostic test for LTBI, but close contact with a person with infectious pulmonary TB and no evidence of active TB **(AII)**; A history of untreated or inadequately treated healed TB (i.e., old fibrotic lesions) regardless of diagnostic tests for LTBI and no evidence of active TB **(AII)**	Isoniazid (INH) 300 mg PO daily **(AII)** or 900 mg PO biw **(BII)** for 9 months – both plus pyridoxine 50 mg PO daily **(BIII)**; or For persons exposed to drug-resistant TB, selection of drugs after consultation with public health authorities **(AII)**	• Rifampin (RIF) 600 mg PO daily x 4 months **(BIII)**; or • Rifabutin (RFB) (dose adjusted based on concomitant ART) x 4 months **(BIII)**
Disseminated *Mycobacterium avium* complex (MAC) disease	CD4+ count <50 cells/μL – after ruling out active MAC infection **(AI)**	Azithromycin 1,200 mg PO once weekly **(AI)**; or Clarithromycin 500 mg PO bid **(AI)**; or Azithromycin 600 mg PO twice weekly **(BIII)**	• RFB 300 mg PO daily **(BI)** (dosage adjustment based on drug-drug interactions with ART); rule out active TB before starting RFB
Streptococcus pneumoniae infection	CD4+ count >200 cells/μL and no receipt of pneumococcal vaccine in the past 5 years **(AII)** CD4+ count <200 cells/μL – vaccination can be offered **(CIII)** In patients who received polysaccharide pneumococcal vaccination (PPV) when CD4+ count <200 cells/μL, but has increased to >200 cells/μL in response to ART **(CIII)**	23-valent PPV 0.5 mL IM x 1 **(BII)** Revaccination every 5 years may be considered **(CIII)**	
Influenza A and B virus infection	All HIV-infected patients **(AIII)**	Inactivated influenza vaccine 0.5 mL IM annually **(AIII)**	
Histoplasma capsulatum infection	CD4+ count ≤150 cells/μL and at high risk because of occupational exposure or live in a community with a hyperendemic rate of histoplasmosis (>10 cases/100 patient-years) **(CI)**	Itraconazole 200 mg PO daily (CI)	
Coccidioidomycosis	Positive IgM or IgG serologic test in a patient from a disease-endemic area; and CD4+ count <250 cells/μL **(CIII)**	Fluconazole 400 mg PO daily **(CIII)** Itraconazole 200 mg PO bid **(CIII)**	

TABLE 1. (*Continued*) Prophylaxis to prevent first episode of opportunistic disease

Pathogen	Indication	First choice	Alternative
Varicella-zoster virus (VZV) infection	Pre-exposure prevention: Patients with CD4+ count ≥200 cells/μL who have not been vaccinated, have no history of varicella or herpes zoster, or who are seronegative for VZV **(CIII)** Note: routine VZV serologic testing in HIV-infected adults is not recommended Post-exposure – close contact with a person who has active varicella or herpes zoster: For susceptible patients (those who have no history of vaccination or of either condition, or are known to be VZV seronegative) **(AIII)**	Pre-exposure prevention: Primary varicella vaccination (Varivax™), 2 doses (0.5 mL SQ) administered 3 months apart **(CIII)** If vaccination results in disease because of vaccine virus, treatment with acyclovir is recommended **(AIII)** Post-exposure therapy: Varicella-zoster immune globulin (VariZIG™) 125 IU per 10 kg (maximum of 625 IU) IM, administered within 96 hours after exposure to a person with active varicella or herpes zoster **(AIII)** Note: As of June 2007, VariZIG can be obtained only under a treatment IND (1-800-843-7477, FFF Enterprises)	• VZV-susceptible household contacts of susceptible HIV-infected persons should be vaccinated to prevent potential transmission of VZV to their HIV-infected contacts **(BIII)** Alternative post-exposure therapy: • Post exposure varicella vaccine (Varivax) 0.5 mL SQ x 2 doses, 3 months apart if CD4+ count >200 cells/μL **(CIII)**; or • Pre-emptive acyclovir 800 mg PO 5x/day for 5 days **(CIII)** • These two alternatives have not been studied in the HIV population
Human Papillomavirus (HPV) infection	Women aged 15–26 yrs **(CIII)**	HPV quadravalent vaccine 0.5 mL IM months 0, 2, and 6 **(CIII)**	
Hepatitis A virus (HAV) infection	HAV-susceptible patients with chronic liver disease, or who are injection-drug users, or men who have sex with men **(AII).** Certain specialists might delay vaccination until CD4+ count >200 cells/μL **(CIII)**	Hepatitis A vaccine 1 mL IM x 2 doses - at 0 & 6–12 months **(AII)** IgG antibody response should be assessed 1 month after vaccination; non-responders should be revaccinated **(BIII)**	
Hepatitis B virus (HBV) infection	All HIV patients without evidence of prior exposure to HBV should be vaccinated with HBV vaccine, including patients with CD4+ count <200 cells/μL **(AII)** *Patients with isolated anti-HBc:* **(BII)** (consider screening for HBV DNA before vaccination to rule out occult chronic HBV infection) *Vaccine non-responders:* Defined as anti-HBs <10 IU/mL 1 month after a vaccination series For patients with low CD4+ count at the time of first vaccination series, certain specialists might delay revaccination until after a sustained increase in CD4+ count with ART.	Hepatitis B vaccine IM (Engerix-B® 20 μg/mL or Recombivax HB® 10 μg/mL) at 0, 1, and 6 months **(AII)** Anti-HBs should be obtained one month after completion of the vaccine series **(BIII)** Revaccinate with a second vaccine series **(BIII)**	Some experts recommend vaccinating with 40 μg doses of either vaccine **(CIII)** Some experts recommend revaccinating with 40 μg doses of either vaccine **(CIII)**
Malaria	Travel to disease-endemic area	Recommendations are the same for HIV-infected and -uninfected patients. One of the following three drugs is usually recommended depending on location: atovaquone/proguanil, doxycycline, or mefloquine. Refer to the following website for the most recent recommendations based on region and drug susceptibility. http://www.cdc.gov/malaria/ **(AIII)**	

Definitions of abbreviations: DS = double strength; PO = by mouth; SS = single strength; bid = twice daily; tiw = 3 times weekly; SQ = subcutaneous; IM = intramuscular

TABLE 2. Drug therapy for treatment and chronic maintenance therapy of AIDS-associated opportunistic infections in adults and adolescents

Opportunistic infection	Preferred therapy, duration of therapy, chronic maintenance	Alternative therapy	Other options/issues
Pneumocystis pneumonia (PCP)	Preferred treatment for moderate to severe PCP ▪ Trimethoprim-sulfamethoxazole (TMP-SMX): [15–20 mg TMP and 75–100 mg SMX]/kg/day IV administered q6h or q8h **(AI)**, may switch to PO after clinical improvement **(AI)** ▪ Duration of therapy: 21 days **(AII)**	Alternative therapy for moderate to severe PCP ▪ Pentamidine 4 mg/kg IV daily infused over ≥60 minutes **(AI)**, certain specialists reduce dose to 3 mg/kg IV daily because of toxicities **(BI)**; or ▪ Primaquine 15–30 mg (base) PO daily plus clindamycin 600–900 mg IV q6h to q8h or clindamycin 300–450 mg PO q6h to q8h **(AI)**	Indications for corticosteroids **(AI)** PaO_2 <70 mmHg at room air or alveolar-arterial O_2 gradient >35 mmHg Prednisone doses (beginning as early as possible and within 72 hours of PCP therapy) **(AI)**: Days 1–5 40 mg PO bid Days 6–10 40 mg PO daily Days 11–21 20 mg PO daily IV methylprednisolone can be administered as 75% of prednisone dose Benefits of corticosteroid if started after 72 hours of treatment is unknown, but a majority of clinicians will use it in patients with moderate to severe PCP **(BIII)** Whenever possible, patients should be tested for G6PD deficiency before use of primaquine
	Preferred treatment for mild to moderate PCP ▪ Same daily dose of TMP-SMX as above, administered PO in 3 divided doses **(AI)**; or ▪ TMP-SMX (160 mg/800 mg or DS) 2 tablets tid **(AI)** ▪ Duration of therapy: 21 days **(AII)**	Alternative therapy for mild-to-moderate PCP ▪ Dapsone 100 mg PO daily and TMP 15 mg/kg/day PO (3 divided dose) **(BI)**; or ▪ Primaquine 15–30 mg (base) PO daily plus clindamycin 300–450 mg PO q6h to q8h **(BI)**; or ▪ Atovaquone 750 mg PO bid with food **(BI)**	
	Preferred secondary prophylaxis ▪ TMP-SMX (160 mg/800 mg or DS) tablet PO daily **(AI)**; or ▪ TMP-SMX (80 mg/400 mg or SS) tablet PO daily **(AI)**	Alternative secondary prophylaxis ▪ TMP-SMX (160 mg/800 mg or DS) PO tiw **(BI)** ▪ Dapsone 50 mg PO bid or 100 mg PO daily **(BI)**; or ▪ Dapsone 50 mg PO daily plus pyrimethamine 50 mg PO weekly plus leucovorin 25 mg PO weekly **(BI)**; or ▪ Dapsone 200 mg PO plus pyrimethamine 75 mg PO plus leucovorin 25 mg PO weekly **(BI)**; or ▪ Aerosolized pentamidine 300 mg every month via Respirgard II™ nebulizer **(BI)**; or ▪ Atovaquone 1,500 mg PO daily **(BI)**; or ▪ Atovaquone 1,500 mg + pyrimethamine 25 mg + leucovorin 10 mg PO daily **(CIII)**	

TABLE 2. (*Continued*) Drug therapy for treatment and chronic maintenance therapy of AIDS-associated opportunistic infections in adults and adolescents

Opportunistic infection	Preferred therapy, duration of therapy, chronic maintenance	Alternative therapy	Other options/issues
Toxoplasma gondii encephalitis (TE)	Preferred therapy ▪ Pyrimethamine 200 mg PO x 1, then 50 mg (<60 kg) to 75 mg (≥60 kg) PO daily plus sulfadiazine 1,000 mg (<60 kg) to 1,500 mg (≥60 kg) PO q6h plus leucovorin 10–25 mg PO daily (can increase 50 mg) **(AI)** Duration for acute therapy ▪ At least 6 weeks **(BII)**; longer duration if clinical or radiologic disease is extensive or response is incomplete at 6 weeks	Alternative therapy regimens • Pyrimethamine (leucovorin)* plus clindamycin 600 mg IV or PO q6h **(AI)**; or • TMP-SMX (5 mg/kg TMP and 25 mg/kg SMX) IV or PO bid **(BI)**; or • Atovaquone 1,500 mg PO bid with food (or nutritional supplement) plus pyrimethamine (leucovorin)* **(BII)**; or • Atovaquone 1,500 mg PO bid with food (or nutritional supplement) plus sulfadiazine 1,000–1,500 mg PO q6h **(BII)**; or • Atovaquone 1,500 mg PO bid with food **(BII)**; or • Pyrimethamine (leucovorin)* plus Azithromycin 900–1200 mg PO daily **(BII)**	Adjunctive corticosteroids (e.g., dexamethasone) should be administered when clinically indicated only for treatment of mass effect attributed to focal lesions or associated edema **(BIII)**; discontinue as soon as clinically feasible Anticonvulsants should be administered to patients with a history of seizures **(AIII)** and continued through the acute treatment; but should not be used prophylactically **(DIII)**
	Preferred chronic maintenance therapy ▪ Pyrimethamine 25–50 mg PO daily plus sulfadiazine 2,000–4,000 mg PO daily (in two to four divided doses) plus leucovorin 10–25 mg PO daily **(AI)**	Alternative chronic maintenance therapy/ secondary prophylaxis • Clindamycin 600 mg PO every 8 hours plus pyrimethamine 25–50 mg PO daily plus leucovorin 10–25 PO daily **(BI)** [should add additional agent to prevent PCP **(AII)**]; or • Atovaquone 750 mg PO every 6–12 hours +/- [(pyrimethamine 25 mg PO daily plus leucovorin 10 mg PO daily) or sulfadiazine 2,000–4,000 mg PO] daily **(BII)**	
Cryptosporidiosis	Preferred therapy ▪ Initiate or optimize ART for immune restoration **(AII)** ▪ Symptomatic treatment of diarrhea **(AIII)** ▪ Aggressive oral or IV rehydration & replacement of electrolyte loss **(AIII)**	Alternative therapy for cryptosporidiosis ▪ A trial of nitazoxanide 500–1,000 mg PO bid with food for 14 days **(CIII)** + optimized ART, symptomatic treatment and rehydration & electrolyte replacement	Use of antimotility agents such as loperamide or tincture of opium might palliate symptoms **(BIII)**

* Pyrimethamine and leucovorin doses – same as in "Preferred therapy" for toxoplasmosis.

TABLE 2. (*Continued*) Drug therapy for treatment and chronic maintenance therapy of AIDS-associated opportunistic infections in adults and adolescents

Opportunistic infection	Preferred therapy, duration of therapy, chronic maintenance	Alternative therapy	Other options/issues
Microsporidiosis	Initiate or optimize ART; immune restoration to CD4+ count >100 cells/μL is associated with resolution of symptoms of enteric microsporidiosis **(AII)**		Severe dehydration, malnutrition, and wasting should be managed by fluid support and nutritional supplement **(AIII)** Antimotility agents can be used for diarrhea control if required **(BIII)**
	Preferred therapy for gastrointestinal infections caused by *Enterocytozoon bienuesi* ▪ Fumagillin 20 mg PO tid (not available in U.S.) **(BII)** ▪ TNP-470 (a synthetic analog of fumagillin) might also be effective (not available in U.S.) **(BIII)**	Alternative therapy for gastrointestinal infections caused by *E. bienuesi* ▪ Nitazoxanide 1,000 mg bid with food for 60 days – effects might be minimal for patients with low CD4+ count **(CIII)**	
	Preferred therapy for disseminated (not ocular) and intestinal infection attributed to microsporidia other than *E. bienuesi* and *Vittaforma corneae* ▪ Albendazole 400 mg PO bid **(AII)**, continue until CD4+ count >200 cells/μL for >6 months after initiation of ART **(BIII)**	Alternative therapy for disseminated disease ▪ Itraconazole 400 mg PO daily plus albendazole 400 mg PO bid for disseminated disease attributed to *Trachipleistophora* or *Anncaliia* **(CIII)**	
	For ocular infection ▪ Topical fumagillin bicylohexylammonium (Fumidil B) 3 mg/mL in saline (fumagillin 70 μg/mL) eye drops - 2 drops every 2 hours for 4 days, then 2 drops qid (investigational use only in U.S.) **(BII)** plus albendazole 400 mg PO bid for management of systemic infection **(BIII)** ▪ Treatment should be continued indefinitely to prevent recurrence or relapse **(BIII)**		

TABLE 2. (*Continued*) Drug therapy for treatment and chronic maintenance therapy of AIDS-associated opportunistic infections in adults and adolescents

Opportunistic infection	Preferred therapy, duration of therapy, chronic maintenance	Alternative therapy	Other options/issues
Mycobacterium tuberculosis (TB)	Empiric treatment should be initiated and continued in HIV-infected persons in whom TB is suspected until all diagnostic work-up is complete **(AII)** **Treatment of drug-susceptible active TB disease** (*refer to Table 3 for dosing recommendations*) Initial phase (2 months) **(AI)** Isoniazid (INH)† + [rifampin (RIF) or rifabutin (RFB)] + pyrazinamide (PZA) + ethambutol (EMB); if drug susceptibility report shows sensitivity to INH & RIF and PZA, then EMB may be discontinued before 2 months of treatment is completed **(AI)** Continuation phase ▪ INH + (RIF or RFB) daily or tiw **(AIII)** or biw (if CD4+ count >100/μL) **(CIII)** Duration of therapy: *Pulmonary TB* – 6 months **(AI)** *Pulmonary TB w/ cavitary lung lesions & (+) culture after 2 months of TB treatment* **(AII)** – 9 months *Extrapulmonary TB w/ CNS, bone, or joint infections* – 9 to 12 months **(AII);** *Extrapulmonary TB in other sites* – 6 to 9 months **(AII)**	**Treatment for drug-resistant active TB** Resistant to INH ▪ Discontinue INH (and streptomycin, if used) ▪ (RIF or RFB) + EMB + PZA for 6 months **(BII)**; or ▪ (RIF or RFB) + EMB for 12 months (preferably with PZA during at least the first 2 months) **(BII)** ▪ A fluoroquinolone may strengthen the regimen for patients with extensive disease **(CIII)** Resistant to rifamycins ▪ INH + PZA + EMB + a fluoroquinolone for 2 months, followed by 10–16 additional months with INH + EMB + fluoroquinolone **(BIII)** ▪ Amikacin or capreomycin may be included in the first 2–3 months for patients with rifamycin resistance & severe disease **(CIII)** Multidrug resistant (MDR, i.e., INH & RIF resistant) or extensively drug resistant (XDR, i.e., resistance to INH & RIF, fluoroquinolone & at least 1 injectable agent) TB ▪ Therapy should be individualized based on resistance pattern and with close consultation with experienced specialist **(AIII)**	Directly observed therapy (DOT) is recommended for all HIV patients undergoing treatment for active TB **(AII)** Initial phase of TB treatment may also be administered 5 days weekly (40 doses) **(AII)**, or tiw (24 doses) **(BII)** by DOT For CNS disease, corticosteroid should be initiated as early as possible and continued for 6–8 weeks **(AII)** RIF is not recommended for patients receiving HIV protease inhibitors (PI) because of its induction of PI metabolism **(EII)** RFB is a less potent CYP 3A4 inducer than RIF and is preferred in patients receiving PIs Rifapentine administered once weekly can result in development of resistance in HIV-infected patients and is not recommended **(EI)** Therapeutic drug monitoring should be considered in patients receiving rifamycin and interacting ART Paradoxical reaction that is not severe may be treated with nonsteroidal anti-inflammatory drugs (NSAIDs) without a change in anti-TB or anti-HIV therapy (**BIII**) For severe paradoxical reaction, may consider prednisone or methylprednisolone 1 mg/kg of body weight, gradually reduced after 1–2 weeks **(BIII)**

† All patients receiving INH should receive pyridoxine 25–50 mg PO daily **(BIII).**

TABLE 2. (*Continued*) Drug therapy for treatment and chronic maintenance therapy of AIDS-associated opportunistic infections in adults and adolescents

Opportunistic infection	Preferred therapy, duration of therapy, chronic maintenance	Alternative therapy	Other options/issues
Disseminated *Mycobacterium avium* complex (MAC) disease	Preferred therapy for disseminated MAC At least 2 drugs as initial therapy with ▪ Clarithromycin 500 mg PO bid **(AI)** + ethambutol 15 mg/kg PO daily **(AI)** Addition of rifabutin may also be considered: ▪ Rifabutin 300 mg PO daily (dosage adjusted may be necessary based on drug-drug interactions) **(CI)**	Alternative therapy for disseminated MAC (e.g., when drug interactions or intolerance precludes the use of clarithromycin) ▪ Azithromycin 500–600 mg + ethambutol 15 mg/kg PO daily **(AII)** Addition of a third or fourth drug should be considered for patients with advanced immunosuppression (CD4+ count <50 cells/μL), high mycobacterial loads (>2 log CFU/mL of blood), or in the absence of effective ART **(CIII)** ▪ Amikacin 10–15 mg/kg IV daily; or ▪ Streptomycin 1 gm IV or IM daily; or ▪ Ciprofloxacin 500–750 mg PO bid; or ▪ Levofloxacin 500 mg PO daily; or ▪ Moxifloxacin 400 mg PO daily	Testing of susceptibility to clarithromycin and azithromycin is recommended **(BIII)** In ART-naïve patients, may consider withholding initiation of ART until after 2 weeks of MAC treatment to lessen drug interactions, reduce pill burden, and potentially lower occurrence of IRIS **(CIII)** NSAIDs may be used for patients who experience moderate to severe symptoms attributed to ART-associated IRIS **(CIII)** If immune reconstitution inflammatory syndrome (IRIS) symptoms persist, short term (4–8 weeks) of systemic corticosteroid (equivalent to 20–40 mg of prednisone) can be used **(CIII)**
	Chronic maintenance therapy (secondary prophylaxis) ▪ Same as treatment drugs and regimens Duration: Lifelong therapy **(AII)**, unless in patients with sustained immune recovery on ART **(BII)**		

TABLE 2. (*Continued*) Drug therapy for treatment and chronic maintenance therapy of AIDS-associated opportunistic infections in adults and adolescents

Opportunistic infection	Preferred therapy, duration of therapy, chronic maintenance	Alternative therapy	Other options/issues
Bacterial respiratory diseases	Preferred empiric outpatient therapy (oral) ▪ A beta-lactam plus a macrolide (azithromycin or clarithromycin) **(AII)** *Preferred beta-lactams*: high-dose amoxicillin or amoxicillin/clavulanate *Alternative beta-lactams*: cefpodoxime or cefuroxime	Alternative empiric outpatient therapy (oral) ▪ A beta-lactam plus doxycycline **(CIII)** *For penicillin-allergic patients or those with beta-lactam use in prior 3 months* ▪ A respiratory fluoroquinolone (levofloxacin 750 mg/day, gemifloxacin, or moxifloxacin) **(AII)**	Patients receiving macrolide for MAC prophylaxis should not receive macrolide monotherapy for empiric treatment of bacterial pneumonia Fluoroquinolones should be used with caution in patients where TB is suspected but is not being treated Empiric therapy with a macrolide alone is not routinely recommended, because of increasing pneumococcal resistance **(DIII)** Once the pathogen has been identified by a reliable microbiologic method, antibiotics should be directed at the pathogen **(BIII)** For patients begun on IV antibiotic therapy, switching to PO should be considered when patient is clinically improved and able to tolerate oral medications Chemoprophylaxis may be considered for patients with frequent recurrences of serious bacterial respiratory infections **(CIII)** Clinicians should be cautious of using antibiotics to prevent recurrences, because of the potential for developing drug resistance and drug toxicities
	Preferred empiric therapy for non-ICU inpatient ▪ A beta-lactam (IV) plus a macrolide **(AII)** *Preferred beta-lactams:* cefotaxime, ceftriaxone, or ampicillin-sulbactam	Alternative empiric therapy for non-ICU inpatient ▪ A beta-lactam (IV) plus doxycycline **(CIII)** *For penicillin-allergic patients or those with beta-lactam use in prior 3 months* ▪ An IV respiratory fluoroquinolone (levofloxacin 750 mg or moxifloxacin) **(AII)**	
	Preferred empiric ICU inpatient therapy ▪ A beta-lactam (IV) plus azithromycin IV **(AII)** or an IV respiratory fluoroquinolone (levofloxacin 750 mg or moxifloxacin) **(AII)** *Preferred beta-lactams*: cefotaxime, ceftriaxone, or ampicillin-sulbactam	Alternative empiric ICU therapy *For penicillin-allergic patients or those with beta-lactam use in prior 3 months* ▪ Aztreonam IV plus an IV respiratory fluoroquinolone **(BIII)**	
	Preferred empiric *Pseudomonas* therapy (if risks present) ▪ An antipneumococcal, antipseudomonal beta-lactam plus either ciprofloxacin or levofloxacin 750 mg/day **(BIII)** *Preferred beta-lactams*: piperacillin-tazobactam, cefepime, imipenem, or meropenem	Alternative empiric *Pseudomonas* therapy ▪ An antipneumococcal, antipseudomonal beta-lactam plus an aminoglycoside plus azithromycin **(BIII)** ▪ Above beta-lactam plus an aminoglycoside plus an antipneumococcal fluoroquinolone* **(BIII)** *For penicillin-allergic patients or those with beta-lactam use in prior 3 months* ▪ Replace the beta-lactam with aztreonam **(BIII)**	
	Preferred empiric methicillin-resistant *Staphylococcus aureus* (if risks present) ▪ Add vancomycin (possibly plus clindamycin) or linezolid alone to above **(BIII)**		

TABLE 2. (*Continued*) Drug therapy for treatment and chronic maintenance therapy of AIDS-associated opportunistic infections in adults and adolescents

Opportunistic infection	Preferred therapy, duration of therapy, chronic maintenance	Alternative therapy	Other options/issues
Bacterial enteric infections: Salmonellosis	Most specialists recommend treatment for all HIV-infected patients with salmonellosis due to the high risk of bacteremia in these patients **(BIII)** Preferred therapy for *Salmonella* gastroenteritis with or without symptomatic bacteremia ▪ Ciprofloxacin 500–750 mg PO bid (or 400 mg IV bid) **(AIII)** Duration for mild gastroenteritis with or without bacteremia ▪ If CD4+ count ≥200/μL: 7–14 days **(BIII)** ▪ If CD4+ count <200/μL: 2–6 weeks **(CIII)** ▪ If recurrent symptomatic septicemia – may need 6 months or more **(CIII)**	Alternative therapy for *Salmonella* gastroenteritis with or without symptomatic bacteremia ▪ Levofloxacin 750 mg or moxifloxacin **(BIII)** ▪ TMP-SMX PO or IV **(BIII)** – if susceptible ▪ Third generation cephalosporin such as ceftriaxone (IV) or cefotaxime (IV) **(BIII)** – if susceptible	The role of long-term secondary prophylaxis for patients with recurrent bacteremia is not well established. Must weigh the benefit against the risks of long-term antibiotic exposure
Bacterial enteric infections: Shigellosis	Preferred therapy for *Shigella* infection ▪ Fluoroquinolone IV or PO **(AIII)** Duration of therapy: *for gastroenteritis:* 3–7 days **(AIII)** *for bacteremia:* 14 days **(BIII)**	Alternative therapy depending on antibiotic susceptibility *For gastroenteritis* ▪ TMP-SMX DS 1 tab PO bid for 3–7 days **(BIII)**; or ▪ Azithromycin 500 mg PO on day 1, then 250 mg PO daily for 4 days **(BIII)**	Therapy is indicated both to shorten the duration of illness and to prevent spread of infection **(AIII)** *Shigella* infections acquired outside of United States have high rates of TMP-SMX resistance
Bacterial enteric infections: Campylobacteriosis	For mild disease Might withhold therapy unless symptoms persist for several days For mild-to-moderate disease ▪ Ciprofloxacin 500 mg PO bid **(BIII)**; or ▪ Azithromycin 500 mg PO daily **(BIII)** Consider addition of an aminoglycoside in bacteremic patients **(CIII)** Duration of therapy: ▪ Mild-to-moderate disease: 7 days **(BIII)** ▪ Bacteremia: at least 2 weeks **(BIII)**		There is an increasing rate of fluoroquinolone resistance Antimicrobial therapy should be modified based on susceptibility reports

TABLE 2. (*Continued*) Drug therapy for treatment and chronic maintenance therapy of AIDS-associated opportunistic infections in adults and adolescents

Opportunistic infection	Preferred therapy, duration of therapy, chronic maintenance	Alternative therapy	Other options/issues
Bartonella infections	Preferred therapy for bacillary angiomatosis, peliosis hepatis, bacteremia, and osteomyelitis ▪ Erythromycin 500 mg PO or IV qid **(AII)**; or ▪ Doxycycline 100 mg PO or IV q12h **(AII)** Duration of therapy: at least 3 months **(AII)** CNS infections and severe infections ▪ Doxycycline 100 mg PO or IV q12h +/- rifampin 300 mg PO or IV q12h **(AIII)** Duration of therapy: 4 months **(AII)** Long-term suppression ▪ With a macrolide or doxycycline for patients with relapse or reinfection as long as the CD4+ count remains <200 cells/μL **(AIII)**	Alternative therapy for bacillary angiomatosis infections, peliosis hepatis, bacteremia, and osteomyelitis ▪ Azithromycin 500 mg PO daily **(BIII)** ▪ Clarithromycin 500 mg PO bid **(BIII)**	Severe Jarisch-Herxheimer-like reaction can occur in the first 48 hours of treatment
Treponema pallidum infection (syphilis)	Preferred therapy early stage (primary, secondary, & early latent syphilis) ▪ Benzathine penicillin G 2.4 million units IM for 1 dose **(AII)** Preferred therapy late-latent disease (>1year or of unknown duration, CSF examination ruled out neurosyphilis) ▪ Benzathine penicillin G 2.4 million units IM weekly for 3 doses **(AIII)** Preferred therapy late-stage (tertiary – cardiovascular or gummatous disease) ▪ Rule out neurosyphilis before therapy with 3 doses of benzathine penicillin and obtain infectious diseases consultation to guide management **(AIII)** Preferred therapy neurosyphilis (including otic and ocular disease) ▪ Aqueous crystalline penicillin G, 18-24 million units per day, administered as 3–4 million units IV q4h or by continuous IV infusion for 10–14 days **(AII)** +/- benzathine penicillin G 2.4 million units IM weekly for 3 doses after completion of IV therapy **(CIII)**	Alternative therapy early stage (primary, secondary, and early latent syphilis) **(BIII)** *For penicillin-allergic patients:* ▪ Doxycycline 100 mg PO bid for 14 days **(BIII)**; or ▪ Ceftriaxone 1 g IM or IV daily for 8–10 days **(BIII)**; or ▪ Azithromycin 2 g PO for 1 dose **(CII)** Alternative therapy late-latent disease (without CNS involvement) *For penicillin-allergic patients:* ▪ Doxycycline 100 mg PO bid for 28 days **(BIII)** Alternative therapy neurosyphilis ▪ Procaine penicillin 2.4 million units IM daily plus probenecid 500 mg PO qid for 10–14 days **(BII)** +/- benzathine penicillin G 2.4 million units IM weekly for 3 doses after completion of above **(CIII)**; or *For penicillin-allergic patients*: ▪ Desensitization to penicillin is the preferred approach **(BIII)**; if not feasible, ▪ Ceftriaxone 2 grams IM or IV daily for 10–14 days **(CIII)**	The efficacy of non-penicillin alternatives has not been evaluated in HIV-infected patients and should be undertaken only with close clinical and serologic monitoring **(BIII)** Combination of procaine penicillin and probenecid is not recommended for patients with history of sulfa allergy **(DIII)** The Jarisch-Herxheimer reaction is an acute febrile reaction accompanied by headache and myalgias that might occur within the first 24 hours after therapy for syphilis

TABLE 2. (*Continued*) Drug therapy for treatment and chronic maintenance therapy of AIDS-associated opportunistic infections in adults and adolescents

Opportunistic infection	Preferred therapy, duration of therapy, chronic maintenance	Alternative therapy	Other options/issues
Candidiasis (mucosal)	Preferred therapy oropharyngeal candidiasis: initial episodes (7–14 day treatment) ▪ Fluconazole 100 mg PO daily **(AI)**; or ▪ Clotrimazole troches 10 mg PO 5 times daily **(BII)**; or ▪ Nystatin suspension 4–6 mL qid or 1–2 flavored pastilles 4–5 times daily **(BII)** ▪ Miconazole mucoadhesive tablet PO daily **(BII)**	Alternative therapy oropharyngeal candidiasis: initial episodes (7–14 day treatment) ▪ Itraconazole oral solution 200 mg PO daily **(BI)**; or ▪ Posaconazole oral solution 400 mg PO bid x 1, then 400 mg daily **(BI)**	Chronic or prolonged use of azoles might promote development of resistance Higher relapse rate of esophageal candidiasis with echinocandins than with fluconazole has been reported Patients with fluconazole refractory oropharyngeal or esophageal candidiasis who responded to echinocandin should be started on voriconazole or posaconazole for secondary prophylaxis until ART produces immune reconstitution **(CI)**
	Preferred therapy esophageal candidiasis (14–21 days) ▪ Fluconazole 100 mg (up to 400 mg) PO or IV daily **(AI)** ▪ Itraconazole oral solution 200 mg PO daily **(AI)**	Alternative therapy esophageal candidiasis (14–21 days) ▪ Voriconazole 200 mg PO or IV bid **(BI)** ▪ Posaconazole 400 mg PO bid **(BI)** ▪ Caspofungin 50 mg IV daily **(BI)** ▪ Micafungin 150 mg IV daily **(BI)** ▪ Anidulafungin 100 mg IV x 1, then 50 mg IV daily **(BI)** ▪ Amphotericin B deoxycholate 0.6 mg/kg IV daily **(BI)**	Suppressive therapy is usually not recommended **(DIII)** unless patients have frequent or severe recurrences. If decision is to use suppressive therapy: Oropharyngeal candidiasis ▪ Fluconazole 100 mg PO tiw **(BI)** ▪ Itraconazole oral solution 200 mg PO daily **(CI)** Esophageal candidiasis ▪ Fluconazole 100–200 mg PO daily **(BI)** ▪ Posaconazole 400 mg PO bid **(BII)**
	Preferred therapy uncomplicated vulvovaginal candidiasis ▪ Oral fluconazole 150 mg for 1 dose **(AII)** ▪ Topical azoles (clotrimazole, butoconazole, miconazole, tioconazole, or terconazole) for 3–7 days **(AII)**	Alternative therapy uncomplicated vulvovaginal candidiasis ▪ Itraconazole oral solution 200 mg PO daily for 3-7 days **(BII)**	Vulvovaginal candidiasis ▪ Fluconazole 150 mg PO once weekly **(CII)** ▪ Daily topical azole **(CII)**
	Preferred therapy fluconazole-refractory oropharyngeal candidiasis or esophageal candidiasis ▪ Itraconazole oral solution ≥200 mg PO daily **(AII)** ▪ Posaconazole oral solution 400 mg PO bid **(AII)**	Alternative therapy fluconazole-refractory oropharyngeal candidiasis or esophageal candidiasis ▪ Amphotericin B deoxycholate 0.3 mg/kg IV daily **(BII)** ▪ Lipid formulation of amphotericin B 3–5 mg/kg IV daily **(BII)** ▪ Anidulafungin 100 mg IV x 1, then 50 mg IV daily **(BII)** ▪ Caspofungin 50 mg IV daily **(CII)** ▪ Micafungin 150 mg IV daily **(CII)** ▪ Voriconazole 200 mg PO or IV bid **(CIII)** *Fluconazole-refractory oropharyngeal candidiasis (not esophageal)* ▪ Amphotericin B oral suspension 100 mg/mL (not available in U.S.) – 1 mL PO qid **(CIII)**	
	Preferred therapy complicated (severe or recurrent) vulvovaginal candidiasis ▪ Fluconazole 150 mg q72h x 2-3 doses **(AII)** ▪ Topical antifungal ≥7 days **(AII)**		

TABLE 2. (*Continued*) Drug therapy for treatment and chronic maintenance therapy of AIDS-associated opportunistic infections in adults and adolescents

Opportunistic infection	Preferred therapy, duration of therapy, chronic maintenance	Alternative therapy	Other options/issues
Cryptococcal meningitis	Preferred induction therapy ▪ Amphotericin B deoxycholate 0.7 mg/kg IV daily plus flucytosine 100 mg/kg PO daily in 4 divided doses for at least 2 weeks **(AI)**; or ▪ Lipid formulation amphotericin B 4–6 mg/kg IV daily (consider for persons who have renal dysfunction on therapy or have high likelihood of renal failure) plus flucytosine 100 mg/kg PO daily in 4 divided doses for at least 2 weeks **(AII)**	Alternative induction therapy ▪ Amphotericin B (deoxycholate or lipid formulation, dose as preferred therapy) plus fluconazole 400 mg PO or IV daily **(BII)** ▪ Amphotericin B (deoxycholate or lipid formulation, dose as preferred therapy) alone **(BII)** ▪ Fluconazole 400–800 mg/day (PO or IV) plus flucytosine 100 mg/kg PO daily in 4 divided doses for 4–6 weeks **(CII)** – for persons unable to tolerate or unresponsive to amphotericin B	Addition of flucytosine to amphotericin B has been associated with more rapid sterilization of CSF and decreased risk for subsequent relapse Patients receiving flucytosine should have blood levels monitored; peak level 2 hours after dose should not exceed 75 μg/mL. Dosage should be adjusted in patients with renal insufficiency. Opening pressure should always be measured when a lumbar puncture (LP) is performed **(AII)**. Repeated LPs or CSF shunting are essential to effectively manage increased intracranial pressure **(BIII)**.
	Preferred consolidation therapy (after at least 2 weeks of successful induction – defined as significant clinical improvement & negative CSF culture) ▪ Fluconazole 400 mg PO daily for 8 weeks **(AI)**	Alternative consolidation therapy ▪ Itraconazole 200 mg PO bid for 8 weeks **(BI)**, or until CD4+ count ≥200 cells/μL for >6 months as a result of ART **(BII)**.	
	Preferred maintenance therapy ▪ Fluconazole 200 mg PO daily **(AI)** lifelong or until CD4+ count ≥200 cells/μL for >6 months as a result of ART **(BII)**	Alternative maintenance therapy ▪ Itraconazole 200 mg PO daily lifelong unless immune reconstitution as a result of potent ART – for patients intolerant of or who failed fluconazole **(BI)**	

TABLE 2. (*Continued*) Drug therapy for treatment and chronic maintenance therapy of AIDS-associated opportunistic infections in adults and adolescents

Opportunistic infection	Preferred therapy, duration of therapy, chronic maintenance	Alternative therapy	Other options/issues
Histoplasma capsulatum infections	Preferred therapy for moderately severe to severe disseminated disease *Induction therapy* (for 2 weeks or until clinically improved) ▪ Liposomal amphotericin B at 3 mg/kg IV daily **(AI)** *Maintenance therapy* ▪ Itraconazole 200 mg PO tid for 3 days, then bid **(AII)** Preferred therapy for less severe disseminated disease *Induction and maintenance therapy* ▪ Itraconazole 200 mg PO tid for 3 days, then 200 mg PO bid **(AII)** Duration of therapy: at least 12 months Preferred therapy for meningitis *Induction therapy* (4–6 weeks) ▪ Liposomal amphotericin B 5 mg/kg/day **(AII)** *Maintenance therapy* ▪ Itraconazole 200 mg PO bid-tid for ≥1 year and until resolution of abnormal CSF findings **(AII)** Preferred therapy for long term suppression therapy In patients with severe disseminated or CNS infection **(AII)** and in patients who relapse despite appropriate therapy **(CIII)** ▪ Itraconazole 200 mg PO daily	Alternative therapy moderately severe to severe disseminated disease *Induction therapy* (for 2 weeks or until clinically improved) ▪ Amphotericin B deoxycholate 0.7 mg/kg IV daily **(BI)** ▪ Amphotericin B lipid complex 5 mg/kg IV daily **(CIII)** *Maintenance therapy* same as "Preferred therapy"	Itraconazole levels should be obtained in all patients to ensure adequate absorption **(AIII)**. Serum concentrations of itraconazole + hydroxyitraconazole should be >1 μg/mL Itraconazole oral solution is preferred over capsule by certain specialists because of improved absorption Acute pulmonary histoplasmosis in HIV-infected patients with CD4+ count >300 cells/μL should be managed as non-immunocompromised host **(AIII)**

TABLE 2. (*Continued*) Drug therapy for treatment and chronic maintenance therapy of AIDS-associated opportunistic infections in adults and adolescents

Opportunistic infection	Preferred therapy, duration of therapy, chronic maintenance	Alternative therapy	Other options/issues
Coccidioidomycosis	Preferred therapy for mild infections (focal pneumonia or positive coccidiodal serologic test alone) ▪ Fluconazole 400 mg PO daily **(BII)**; or ▪ Itraconazole 200 mg PO tid x 3 days, then 200 mg bid **(BII)**		Certain patients with meningitis may develop hydrocephalus and require CSF shunting Therapy should be continued indefinitely for patients with diffuse pulmonary or disseminated diseases as relapse can occur in 25%–33% in HIV-negative patients **(AIII)**
	Preferred therapy for severe, nonmeningeal infection (diffuse pulmonary or severely ill patients with extrathoracic disseminated disease): acute phase ▪ Amphotericin B deoxycholate 0.7–1.0 mg/kg IV daily **(AII)** ▪ Lipid formulation amphotericin B 4–6 mg/kg IV daily **(AIII)** Duration of therapy: until clinical improvement, then switch to azole	Alternative therapy for severe nonmeningeal infection (diffuse pulmonary or disseminated disease): acute phase ▪ Certain specialists add triazole to amphotericin B therapy and continue triazole once amphotericin B is stopped **(BIII)**	Therapy should be lifelong in patients with meningeal infections as relapse occurred in 80% of HIV-infected patients after discontinuation of triazole therapy **(AII)** Case reports of successful therapy with voriconazole and posaconazole are available.
	Preferred therapy for meningeal infections ▪ Fluconazole 400–800 mg PO or IV daily **(AII)**	Alternative therapy for meningeal infections ▪ Itraconazole 200 mg PO tid x 3 days, then 200 mg PO bid **(BII)** ▪ Intrathecal amphotericin B when triazole antifungals are not effective **(AIII)**	
	Maintenance therapy (for all cases) ▪ Fluconazole 400 mg PO daily **(AII)**; or ▪ Itraconazole 200 mg PO bid **(AII)**		
Aspergillosis, invasive	Preferred therapy ▪ Voriconazole 6 mg/kg q12h x 1 day, then 4 mg/kg q12h IV **(BIII)**, followed by voriconazole PO 200 mg q12h after clinical improvement Duration of therapy: until CD4+ count >200 cells/μL and with evidence of clinical response	Alternative therapy ▪ Amphotericin B deoxycholate 1 mg/kg/day IV **(AIII)**; or ▪ Lipid formulation of amphotericin B 5 mg/kg/day IV **(AIII)** ▪ Caspofungin 70 mg IV x 1, then 50 mg IV daily **(BII)** ▪ Posaconazole 400 mg bid PO **(BII)**	Potential for significant pharmacokinetic interactions between PIs or NNRTIs with voriconazole; it should be used cautiously in these situations. Consider therapeutic drug monitoring and dosage adjustment if necessary.

TABLE 2. (*Continued*) Drug therapy for treatment and chronic maintenance therapy of AIDS-associated opportunistic infections in adults and adolescents

Opportunistic infection	Preferred therapy, duration of therapy, chronic maintenance	Alternative therapy	Other options/issues
Cytomegalovirus (CMV) disease	Preferred therapy for CMV retinitis *For immediate sight-threatening lesions* ▪ Ganciclovir intraocular implant + valganciclovir 900 mg PO (bid for 14–21 days, then once daily) **(AI)** ▪ One dose of intravitreal ganciclovir may be administered immediately after diagnosis until ganciclovir implant can be placed **(CIII)** *For small peripheral lesions* ▪ Valganciclovir 900 mg PO bid for 14–21 days, then 900 mg PO daily **(BII)**	Alternative therapy for CMV retinitis ▪ Ganciclovir 5 mg/kg IV q12h for 14–21 days, then 5 mg/kg IV daily **(AI)**; or ▪ Ganciclovir 5 mg/kg IV q12h for 14–21 days, then valganciclovir 900 mg PO daily **(AI)**; or ▪ Foscarnet 60 mg/kg IV q8h or 90 mg/kg IV q12h for 14–21 days, then 90–120 mg/kg IV q24h **(AI)**; or ▪ Cidofovir 5 mg/kg/week IV for 2 weeks, then 5 mg/kg every other week with saline hydration before and after therapy and probenecid 2 g PO 3 hours before the dose followed by 1 g PO 2 hours after the dose, and 1 g PO 8 hours after the dose (total of 4 g) **(AI)** Note: This regimen should be avoided in patients with sulfa allergy because of cross hypersensitivity with probenecid	The choice of initial therapy for CMV retinitis should be individualized, based on location and severity of the lesion(s), level of immunosuppression, and other factors such as concomitant medications and ability to adhere to treatment **(AIII)** Initial therapy in patients with CMV retinitis, esophagitis, colitis, and pneumonitis should include initiation or optimization of ART **(BIII)** In patients with CMV neurological disease, localized morbidity might occur because of IRIS, a brief delay in initiation of ART until clinical improvement might be prudent **(CIII)** Maintenance therapy for CMV retinitis can be safely discontinued in patients with inactive disease and sustained CD4+ count (>100 cells/mm^3 for ≥3–6 months); consultation with ophthalmologist is advised **(BII)** Patients with CMV retinitis who discontinued maintenance therapy should undergo regular eye examination, optimally every 3 months, for early detection of relapse or immune recovery uveitis (IRU) **(AIII)** IRU might develop in the setting of immune reconstitution. Treatment of IRU: periocular corticosteroid or short courses of systemic steroid
	Preferred chronic maintenance therapy (secondary prophylaxis) for CMV retinitis ▪ Valganciclovir 900 mg PO daily **(AI)**; or ▪ Ganciclovir implant (may be replaced every 6–8 months if CD4+ count remains <100 cells/μL) + valganciclovir 900 mg PO daily until immune recovery **(BIII)**	Alternative chronic maintenance (secondary prophylaxis) for CMV retinitis ▪ Ganciclovir 5 mg/kg IV 5–7 times weekly **(AI)**; or ▪ Foscarnet 90–120 mg/kg body weight IV once daily **(AI)**; or ▪ Cidofovir 5 mg/kg body weight IV every other week with saline hydration and probenecid as above **(AI)**	
	Preferred therapy for CMV esophagitis or colitis ▪ Ganciclovir IV or foscarnet IV for 21–28 days or until resolution of signs and symptoms **(BII)** ▪ Oral valganciclovir may be used if symptoms are not severe enough to interfere with oral absorption **(BII)** ▪ Maintenance therapy is usually not necessary, but should be considered after relapses **(BII)**		
	Preferred therapy CMV pneumonitis ▪ Treatment should be considered in patients with histologic evidence of CMV pneumonitis and who do not respond to treatment of other pathogens **(AIII)** ▪ The role of maintenance therapy has not been established **(CIII)**		
	Preferred therapy CMV neurological disease *Treatment should be initiated promptly* ▪ Combination of ganciclovir IV + foscarnet IV to stabilize disease and maximize response, continue until symptomatic improvement **(BII)** ▪ Maintenance therapy (with valganciclovir PO + IV foscarnet) should be continued for life unless evidence of immune recovery is evident **(BII)**		

TABLE 2. (*Continued*) Drug therapy for treatment and chronic maintenance therapy of AIDS-associated opportunistic infections in adults and adolescents

Opportunistic infection	Preferred therapy, duration of therapy, chronic maintenance	Alternative therapy	Other options/issues
Herpes simplex virus (HSV) disease	Preferred therapy for orolabial lesions and initial or recurrent genital HSV ▪ Valacyclovir 1 g PO bid, famciclovir 500 mg PO bid, or acyclovir 400 mg PO tid **(AI)** Duration of therapy: ▪ Orolabial HSV: 5–10 days **(AII)** ▪ Genital HSV: 5–14 days **(AI)** Preferred therapy for severe mucocutaneous HSV infections ▪ Initial therapy acyclovir 5 mg/kg IV q8h **(AII)** ▪ After lesions began to regress, change to PO therapy as above **(AI)**. Continue therapy until lesions have completely healed.		
	Preferred therapy for acyclovir-resistant mucocutaneous HSV infections ▪ Foscarnet 80–120 mg/kg/day IV in 2–3 divided doses until clinical response **(AI)**	Alternative therapy for acyclovir-resistant mucocutaneous HSV infections **(CIII)** ▪ Topical trifluridine ▪ Topical cidofovir ▪ Topical imiquimod Duration of therapy: 21–28 days or longer	Topical formulations of neither trifluridine nor cidofovir are commercially available in the U.S. Extemporaneous compounding of topical products can be prepared using trifluridine ophthalmic solution and the intravenous formulation of cidofovir
	Preferred therapy for HSV encephalitis ▪ Acyclovir 10 mg/kg IV q8h for 21 days **(AII)** Suppressive therapy (For patients with frequent or severe recurrences of genital herpes) **(AI)** ▪ Valacyclovir 500 mg PO bid **(AI)** ▪ Famciclovir 500 mg PO bid **(AI)** ▪ Acyclovir 400 mg PO bid **(AI)**		
HHV-6 infection	If HHV-6 has been identified as cause of disease in HIV-infected patients, use same drugs and doses as treatment for CMV disease **(CIII)** ▪ Ganciclovir (or valganciclovir) ▪ Foscarnet		

TABLE 2. (*Continued*) Drug therapy for treatment and chronic maintenance therapy of AIDS-associated opportunistic infections in adults and adolescents

Opportunistic infection	Preferred therapy, duration of therapy, chronic maintenance	Alternative therapy	Other options/issues
Varicella zoster virus (VZV) disease	Varicella (chickenpox) *Uncomplicated cases* ▪ Acyclovir (20 mg/kg body weight up to a maximum of 800 mg PO 5x daily), valacyclovir 1,000 mg PO tid, or famciclovir 500 mg PO tid x 5–7 days **(AII)** *Severe or complicated cases* ▪ Acyclovir 10–15 mg/kg IV q8h x 7–10 days **(AIII)** ▪ May switch to oral acyclovir, famciclovir, or valacyclovir after defervescence if no evidence of visceral involvement is evident **(AIII)** Herpes zoster (shingles) *Acute localized dermatomal* ▪ Valacyclovir 1g tid or famciclovir 500 mg tid, or acyclovir 800 mg PO 5x daily x 7–10 days **(AII)**, longer duration should be considered if lesions are slow to resolve *Extensive cutaneous lesion or visceral involvement* ▪ Acyclovir 10–15 mg/kg IV q8h until clinical improvement is evident **(AII)** ▪ Switch to oral therapy (valacyclovir 1,000 mg tid or famciclovir 500 mg tid, or acyclovir 800 mg PO 5x daily) after clinical improvement is evident, to complete a 10–14 day course **(AIII)** Progressive outer retinal necrosis (PORN) ▪ Ganciclovir 5 mg/kg IV q12h, plus foscarnet 90 mg/kg IV q12h, plus ganciclovir 2 mg/0.05mL intravitreal twice weekly, and/or foscarnet 1.2 mg/0.05mL intravitreal twice weekly **(AIII)** ▪ Optimization of ART **(AIII)** Acute retinal necrosis (ARN) ▪ Acyclovir 10 mg/kg IV q8h x 10–14 days, followed by valacyclovir 1,000 mg PO tid x 6 weeks **(AIII)**	Infection caused by acyclovir-resistant VZV ▪ Foscarnet 90 mg/kg IV q12h **(AII)**	Involvement of an experienced ophthalmologist with management of VZV retinitis is strongly recommended **(AIII)** Corticosteroid therapy for herpes zoster is not recommended **(DIII)**

TABLE 2. (*Continued*) Drug therapy for treatment and chronic maintenance therapy of AIDS-associated opportunistic infections in adults and adolescents

Opportunistic infection	Preferred therapy, duration of therapy, chronic maintenance	Alternative therapy	Other options/issues
HHV-8 diseases (*Kaposi's Sarcoma [KS], primary effusion lymphoma [PEL], multicentric Castleman's disease [MCD],)*	Initiation or optimization of ART should be done for all patients with KS, PEL, or MCD **(BII)** Preferred therapy for visceral KS **(BII),** disseminated cutaneous KS **(CIII)**, and PEL **(BIII)** ▪ Chemotherapy + ART **(BII)** ▪ Oral valganciclovir or IV ganciclovir might be useful as adjunctive therapy in PEL **(BII)** Preferred therapy for MCD ▪ Valganciclovir 900 mg PO bid **(BII)**; or ▪ Ganciclovir 5 mg/kg IV q12h **(BII)**	Alternative therapy for MCD Rituximab, 375 mg/m^2 given weekly x 4–8 weeks, may be an alternative to antiviral therapy **(BII)**	
Human papillomavirus disease	Treatment of condyloma acuminata (genital warts) Patient-applied therapy ▪ Podofilox 0.5% solution or 0.5% gel – apply to all lesions bid x 3 consecutive days, followed by 4 days of no therapy, repeat weekly for up to 4 cycles **(BIII)**; or ▪ Imiquimod 5% cream – apply to lesion at bedtime and remove in the morning on 3 nonconsecutive nights weekly for up to 16 weeks. Each treatment should be washed with soap and water 6–10 hours after application **(BII)**	Provider-applied therapy ▪ Cryotherapy (liquid nitrogen or cryoprobe) – apply until each lesion is thoroughly frozen; repeat every 1–2 weeks. Some providers allow the lesion to thaw, then freeze a 2nd time in each session **(BIII)**. ▪ Trichloroacetic acid or bicloroacetic acid cauterization – 80%–90% aqueous solution, apply to each lesion, repeat weekly for 3–6 weeks **(BIII)** ▪ Surgical excision **(BIII)** or laser surgery **(CIII)** ▪ Podophyllin resin 10%–25% suspension in tincture of benzoin – apply to all lesions, then wash off a few hours later, repeat weekly for 3–6 weeks **(CIII)**	Intralesional interferon-alpha is usually not recommended because of high cost, difficult administration, and potential for systemic side effects **(DIII)** The rate of recurrence of genital warts is high, despite treatment

TABLE 2. (*Continued*) Drug therapy for treatment and chronic maintenance therapy of AIDS-associated opportunistic infections in adults and adolescents

Opportunistic infection	Preferred therapy, duration of therapy, chronic maintenance	Alternative therapy	Other options/issues
Hepatitis B virus (HBV) disease	Therapy for patients who require ART ▪ Patients should be treated with agents active against both HIV and HBV or with agents with independent activity against each virus **(CIII)** ▪ Consider tenofovir + emtricitabine as part of HIV and HBV regimen **(CIII)** *Lamivudine or emtricitabine-naïve patients* ▪ [Lamivudine 150 mg PO bid (or 300 mg PO daily) or emtricitabine 200 mg PO daily] + tenofovir (TDF) 300 mg PO daily **(CIII)** (+ additional agent[s] active against HIV) *Lamivudine or emtricitabine-experienced patients with detectable HBV DNA (assume lamivudine-resistance)* ▪ *If not on TDF*: Add TDF 300 mg PO daily as part of an ART regimen + lamivudine or emtricitabine **(CIII)**; or ▪ Adefovir 10 mg PO daily + lamivudine or emtricitabine + other combination ART **(BII)**; or ▪ Entecavir 1 mg PO daily can be considered in patients with complete HIV suppression (while on ART) who do not demonstrate YMDD (M204V/I) motif mutations in HBV DNA **(CIII)** Duration of therapy: Because of the high rates of relapse, certain specialists recommend continuing therapy indefinitely **(CIII)**	Treatment for patients who do not require ART ▪ Use agents with sole activity against HBV and with the least potential of selecting HIV resistance mutations **(BIII)** ▪ Consider early initiation of ART, especially for patients with high HBV DNA *For patients with CD4+ count >350 cells/μL, HBeAg (-), HBV DNA >2,000 IU/mL (>20,000 copies/mL)* ▪ Adefovir 10 mg PO daily **(CIII)** *For patients with CD4+ count >350 cells/μL, HBeAg (+), HBV DNA >20,000 IU/mL (>200,000 copies/mL), and elevated ALT* ▪ Peginterferon alfa-2a 180 μg SQ weekly **(CIII)** x 48 weeks – with careful follow-up of HBeAg conversion	Emtricitabine, entecavir, lamivudine, or tenofovir should not be used for the treatment of HBV infection in patients who are not receiving combination ART **(EII)** Among patients coinfected with HIV, HBV, and HCV, consideration of starting ART should be the first priority. If ART is not required, an interferon-based regimen, which suppresses both HCV & HBV, should be considered **(CIII)** If IFN-based treatment for HCV has failed, treatment of chronic HBV with nucleoside or nucleotide analogs is recommended **(CIII)** Cross-resistance to emtricitabine or telbivudine should be assumed in patients with suspected or proven 3TC resistance When changing ART regimens, continue agents with anti-HBV activity because of the risk of IRIS If anti-HBV therapy is discontinued and a flare occurs, therapy should be reinstituted, as it can be potentially life saving **(BIII)**
Hepatitis C virus (HCV) disease	Genotype 1, 4, 5, or 6 **(AI)** ▪ Peginterferon alfa-2a 180 μg SQ weekly, or ▪ Peginterferon alfa-2b 1.5 mg/kg SQ weekly + ▪ Ribavirin PO (wt-based dosing) **(AII)** <75 kg: 600 mg qAM and 400 mg qPM; ≥75 kg: 600 mg qAM and 600 mg qPM Genotype 2 or 3 **(AI)** ▪ Peginterferon alfa-2a 180μg SQ weekly, or ▪ Peginterferon alfa-2b 1.5 mg/kg SQ weekly + ▪ Ribavirin (fixed dose) PO 400 mg qAM and 400 mg qPM Duration of therapy: ▪ 48 weeks – genotypes 1 or 4, 5 or 6 **(AI)** and genotypes 2 and 3 **(BII)** ▪ At least 24 weeks – treatment of acute HCV infection (<6 months from HCV exposure) **(BIII)**	In patients for whom ribavirin is contraindicated (e.g. unstable cardiopulmonary disease, pre-existing anemia unresponsive to erythropoietin, renal failure, or hemoglobinopathy) ▪ Peginterferon alfa-2a 180 μg SQ weekly **(AII)**, or ▪ Peginterferon alfa-2b 1.5 μg/kg SQ weekly **(AII)** In patients with decompensated liver disease ▪ Liver transplantation if feasible **(CIII)**	For patients with CD4+ count <200 cells/μL, initiation of ART may be considered before HCV treatment **(CIII)** Didanosine + ribavirin may lead to increased mitochondrial toxicities; concomitant use is contraindicated **(EI)**. HCV therapy is not recommended in patients with hepatic decompensation. Liver transplantation, if feasible, should be the primary treatment option **(CIII)**. Interferon is abortifacient in high doses and ribavirin is teratogenic. HCV treatment is not recommended in pregnant women or women who are not willing to use birth control **(EIII)**.

TABLE 2. (*Continued*) Drug therapy for treatment and chronic maintenance therapy of AIDS-associated opportunistic infections in adults and adolescents

Opportunistic infection	Preferred therapy, duration of therapy, chronic maintenance	Alternative therapy	Other options/issues
Progressive multifocal leukoencephalopathy (JC virus infections)	Initiate antiretroviral therapy in ART-naïve patients **(AII)** Optimize ART in patients who develop PML in phase of HIV viremia on antiretroviral therapy **(AIII)**		Some patients might experience a remission after initiation of ART. Although their neurological deficits frequently persist, disease progression remits. Corticosteroids may be used in patients with progressive clinical deficits and neuroimaging features suggesting inflammatory disease (e.g., edema, swelling, and contrast enhancement) as a result of initiating ART **(BIII)**
Geographic opportunistic infections of specific consideration			
Malaria			
Uncomplicated malaria from *Plasmodium falciparum* or unknown malaria species	Preferred therapy for chloroquine-sensitive infection (north of the Panama Canal) ▪ Chloroquine phosphate 1,000 mg PO (=600 mg chloroquine base) once, then 500 mg PO (=300 mg chloroquine base) at 6, 24, and 48 hours ▪ Total dose = chloroquine phosphate 2,500 mg	Alternative therapy for chloroquine-sensitive infection (north of the Panama Canal) No alternative listed	Treatment recommendations for HIV-infected patients are the same as HIV non-infected patients. For most updated treatment recommendations for specific region, clinicians should refer to the following web link: http://www.cdc.gov/malaria/ or call the CDC Malaria Hotline: 770-488-7788 - M-F 8 AM-4:30 PM ET 770-488-7100 - after hours
	Preferred therapy for chloroquine-resistant infections (all other malaria areas or unknown region) ▪ Atovaquone-proguanil (250 mg/100 mg) – 4 tablet PO daily x 3 days	Alternative therapy for chloroquine-resistant infections (all other malaria areas or unknown region) ▪ Mefloquine 750 mg PO x 1, then 500 mg administered 12 hrs later, total dose = 1,250 mg ▪ Quinine sulfate 650 mg PO q8h x 3 days (infections acquired outside of southeast Asia) to 7 days (infections acquired in southeast Asia) + (doxycycline 100 mg PO q12h x 7 days or clindamycin 20 mg base/kg/day (in 3 divided doses) PO x 7 days)	
Severe malaria from all regions	Preferred therapy ▪ Quinidine gluconate 10 mg/kg IV over 1–2 hours, then 0.02 mg/kg/min infusion (quinidine 6.25 mg base/kg IV over 1–2 hours, then 0.0125 mg/kg/min) for ≥24 hours with cardiac monitoring + ▪ Doxycycline 100 mg PO or IV q12h x 7 days; or ▪ Clindamycin 20 mg base/kg/day (in 3 divided doses) PO or 10 mg base/kg loading dose IV followed by 5 mg base/kg IV q8h; switch to PO clindamycin (dose as above) as soon as patient can take PO medication - for a total course of 7 days	Alternative therapy ▪ Artesunate 2.4 mg/kg IV bolus at 0, 12, and 24 hours, then daily Duration of therapy: 7 days for Southeast Asia and Oceania and 3 days for other areas When able to take PO, switch to: ▪ Atovaquone-proquanil, mefloquine, or doxycycline (doses as listed above)	Intravenous artesunate is available from CDC quarantine stations (CDC Malaria Hotline 770-488-7788)

TABLE 2. (*Continued*) Drug therapy for treatment and chronic maintenance therapy of AIDS-associated opportunistic infections in adults and adolescents

Opportunistic infection	Preferred therapy, duration of therapy, chronic maintenance	Alternative therapy	Other options/issues
Malaria from: *P. vivax* *P. ovale* *P. malariae*	All regions use the following regimens (except for Papua New Guinea and Indonesia, in which case treat as for chloroquine-resistant *P. falciparum* malaria as above) ▪ Chloroquine phosphate 1000 mg PO x 1, then 500 mg PO at 6, 24, and 48 hours, total dose = 2,500 mg; then ▪ Anti-relapse therapy (after checking G6PD status): primaquine 30 mg base PO daily x 14 days		G6PD status should be checked before initiation of primaquine
Penicilliosis	Acute infection in severely ill patients ▪ Amphotericin B deoxycholate 0.6 mg/kg/day IV for 2 weeks; followed by itraconazole 400 mg PO daily for 10 weeks **(AII)** Mild disease ▪ Itraconazole 400 mg PO daily for 8 weeks **(BII)** Chronic maintenance therapy (secondary prophylaxis) ▪ Itraconazole 200 mg PO daily **(AI)**		ART should be administered according to standard of care in the community; consideration should be given to simultaneously initiating ART and treatment for penicilliosis **(CIII)**
Leishmaniasis, visceral	Preferred therapy for initial infection ▪ Liposomal amphotericin B or amphotericin B lipid complex **(AII)** 2–4 mg/kg IV daily x 10 days; or interrupted schedule (e.g., 4 mg/kg on days 1–5, 10, 17, 24, 31, 38) to achieve total dose of 20–60 mg/kg **(BII)**	Alternative therapy for initial infection ▪ Amphotericin B deoxycholate 0.5–1.0 mg/kg IV daily for total dose of 1.5–2.0 grams **(BII)**; or ▪ Sodium stibogluconate (pentavalent antimony) **(AII)** 20 mg/kg body weight IV or IM daily for 3–4 weeks. (Contact the CDC Drug Service at 404-639-3670 or drugservice@cdc.gov)	ART should be initiated or optimized **(AII)** Parenteral paromomycin has been proven effective in HIV-negative patients in India - may be available as an alternative in India in the future **(BI)**
	Preferred chronic maintenance therapy (secondary prophylaxis) – especially in patients with CD4+ count <200 cells/μL ▪ Liposomal amphotericin B 4 mg/kg every 2–4 weeks **(AII)**	Alternative chronic maintenance therapy (secondary prophylaxis) ▪ Amphotericin B Lipid Complex **(AII)** 3–4 mg/kg every 2–4 weeks **(AII)** ▪ Sodium stibogluconate 20 mg/kg IV or IM every 4 weeks **(AII)**	Alternative regimens for treatment failure Miltefosine 100 mg PO daily for 4 weeks (available in Europe via compassionate use) **(CIII)**
Leishmaniasis, cutaneous	Preferred therapy for acute infection ▪ Liposomal amphotericin B 2–4 mg/kg IV daily for 10 days or interrupted schedule (e.g., 4 mg/kg on days 1–5, 10, 17, 24, 31, 38) to achieve total dose of 20–60 mg/kg **(BIII)**; or ▪ Sodium stibogluconate 20 mg/kg IV or IM daily for 3–4 weeks **(BIII)**	Alternative therapy for acute infection Choice dependent on species of *Leishmania* Other options include oral miltefosine, topical paromomycin, intralesional pentavalent antimony, and local heat therapy	

TABLE 2. (*Continued*) Drug therapy for treatment and chronic maintenance therapy of AIDS-associated opportunistic infections in adults and adolescents

Opportunistic infection	Preferred therapy, duration of therapy, chronic maintenance	Alternative therapy	Other options/issues
Chagas disease (American trypanosomiasis)	Preferred therapy for acute, early chronic, and reactivated disease ▪ Benznidazole 5–8 mg/kg/day PO in 2 divided doses for 30–60 days **(BIII)** (not commercially available in the U.S., contact the CDC Drug Service at 404-639-3670 or drugservice@cdc.gov)	Alternative therapy ▪ Nifurtimox 8–10 mg/kg/day PO for 90–120 days **(CIII)** (Contact the CDC Drug Service at 404-639-3670 or drugservice@cdc.gov)	Duration of therapy has not been studied in HIV-infected patients Initiation or optimization of ART in patients undergoing treatment for Chagas disease, once the patient is clinically stable **(AIII)**
Isospora belli infection	Preferred therapy for acute infection: ▪ TMP-SMX **(AI)** (160 mg/800 mg) PO (or IV) qid for 10 days **(AII);** or ▪ TMP-SMX (160 mg/800 mg) PO (or IV) bid for 7–10 days **(BI)** ▪ May increase daily dose and/or duration (up to 3–4 weeks) if symptoms worsen or persist **(BIII)**	Alternative therapy for acute infection ▪ Pyrimethamine 50–75 mg PO daily plus leucovorin 10–25 mg PO daily **(BIII)**; or ▪ Ciprofloxacin 500 mg PO bid x 7 days **(CI)** – as a second line alternative	Fluid and electrolyte management in patients with dehydration **(AIII)** Nutritional supplementation for malnourished patients **(AIII)** Immune reconstitution with ART may result in fewer relapses **(AIII)**
	Preferred chronic maintenance therapy (secondary prophylaxis) In patients with CD4+ count <200/μL, ▪ TMP-SMX (160 mg/800 mg) PO tiw **(AI)**	Alternative chronic maintenance therapy (secondary prophylaxis) ▪ TMP-SMX (160 mg/800 mg) PO daily or (320 mg/1600 mg) tiw **(BIII)** ▪ Pyrimethamine 25 mg PO daily + leucovorin 5–10 mg PO daily **(BIII)** ▪ Ciprofloxacin 500 mg tiw **(CI)** – as a second line alternative	

ART = antiretroviral therapy; bid = twice a day; biw = twice weekly; g = gram; IM = intramuscular; IV = intravenous; μg = microgram; mg = milligram; PO = oral; qAM = every morning; qid = four times a day; q'n'h = every 'n' hour; qPM = every evening; SQ = subcutaneous; tid = three times daily, tiw = three times weekly

TABLE 3. Recommended doses of first-line antituberculosis drugs for adults*

Drug	Daily	2x/wk (not recommended for patients with CD4+ count <100 cells/μL)	3x/wk
Isoniazid	5 mg/kg (usual dose 300 mg)	15 mg/kg (usual dose 900 mg)	15 mg/kg (usual dose 900 mg)
Rifampin [NOTE: rifampin is not recommended in patients receiving HIV protease inhibitor(s) (PI) or the CCR5 antagonist maraviroc]	10 mg/kg (usual dose 600 mg)	10 mg/kg (usual dose 600 mg)	10 mg/kg (usual dose 600 mg)
Rifabutin (w/o HIV PIs or NNRTI§)	5 mg/kg (usual dose 300 mg)	5 mg/kg (usual dose 300 mg)	5 mg/kg (usual dose 300 mg)
w/ HIV protease inhibitors	150 mg†	Not recommended†	150 mg†
w/ efavirenz	450–600 mg	450–600 mg	450–600 mg
Streptomycin/amikacin/ kanamycin	15 mg/kg	25 mg/kg	25 mg/kg
Pyrazinamide			
40–55 kg body weight	1,000 mg (18.2–25.0 mg/kg)	2,000 mg (36.4–50.0 mg/kg)	1,500 mg (27.3–37.5 mg/kg)
56–75 kg body weight	1,500 mg (20.0–26.8 mg/kg)	3,000 mg (40.0–53.6 mg/kg)	2,500 mg (33.3–44.6 mg/kg)
>75 kg body weight	2,000 mg (22.2–26.3 mg/kg)	4,000 mg (44.4–52.6 mg/kg)	3,000 mg (33.3–44.6 mg/kg)
Ethambutol			
40-55 kg body weight	800 mg (14.5–20.0 mg/kg)	2,000 mg (36.4–50.0 mg/kg)	1,200 mg/kg (21.8–30.0 mg/kg)
56-75 kg body weight	1,200 mg (16.0–21.0 mg/kg)	2,800 mg (37.3–50.0 mg/kg)	2,000 mg/kg (26.7–35.7 mg/kg)
>75 kg body weight	1,600 mg (17.8–21.0 mg/kg)	4,000 mg (44.4–52.6 mg/kg)	2,400 mg/kg (26.7–31.6 mg/kg)

* Some experts recommend that for severe tuberculosis infection (e.g., CNS, pericardial disease) considerations should be given to the use of adjuvant corticosteroids. The dosing and taper schedule should be individualized according to severity of disease and adjusted, as needed, in response to treatment.
† Acquired rifamycin resistance has been reported in patients with inadequate rifabutin levels while on 150 mg twice weekly dosing together with ritonavir-boosted PIs. May consider therapeutic drug monitoring when rifabutin is used with a ritonavir-boosted PI and adjust dose accordingly.
§ Non-nucleoside reverse transcriptase inhibitor.

TABLE 4. Criteria for discontinuing and restarting opportunistic infection prophylaxis for adults and adolescents with human immunodeficiency virus infection

Opportunistic infection	Criteria for discontinuing primary prophylaxis	Criteria for restarting primary prophylaxis	Criteria for discontinuing secondary prophylaxis/chronic maintenance therapy	Criteria for restarting secondary prophylaxis/ chronic maintenance
Pneumocystis pneumonia (PCP)	CD4+ count >200 cells/μL for >3 months in response to antiretroviral therapy (ART) **(AI)**	CD4+ count <200 cells/μL **(AIII)**	CD4+ count increased from <200 cells/μL to >200 cells/μL for ≥3 months in response to ART **(BII)** If PCP is diagnosed when CD4+ count >200 cells/μL, prophylaxis should probably be continued for life regardless of CD4+ count rise in response to ART **(CIII)**	CD4+ count <200 cells/μL **(AIII)**, or if PCP recurred at a CD4+ count >200 cells/ μL **(CIII)**
Toxoplasma gondii encephalitis (TE)	CD4+ count >200 cells/μL for >3 months in response to ART **(AI)**	CD4+ count <100–200 cells/μL **(AIII)**	Successfully completed initial therapy, remain asymptomatic of signs and symptoms of TE, and CD4+ count >200 cells/μL for >6 months in response to ART **(BI)**	CD4+ count <200 cells/μL **(AIII)**
Microsporidiosis	Not applicable	Not applicable	No signs and symptoms of non-ocular microsporidiosis and CD4+ count >200 cells/μL for >6 months in response to ART **(BIII)** Patients with ocular microsporidiosis should be on therapy indefinitely regardless of CD4+ count **(BIII)**	No recommendation
Disseminated *Mycobacterium avium* complex (MAC) disease	CD4+ count >100 cells/μL for ≥3 months in response to ART **(AI)**	CD4+ count <50 cells/μL **(AIII)**	If fulfill the following criteria **(BII)** • Completed ≥12 months therapy, and • No signs & symptoms of MAC, and • Have sustained (≥6 months) CD4+ count >100 cells/μL in response to ART	CD4+ count <100 cells/μL **(AIII)**
Bartonellosis	Not applicable	Not applicable	If fulfill the following criteria **(CIII)**: • Received 3–4 months of treatment • CD4+ count >200 cells/μL for ≥6 months • Certain specialists would only discontinue therapy if *Bartonella* titers have also decreased by fourfold	No recommendation
Mucosal candidiasis	Not applicable	Not applicable	If used, reasonable to discontinue when CD4+ count >200 cells/μL **(CIII)**	No recommendation
Cryptococcal meningitis	Not applicable	Not applicable	If fulfill the following criteria **(BII)** • Completed course of initial therapy • Remain asymptomatic of cryptococcosis • CD4+ count ≥200 cells/μL for >6 months in response to ART Certain specialists would perform a lumbar puncture to determine if cerebrospinal fluid is culture- and antigen-negative before stopping therapy **(CIII)**	CD4+ count <200 cells/μL **(AIII)**
Histoplasma capsulatum infection	If used, CD4+ count >150 cells/ μL for 6 months on ART **(BIII)**	For patients at high risk for acquiring histoplasmosis, restart at CD4+ count ≤150 cells/μL **(CIII)**	If fulfill the following criteria **(AI)** • Received itraconazole for ≥1 year • Negative blood cultures • CD4+ count >150 cells/μL for ≥6 months in response to ART • Serum *Histoplasma* antigen <2 units	CD4+ count ≤150 cells/μL **(BIII)**

TABLE 4. (*Continued*) Criteria for discontinuing and restarting opportunistic infection prophylaxis for adults and adolescents with human immunodeficiency virus infection

Opportunistic infection	Criteria for discontinuing primary prophylaxis	Criteria for restarting primary prophylaxis	Criteria for discontinuing secondary prophylaxis/chronic maintenance therapy	Criteria for restarting secondary prophylaxis/ chronic maintenance
Coccidioidomycosis	If used, CD4+ count ≥250 cells/ μL for ≥6 months **(CIII)**	If used, restart at CD4+ count <250 cells/μL **(BIII)**	**Only for patients with focal coccidioidal pneumonia (CIII)**: • Clinically responded to ≥12 months of antifungal therapy • CD4+ count >250 cells/μL • Receiving ART Suppressive therapy should be continued indefinitely, even with increase in CD4+ count on ART for patients with diffuse pulmonary **(AIII)**, disseminated **(AIII)**, or meningeal diseases **(AII)**	No recommendation
Cytomegalovirus retinitis	Not applicable	Not applicable	• CD4+ count >100 cells/μL for >3–6 months in response to ART **(BII)**. Therapy should be discontinued only after consultation with an ophthalmologist, taking into account magnitude and duration of CD4+ count increase, anatomic location of the lesions, vision in the contralateral eye, and the feasibility of regular ophthalmologic monitoring **(BII)**. • Routine (every 3 months) ophthalmologic follow-up is recommended for early detection of relapse or immune restoration uveitis **(AII)**	CD4+ count <100 cells/μL **(AIII)**
Penicillium marneffei infection	Not applicable	Not applicable	CD4+ count >100 cells/μL for ≥6 months in response to ART **(BII)**	CD4+ count <100 cells/μL **(AIII)** or if penicilliosis recurs at CD4+ count >100 cells/ μL **(CIII)**
Visceral leishmaniasis	Not applicable	Not applicable	Sustained (>3–6 months) increase in CD4+ count to >350 cells/μL in response to ART **(CIII)**	No recommendation
Isospora belli infection	Not applicable	Not applicable	Sustained increase in CD4+ count to >200 cells/μL for >6 months in response to ART and without evidence of *I. belli* infection **(BIII)**	No recommendation

TABLE 5. Common toxicities of agents for treatment and prevention of opportunistic infections

Drug class	Drugs	Toxicities
Anti-fungal agents	Amphotericin B deoxycholate and lipid formulations	Nephrotoxicity, infusion-related reactions (fever, chills, rigors, back pain, rarely, hypotension), electrolyte imbalances, anemia, thrombophlebitis, nausea, vomiting, hypertension. Lipid formulations might have lower incidence of nephrotoxicity and infusion-related reactions.
	Anidulafungin	Hepatotoxicity, histamine-related infusion reactions (flushing, rash, pruritus, hypotension, dyspnea; rare if infusion rate <1.1 mg/min), hypokalemia, diarrhea, deep vein thrombosis (rare)
	Caspofungin	Headache, thrombophlebitis, facial flushing, erythema, rash, infusion-related reactions (flushing, rash, pruritus, hypotension, dyspnea), hypokalemia, fever, hepatotoxicity
	Clotrimazole (troche)	Nausea, vomiting, diarrhea, anorexia, metallic taste, increase in serum transaminases
	Flucytosine	Bone marrow suppression, diarrhea, nausea, vomiting
	Fluconazole	Hepatotoxicity, rash
	Itraconazole	Hepatotoxicity, congestive heart failure, edema, hypokalemia, nausea, vomiting, diarrhea, abdominal pain, rash
	Micafungin	Hypersensitivity reaction (anaphylaxis and anaphylactoid reactions, rash, pruritus, facial flushing), hepatotoxicity, hemolysis, leukopenia, thrombophlebitis, nausea, vomiting, diarrhea, hypokalemia
	Nystatin (oral preparations)	Nausea, vomiting, anorexia, diarrhea, hypersensitivity reaction (rare)
	Posaconazole	Nausea, vomiting, diarrhea, abdominal pain, hepatotoxicity, edema, hypokalemia, QTc prolongation, rash
	Voriconazole	Visual disturbances, photosensitivity, rash, hepatotoxicity, peripheral edema, headache, delirium, hallucination, QTc prolongation, arrhythmias, hypotension
Anti-*Pneumocystis* pneumonia (PCP) agents	Atovaquone	Diarrhea, rash, nausea, vomiting, headache, hyponatremia, hyperglycemia, fever
	Clindamycin	Diarrhea, pseudomembranous colitis, rash
	Dapsone	Methemoglobinemia, hemolytic anemia (especially in patients with G-6-PD deficiency), neutropenia, rash, fever, hepatitis, hyperkalemia, peripheral neuropathy, hepatotoxicity
	Pentamidine	IV infusion: Nephrotoxicity, infusion-related hypotension, arrhythmias, pancreatitis, hypoglycemia, diabetes mellitus, hepatitis, electrolyte abnormalities Aerosolized therapy: Brochospasm, cough, dyspnea, tachypnea, metallic taste, pneumothorax (rare)
	Primaquine	Methemoglobinemia, hemolytic anemia (especially in patients with G-6-PD deficiency), abdominal cramps, nausea, vomiting
	Trimethoprim-sulfamethoxazole (TMP-SMX)	Rash, Stevens-Johnson Syndrome, bone marrow suppression, hepatotoxicity, increase in serum creatinine, nausea, vomiting, crystalluria, hyperkalemia
Antitoxoplasmosis agents (for atovaquone, clindamycin, and TMP-SMX, see Agents for PCP, above)	Pyrimethamine	Neutropenia, thrombocytopenia, megaloblastic anemia, rash
	Sulfadiazine	Rash, Stevens-Johnson Syndrome, bone marrow suppression, crystalluria, renal insufficiency, nausea, vomiting

TABLE 5. (*Continued*) Common toxicities of agents for treatment and prevention of opportunistic infections

Drug class	Drugs	Toxicities
Antimycobacterial agents	Amikacin	Nephrotoxicity, ototoxicity (both hearing loss and vestibular toxicity are possible)
	Azithromycin	Hepatotoxicity, ototoxicity (with prolonged use), rash, urticaria, pruritus, nausea, vomiting, abdominal pain, diarrhea
	Capreomycin	Nephrotoxicity, ototoxicity (both hearing loss and vestibular toxicity are possible). Intramuscular injections: injection-site reactions, pain
	Ciprofloxacin/ levofloxacin/ ofloxacin/ moxifloxacin	Nausea, vomiting, abdominal pain, diarrhea, headache, dizziness, sleep disturbances, tendonitis, photosensitivity, hypoglycemia, neurotoxicity (especially with high dose or in patients with renal dysfunction)
	Clarithromycin	Hepatotoxicity, ototoxicity (with high doses), headache, nausea, vomiting, abdominal cramps, diarrhea, rash
	Cycloserine	Neuropsychiatric toxicities (headache, somnolence, vertigo, tremor, dysarthria, irritability, confusion, paranoia, psychosis)
	Ethambutol	Optic neuritis, peripheral neuropathy, headache, nausea, vomiting, anorexia, hepatotoxicity, hyperuricemia, rash
	Ethionamide	Gastrointestinal side effects (dose related): nausea, vomiting, abdominal pain, metallic taste, anorexia; dizziness; drowsiness; depression; hepatotoxicity
	Isoniazid	Hepatotoxicity, peripheral neuropathy, optic neuritis
	Pyrazinamide	Hepatotoxicity, hyperuricemia, arthralgia, nausea, vomiting
	Rifabutin	Hepatotoxicity, uveitis, neutropenia, red-orange discoloration of body fluids, rash, arthralgia, anemia, thrombocytopenia
	Rifampin	Hepatotoxicity, red-orange discoloration of body fluids, thrombocytopenia, hemolytic anemia, rash, flu-like syndrome
	Streptomycin	Nephrotoxicity, ototoxicity (both hearing loss and vestibular toxicity are possible) Intramuscular injections: injection-site reactions, pain

TABLE 5. (*Continued*) Common toxicities of agents for treatment and prevention of opportunistic infections

Drug class	Drugs	Toxicities
Antiviral agents	Acyclovir	Crystalluria (with high dose or renal impairment), nausea, vomiting, neurotoxicity (high doses, especially in patients with renal impairment; agitation, confusion, hallucination, seizure, coma), nephrotoxicity (particularly after rapid IV infusion), thrombophlebitis at peripheral intravenous infusion site
	Adefovir	Nephrotoxicity, nausea, vomiting, asthenia
	Cidofovir	Nephrotoxicity, proteinuria, ocular hypotony, anterior uveitis/iritis, neutropenia, metabolic acidosis, asthenia. Side effects most likely related to co-administration of probenecid: rash, nausea, vomiting, anorexia
	Emtricitabine	Headache, nausea, hyperpigmentation, diarrhea, rash
	Entecavir	Headache, fatigue, dizziness, nausea
	Famciclovir	Headache, nausea, vomiting, anorexia
	Foscarnet	Nephrotoxicity, electrolyte imbalances (hypocalcemia, hypomagnesemia, hypophosphatemia, hyperphosphatemia, hypokalemia), penile ulceration, nausea, vomiting, anorexia, headache, seizure, thrombophlebitis
	Ganciclovir	Neutropenia, thrombocytopenia, anemia, IV-site-associated thrombophlebitis, confusion.
	Interferon-alfa and peginterferon-alfa	Influenza-like syndrome (fever, headache, fatigue, and myalgia), neuropsychiatric disorders (depression and suicidal ideation), neutropenia, thrombocytopenia, thyroid dysfunction, injection-site reactions, alopecia, nausea, anorexia, diarrhea, weight loss, development or exacerbation of autoimmune disorders, ophthalmologic disorders (retinal hemorrhage, retinal artery or vein obstructions, and cotton wool spots)
	Lamivudine	Nausea, vomiting
	Ribavirin	Hemolytic anemia, hyperbilirubinemia, nausea, vomiting, anorexia, dyspepsia, rash
	Telbuvidine	Nausea, vomiting, abdominal pain, increase in creatine kinase, headache, dizziness
	Tenofovir	Nausea, asthenia, renal insufficiency, hypophosphatemia, decrease in bone mineral density
	Valacyclovir	Nausea, vomiting, headache crystalluria (with high dose or renal impairment), neurotoxicity (high doses, especially in patients with renal impairment; agitation, confusion, hallucination, seizure, coma); at a high dose of 8 g/day: thrombotic thrombocytopenic purpura/hemolytic uremic syndrome reported in advanced human immunodeficiency virus patients and in transplant recipients
	Valganciclovir	Neutropenia, thrombocytopenia, anemia, nausea, confusion

TABLE 5. (*Continued*) Common toxicities of agents for treatment and prevention of opportunistic infections

Drug class	Drugs	Toxicities
Antiparasitic agents	Albendazole	Nausea, vomiting, hepatotoxicity, hypersensitivity reaction, neutropenia, dizziness, headache, reversible alopecia
	Atovaquone-proguanil	Pruiritis, abdominal pain, vomiting, diarrhea, anorexia, erythema multiformae, asthenia, dizziness, headache, oral ulcers
	Benznidazole	Peripheral neuropathy, bone marrow suppression, rash
	Chloroquine & hydroxychloroquine	Headache, pruritus, skin pigmentation, nausea, vomiting, anorexia, photosensitivity, visual disturbances, QTc prolongation, neuromyopathy (rarely with long-term use)
	Fumagillin (investigational)	Oral therapy: neutropenia, thrombocytopenia, vertigo, nausea, vomiting, diarrhea, anorexia, abdominal cramps Ocular therapy: minimal systemic effect or local effect
	Mefloquine	Depression, psychosis, rash, vomiting, epigastric pain, nausea, agitation, dizziness, headache, insomnia, abnormal dreams, arrhythmias
	Miltefosine	Nausea, vomiting, leukocytosis, thrombocytosis, nephrotoxicity, retinal degeneration, diarrhea
	Nifurtimox	Rash, nausea, vomiting, anorexia, neuropsychiatric symptoms, hepatotoxiicty, arthralgia, myalgia,
	Nitazoxanide	Nausea, vomiting, diarrhea, abdominal pain, hypotension, headache
	Pentavalent antimony (sodium stibogluconate)	Nausea, vomiting, abdominal pain, anorexia, pancreatitis, hepatotoxicity, arthralgia, myalgia, ECG changes (with higher than 20 mg/kg dose), rash, thrombophlebitis, leukopenia, anemia, thrombocytopenia
	Quinidine glucuronate	QTc prolongation, lightheadedness, diarrhea, cramping, palpitation headache, rash
	Quinine	Headache, nausea, vomiting, diarrhea, tinnitus, blurred vision, cinchonism, hypersensitivity reaction
	Tetracycline	Photosensitivity, tooth discoloration if taken by infants and children, pruritus, nausea, vomiting, diarrhea, hepatotoxicity, rash
Treatment for syphilis (for azithromycin, see Antimycobacterial agents, above)	Ceftriaxone	Cholelithiasis, rash Intramuscular injections: injection-site reactions, pain
	Doxycycline	Photosensitivity reaction, nausea, vomiting, diarrhea, esophageal ulceration, thrombophlebitis (with IV infusion)
	Penicillin G	All penicillin G preparations: Hypersensitivity reactions (immediate or delayed reaction), bone marrow suppression (rare), drug fever Benzathine penicillin G: Injection-site reactions (pain and erythema) Procaine penicillin G: Injection-site reactions (pain and erythema) Aqueous crystalline penicillin G: Thrombophlebitis, neurotoxicity at high doses (especially in patients with renal dysfunction)
Other antibacterial agents	Erythromycin	Nausea, vomiting, abdominal pain, hepatotoxicity, cholestatic jaundice, ototoxicity (hearing loss, tinnitus), rash, cardiac arrhythmia

TABLE 6. Substantial pharmacokinetic drug-drug interactions for drugs used in the treatment of opportunistic infections

Drugs	Interacting with	Mechanism/effects	Recommendations
Acyclovir	Probenecid (with cidofovir)	Probenecid might decrease renal clearance of acyclovir by 32%, increasing acyclovir area under the concentration curve (AUC)	No dosage adjustment; monitor for acyclovir toxicities
Atovaquone	Rifabutin	Atovaquone concentration (conc.) decreased 34%; Rifabutin conc. decreased 19%	This combination should be avoided
	Rifampin	Atovaquone conc. decreased 52%; Rifampin conc. increased 37%	This combination should be avoided
	Tetracycline	Atovaquone conc. decreased 40%	This combination should be avoided; interaction study with doxycycline not available
	Zidovudine	Zidovudine AUC increased 31%, possibly because of atovaquone inhibition of zidovudine glucuronidation	No dosage adjustment recommended, monitor for zidovudine toxicities
Caspofungin	Efavirenz, nevirapine, nelfinavir	Possible decreases in caspofungin conc. based on regression analyses of patient pharmacokinetic data; no formal pharmacokinetic study available	Manufacturer recommends considering increasing maintenance dose of caspofungin to 70 mg/day when co-administered with the interacting drugs
	Rifampin	Caspofungin conc. decreased 30%	Caspofungin dose should be increased to 70 mg/day
Cidofovir (plus probenecid)	Acyclovir, cephalosporins, dapsone, fluoroquinolones, ganciclovir, penicillins, valacyclovir, valganciclovir, zidovudine	Probenecid might decrease renal clearance of these drugs, increasing plasma conc.	Because of the infrequent dosing of probenecid when used with cidofovir, no dosage adjustment is necessary for interacting drugs; monitor for dose-related toxicities
Ciprofloxacin	Didanosine buffered formulations	Decreased ciprofloxacin absorption attributed to chelation with magnesium-aluminum buffer	Administer didanosine buffered preparation at least 2 hours after or 6 hours before ciprofloxacin
	Cidofovir (plus probenecid)	Probenecid might reduce renal clearance of ciprofloxacin, increasing plasma conc.	No dosage adjustment necessary; monitor for ciprofloxacin toxicities

TABLE 6. (*Continued*) Substantial pharmacokinetic drug-drug interactions for drugs used in the treatment of opportunistic infections

Drugs	Interacting with	Mechanism/effects	Recommendations
Clarithromycin (CYP3A4 inhibitor and substrate)	Atazanavir	Atazanavir minimum conc. (Cmin) increased 91%; Clarithromycin AUC increased 94%; Cmin increased 160%	Because of concerns about QTc prolongation, decrease clarithromycin dose 50% or switch to azithromycin
	Delavirdine	Delavirdine AUC increased 44%; clarithromycin AUC increased 100% and 14-OH clarithromycin AUC decreased 75%	No dosage adjustment recommended; might consider clarithromycin dose adjustment in patients with renal insufficiency; monitor for clarithromycin toxicities; or switch to azithromycin
	Darunavir	Clarithomycin AUC increased 57%; Cmin increased 174%	No dosage change in patients with normal renal function. *CrCl (mL/min)* — *Clarithromycin* 30-60 — decrease dose by 50% <30 — decrease dose by 75%
	Efavirenz	Clarithromycin AUC decreased 39%; 14-OH clarithromycin AUC increased 34%	Significance unknown, no dosage adjustment recommended; some recommend switching to azithromycin
	Etravirine	Clarithromycin AUC decreased 39%, 14-OH clarithromycin AUC increased by 21%; etravirine Cmin increased by 46%; AUC increased 42%	Alternative to clarithromycin should be considered
	Itraconazole	Possible bi-directional CYP3A4 inhibition and increased AUC of both drugs	Monitor for toxicities of both itraconazole and clarithromycin or switch to azithromycin
	Lopinavir/ritonavir	Increased clarithromycin AUC and decrease in 14-OH clarithromycin AUC	No dosage change in patients with normal renal function. *CrCl (mL/min)* — *Clarithromycin* 30-60 — decrease dose by 50% <30 — decrease dose by 75%
	Maraviroc	Potential for inhibition of maraviroc metabolism	Maraviroc: Reduce dose to 150 mg bid or switch clarithromycin to azithromycin

TABLE 6. (*Continued*) Substantial pharmacokinetic drug-drug interactions for drugs used in the treatment of opportunistic infections

Drugs	Interacting with	Mechanism/effects	Recommendations
Clarithromycin (CYP3A4 inhibitor and substrate) (*Continued*)	Rifabutin	Clarithromycin AUC decreased by 44%; rifabutin AUC increased 76%–99%	Might need clarithromycin dose increase and decrease rifabutin dose; might result in increased rifabutin toxicities; some recommend switching to azithromycin
	Rifampin	Decreased mean clarithromycin conc. by 87%	This combination should be avoided; consider switching to azithromycin
	Ritonavir	Clarithromycin AUC increased 77% and decrease in 14-OH clarithromycin AUC	No dosage change in patients with normal renal function. *CrCl (mL/min)* — *Clarithromycin* 30–60 — decrease dose 50% < 30 — decrease dose 75%
	Tipranavir	Clarithromycin AUC: increased 19%; Cmin: increased 68% 14-hydroxyclarithromycin AUC: decreased 97%; Cmin: decreased 95% Tipranavir AUC: increased 66%; Cmax: increased 40%; Cmin: increased 100%	Monitor for tipranavir toxicity and possible decreased clarithromycin effects
Dapsone	Rifampin	Decreased dapsone level 7–10-fold and dapsone half-life ($t_{1/2}$) decreased from 24 to 11 hours	Reduced dapsone activities; might consider increasing dapsone dose or use alternative agent
Doxycycline	Atovaquone	Tetracycline decreased atovaquone conc. 40%; effect of doxycycline on atovaquone unknown	Until doxycycline-atovaquone interaction data become available, avoid this combination if possible
	Didanosine buffered formulations	Decreased doxycycline absorption attributed to chelation with magnesium-aluminum buffer	Separate doxycycline with didanosine by at least 2 hours or use didanosine enteric-coated capsule
	Rifampin	Increased doxycycline clearance, decreased $t_{1/2}$ and AUC	Potential for decreased doxycycline efficacy, monitor closely for therapeutic failure
Erythromycin (CYP3A4 inhibitor)	Itraconazole	Potential for bi-directional inhibition of hepatic metabolism and increased serum conc. of both	Monitor for toxicities of both drugs
Fluconazole (CYP3A4 inhibitor)	Nevirapine	Nevirapine conc. increased by 100% compared with historic control	Recommended monitor for nevirapine toxicity
	Rifabutin	Rifabutin AUC increased 80%; no effect on fluconazole levels	Monitor for rifabutin toxicity or might consider dose reduction to 150 mg/day
	Rifampin	Fluconazole AUC decreased by 23%–56%; no change in rifampin conc.	Monitor for antifungal efficacy, might need to increase fluconazole dose
	Saquinavir	Saquinavir AUC increased 50%	Clinical significance unknown
	Tipranavir	Tipranavir AUC increased 50%; Cmin increased 69%	Monitor for tipranavir toxicity; fluconazole doses >200 mg/day not recommended
	Zidovudine	Fluconazole decreased glucuronidation of zidovudine; fluconazole 400 mg/day results in increased zidovudine AUC by 74%	Monitor for zidovudine toxicities

TABLE 6. (*Continued*) Substantial pharmacokinetic drug-drug interactions for drugs used in the treatment of opportunistic infections

Drugs	Interacting with	Mechanism/effects	Recommendations
Ganciclovir	Didanosine buffered formulations (study with enteric coated didanosine has not been done)	Didanosine AUC increased 78% with IV ganciclovir and increased 111% with oral ganciclovir	Might consider reducing didanosine dose; monitor for didanosine toxicities
	Cidofovir (plus probenecid)	Probenecid might decrease ganciclovir clearance and increase ganciclovir conc.	Because of the infrequent dosing of probenecid when used with cidofovir, no dosage adjustment is necessary; monitor for dose-related toxicities
Itraconazole (CYP3A4 inhibitor and substrate)	Clarithromycin	Potential for bi-directional inhibition of CYP3A4 metabolism with increased AUC of itraconazole and/or interacting drug(s)	Monitor for toxicities of clarithromycin; monitor itraconazole level and toxicities; or switch to azithromycin
	Delavirdine	Potential for bi-directional inhibition of CYP3A4 metabolism with increased AUC of itraconazole and/or delavirdine	Monitor for toxicities of delavirdine; monitor itraconazole level and toxicities
	Didanosine buffered preparation	Might decrease itraconazole oral absorption because of increased gastric pH from antacid in the didanosine preparation	Administer itraconazole at least 2–4 hours before didanosine buffered tablets, use didanosine enteric coated capsule, or take itraconazole with cola beverage to decrease gastric pH
	Efavirenz	Decreased itraconazole conc.	Monitor itraconazole level and adjust dose accordingly
	Erythromycin	Potential for bi-directional inhibition of CYP3A4 metabolism with increased AUC of itraconazole and/or erythromycin	Monitor for toxicities of erythromycin; monitor itraconazole level and toxicities
	Etravirine	Etravirine concentration may be increased, itraconazole concentration may be decreased. Extent of the interaction unknown.	Dose adjustment with itraconazole might be necessary – depending on the presence of other concomitant antiretrovirals (e.g., protease inhibitors). Monitor itraconazole level and dose adjust accordingly
	Maraviroc	Potential for inhibition of maraviroc metabolism	Maraviroc: Reduce dose to 150 mg bid
	Nevirapine	Potential for induction of itraconazole metabolism and decrease in itraconazole conc.	Monitor itraconazole level and adjust accordingly; monitor therapeutic efficacy
	Protease inhibitors other than ritonavir	Potential for bi-directional inhibition of CYP3A4 metabolism with increased AUC of itraconazole and/or PIs	Monitor for toxicities of protease inhibitors; monitor itraconazole level and toxicities (especially in patients with ritonavir-boosted PI regimens)
	Rifabutin	Decrease in itraconazole conc. by 70%; potential for inhibition of rifabutin metabolism and increased rifabutin conc.	Avoid concomitant use if possible; if the combination is to be used, monitor itraconazole level and adjust dose accordingly; monitor for rifabutin toxicity, consider monitoring rifabutin conc.
	Rifampin	Itraconazole AUC decreased 64%–88%; no change in rifampin conc.	Avoid concomitant use if possible. If the combination is to be used, monitor itraconazole level and adjust dose accordingly; monitor therapeutic response
	Ritonavir	Potential for substantial increase in itraconazole conc.	Might require reduced itraconazole dose; monitor itraconazole level and toxicities

TABLE 6. (*Continued*) Substantial pharmacokinetic drug-drug interactions for drugs used in the treatment of opportunistic infections

Drugs	Interacting with	Mechanism/effects	Recommendations
Ketoconazole (CYP3A4 substrate)	Darunavir	Darunavir AUC increased 42%; Cmin increased 73%; ketoconazole AUC increased 212%; Cmin increased 868%	Combination not recommended
	Delavirdine	Delavirdine Cmin increased 50%	Monitor for delavirdine toxicities
	Didanosine buffered formulations	Might decrease oral absorption of ketoconazole because of increased gastric pH from antacid in the didanosine preparation	Space doses of ketoconazole and didanosine by at least 2 hours or administer ketoconazole with cola beverage to decrease pH
	Etravirine	Etravirine concentration may be increased, ketonconazole concentration may be decreased. Extent of interaction unknown.	Magnitude of the interaction also depends on concomitant drugs used. Use with caution or use alternative agents.
	Fosamprenavir	Amprenavir AUC increased 31%; ketoconazole AUC increased 44%	Monitor for toxicities of each drug
	Indinavir	Indinavir AUC increased 68%; no substantial change in ketoconazole conc.	Decrease indinavir dose to 600 mg every 8 hours
	Lopinavir/ritonavir	Ketoconazole AUC increased threefold; no substantial change in lopinavir pharmacokinetics	Decrease ketoconazole dose and monitor for toxicities
	Maraviroc	Maraviroc AUC increased 400%	Reduce maraviroc dosage to 150 mg twice daily
	Nevirapine	Ketoconazole AUC decreased 63%; nevirapine AUC increased 15%–30%	Consider alternative antifungal or monitor for ketoconazole efficacy
	Rifabutin	Possible increase in rifabutin conc. and decrease in ketoconazole conc.	Monitor for rifabutin toxicities and ketoconazole efficacy
	Rifampin	Ketoconazole levels decreased 50%	Avoid concomitant use if possible; consider alternative antifungal and/or antimycobacterial agent(s)
	Ritonavir	Ketoconazole AUC increased 3.4-fold	Ketoconazole dose >200 mg/day not recommended; monitor for ketoconazole toxicities
	Tipranavir/ritonavir	Possible increase in ketoconazole conc.	Use with caution; ketoconazole doses >200 mg/day not recommended
Mefloquine	Ritonavir	Ritonavir AUC decreased 31%, and Cmin: decreased 43%; No substantial change in mefloquine pharmacokinetics	Avoid combination if possible. If used, monitor for signs of antiretroviral failure.
Posaconazole	Etravirine	Etravirine concentration may be increased, posaconazole concentration unchanged	No dosage adjustment necessary
	Rifabutin	Posaconazole AUC decreased 49%; rifabutin AUC increased 72%	Avoid concomitant use if possible, or monitor drug concentrations and adjust doses accordingly
	Rifampin	Posaconazole level may be reduced significantly	Avoid combination if possible, if used, monitor posaconazole level and adjust dose if necessary
Pyrazinamide	Zidovudine	Decreased pyrazinamide conc. in one study	Monitor therapeutic efficacy or consider monitoring pyrazinamide level

TABLE 6. (*Continued*) Substantial pharmacokinetic drug-drug interactions for drugs used in the treatment of opportunistic infections

Drugs	Interacting with	Mechanism/effects	Recommendations
Ribavirin	Didanosine	Increased intracellular levels of dideoxyadenosine triphosphate (ddA-TP)	This combination should be avoided; increased didanosine (ddI)-associated mitochondrial toxicities
	Zidovudine	Decreased intracellular activities of zidovudine against HIV in vitro	Potential for worsening of HIV suppression; monitoring HIV viral load
Rifabutin* (CYP3A4 inducer and substrate)	Atazanavir	Rifabutin AUC increased 210%; Cmin increased 343%; minimal change in atazanavir pharmacokinetics	Decrease rifabutin dose to 150 mg tiw, or adjust dose based on rifabutin level*
	Atovaquone	Atovaquone conc. decreased 34%; rifabutin conc. decreased 19%	This combination should be avoided
	Clarithromycin	Rifabutin AUC increased 76% because of inhibition of hepatic metabolism; clarithromycin AUC might be reduced	Consider reducing rifabutin dose, monitor for rifabutin toxicities, or switching macrolide to azithromycin
	Darunavir	Darunavir might inhibit metabolism of rifabutin	Decrease rifabutin dose to 150 mg tiw, or adjust dose based on rifabutin level*
	Delavirdine	Delavirdine AUC decreased 80%; rifabutin AUC increased 100%	This combination should be avoided
	Didanosine buffered formulation	Decreased rifabutin oral absorption	Space rifabutin and didanosine buffered formulation apart by at least 2 hours or use enteric coated didanosine capsule
	Efavirenz	Rifabutin AUC decreased 38%; no change in efavirenz conc.	Increase rifabutin dose to 450–600 mg/day or 600 mg two to three times weekly; effect of efavirenz + PI(s) on rifabutin conc. has not been studied
	Etravirine	Etravirine Cmin decreased by 35% and AUC decreased by 37%; rifabutin AUC decreased by 17%	Use standard rifabutin dose of 300 mg daily if it is not used with a ritonavir-boosted PI. In patients receiving ritonavir-boosted darunavir or saquinavir, if rifabutin is needed, consider alternative antiretroviral to etravirine.
	Fluconazole	Rifabutin AUC increased 80% because of inhibition of hepatic metabolism	Consider reducing rifabutin dose to 150 mg daily and monitor rifabutin level or monitor for rifabutin toxicities

* Acquired rifamycin resistance has been reported when ritonavir-boosted PIs are used with rifabutin 150 mg twice weekly. Consider therapeutic drug monitoring and adjust rifabutin dose based on levels

TABLE 6. (*Continued*) Substantial pharmacokinetic drug-drug interactions for drugs used in the treatment of opportunistic infections

Drugs	Interacting with	Mechanism/effects	Recommendations
Rifabutin* (CYP3A4 inducer and substrate) (*Continued*)	Fosamprenavir	Rifabutin AUC increased 193%; no change in amprenavir conc.	Decrease rifabutin dose to 150 mg tiw, or adjust dose based on rifabutin level*
	Itraconazole	Itraconazole conc. decreased by 70%; potential for inhibition of rifabutin metabolism and increased rifabutin conc.	Avoid concomitant use if possible; if the combination is to be used, monitor itraconazole and rifabutin level and adjust dose accordingly; monitor for rifabutin toxicity
	Indinavir	Rifabutin AUC increased 204%; indinavir AUC decreased 32%	Decrease rifabutin dose to 150 mg tiw, or adjust dose based on rifabutin level and increase unboosted indinavir dose to 1,000 mg every 8 hours*
	Ketoconazole	Possible increase in rifabutin conc. and decrease in ketoconazole conc.	Monitor for rifabutin toxicities and ketoconazole efficacy
	Lopinavir/ritonavir	Rifabutin AUC increased 303%; 25-O-des-acetyl rifabutin AUC increased 47.5-fold	Decrease rifabutin dose to 150 mg tiw, or adjust dose based on rifabutin level*
	Nelfinavir	Rifabutin AUC increased 207%; insignificant change in nelfinavir conc.	Decrease rifabutin dose to 150 mg tiw, or adjust dose based on rifabutin level*
	Posaconazole	Posaconazole AUC decreases 49%; Rifabutin AUC increases 72%	Avoid concomitant use if possible; otherwise, monitor posaconazole and rifabutin level and adjust dose and monitor clinical responses of each
	Ritonavir	Rifabutin AUC increased 430%; no change in ritonavir conc.	Decrease rifabutin dose to 150 mg tiw, or adjust dose based on rifabutin level*
	Saquinavir	Saquinavir AUC decreased 43%; no change in rifabutin conc.	Saquinavir should not be used without ritonavir-boosting. Decrease rifabutin dose to 150 mg tiw, or adjust dose based on rifabutin level*
	Tipranavir/ritonavir	Rifabutin AUC: increased 190%; Cmin: increased 114%; 25-O-desacetyl-rifabutin AUC: increased 1971%; Cmin: increased 683%	Decrease rifabutin dose to 150 mg tiw, or adjust dose based on rifabutin level*
	Voriconazole	Voriconazole AUC decreased 79%; rifabutin AUC increased threefold	This combination should be avoided; if used in combination, monitor voriconazole and rifabutin levels, clinical responses, and toxicities

* Acquired rifamycin resistance has been reported when ritonavir-boosted PIs are used with rifabutin 150 mg twice weekly. Consider therapeutic drug monitoring and adjust rifabutin dose based on levels

TABLE 6. (*Continued*) Substantial pharmacokinetic drug-drug interactions for drugs used in the treatment of opportunistic infections

Drugs	Interacting with	Mechanism/effects	Recommendations
Rifampin (Potent CYP3A4 & UGT1A1 inducer)	Atazanavir	Substantial decrease in atazanavir Cmin and AUC despite double dosing or boosting with ritonavir	This combination should be avoided
	Atovaquone	Atovaquone conc. decreased 52%; rifampin conc. increased 37%	This combination should be avoided
	Caspofungin	Caspofungin conc. decreased 30%	Caspofungin dose should be increased to 70 mg/day
	Clarithromycin	Decreased mean clarithromycin conc. 87%	This combination should be avoided; consider switching clarithromycin to azithromycin
	Dapsone	Dapsone half-life decreased from 24 to 11 hr; Reduced dapsone activity expected	Consider alternative to dapsone; rifabutin might be an alternative
	Darunavir	Potential substantial decrease in darunavir concentration	This combination should be avoided
	Delavirdine	Delavirdine AUC decreased 95%; no change in rifampin conc.	This combination should be avoided
	Efavirenz	Efavirenz AUC decreased 22%; no change in rifampin conc.	No dosage adjustment or consider increasing efavirenz dose to 800 mg/day or monitor efavirenz concentration
	Etravirine	Potential significant decrease in etravirine concentration	This combination should be avoided
	Fluconazole	Fluconazole AUC decreased by 23%–56%; no change in rifampin conc.	Might need to increase fluconazole dose
	Fosamprenavir	Amprenavir AUC decreased 82%, Cmin decreased 92%; no change in rifampin conc.	This combination should be avoided; effect of rifampin on ritonavir and amprenavir has not been studied

TABLE 6. (*Continued*) Substantial pharmacokinetic drug-drug interactions for drugs used in the treatment of opportunistic infections

Drugs	Interacting with	Mechanism/effects	Recommendations
Rifampin (Potent CYP3A4 & UGT1A1 inducer) (*Continued*)	Indinavir	Indinavir AUC decreased 89%; rifampin conc. slightly increased	This combination should be avoided
	Itraconazole	Itraconazole AUC decreased 64%–88%; no change in rifampin conc.	Avoid concomitant use if possible; if the combination is to be used, monitor itraconazole level and adjust dose accordingly; monitor clinical response
	Ketoconazole	Ketoconazole levels decreased 50%	Avoid concomitant use if possible; consider alternative antifungal and/or antimycobacterial agent(s)
	Lopinavir/ritonavir	Lopinavir AUC decreased 75% and Cmin decreased 99%; rifampin AUC might be increased	This combination should be avoided
	Maraviroc	Maraviroc AUC decreased 63%, Cmin decreased 67%	This combination should be avoided
	Nelfinavir	Nelfinavir AUC decreased 82%; no change in rifampin conc.	This combination should be avoided
	Nevirapine	Nevirapine maximum concentration (Cmax) and AUC decreased by >50%; no change in rifampin conc.	This combination should be used with caution; monitor antiretroviral response
	Posaconazole	Posaconazole level may be reduced substantially	Avoid combination if possible, if used, monitor posaconazole level and adjust dose if necessary
	Raltegravir	Rifampin induces raltegravir glucuronidation via UGT1A1 enzyme – reducing AUC by 40% & Cmin by 60%	Increase raltegravir dose to 800 mg PO bid
	Ritonavir 600 mg BID	Ritonavir AUC decreased 35%; no change in rifampin conc.	Monitor for antiretroviral activity of ritonavir
	Saquinavir	Saquinavir AUC decreased 84%; no change in rifampin conc.	This combination should be avoided due to pharmacokinetic interaction; rifampin use with ritonavir-boosed saquinavir is contraindicated because of high incidence of serious hepatotoxicity
	Tipranavir	Potentially substantial decrease in tipranavir concentration	This combination should be avoided
	Voriconazole	Voriconazole AUC decreased 96%	This combination should be avoided
	Zidovudine	Rifampin increased zidovudine glucuronidation, decreasing zidouvdine AUC 47%	Monitor for zidovudine efficacy

TABLE 6. (*Continued*) Substantial pharmacokinetic drug-drug interactions for drugs used in the treatment of opportunistic infections

Drugs	Interacting with	Mechanism/effects	Recommendations
Tenofovir	Acyclovir, cidofovir, ganciclovir, valacyclovir, valganciclovir	Potential for compete active tubular secretion of these drugs	Monitor for toxicities of these drugs and tenofovir
	Atazanavir	Atazanavir Cmin decreased 40%; mechanism unknown	Co-administer with ritonavir at a dose of ritonavir 100 mg daily plus atazanavir 300 mg daily
	Didanosine	Increased didanosine AUC by 44%–60%; no change in tenofovir AUC	Reduce didanosine dose (from 400 mg to 250 mg in patients weighing >60 mg); monitor for didanosine-associated toxicities; discontinue didanosine if serious toxicity occurs
	Lopinavir/ritonavir	Tenofovir AUC increased by 34%	Significance unknown, monitor for tenofovir toxicities
Valganciclovir	Cidofovir (plus probenecid)	Probenecid might decrease ganciclovir renal clearance and increase ganciclovir conc.	Because of the infrequent dosing of probenecid when used with cidofovir, no dosage adjustment is necessary; monitor for dose-related toxicities
	Didanosine buffered formulation	Oral ganciclovir increased didanosine AUC 111%	Monitor for didanosine toxicities; study with valganciclovir and didanosine enteric coated formuation has not been done
Voriconazole (CYP 2C9, 2C19, & 3A4 substrate and inhibitor)	Atazanavir	Voriconazole AUC: decreased 39%	Avoid combination if possible
	Delavirdine	Potential bi-directional inhibition of metabolism, increasing conc. of both	No formal interaction studies; monitor for toxicities
	Efavirenz	Voriconazole Cmax decreased 61%; AUC decreased 77%; efavirenz Cmax increased 98% and AUC increased 44%	Do not coadminister at standard doses; increase voriconazole to 400 mg Q12H and decrease efavirenz to 300 mg QHS
	Etravirine	Potential for increase of both etravirine and voriconazole concentration	Monitor for voriconazole toxicities. Consider therapeutic drug monitoring and adjust dose accordingly.
	Nevirapine	Potential induction of voriconazole metabolism, decreasing voriconazole conc.	No formal interaction studies; monitor for therapeutic failure of voriconazole; consider monitoring voriconazole level
	Protease inhibitors (except atazanavir and ritonavir)	Potential bi-directional inhibition of metabolism, increasing conc. of both drugs; indinavir and voriconazole lead to no substantial interaction	No formal interaction studies; monitor for toxicities, consider therapeutic drug monitoring
	Rifabutin	Voriconazole AUC decreased 79%; Rifabutin AUC increased 3-fold	This combination should be avoided
	Rifampin	Voriconazole AUC decreased 96%	This combination should be avoided
	Ritonavir	Ritonavir 400 mg q12h: Voriconazole AUC decreased 82% Ritonavir 100 mg q12h: Voriconazole AUC decreased by 39%	Avoid combination if possible, esp. ritonavir dose at 400 mg q12h. If use with ritonavir 100 mg q12h, consider monitoring voriconazole level and adjust dose accordingly.

.

TABLE 7. Antiretroviral anti-infective drug combinations that should be avoided*

First Drug	Second Drug	Reason
Ribavirin	Didanosine	Increased intracellular levels of ddA-TP, increase in ddI-associated mitochondrial toxicities (e.g., lactic acidosis, pancreatitis, and peripheral neuropathy)
Rifabutin	Atovaquone	Atovaquone concentration (conc.) decreased 34%; rifabutin conc. decreased 19%
	Delavirdine	Delavirdine area under the conc. curve (AUC) decreased 90%; rifabutin AUC increased 100%
	Etravirine (use with darunavir/ritonavir or saquinavir/ritonavir)	If rifabutin therapy is needed, consider alternative antiretroviral to etravirine – as rifabutin might reduce etravirine concentration.
	Itraconazole	Itraconazole conc. decreased 70%; potential for inhibition of rifabutin metabolism and increased rifabutin conc.
	Posaconazole	Posaconazole AUC decreased by 49%; rifabutin AUC increased by 72%
	Voriconazole	Voriconazole AUC decreased 79%; rifabutin AUC increased threefold
Rifampin	Atazanavir	Pharmacokinetic data not available; expect rifampin to decrease atazanavir concentrations substantially, as seen with other protease inhibitors
	Atovaquone	Atovaquone conc. decreased 52%; rifampin conc. increased 37%
	Clarithromycin	Mean clarithromycin conc. decreased 87%
	Darunavir	Pharmacokinetic study not available; expect rifampin to decrease darunavir concentration substantially, as seen with other protease inhibitors
	Delavirdine	Delavirdine AUC decreased 95%; no change in rifampin conc.
	Etravirine	Pharmacokinetic data not available; expect rifampin to decrease etravirine concentrations substantially
	Fosamprenavir	No study done with fosamprenavir; amprenavir AUC decreased 82%; Cmin decreased 92%
	Indinavir	Indinavir AUC decreased 89%; rifampin conc. slightly increased
	Itraconazole	Itraconazole AUC decreased 64%–88%; no change in rifampin conc.
	Ketoconazole	Ketoconazole levels decreased 50%; rifampin maximum concentration (Cmax) decreased 40%–50% probably because of impaired rifampin oral absorption
	Lopinavir/ritonavir	Lopinavir AUC decreased 75% and Cmin decreased 99%; rifampin AUC might be increased
	Maraviroc	Maraviroc AUC decreased 63%, Cmin decreased 67%
	Nelfinavir	Nelfinavir AUC decreased 82%; no change in rifampin conc.
	Posaconazole	Posaconazole concentration may be decreased substantially
	Saquinavir	Saquinavir AUC decreased 82%; no change in rifampin concentration
	Tipranavir	Pharmacokinetic study not available; expect rifampin to decrease tipranavir concentration substantially, as seen with other protease inhibitors
	Voriconazole	Voriconazole AUC decreased 96%
Voriconazole	Ritonavir 400 mg q12h	Voriconazole AUC decreased 82%

Note: In some cases, the benefit of concomitant use of these agents may outweigh the risks. If possible, monitor drug concentrations and adjust doses accordingly; also monitor clinical responses or toxicities.

TABLE 8. Dosage adjustment in renal insufficiency

Drugs	Normal dose	Dosage adjustment in renal insufficiency: Creatinine clearance (mL/min)	Dosage adjustment in renal insufficiency: Dose
Acyclovir	IV dose for serious HSV/VZV infections: 10 mg/kg body weight q8h PO dose for herpes zoster: 800 mg q4h (5x/day)	25–50 10–25 0–10 hemodialysis 10–25 0–10	10 mg/kg body weight q12h 10 mg/kg q24h 5 mg/kg q24h adminster additional dose post dialysis 800 mg q8h 800 mg q12h
Amikacin	IV 15 mg/kg/day or 25 mg/kg tiw		25 mg/kg tiw initially, adjust to achieve target peak concentration while allowing sufficient time for clearance. TDM is recommended.
Amphotericin B	0.5–1.0 mg/kg/day IV (amphotericin B deoxycholate); or 3–6 mg/kg/day IV (lipid formulation)		No dosage adjustment necessary; alternative antifungals might be considered if renal insufficiency occurs during therapy
Chloroquine	600 mg (2 tabs) STAT dose followed by 300 mg (1 tab) at 6, 24, and 48 hours for a total dose of 1500 mg	<10	50% of dose
Cidofovir	5 mg/kg IV two times each week, then every 2 weeks (with probenecid & hydration)	If serum creatinine increases 0.3–0.4 mg/dL >baseline; If serum creatinine increases ≥0.5 mg/dL >baseline or ≥3+ proteinuria	3 mg/kg per dose Discontinue therapy
Ciprofloxacin	500 mg PO bid	30–50 5–29 Patients on hemodialysis or peritoneal dialysis	250 mg q12hr 250 mg q18h (or 375 mg q24h) 250 mg q24hr (administered after dialysis)
Clarithromycin	500 mg PO bid	<30	250 mg bid or 500 mg daily
Emtricitabine	200 mg once daily	30–49 15–29 <15 or hemodialysis	200 mg q48h 200 mg q72h 200 mg q96h
Emtricitabine/tenofovir	200 mg/300 mg PO one tablet daily	30–49 <30 or hemodialysis	One tablet q48h Coformulated tablet should not be used. Use individual formulation and dose adjust according to recommendations.
Entecavir	Usual dose: 0.5 mg once daily; Lamivudine (3TC)-refractory HBV: 1 mg once daily	30–<50 10–<30 <10 or hemodialysis or CAPD	Usual: 0.25 mg daily; 0.15 mg daily; 0.05 mg daily 3TC-refractory: 0.5 mg daily; 0.3 mg daily; 0.1 mg daily
Ethambutol	15–20 mg/kg q24h PO	10–50 <10 hemodialysis	15–20 mg/kg q24-36h 15–20 mg/kg q48h 15–20 mg/kg tiw after hemodialysis TDM may be considered
Fluconazole	200–800 mg PO or IV daily	≥50 <50 hemodialysis	Full dose 50% of full dose Full dose after dialysis

TABLE 8. (*Continued*) Dosage adjustment in renal insufficiency

Drugs	Normal dose	Dosage adjustment in renal insufficiency	
		Creatinine clearance (mL/min)	Dose
Flucytosine	25 mg/kg PO q6h	20–40 10–20 hemodialysis	25 mg/kg q12h 25 mg/kg q24h 25–50 mg/kg q48–72h (after hemodialysis)
Foscarnet	120–180 mg/kg/day	Dosage adjustment according to calculated CrCl/kg; consult package labeling for dosing table	
Ganciclovir	Induction therapy: 5 mg/kg IV q12h	50–69 25–49 10–24 <10 or on hemodialysis	2.5 mg/kg q12h 2.5 mg/kg q24h 1.25 mg/kg q24h 1.25 mg/kg tiw after dialysis
	Maintenance Therapy: 5 mg/kg IV q24h	50–69 25–49 10–24 <10 or on hemodialysis	2.5 mg/kg q24h 1.25 mg/kg q24h 0.625 mg/kg q24h 0.625 mg/kg tiw after dialysis
Lamivudine	For HIV/HBV-coinfected patients: 150 mg bid or 300 mg daily	30–49 15–29 5–14 <5 or on hemodialysis	150 mg daily 150 mg x 1, then 100 mg daily 150 mg x 1, then 50 mg daily 50 mg x 1, then 25 mg daily
Levofloxacin	500–750 mg PO daily		750–1000 mg 3x weekly, adjust dosing based on TDM may be considered
Aqueous penicillin G	Neurosyphilis or Ocular syphilis: 3–4 milion units (MU) IV q4h	10–50 <10 Hemodialysis	2–3 MU q4h 1 MU q4-6h 1 MU q4-6h
Quinidine glucuronate	324–972 mg PO q8–12h	<10 Hemodialysis	75% of normal dose 75% of normal dose, schedule timing of dose after dialysis
Quinine sulfate	650 mg PO q8h for 3–7 days	10–50 <10	q8–12h or 75% of normal dose q24h
Ribavirin	1,000–1,200 mg/day in 2 divided doses (based on weight)	<50	Not recommended
Rifabutin	300 mg daily (or adjustment based on drug-drug interaction)	<30	Usually, no dosage change is necessary, some suggest 50% of dose or may consider TDM*
Streptomycin	15 mg/kg IM or IV q24h or 25 mg/kg tiw IM or IV		25 mg/kg tiw initially, adjust to achieve target peak concentration while allowing sufficient time for clearance. TDM is recommended
Sulfamethoxazole/ trimethoprim	15–20 mg/kg/day (of TMP) IV or PO in 3–4 divided doses	15–30 <15 Hemodialysis	5 mg/kg q6–8h x 48 hr, then 3.5–5 mg/kg q12h 7–10 mg/kg/day in 1–2 divided doses 7–10 mg/kg after dialysis

Note: To prevent underdosing, certain specialists prefer to use standard dose and measure drug levels.

TABLE 8. (*Continued*) Dosage adjustment in renal insufficiency

Drugs	Normal dose	Dosage adjustment in renal insufficiency	
		Creatinine clearance (mL/min)	Dose
Telbuvidine	600 mg PO daily	30–49 <30 (not on hemodialysis) Hemodialysis	600 mg q48h 600 mg q72h 600 mg q96h (dose after dialysis)
Tenofovir	For HIV (in HBV patients): 300 mg PO daily	30–49 10–29 End stage renal disease or hemodialysis	300 mg q48h 300 mg twice weekly 300 mg once weekly
Tetracycline	250 mg PO q6h x 7 days	10–49 <10 Hemodialysis	Adminster q12–24h Administer q24h Administer q24h, schedule timing of dose after dialysis
Valacyclovir	For herpes zoster 1 g PO tid	30–49 10–29 <10 Hemodialysis	1 g PO q12h 1 g PO q24h 500 mg PO q24h 500 mg PO q24h, schedule timing of dose after dialysis
Valganciclovir	900 mg PO bid (induction) 900 mg PO daily (maintenance)		Induction / Maintenance
		40–59 25–39 10–25 Hemodialysis	450 mg bid / 450 mg daily 450 mg daily / 450 mg qod 450 mg qod / 450 mg biw Not recommended / Not recommended
Voriconazole	IV dose: 6 mg/kg body weight g12h as loading dose, then 4 mg/kg q12h	≤50	Consider switching to PO dosing; SBECD vehicle might accumulate in patients with renal insufficiency

Definitions of abbreviations: bid = twice a day; IV=intravenous; q'n'h = every "n" hour; PO = by mouth; TDM = therapeutic drug monitoring; tid = three times daily; tiw = three times weekly; MU = million units; HSV/VZV = herpes simplex virus/varicella-zoster virus; HBV - hepatitis B virus.

TABLE 9. Summary of pre-clinical and human data on and indications for opportunistic infection drugs during pregnancy

Drug	FDA category	Pertinent animal reproductive and human pregnancy data	Recommended use during pregnancy
Acyclovir	B	No teratogenicity in mice, rats, rabbits at human levels. Large experience in pregnancy (>700 first-trimester exposures reported to registry); well-tolerated.	Treatment of frequent or severe symptomatic herpes outbreaks or varicella
Adefovir	C	Embryotoxic in mice; caused thymic lymphoid destruction in neonatal mice. Limited experience with human use in pregnancy.	Not recommended; report exposures during pregnancy to Antiretroviral Pregnancy Registry: http://www.APRegistry.com
Albendazole	C	Embryotoxic and teratogenic (skeletal malformations) in rats and rabbits but not in mice or cows. Limited experience in human pregnancy.	Not recommended. Primary therapy for microsporidosis in pregnancy should be antiretroviral therapy (ART).
Amikacin	C	Not teratogenic in animals. Theoretical risk for ototoxicty in fetus; reported with streptomycin but not amikacin.	Drug resistant tuberculosis, severe *Mycobacterium avium* (MAC) complex infections
Amoxicillin, amoxicillin/clavulanate, ampicillin/sulbactam	B	Not teratogenic in animals. Large experience in human pregnancy does not suggest an increase in adverse events.	Susceptible bacterial infections
Amphotericin B	B	Not teratogenic in animals or in human experience. Preferred over azole antifungals in first trimester if similar efficacy expected.	Documented invasive fungal disease
Antimonials, pentavalent (sodium stibogluconate, meglumine)	Not FDA approved	Antimony not teratogenic in rats, chicks, sheep. Three cases reported of use in human pregnancy in second trimester with good outcome. Labeled as contraindicated in pregnancy.	Therapy of visceral leishmaniasis not responsive to amphotericin B or pentamidine
Artesunate, artemether	Not FDA approved	Embryotoxicity, cardiovascular and skeletal anomalies in rats and rabbits. Limited human experience.	Pending more data, use for malaria in pregnancy only if other drugs not available or have failed.
Atovaquone	C	Not teratogenic in rats or rabbits, limited human experience	Alternate agent for *Pneumocystis jiroveci* pneumonia (PCP), *Toxoplasma gondii* infections
Azithromycin	B	Not teratogenic in animals. Moderate experience with use in human pregnancy does not suggest adverse events.	Preferred agent for MAC prophylaxis or treatment (with ethambutol), *Chlamydia trachomatis* infection in pregnancy.
Aztreonam	B	Not teratogenic in rats, rabbits. Limited human experience but other beta-lactam antibiotics have not been associated with adverse pregnancy outcomes.	Susceptible bacterial infections
Benznidazole	Not FDA approved	No animal studies. Increase in chromosomal aberrations in children with treatment; uncertain significance. No human pregnancy data.	Not indicated for chronic *Trypanosoma cruzi* in pregnancy. Seek expert consultation if acute or symptomatic infection in pregnancy requiring treatment.
Capreomycin	C	Increase in skeletal variants in rats. Limited experience in human pregnancy; theoretical risk for fetal ototoxicity.	Drug-resistant tuberculosis
Caspofungin	C	Embryotoxic, skeletal defects in rats, rabbits. No experience with human use.	Invasive *Candida* or *Aspergillus* infections refractory to amphotericin and azoles
Cephalosporins	B	Not teratogenic in animals. Large experience in human pregnancy has not suggested increase in adverse outcomes.	Bacterial infections; alternate treatment for MAC

TABLE 9. (*Continued*) Summary of pre-clinical and human data on and indications for opportunistic infection drugs during pregnancy

Drug	FDA category	Pertinent animal reproductive and human pregnancy data	Recommended use during pregnancy
Chloroquine	C	Associated with anophthalmia, micro-ophthalmia at fetotoxic doses in animals. Not associated with increased risk in human pregnancy at doses used for malaria.	Drug of choice for malaria prophylaxis and treatment of sensitive species in pregnancy
Cidofovir	C	Embryotoxic and teratogenic (meningocele, skeletal abnormalities) in rats and rabbits. No experience in human pregnancy.	Not recommended
Ciprofloxacin, other quinolones	C	Arthropathy in immature animals; not embryotoxic or teratogenic in mice, rats, rabbits, or monkeys. Approximately 400 cases of quinolone use in human pregnancy have not been associated with arthropathy or birth defects.	Severe MAC infections; multidrug-resistant tuberculosis, anthrax
Clarithromycin	C	Cardiovascular defects noted in one strain of rats and cleft palate in mice, not teratogenic in rabbits or monkeys. Two human studies, each with >100 first-trimester exposures, did not indicate increase in defects, but one study found an increase in spontaneous abortion.	Treatment or secondary MAC prophylaxis if other choices exhausted
Clindamycin	B	No concerns specific to pregnancy in animal or human studies	Treatment of anaerobic bacterial infections and used with quinine for chloroquine resistant malaria; alternate agent for secondary prophylaxis of *Toxoplasma* encephalitis
Clofazimine	C	Not teratogenic in mice, rats, or rabbits. Limited experience reported (19 cases); no anomalies noted but red-brown skin discoloration reported in several infants exposed throughout pregnancy.	No indications
Clotrimazole troches	C	Not teratogenic in animals at exposures expected from treatment of oral or vaginal *Candida*. No increase in adverse pregnancy outcomes with vaginal use.	Oral *Candida* infections and prophylaxis
Cycloserine	C	No data available from animal or human studies	Drug-resistant tuberculosis
Dapsone	C	No animal data. Limited human experience does not suggest teratogenicity; might displace bound bilirubin in the neonate, increasing the risk for kernicterus.	Alternate choice for primary or secondary PCP prophylaxis
Diphenoxylate	C	Limited animal and human data do not indicate teratogenicity	Symptomatic treatment of diarrhea
Doxycycline, other tetracyclines	D	Risk for hepatic toxicity increased with tetracyclines in pregnancy; staining of fetal bones and teeth contraindicate use in pregnancy	No indications
Emtricitabine	B	No concerns in pregnancy from limited animal and human data	As part of combination antiretroviral regimen for treatment of HIV, hepatitis B. Report exposures during pregnancy to Antiretroviral Pregnancy Registry: http://www.APRegistry.com.

TABLE 9. (*Continued*) Summary of pre-clinical and human data on and indications for opportunistic infection drugs during pregnancy

Drug	FDA category	Pertinent animal reproductive and human pregnancy data	Recommended use during pregnancy
Entecavir	C	Animal data do not suggest teratogenicity at human doses; no experience in human pregnancy.	Not indicated. Use antiretroviral agents active against both HIV and hepatitis B. Report exposures during pregnancy to Antiretroviral Pregnancy Registry: http://www.APRegistry.com.
Erythromycin	B	Hepatotoxicity with erythromycin estolate in pregnancy; other forms acceptable; no evidence of teratogenicity	Bacterial and chlamydial infections
Ethambutol	B	Teratogenic, at high doses, in mice, rats, rabbits. No evidence of teratogenicity in 320 cases of human use for treatment of tuberculosis.	Active tuberculosis and MAC treatment; avoid in first trimester if possible
Ethionamide	C	Increased rate of defects (omphalocele, exencephaly, cleft palate) in rats, mice, and rabbits with high doses; not seen with usual human doses. Limited human data.	Active tuberculosis; avoid in first trimester if possible
Famciclovir	B	No evidence of teratogenicity in rats or rabbits, limited human experience	Recurrent genital herpes and primary varicella infection. Report exposures during pregnancy to the Famvir Pregnancy Registry (1-888-669-6682).
Fluconazole	C	Abnormal ossification, structural defects in rats, mice at high doses. Case reports of rare pattern of craniofacial, skeletal and other abnormalities in five infants born to four women with prolonged exposure during pregnancy; no increase in defects seen in several series after single-dose treatment.	Single dose may be used for treatment of vaginal *Candida* though topical therapy preferred. Not recommended for prophylaxis during pregnancy. Can be used for invasive fungal infections after the first trimester; amphotericin B preferred in first trimester if similar efficacy expected.
Flucytosine	C	Facial clefts and skeletal defects in rats; no defects in mice, rabbits. No reports of use in first trimester of human pregnancy; might be metabolized to 5-fluorouracil, which is teratogenic in animals and possibly in humans.	Use after first trimester if indicated for life-threatening fungal infections
Fomivirsen	C	No animal studies; no data in human pregnancy. Intravitreous injection probably safe in pregnancy as minimal systemic levels.	Treatment of intraocular cytomegalovirus (CMV) infection
Foscarnet	C	Teratogenic in rats, rabbits. Single case report of use in human pregnancy in third trimester.	Alternate agent for treatment or secondary prophylaxis of life-threatening or sight-threatening CMV infection
Fumagillin	Not FDA approved	Caused complete litter destruction or growth retardation in rats, depending on when administered. No data in human pregnancy.	Topical solution may be used for ocular microsporidial infections
Ganciclovir, valganciclovir	C	Embryotoxic in rabbits and mice; teratogenic in rabbits (cleft palate, anophthalmia, aplastic kidney and pancreas, hydrocephalus). Case reports of safe use in human pregnancy after transplants, treatment of fetal CMV.	Treatment or secondary prophylaxis of life-threatening or sight-threatening CMV infection. Preferred agent for therapy in children
Granulocyte colony stimulating factor (GMCSF)	C	Not teratogenic in rats and rabbits. Case reports of use in human pregnancy without adverse effects.	Treatment of leucopenia
Imipenem	C	Not teratogenic in animals; limited human experience.	Serious bacterial infections
Imiquimod	B	No teratogenicity in rats and rabbits; eight case reports of human use, only two in first trimester	Because of limited experience, other treatment modalities such as cryotherapy or trichloracetic acid recommended for wart treatment during pregnancy

TABLE 9. (*Continued*) Summary of pre-clinical and human data on and indications for opportunistic infection drugs during pregnancy

Drug	FDA category	Pertinent animal reproductive and human pregnancy data	Recommended use during pregnancy
Influenza vaccine	C	Not teratogenic. Live vaccines, including intranasal influenza vaccine, are contraindicated in pregnancy.	All pregnant women should receive injectable influenza vaccine because of the increased risk of complications of influenza during pregnancy. HIV-infected women should be on ART before vaccination to limit potential increases in HIV RNA levels with immunization.
Interferons: alfa, beta, gamma	C	Abortifacient at high doses in monkeys, mice; not teratogenic in monkeys, mice, rats, or rabbits. Approximately 30 cases of use of interferon-alfa in pregnancy reported; 14 in first trimester without increase in anomalies; possible increased risk for intrauterine growth retardation.	Not indicated; treatment of hepatitis C should be delayed until after delivery
Isoniazid	C	Not teratogenic in animals. Possible increased risk for hepatotoxicity during pregnancy; prophylactic pyridoxine, 50 mg/day, should be administered to prevent neurotoxicity.	Active tuberculosis; prophylaxis for exposure or skin-test conversion
Itraconazole	C	Teratogenic in rats and mice at high doses. Case reports of craniofacial, skeletal abnormalities in humans with prolonged fluconazole exposure during pregnancy; no increase in defect rate noted among 156 infants born after first-trimester itraconazole exposure.	Only for documented systemic fungal disease, not prophylaxis. Consider using amphotericin B in first trimester if similar efficacy expected.
Kanamycin	D	Associated with club feet in mice, inner ear changes in multiple species. Hearing loss in 2.3% of 391 children after long-term in utero therapy.	Drug-resistant tuberculosis
Ketoconazole	C	Teratogenic in rats, increased fetal death in mice, rabbits. Inhibits androgen and corticosteroid synthesis; might affect fetal male genital development; case reports of craniofacial, skeletal abnormalities in humans with prolonged fluconazole exposure during pregnancy.	None
Lamivudine	C	Not teratogenic in animals. No evidence of teratogenicity with >1900 first-trimester exposures reported to Antiretroviral Pregnancy Registry.	HIV and Hepatitis B therapy, only as part of a combination antiretroviral regimen. Report exposures to Antiretroviral Pregnancy Registry: http://www.APRegistry.com.
Leucovorin (folinic acid)	C	Prevents birth defects of valproic acid, methotrexate, phenytoin, aminopterin in animal models. No evidence of harm in human pregnancies.	Use with pyrimethamine if use of pyrimethamine cannot be avoided
Linezolid	C	Not teratogenic in animals. Decreased fetal weight and neonatal survival at ~ human exposures. Limited human experience.	Serious bacterial infections
Loperamide	B	Not teratogenic in animals. No increase in birth defects among infants born to 89 women with first-trimester exposure.	Symptomatic treatment of diarrhea
Mefloquine	C	Animal data and human data do not suggest an increased risk of birth defects, but miscarriage and stillbirth might be increased.	Second line therapy of chloroquine-resistant malaria in pregnancy, if quinine/clindamycin not available or not tolerated. Weekly as prophylaxis in areas with chloroquine-resistant malaria.
Megalamine antimonate	Not FDA approved	See "Antimonials, pentvalent"	
Meripenam	B	Not teratogenic in animals; limited human experience	Serious bacterial infections

TABLE 9. (*Continued*) Summary of pre-clinical and human data on and indications for opportunistic infection drugs during pregnancy

Drug	FDA category	Pertinent animal reproductive and human pregnancy data	Recommended use during pregnancy
Metronidazole	B	Multiple studies do not indicate teratogenicity; one study with positive findings in rodents, guinea pigs. Studies in several hundred women with first trimester exposure found no increase in birth defects.	Anaerobic bacterial infections, bacterial vaginosis, trichomoniasis, giardiasis, amebiasis
Micafungin	C	Teratogenic in rabbits; no human experience	Not recommended
Miltefosine	Not FDA approved	Embryotoxic in rats, rabbits; teratogenic in rats. No experience with human use.	Not recommended
Nifurtimox	Not FDA approved	Not teratogenic in mice and rats. Increased chromosomal aberrations in children receiving treatment; uncertain significance. No experience in human pregnancy.	Not indicated in chronic infection; seek expert consultation if acute infection or symptomatic reactivation of *T. cruzi* in pregnancy
Nitazoxanide	B	Not teratogenic in animals; no human data	Severely symptomatic cryptosporidiosis after the first trimester
Para-amino salicylic acid (PAS)	C	Occipital bone defects in one study in rats; not teratogenic in rabbits. Possible increase in limb, ear anomalies in one study with 143 first trimester exposures; no specific pattern of defects noted, several studies did not find increased risk.	Drug-resistant tuberculosis
Paromomycin	C	Not teratogenic in mice and rabbits. Limited human experience, but poor oral absorption makes toxicity, teratogenicity unlikely.	Amebic intestinal infections, possibly cryptosporidiosis
Penicillin	B	Not teratogenic in multiple animal species. Experience with use in human pregnancy does not suggest teratogenicity, other adverse outcomes.	Syphilis, other susceptible bacterial infections
Pentamidine	C	Embryocidal but not teratogenic in rats, rabbits with systemic use. Limited systemic absorption with aerosol use; limited experience with systemic use in pregnancy.	Alternate therapy for PCP and leishmaniasis
Piperacillin-tazobactam	B	Not teratogenic in limited animal studies. Limited experience in pregnancy but penicillins generally considered safe.	Bacterial infections
Pneumococcal vaccine	C	No studies in animals or human pregnancy. Polysaccharide vaccines generally considered safe in pregnancy.	Initial or booster dose for prevention of invasive pneumococcal infections. HIV-infected pregnant women should be on highly-aggressive antiretroviral therapy before vaccination to limit potential increases in HIV ribonucleic acid levels with immunization.
Podophyllin, podofilox	C	Increased embryonic and fetal deaths in rats, mice but not teratogenic. Case reports of maternal, fetal deaths after use of podophyllin resin in pregnancy; no clear increase in birth defects with first-trimester exposure.	Because alternative treatments for genital warts in pregnancy are available, use not recommended; inadvertent use in early pregnancy is not indication for abortion
Posaconazole	C	Embryotoxic in rabbits; teratogenic in rats at similar to human exposures. No experience in human pregnancy.	Not recommended

TABLE 9. (*Continued*) Summary of pre-clinical and human data on and indications for opportunistic infection drugs during pregnancy

Drug	FDA category	Pertinent animal reproductive and human pregnancy data	Recommended use during pregnancy
Prednisone	B	Dose-dependent increased risk for cleft palate in mice, rabbits, hamsters; dose dependent increase in genital anomalies in mice. Human data inconsistent regarding increased risk for cleft palate. Risk for growth retardation, low birthweight might be increased with chronic use; monitor for hyperglycemia with use in third trimester.	Adjunctive therapy for severe PCP; multiple other non-HIV-related indications
Primaquine	C	No animal data. Limited experience with use in human pregnancy; theoretical risk for hemolytic anemia if fetus has G6PD deficiency.	Alternate therapy for PCP, chloroquine-resistant malaria
Proquanil	C	Not teratogenic in animals. Widely used in malaria-endemic areas with no clear increase in adverse outcomes.	Not recommended alone or in combination with atovaquone as primary therapy or prophylaxis of malaria
Pyrazinamide	C	Not teratogenic in mice. Limited experience with use in human pregnancy.	Active tuberculosis
Pyrimethamine	C	Teratogenic in mice, rats, hamsters (cleft palate, neural tube defects, and limb anomalies). Limited human data have not suggested an increased risk for birth defects; since folate antagonist, use with leucovorin.	Treatment and secondary prophylaxis of toxoplasmic encephalitis; alternate treatment of PCP
Quinidine gluconate	C	Generally considered safe in pregnancy; high doses associated with preterm labor. One case of fetal eighth nerve damage reported.	Alternate treatment of malaria, control of fetal arrhythmias
Quinine sulfate	C	High doses, often taken as an abortifacient, have been associated with birth defects, especially deafness, in humans and animals. Therapeutic doses have not been associated with an increased risk of defects in humans or animals. Monitor for hypoglycemia.	Treatment of chloroquine-resistant malaria
Ribavirin	X	Dose-dependent risk for multiple defects (craniofacial, central nervous system, skeletal, anophthalmia) in rats, mice, hamsters starting at below human doses. Reports of treatment during second half of pregnancy among nine women without incident; contraindicated in first trimester.	Contraindicated in early pregnancy; no clear indications in pregnancy
Rifabutin	B	Not teratogenic in rats and rabbits; no specific concerns for human pregnancy	Treatment or prophylaxis of MAC, active tuberculosis
Rifampin	C	Teratogenic in mice (cleft palate) and rats (spina bifida) but not in rabbits. No clear teratogenicity in humans.	Active tuberculosis
Sodium stibogluconate	Not FDA approved	See "Antimonials, pentavalent"	
Streptomycin	D	No teratogenicity in mice, rats, guinea pigs. Possible increased risk for deafness and VIII nerve damage; no evidence of other defects.	Alternate therapy for active tuberculosis
Sulfadiazine	B	Sulfonamides teratogenic in some animal studies. No clear teratogenicity among humans; potential for increased jaundice, kernicterus if used near delivery.	Secondary prophylaxis of toxoplasmic encephalitis

TABLE 9. (*Continued*) Summary of pre-clinical and human data on and indications for opportunistic infection drugs during pregnancy

Drug	FDA category	Pertinent animal reproductive and human pregnancy data	Recommended use during pregnancy
Telbivudine	B	Not teratogenic in rats, rabbits. Limited experience in human pregnancy.	Not indicated. Use antiretroviral agents active against both HIV and hepatitis B. Report exposures during pregnancy to Antiretroviral Pregnancy Registry: http://www.APRegistry.com.
Tenofovir	B	No evidence of birth defects in rats, rabbits, or monkeys at high doses; chronic administration in immature animals of multiple species at 6–50 times human doses has led to dose-specific bone changes ranging from decreased mineral density to severe osteomalacia and fractures. Clinical studies in humans (particularly children) show bone demineralization with chronic use; clinical significance unknown.	Possible component of ART regimen in pregnant women with hepatitis B coinfection requiring therapy. Report exposures during pregnancy to Antiretroviral Pregnancy Registry: http://www.APRegistry.com.
Trichloracetic acid, bichloracetic acid	Not rated	No studies. Used topically so no systemic absorption expected.	Topical therapy of non-cervical genital warts
Trifluridine	C	Not teratogenic in rats, rabbits. Minimal systemic absorption expected with topical ocular use.	Topical agent for treatment of ocular herpes infections
Trimethoprim-sulfamethoxazole (TMP-SMX)	C	Teratogenic in rats and mice. Possible increase in congenital cardiac defects, facial clefts, neural tube and urinary defects with first trimester use. Unclear if higher levels of folate supplementation lower risk. Potential for increased jaundice, kernicterus if used near delivery.	Therapy of PCP during pregnancy. Primary and secondary PCP prophylaxis in the second and third trimester; consider aerosolized pentamidine in first trimester. Recommend fetal ultrasound at 18–20 weeks after first trimester exposure.
Valacyclovir	B	Not teratogenic in mice, rats, and rabbits. Experience with valacyclovir in pregnancy limited; prodrug of acyclovir, which is considered safe for use in pregnancy.	Treatment of herpes simplex virus and varicella infections in pregnancy
Vancomycin	C	Not teratogenic in rats, rabbits. Limited human experience.	Serious bacterial infections
Voriconazole	D	Embryotoxic in rats, rabbits. Teratogenic in rats (cleft palate, hydronephrosis, ossification defects). No experience with human use.	Not recommended

TABLE 10. Comparative characteristics of TST with IGRAs*

Performance and operational characteristics	TST	RD1-based-IFN-γ assay	
		QFT®-Gold/ QFT®-Gold In-tube	T-SPOT™.*TB*
Estimated sensitivity (in patients with active TB)	~70% (lower in immunocompromised populations)	76%–80% (inadequate data in immunocompromised populations)	87%–88%
Estimated specificity (in healthy persons with no known TB disease/exposure)	56%–95%	97%	92%
Cross reactivity with BCG	Yes, if vaccinated after infancy	No	No
Cross reactivity with nontuberculous mycobacteria	Yes	Less likely	Less likely
Association between test positivity and subsequent risk of active TB during follow-up	Moderate-to-strong positive association	Insufficient evidence	Insufficient evidence
Correlation with *Mycobacterium tuberculosis* exposure	Yes	Yes (correlated better with exposure than TST in some head-to-head comparisons)	Yes (correlated better with exposure than TST in some head-to-head comparisons)
Benefits of treating test positives (based on randomized controlled trials)	Yes	No evidence	No evidence
Reliability (reproducibility)	Moderate	Limited evidence but might be high	Limited evidence but might be high
Inter-reader variability	Yes	No	Variation in counting spots (if read manually)
Boosting phenomenon	Yes	No	No
Potential for conversions and reversions	Yes	Yes	Yes
Adverse reactions	Yes	No	No
Patient visits to complete testing protocol	Two to four	One	One
Material costs	Low (TST antigen requires refrigeration)	Moderate (QFT®-Gold In-tube less complex than QFT®-Gold)	High
Sample processing and assay complexity	NA	Moderate	High
Laboratory infrastructure required	No	Yes	Yes
Time to obtain a result	48–72 hours	24–48 hours, longer if assays batched	24–48 hours, longer if assays batched
Trained personnel required	Yes	Yes	Yes

Definition of abbreviations: IGRA = Interferon gamma release assays; TST = tuberculin skin test; QFT-Gold = QuantiFERON®-TB Gold; IFNY = interferon-y; BCG = bacillus Calmette-Guerin; TB = tuberculosis.

* Adapted from Nahid P, Pai M, and Hopewell, PC. Advances in the diagnosis and treatment of tuberculosis. Proc Am Thorac Soc 2006;3:103–10.

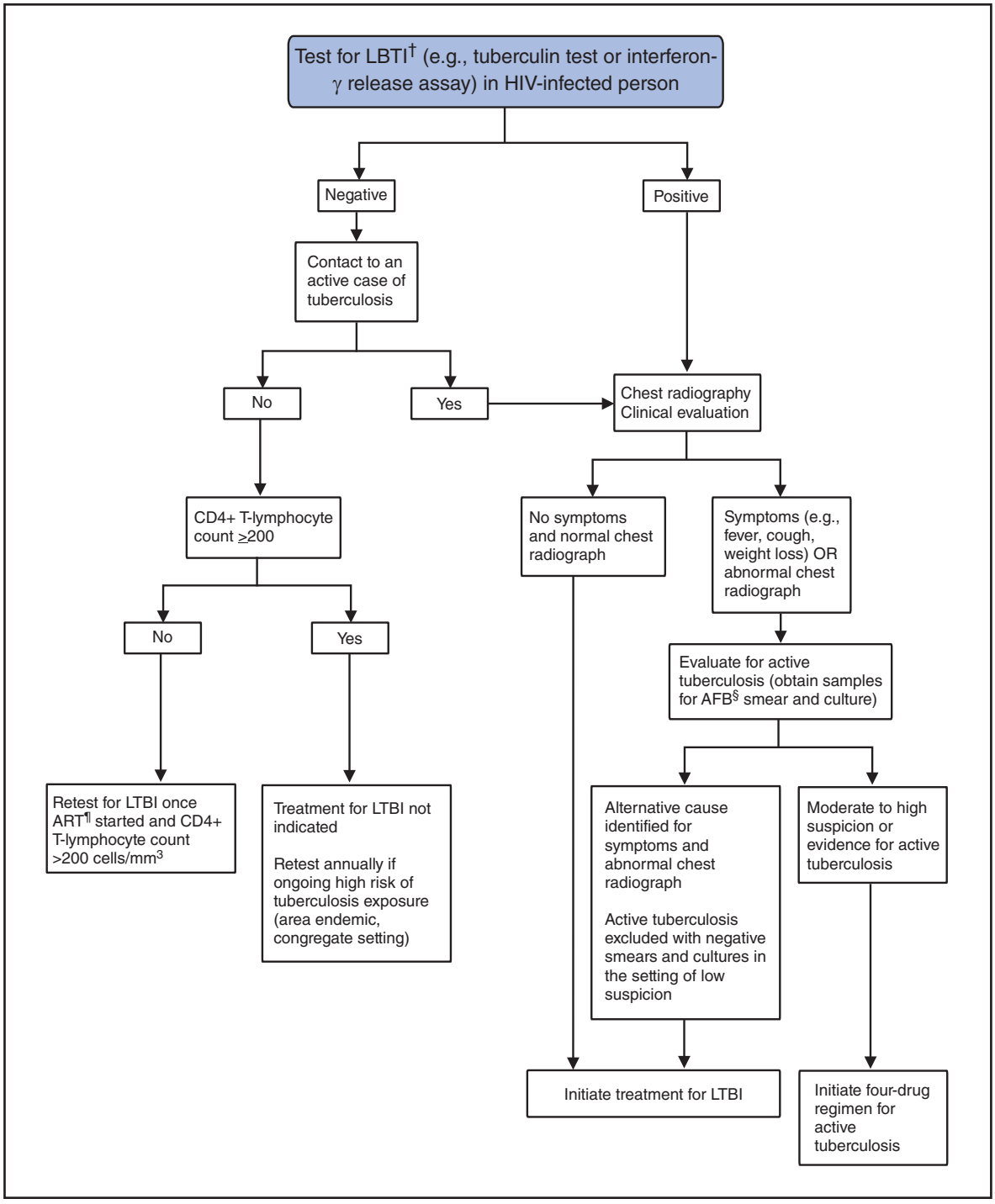
TABLE 11. Cytology and histology terms for papanicolou smears and cervical, vaginal, and anal tissue samples

Cytology (Bethesda System 2001)*	Tissue histology Dysplasia)	Tissue histology (Cervical, vaginal, vulvar, and anal intraepithelial neoplasia system)
Negative for intraepithelial lesion of malignancy	Normal	Normal
Unsatisfactory	Unsatisfactory	Unsatisfactory
Atypical squamous cells – undetermined significance	No term	No term
Atypical squamous cells – cannot exclude high-grade squamous intraepithelial lesion (HSIL)	No term	No term
Low-grade squamous intraepithelial lesion (LSIL)	Mild	CIN I, VAIN I, VIN I, AIN I
HSIL	Moderate	CIN II, VAIN II, VIN II, AIN II
	Severe	CIN III, VAIN III, VIN III, AIN III
	CIS (carcinoma in situ)	CIN III, VAIN III, VIN III, AIN III
Carcinoma	Carcinoma	Carcinoma

Definition of abbreviations: CIN = cervical intraepithelial neoplasia; VAIN = vaginal intraepithelial neoplasia; VIN - vulvar intraepithelial neoplasia; AIN = anal intraepithelial neoplasia.

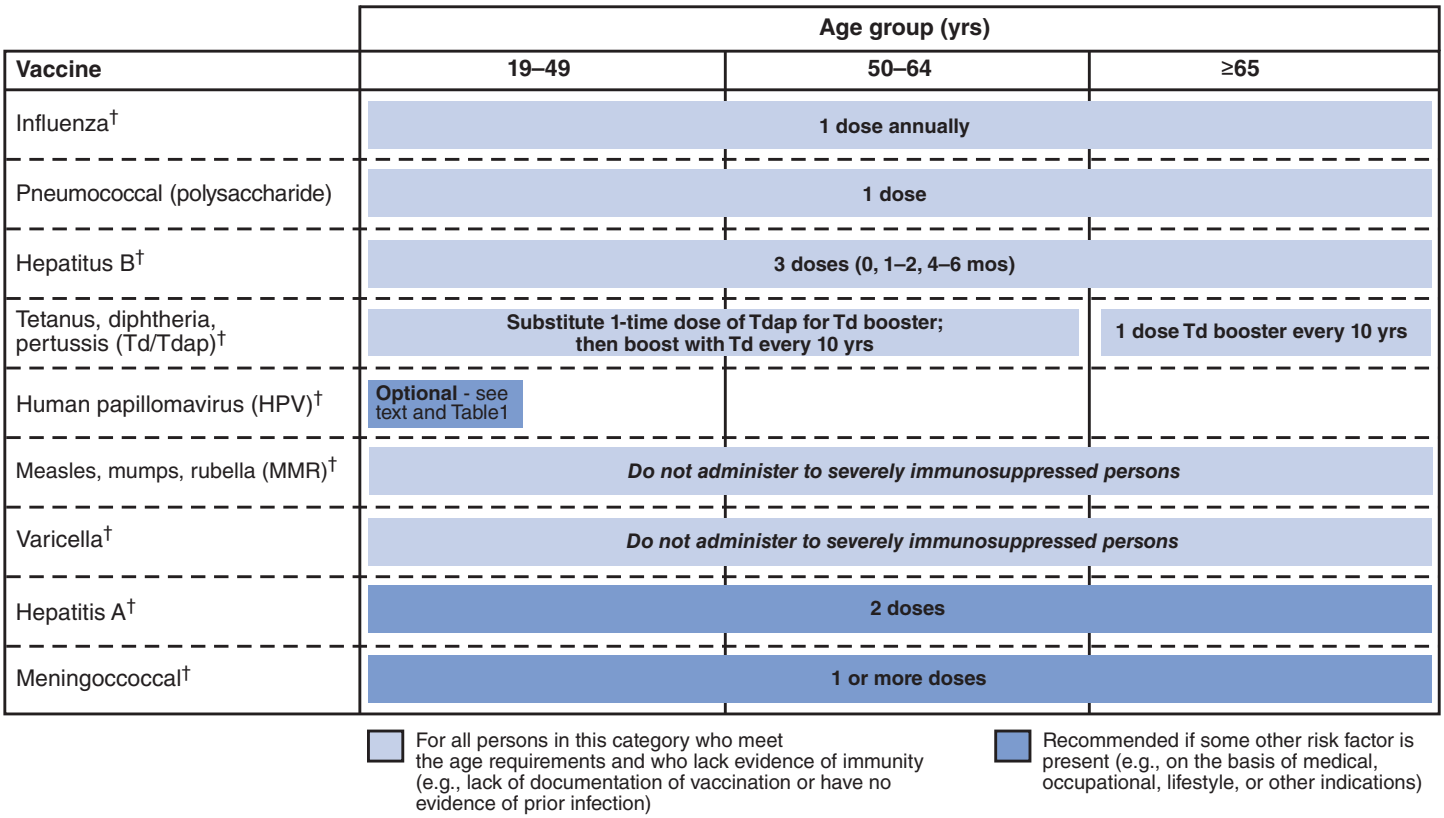
* Adapted from Solomm D, Davey D, Kurman R, Monarty A, O'Connor D, Prey M. The 2001 Bethesda System: terminology for reporting results of cervical cytology. JAMA 2002; 287:2114–9.

FIGURE 1. Schema for the diagnosis of latent tuberculosis infection*



* Adapted from Jasmer RM, Nahid P, Hopewell PC. Clinical practice. Latent tuberculosis infection. N Engl J Med 2002;347(23):1860–6.
† Latent tuberculosis infection
§ Acid-fast bacillus
¶ Antiretroviral therapy

FIGURE 2. Immunization schedule for adults infected with human immunodeficiency virus (HIV)*



* Adapted from the Advisory Committee on Immunization Practices (ACIP) Adult Immunization Schedule. For detailed information on immunization against influenza, pneumococcal disease, hepatitis B, human papillomavirus, varicella, and hepatitis A, see disease-specific sections in the text and in Table 1. For information on immunization against tetanus, diphtheria, pertussis, measles, mumps, rubella, and meningococcal disease, refer to recommendations of the ACIP (www.cdc.gov/vaccines/pubs/ACIP-list.htm).

† Covered by the Vaccine Injury Compensation Program.

Appendix

Recommendations to Help Patients Avoid Exposure to or Infection from Opportunistic Pathogens*

Sexual Exposures

Male latex condoms, when used consistently and correctly during every act of sexual intercourse, are highly effective in preventing the sexual transmission of HIV and can reduce the risk for acquiring other sexually transmitted infections, including syphilis, chlamydia, gonorrhea, and trichomoniasis. Condom use might reduce the risk for transmission of herpes simplex virus and human papillomavirus **(AII)**, although data are more limited. Data regarding the use and efficacy of female condoms are limited **(BIII)**. Spermacides containing nonoxynol-9 (N-9) are not effective for HIV/STD prevention and should not be used as a microbicide or lubricant during vaginal or anal intercourse **(EII)**.

As with many non-sexually transmitted opportunistic infections, intercurrent infections with sexually transmitted pathogens (especially pathogens that cause genital ulcers such as herpes simplex, syphilis, and chancroid) can stimulate increases in HIV viral load and consequent declines in $CD4^+$ count. Furthermore, acquisition of STDs by HIV-infected patients indicates participation in high-risk sexual behavior capable of transmitting HIV to others, the risk for which is substantially increased in the presence of genital tract inflammation (e.g., from gonorrhea or chlamydia) and genital ulcer disease (e.g., HSV-2 infection, syphilis) (*1-5*). All patients, including patients who are asymptomatic, should be screened at least once for STDs. Screening should include testing for syphilis **(AII)**, trichomoniasis in women **(AII)**, urogenital gonorrhea and chlamydia **(BII)**, and oral and rectal gonorrhea and chlamydia for patients reporting receptive sex at these anatomic sites **(BII)** (*6,7*). Nucleic acid amplification testing methods can be more sensitive and specific than traditional culture methods and might be more acceptable to patients. Detailed recommendations for STD testing in HIV-infected persons can be found at the following site: http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5212a1.htm. For all sexually active patients, STD screening should be repeated at least annually and whenever a patient reports high-risk sexual behaviors or symptoms **(BIII)**. In addition to identifying and treating STDs, providers should screen HIV-infected patients for risk behaviors; communicate prevention messages; discuss sexual and drug-use behaviors; positively reinforce safer behaviors; refer patients for services such as substance abuse treatment; and facilitate partner notification, counseling, and testing **(AII)**.

Patients should avoid sex practices that might result in oral exposure to feces (e.g., oral-anal contact) to reduce the risk for intestinal infections (e.g., cryptosporidiosis, shigellosis, campylobacteriosis, amebiasis, giardiasis, LGV serovars of *C. trachomatis* and hepatitis A) **(BIII)**. Latex condom use alone might not reduce the risk for acquiring these fecal-orally transmitted pathogens. Persons who wish to reduce their risk for exposure might consider using dental dams or similar barrier methods for oral-anal and oral-genital contact, changing condoms after anal intercourse, and wearing latex gloves during digital-anal contact. Frequent washing of hands and genitals with warm soapy water during and after activities that might bring these body parts in contact with feces might further reduce risk for illness **(CIII)**.

Hepatitis B vaccination is recommended for all susceptible (hepatitis B core antibody-negative) HIV-infected patients **(AII)**. Hepatitis A vaccination is recommended for all susceptible men who have sex with men, as well as others with indications for hepatitis A virus vaccine (e.g., injection-drug users, persons with chronic liver disease or who are infected with hepatitis B and/or C) **(AII)**.

Injection-Drug–Use Exposures

Injection-drug use is a complex behavior that puts HIV-infected persons at risk for hepatitis B virus and hepatitis C virus infection; additional, possibly drug-resistant strains of HIV; and other bloodborne pathogens. Providers should assess a person's readiness to change this practice and encourage activities to provide education and support directed at recovery. Patients should be counseled to stop using injection drugs **(AIII)** and to enter and complete substance abuse treatment, including relapse prevention programs (*8*) **(AIII)**.

For patients who continue to inject drugs, health-care providers should advise them to adhere to the following practices:

- Never reuse or share syringes, needles, water, or drug- preparation equipment; if injection equipment that has been used by other persons is shared, the implements should first be cleaned with bleach and water before use (**AI**).
- Use only sterile syringes obtained from a reliable source (e.g., pharmacies or syringe-exchange programs) (**BIII**).

* Letters and Roman numerals in parentheses indicate the strength of the recommendation and the quality of evidence supporting it (see Box in Introduction).

- Use sterile (e.g., boiled) water to prepare drugs, and if this is not feasible, use clean water from a reliable source (e.g., fresh tap water); use a new or disinfected container (i.e., cooker) and a new filter (i.e., cotton) to prepare drugs (**BIII**).
- Clean the injection site with a new alcohol swab before injection (**BIII**).
- Safely dispose of syringes after one use (**BIII**).

All susceptible injection-drug–users should be vaccinated against hepatitis B **(BII)** and hepatitis A **(BIII)**.

Environmental and Occupational Exposures

Certain activities or types of employment might increase the risk for exposure to tuberculosis. These include volunteer work or employment in health-care facilities, correctional institutions, and shelters for the homeless, and other settings identified as high risk by local health authorities. Decisions regarding whether to continue with such activities should be made in conjunction with a health-care provider and should be based on such factors as the patient's specific duties in the workplace, the prevalence of tuberculosis in the community, and the degree to which precautions designed to prevent the transmission of tuberculosis are taken in the workplace **(BIII)**. These decisions will affect the frequency with which the patient should be screened for tuberculosis. Day care providers and parents of children in child care are at increased risk for acquiring cytomegalovirus infection, cryptosporidiosis, and other infections (e.g., hepatitis A, giardiasis) from children. The risk for acquiring infection can be diminished by optimal hygienic practices (e.g., handwashing) after fecal contact (e.g., during diaper changing) and after contact with urine or saliva **(AII)**.

Occupations involving contact with animals (e.g., veterinary work and employment in pet stores, farms, or slaughterhouses) might pose a risk for cryptosporidiosis, toxoplasmosis, salmonellosis, campylobacteriosis, or *Bartonella* infection and other infections of concern to any immunocompromised host (e.g., leptospirosis, brucellosis, *Capnocytophaga* spp.). However, available data are insufficient to justify a recommendation against HIV-infected persons working in such settings.

Contact with young farm animals, specifically animals with diarrhea, should be avoided to reduce the risk for cryptosporidiosis **(BII)**. Since soils and sands can be contaminated with *Toxoplasma gondii* and *Cryptosporidium parvum*, persons who have extended contact with these materials (e.g., gardening; playing in or cleaning sandboxes) should wash their hands thoroughly with soap and water following exposure **(BIII)**. In areas where histoplasmosis is endemic, patients should avoid activities known to be associated with increased risk (e.g., creating dust when working with surface soil; cleaning chicken coops that are heavily contaminated with compost droppings; disturbing soil beneath bird-roosting sites; cleaning, remodeling or demolishing old buildings; and cave exploring) (**CIII**). In areas where coccidioidomycosis is endemic, when possible, patients should avoid activities associated with increased risk, including those involving extensive exposure to disturbed native soil (e.g., building excavation sites, during dust storms) (**CIII**).

Pet-Related Exposures

Health-care providers should advise HIV-infected persons of the potential risk posed by pet ownership. However, they should be sensitive to the possible psychological benefits of pet ownership and should not routinely advise HIV-infected persons to part with their pets **(DIII)**. Specifically, providers should advise HIV-infected patients of the following precautions (*9*).

General

Veterinary care should be sought when a pet develops diarrheal illness. If possible, HIV-infected persons should avoid contact with animals that have diarrhea **(BIII)**. A fecal sample should be obtained from animals with diarrhea and examined for *Cryptosporidium*, *Salmonella*, *Campylobacter*, and Shiga toxin-producing *Escherichia coli* **(BIII)**.

When obtaining a new pet, HIV-infected patients should avoid animals aged <6 months (or <1 year for cats) and specifically animals with diarrhea **(BIII)**. Because the hygienic and sanitary conditions in pet-breeding facilities, pet stores, and animal shelters are variable, patients should be cautious when obtaining pets from these sources. Stray animals should be avoided. Animals aged <6 months, and specifically those with diarrhea, should be examined by a veterinarian for *Cryptosporidium*, *Salmonella*, *Campylobacter*, and Shiga toxin-producing *Escherichia coli* **(BIII)**.

Patients should wash their hands after handling pets, including before eating, and avoid contact with pets' feces to reduce the risk for cryptosporidiosis, salmonellosis, campylobacteriosis, and *E. coli* infection **(BIII)**.

Patients should avoid all animal bite wounds to reduce the risk for infection. Patients should also not allow pets, particularly cats, to lick patients' open cuts or wounds. Patients should wash all animal bites, animal scratches, or wounds licked by animals promptly with soap and water **(CIII)** and seek medical attention **(BIII)**. A 3- to 7-day course of antimicrobial therapy might be recommended if the wounds are moderate or severe, demonstrate crush injury and edema, involve the bones of a

joint, involve a puncture of the skin near a joint, or involve a puncture of a joint directly **(CIII)**.

Cats

Patients should be aware that cat ownership increases their risk for toxoplasmosis and *Bartonella* infection, and enteric infections **(CIII)**. Patients who elect to obtain a cat should adopt or purchase an animal aged >1 year and in good health to reduce the risk for cryptosporidiosis, *Bartonella* infection, salmonellosis, campylobacteriosis, and *E. coli* infection **(BII)**.

Litter boxes should be cleaned daily, preferably by an HIV-negative, nonpregnant person; if HIV-infected patients perform this task, their hands should be washed thoroughly afterward to reduce the risk for toxoplasmosis **(BIII)**. To further reduce the risk for toxoplasmosis, HIV-infected patients should keep cats indoors, not allow them to hunt, and not feed them raw or undercooked meat **(BIII)**. Although declawing is not usually advised, patients should avoid activities that might result in cat scratches or bites to reduce the risk for *Bartonella* infection **(BII)**. Patients should also wash sites of cat scratches or bites promptly **(CIII)** and should not allow cats to lick patients' open cuts or wounds **(BIII)**.

Care of cats should include flea control to reduce the risk for *Bartonella* infection **(CIII)**. Testing cats for toxoplasmosis **(EII)** or *Bartonella* infection **(DII)** is not recommended.

Birds

Screening healthy birds for *Cryptococcus neoformans*, *Mycobacterium avium,* or *Histoplasma capsulatum* is not recommended **(DIII)**.

Other

Contact with reptiles (e.g., snakes, lizards, iguanas, and turtles) and chicks and ducklings should be avoided to reduce the risk for salmonellosis **(BIII)**. Gloves should be used during aquarium cleaning to reduce the risk for infection with *Mycobacterium marinum* **(BIII)**. Contact with exotic pets (e.g., nonhuman primates) should be avoided **(CIII)**.

Food- and Water-Related Exposures

HIV-infected persons should avoid eating certain foods, including foods that might contain raw eggs (e.g., certain preparations of hollandaise sauce, Caesar and other salad dressings, certain mayonnaises, uncooked cookie and cake batter, and eggnog); raw or undercooked poultry, meat, seafood (raw shellfish in particular); unpasteurized dairy products; unpasteurized fruit juice; and raw seed sprouts (e.g., alfalfa sprouts or mung bean sprouts). Poultry and meat are safest when adequate cooking is confirmed with a thermometer (165º F [74º F]). If a thermometer is not used, the risk for illness is decreased by eating poultry and meat that have no trace of pink. However, color change of meat (e.g., absence of pink) does not always correlate with internal temperature. Produce items should be washed thoroughly **(BIII)**; providers may wish to advise patients that produce is safest when cooked **(CIII)**.

Cross-contamination of foods should be avoided. Uncooked meats should not be allowed to come in contact with other foods; hands, cutting boards, counters, and knives and other utensils should be washed thoroughly after contact with uncooked foods **(BIII)**.

Although incidence of listeriosis is low, it is a serious disease that occurs unusually frequently among HIV-infected persons who are severely immunosuppressed. An immunosuppressed, HIV-infected person who wishes to reduce the risk for acquiring listeriosis as much as possible can do the following **(CIII)**:

- Avoid soft cheeses (e.g., feta, Brie, Camembert, blue-veined, and Mexican queso fresco cheese). Hard cheeses, processed cheeses, cream cheese, including slices and spreads, cottage cheese, or yogurt need not be avoided.
- Cook leftover foods or ready-to-eat foods (e.g., hot dogs) until steaming hot before eating.
- Avoid foods from delicatessen counters (e.g., prepared salads, meats, cheeses) or heat/reheat these foods until steaming before eating.
- Avoid refrigerated pâtés and other meat spreads, or heat/reheat these foods until steaming; canned or shelf-stable pâté and meat spreads need not be avoided.
- Avoid raw or unpasteurized milk, including goat's milk, or foods that contain unpasteurized milk or milk products.

Patients should not drink water directly from lakes or rivers because of the risk for

cryptosporidiosis, giardiasis, and toxoplasmosis **(AIII)**. Waterborne infection also might result from swallowing water during recreational activities. Patients should avoid swimming in water that is probably contaminated with human or animal waste and should avoid swallowing water during swimming **(BII)**.

During outbreaks or in other situations in which a community boil-water advisory is issued, boiling water for >1 minute will eliminate the risk for acquiring cryptosporidiosis **(AI)**. Using submicron, personal-use water filters (home/office types) or drinking bottled water might also reduce the risk **(CIII)**. Available data are inadequate to support a recommendation that all HIV-infected persons boil or otherwise avoid drinking tap water in nonoutbreak settings. However, persons who wish to take independent action to reduce their risk for waterborne cryptosporidiosis might take precautions similar to those recommended during outbreaks. Such decisions are best made in conjunction with a health-care provider. Persons

who opt for a personal-use filter or bottled water should be aware of the complexities involved in selecting the appropriate products, the lack of enforceable standards for destruction or removal of oocysts, product cost, and the difficulty of using these products consistently. Patients taking precautions to avoid acquiring cryptosporidiosis from drinking water should be advised that ice made from contaminated tap water also can be a source of infection **(BII)**. Such persons should be aware that fountain beverages served in restaurants, bars, theaters, and other public places also might pose a risk, because these beverages, and the ice they might contain, are usually made from tap water. Nationally distributed brands of bottled or canned carbonated soft drinks are safe to drink. Commercially packaged, noncarbonated soft drinks and fruit juices that do not require refrigeration until after they are opened (i.e., those that can be stored unrefrigerated on grocery shelves) also are safe. Nationally distributed brands of frozen fruit juice concentrate are safe if they are reconstituted by users with water from a safe source. Fruit juices that must be kept refrigerated from the time they are processed to the time of consumption might be either fresh (i.e., unpasteurized) or heat treated (i.e., pasteurized); only juices labeled as pasteurized should be considered free of risk from *Cryptosporidium* and other disease agents. Other pasteurized beverages and beers also are considered safe. No data are available concerning survival of *Cryptosporidium* oocysts in wine.

Travel-Related Exposures

Travel, specifically to developing countries, might result in substantial risks of the exposure of HIV-infected persons to opportunistic pathogens, especially for patients who are severely immunosuppressed. Health-care providers or specialists in travel medicine should be consulted to help patients plan itineraries **(BIII)**.

During travel to developing countries, HIV-infected persons are at a higher risk for foodborne and waterborne infections than they are in the United States. Foods and beverages, specifically raw fruits and vegetables, raw or undercooked seafood or meat, tap water, ice made with tap water, unpasteurized milk and dairy products, and items purchased from street vendors, might be contaminated. Items that are usually safe to consume include steaming hot foods, fruits that are peeled by the traveler, bottled (including carbonated) beverages, hot coffee or tea, beer, wine, and water brought to a rolling boil for ≥1 minute **(AII)**. Treating water with iodine or chlorine might not be as effective as boiling but can be used, perhaps in conjunction with filtration, when boiling is not practical **(BIII)**.

Waterborne infections might result from swallowing water during recreational activities. To reduce the risk for cryptosporidiosis, giardiasis, and toxoplasmosis, patients should avoid swallowing water during swimming and should not swim in water that might be contaminated (e.g., with sewage or animal waste) **(BII)**.

Antimicrobial prophylaxis for traveler's diarrhea is not recommended routinely for HIV-infected persons traveling to developing countries **(DIII)**. Such preventive therapy can have adverse effects and can promote the emergence of drug-resistant organisms. Nonetheless, studies (none involving an HIV-infected population) have reported that prophylaxis can reduce the risk for diarrhea among travelers. Under selected circumstances (e.g., those in which the risk for infection is high and the period of travel brief), the health-care provider and patient might weigh the potential risks and benefits and decide that antibiotic prophylaxis is warranted (**CIII**). For those persons to whom prophylaxis is offered, fluoroquinolones (e.g., ciprofloxacin [500 mg daily]) or rifaximin (200 mg daily) can be considered (**CIII**). Fluoroquinolones should not be administered to pregnant women and increasing resistance of bacterial enteric pathogens to fluoroquinolone might limit their future benefit for traveler's diarrhea. Prophylaxis with trimethoprim-sulfamethoxazole (TMP-SMX) (one double-strength tablet daily) also has been demonstrated to be effective, but resistance to this drug is widespread, and it is no longer recommended in many tropical areas.

HIV-infected travelers to developing countries should carry a sufficient supply of an antimicrobial agent to be taken empirically if diarrhea occurs **(BIII)**. One appropriate regimen is 500 mg of ciprofloxacin twice daily for 3–7 days. An alternative to fluoroquinolones in regions with fluoroquinolone resistance is azithromycin. Alternative antibiotics (e.g., azithromycin) should be considered as empirical therapy for use by pregnant women **(CIII)**. Travelers should consult a physician if their diarrhea is severe and does not respond to empirical therapy, if their stools contain blood, if fever is accompanied by shaking chills, or if dehydration occurs. Antiperistaltic agents (e.g., diphenoxylate and loperamide) are used for treating diarrhea; however, they should not be used by patients with high fever or with blood in the stool, and their use should be discontinued if symptoms persist >48 hours **(AII)**.

Travelers should be advised concerning other preventive measures appropriate for anticipated exposures (e.g., chemoprophylaxis for malaria, protection against arthropod vectors, treatment with immune globulin, and vaccination) **(AII)**. They should avoid direct contact of the skin with soil or sand (e.g., by wearing shoes and protective clothing and by using towels on beaches) in areas where fecal contamination of soil is likely **(BIII)**.

Live-virus vaccines should be avoided **(EII)**. One exception is measles vaccine, which is recommended for nonimmune

persons. However, measles vaccine is not recommended for persons who are severely immunosuppressed **(DIII)**; immune globulin should be considered for measles-susceptible, severely immunosuppressed persons who are anticipating travel to measles-endemic countries **(BIII)**. Another exception is varicella vaccine, which can be administered to asymptomatic nonimmunosuppressed adults who are susceptible to varicella virus infection **(BII)**. Inactivated (killed) poliovirus vaccine should be used instead of oral (live) poliovirus vaccine, which is contraindicated for HIV-infected persons. Persons at risk for exposure to typhoid fever should be administered an inactivated parenteral typhoid vaccine instead of the live-attenuated oral preparation. Yellow fever vaccine is a live-virus vaccine with uncertain safety and efficacy among HIV-infected persons. Travelers with asymptomatic HIV infection who cannot avoid potential exposure to yellow fever should be offered vaccination. If travel to a zone with yellow fever is necessary and vaccination is not administered, patients should be advised of the risk, instructed in methods for avoiding the bites of vector mosquitoes, and provided a vaccination waiver letter.

Killed and recombinant vaccines (e.g., influenza, diphtheria-tetanus, rabies, hepatitis A, hepatitis B, Japanese encephalitis, meningococcal vaccines) should usually be used for HIV-infected persons just as they would be used for non-HIV–infected persons anticipating travel **(BIII)**. Preparation for travel should include a review and updating of routine vaccinations, including diphtheria, tetanus, acellular pertussis, and influenza. Available cholera vaccine, which is not currently sold in the United States, is not recommended for travelers following a routine tourist itinerary, even if travel includes countries reporting cases of cholera **(DII)**.

Travelers should be informed regarding other area-specific risks and instructed in ways to reduce those risks **(BIII)**. Geographically focal opportunistic infections that pose an increased risk to HIV-infected persons include visceral leishmaniasis (a protozoan infection transmitted by the sandfly) and different fungal infections (e.g., *Penicillium marneffei* infection, coccidioidomycosis, and histoplasmosis). Several tropical and developing areas and some developed nations have high rates of tuberculosis.

CDC maintains a website accessible to travelers and their care providers at www.cdc.gov/travel and regularly publishes recommendations for prevention of disease while traveling (CDC Health Information for International Travel 2008, a.k.a. the Yellow Book). This information can be found at the same website, which allows users to locate prevention recommendations according to geographic destination and to find updates on international disease outbreaks that might pose a health threat to travelers. A detailed review of concerns faced by immunocompromised persons traveling abroad is available at this website and in the Yellow Book (Chapter 9) (*10*).

References

1. Fleming DT, Wasserheit JN. From epidemiological synergy to public health policy and practice: the contribution of other sexually transmitted diseases to sexual transmission of HIV infection. Sex Transm Infect 1999;75:3–17.
2. Rottingen JA, Cameron DW, Garnett GP. A systematic review of the epidemiologic interactions between classic sexually transmitted diseases and HIV: how much really is known? Sex Transm Dis 2001;28:579–97.
3. McClelland RS, Wang CC, Mandaliya K, et al. Treatment of cervicitis is associated with decreased cervical shedding of HIV-1. AIDS 2001;15:105–10.
4. Cohen MS, Hoffman IF, Royce RA, et al. Reduction of concentration of HIV-1 in semen after treatment of urethritis: implications for prevention of sexual transmission of HIV-1. AIDSCAP Malawi Research Group. Lancet 1997 349:1868–73.
5. Ghys PD, Fransen K, Diallo MO, et al. The associations between cervicovaginal HIV shedding, sexually transmitted diseases and immunosuppression in female sex workers in Abidjan, Côte d'Ivoire. AIDS 1997;11:85–93.
6. CDC. Incorporating HIV prevention into the medical care of persons living with HIV. Recommendations of CDC, the Health Resources and Services Administration, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. MMWR 2003; 52(No. RR-12).
7. CDC. Sexually transmitted diseases treatment guidelines, 2006. MMWR 2006;55(No.RR-11).
8. CDC. HIV prevention bulletin: medical advice for persons who inject illicit drugs—May 9, 1997. Available at http://www.cdcnpin.org/Reports/MedAdv.pdf.
9. CDC. USPHS/IDSA guidelines for the prevention of oppurtunistic infections in persons infected with human immunodeficiency virus. MMWR 1999;48(No.RR-10).
10. CDC. Health information for international travel, 2008. Atlanta, GA: US Department of Health and Human Services, Pubic Health Service. Available at http://www.cdc.gov/travel/contentYellowBook.aspx. 2007.

Acronyms

ABG	arterial blood gas
ABLC	amphotericin B liquid complex
ACG	atypical glandular cells
ACTG	AIDS Clinical Trials Group
ACTs	artemisinin-containing combination therapies
AFB	acid-fast bacillus (*pl.* bacilli)
AFP	alpha fetoprotein
AIN	anal intraepithelial neoplasia
ALT	alanine aminotransferase
Anti-HBc	anti-hepatitis B core antibody
Anti-HBs	anti-hepatitis B surface antibody
APR	Antiretroviral Pregnancy Registry
ARN	acute retinal necrosis
ART	antiretroviral therapy
ARV	antiretroviral
ASC-H	atypical squamous cells, cannot rule out high grade lesions
ASC-US	atypical squamous cells of undetermined significance
ASCCP	American Society for Colposcopy and Cervical Pathology
AST	aspartate aminotransferase
BA	bacillary angiomatosis
BCG	bacillus Calmette-Guérin
bDNA	branched DNA
CAP	community-acquired pneumonia
ccDNA	closed circular DNA
CDC	Centers for Disease Control and Prevention
CES-D	Center for Epidemiologic Studies Depression Scale
CIN	cervical intraepithelial neoplasia
CLEAR	Collaborative Exchange on Antifungal Research
CMV	cytomegalovirus
CNS	central nervous system
CPT score	Child-Pugh-Turcotte score
CSF	cerebrospinal fluid
CT	computed tomography
DNA	deoxyribonucleic acid
DOT	directly observed therapy
DRSP	drug-resistant *Streptococcus pneumoniae*
EBV	Epstein-Barr virus
EDTA	ethylenediaminetetraacetic acid
EGD	esophagogastroduodenoscopy
ELISA	enzyme-linked immunosorbent assay
EMB	ethambutol
ESLD	end-stage liver disease
EVR	early virologic response
FDA	Food and Drug Administration
FLAIR	fluid attenuated inversion recovery
HAART	highly active antiretroviral therapy
HAV	hepatitis A virus
HBeAG	hepatitis B virus e antigen
HBIG	hepatitis B virus immunoglobulin
HBsAg	hepatitis B virus surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HDV	hepatitis delta virus
HHV-6	human herpesvirus 6
HHV-7	human herpesvirus 7
HHV-8	human herpesvirus 8
HIV	human immunodeficiency virus
HIVMA	HIV Medical Association
HPV	human papillomavirus
HRA	high-resolution anoscopy
HSIL	high-grade squamous intraepithelial lesion
HSV-1	human herpes simplex virus type 1
HSV-2	human herpes simplex virus type 1
ICP	intracranial pressure
ICU	intensive care unit
IDSA	Infectious Diseases Society of America
IDU	intravenous- or injection-drug user
IFN	interferon
IgG	immunoglobulin G
IgM	immunoglobulin M
IGRA	interferon-gamma release assay
INH	isoniazid
INR	International Normalized Ratio
IRD	immune reconstitution disease
IRIS	immune reconstitution inflammatory syndrome
IRU	immune recovery uveitis
IV	intravenous
JCV	JC virus
KOH	potassium hydroxide
KS	Kaposi's sarcoma
KSHV	Kaposi's sarcoma-associated virus (aka HHV-8)
LEEP	loop electrosurgical excision procedure
LSIL	low-grade squamous intraepithelial lesion

LTBI	latent tuberculosis infection
MAC	*Mycobacterium avium* complex
MCD	Multicentric Castleman's disease
MDR	multidrug resistant (aka multiple drug-resistant)
MELD	Model for End-stage Liver Disease
MRI	magnetic resonance imaging
MSM	men who have sex with men
MTCT	mother-to-child transmission
MU	million units
NAA	nucleic acid amplification
NEP	needle exchange program
NIH	National Institutes of Health
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
OARAC	Office of AIDS Research Advisory Council
OI	opportunistic infection
PCP	*Pneumocystis* pneumonia (formerly *P. carinii* [now *jirovecii*] pneumonia)
PCR	polymerase chain reaction
pegIFN	pegylated interferon
PEL	primary effusion lymphoma
PET	positron emission tomography
PI	protease inhibitor
PML	progressive multifocal leukoencephalopathy
PORN	progressive outer retinal necrosis
PPD	purified protein derivative
PPV	polysaccharide pneumococcal vaccine
PZA	pyrazinamide
RBV	ribavirin
RIF	rifampin
RFB	rifabutin
RNA	ribonucleic acid
RPR	rapid plasma reagin
RRP	recurrent respiratory papillomatosis
RT-PCR	reverse transcriptase-polymerase chain reaction
SAAG	serum-ascites albumin gradient
SBP	spontaneous bacterial peritonitis
SIRS	systemic inflammatory response syndrome
SLE	systemic lupus erythematosus
SP	sulfadoxine-pyrimethamine
SPECT	single-photon emission computed tomography
SVR	sustained virologic response
TB	tuberculosis
TE	*Toxoplasma gondii* encephalitis
TMP-SMX	trimethoprim-sulfamethoxazole
TSH	thyroid stimulating hormone
TST	tuberculin skin test
VAIN	vaginal intraepithelial neoplasia
VDRL	Venereal Disease Research Laboratory
VIN	vulvar intraepithelial neoplasia
VZV	varicella-zoster virus
WBC	white blood cell
WHO	World Health Organization
XDR	extensively drug resistant
YMDD	tyrosine-methionine-aspartate-aspartate

DHHS Panel on Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents, June 18, 2008

Co-Chairs, Henry Masur, MD, National Institutes of Health, DHHS, Bethesda, MD, Jonathan E. Kaplan, MD, Centers for Disease Control and Prevention, DHHS, Atlanta, GA, King K. Holmes, MD, PhD, University of Washington, Seattle, WA, Constance Benson, MD, University of California San Diego, CA

Editors, John T. Brooks, MD, Centers for Disease Control and Prevention, DHHS, Atlanta, GA, Alice Pau, PharmD, National Institutes of Health, DHHS, Bethesda, MD

Working Groups

Introduction, Leaders, Jonathan E. Kaplan, MD, Centers for Disease Control and Prevention, DHHS, Atlanta, GA, Constance Benson, MD, University of California San Diego, CA, John T. Brooks, MD and Judith Currier, MD, University of California Los Angeles, CA

Pneumocystis **Pneumonia, Leader,** Joseph Kovacs, MD, National Institutes of Health, DHHS, Bethesda, MD, **Members,** Hansjakob Furrer, MD, University Hospital and University of Bern, Switzerland, Laurence Huang, MD, San Francisco General Hospital, San Francisco, CA, Alison Morris, MD,MS, University of Pittsburgh Medical School, Pittsburgh, PA, Caryn G. Morse, MD, National Institutes of Health, DHHS, Bethesda, MD

Toxoplasma gondii **Encephalitis, Leader,** Joseph Kovacs, MD, National Institutes of Health, DHHS, Bethesda, MD, **Members,** Letha Healey, MD, National Institutes of Health, DHHS, Bethesda, MD, Daniel Podzamczer, MD, Hospital Universitari de Bellvitge, Spain, José Miró, MD, PhD, Hospital Clinic- IDIBAPS. University of Barcelona, Spain

Cryptosporidiosis, Bacterial Enteric Infections, Leader, Timothy Flanigan, MD, Brown Medical School, Providence, RI, **Members,** John T. Brooks, MD, Centers for Disease Control and Prevention, DHHS, Atlanta, GA, Cynthia L. Sears, MD, Johns Hopkins School of Medicine, Baltimore, MD, Christine Wanke, MD, Tufts University School of Medicine, Boston, MA, Clinton White, MD, University of Texas Medical Branch, Galveston, TX

Microsporidiosis, Leader, Louis Weiss, MD, MPH, Albert Einstein College of Medicine, Bronx, NY, **Members,** Elizabeth S. Didier, PhD, Tulane National Primate Research Center, Covington, LA, Caspar Franzen, MD, Universität Regensburg, Germany,

Mycobacterium tuberculosis **Infection and Disease, Leaders,** Alyssa Finlay, MD, Centers for Disease Control and Prevention, DHHS, Atlanta, GA, M. Elsa Villarino, MD, Centers for Disease Control and Prevention, DHHS, Atlanta, GA, **Members,** Hansjakob Furrer, MD, University Hospital and University of Bern, Switzerland, José M. Miró, MD, PhD, Hospital Clinic- IDIBAPS. University of Barcelona, Spain, Payam Nahid, MD, MPH, University of California San Francisco at San Francisco General Hospital, CA, Kent Sepkowitz, MD, Memorial Sloan Kettering Cancer Center, New York, NY, Sophia Siddiqui, MD, National Institutes of Health, DHHS, Bethesda, MD

Disseminated *Mycobacterium avium* Complex Disease, Leader, Fred Gordin, MD, Veterans Affairs Medical Center, Washington, DC, **Members,** David Cohn, MD, Denver Public Health, Denver, CO, Judith Currier, MD, University of California Los Angeles, CA, Susan Dorman, MD, Johns Hopkins University School of Medicine, Baltimore, MD, Robert Horsburgh, MD, Boston University School of Public Health, Boston, MA

Bacterial Respiratory Disease, Leader, Laurence Huang, MD, San Francisco General Hospital, San Francisco, CA, **Members,** Robert F. Miller, MD, University College London, United Kingdom, Alison Morris, MD, MS, University of Pittsburgh Medical School, Pittsburgh, PA, Michael S. Niederman, MD, Winthrop-University Hospital, Mineola, NY

Bacterial Enteric Infections, Leader, John T. Brooks, MD, Centers for Disease Control and Prevention, DHHS, Atlanta, GA, **Members,** Cynthia L. Sears, MD, Johns Hopkins School of Medicine, Baltimore, MD, Christine Wanke, MD, Tufts University School of Medicine, Boston, MA, Clinton White, MD, University of Texas Medical Branch, Galveston, TX

Bartonellosis, **Leader,** Jane Koehler, MD, University of California San Francisco, CA **Members,** Nesli Basgoz, MD, Massachusetts General Hospital, Harvard Medical School, Boston, MA, Lynn Guptill-Yoran, DVM, PhD, Purdue University School of Veterinary Medicine, West Lafayette, IN, James Oleske, MD, University of Medicine and Dentistry of New Jersey, Newark, NJ

Syphilis, Leader, Kimberly Workowski, MD, Emory University, Atlanta, GA, **Members,** Michael Augenbraun, MD, SUNY Downstate Medical Center, Brooklyn, NY, Edward Hook III, MD, University of Alabama, Birmingham, AL, Peter Leone, MD, University of North Carolina, Chapel Hill, NC, Anne Rompalo, MD, Johns Hopkins School of Medicine, Baltimore, MD, Bradley Stoner, MD, PhD, Washington University in St. Louis, St. Louis, MO, George Wendel, MD, University of Texas Southwestern Medical School, Dallas, TX

Mucocutaneous Candidiasis, Leader, Jack Sobel, MD, Wayne State University Medical Center, Detroit, MI, **Members,** Luis Ostrosky-Zeichner, MD, University of Texas Health Science Center, Houston, TX, Sanjay G. Revankar, MD, Wayne State University School of Medicine, Detroit, MI, Jose A. Vazquez, MD, Henry Ford Health System, Detroit, MI

Cryptococcosis, Histoplasmosis, Coccidomycosis, and Aspergillosis,, Leader, Neil Ampel, MD, Southern Arizona Veterans Affairs Health Care System, Tucson, AZ, **Members,** Carol A. Kauffman, MD, University of Michigan, Veterans Affairs Ann Arbor Healthcare System, MI, Peter G. Pappas, MD, University of Alabama School of Medicine, Birmingham, AL

Cytomegalovirus Disease, Leader, Paul D. Griffiths, MD, DSc, Royal Free and University College Medical School, United Kingdom, **Members,** Henry H. Balfour, Jr., MD, University of Minnesota, Minneapolis, MN, Douglas Jabs, MD, The Mount Sinai School of Medicine, New York, NY, Michael Polis, MD, National Institutes of Health, DHHS, Bethesda, MD, Stephen Spector, MD, University of California, San Diego, San Diego, CA

Herpes Simplex Virus Disease, HHV-6 and HHV-7, Varicella-Zoster Virus Diseases, and Human Herpesvirus-8 Disease, Leaders, John W. Gnann, Jr., MD, University of Alabama, Birmingham, AL, Anna Wald, MD, University of Washington, Seattle, WA, **Members,** Corey Casper, MD, MPH, University of Washington, Seattle, WA, David W. Kimberlin, MD, University of Alabama, Birmingham, AL, Peter Leone, MD, University of North Carolina, Chapel Hill, NC

Human Papillomavirus, Leader, Joel Palefsky, MD, University of California, San Francisco, San Francisco, CA, **Members,** Susan Cu-Uvin, MD, Brown Center for AIDS Research, Providence, RI, Eileen F. Dunne MD, MPH, Centers for Disease Control and Prevention, DHHS, Atlanta, GA, Kenneth H. Fife, MD, PhD, Indiana University School of Medicine, Indianapolis, IN, Kathleen Squires, MD, Jefferson Medical College, Philadelphia, PA, Howard D. Strickler, MD, MPH, Albert Einstein College of Medicine, Bronx, NY

Hepatitis B Virus Infection, Leader, Kenneth Sherman, MD, PhD, University of Cincinnati, Cincinnati, OH, **Members,** Barbara McGovern, MD, Tufts University School of Medicine, Jamaica Plain, MA, Mindie Nguyen, MD, MAS, Stanford University, Palo Alto, CA, Marion Peters, MD, University of California, San Francisco, San Francisco, CA

Hepatitis C Virus Infection, Leader, Mark Sulkowski, MD, Johns Hopkins University, Baltimore, MD, **Members,** Raymond Chung, MD, Massachusetts General Hospital, Boston, MA, Mamta Jain, MD, University of Texas Southwestern Medical Center, Dallas, TX, Margaret James Koziel, MD, Beth Israel Deaconess Medical Center, Boston, MA, Andrew Talal, MD, MPH, Weill Medical College of Cornell University, New York, NY

Progressive Multifocal Leukoencephalopathy/JC Virus Infection, Leader, Richard W. Price, MD, University of California San Francisco, San Francisco, CA, **Members,** Paola Cinque, MD, PhD , San Raffaele Scientific Institute, Milan, Italy, Igor J. Koralnik, MD, Beth Israel Deaconess Medical Center, Boston, MA, Christina M. Marra, MD, University of Washington, Seattle, WA, José M. Miró, MD, PhD, Hospital Clinic- IDIBAPS. University of Barcelona, Spain

Geographic OIs of Specific Consideration, Leaders, Monica Parise, MD, Centers for Disease Control and Prevention, DHHS, Atlanta, GA, Pacharee Kantipong, (penicilliosis), MD, Chiangrai Regional Hospital, Thailand, **Members,** Jorge Alvar, MD, World Health Organization, Geneva, Caryn Bern, MD, Centers for Disease Control and Prevention, DHHS , Atlanta, GA, Suwat Chariyalertsak, MD, DrPH, Chiang Mai University, Thailand, Barbara Herwaldt, MD, MPH, Centers for Disease Control and Prevention, DHHS, Atlanta, GA, James Maguire, MD, MPH, Brigham and Women's Hospital, Baltimore, MD, Anne Moore, MD, PhD, Centers for Disease Control and Prevention, DHHS, Atlanta, GA, Larry Slutsker, MD, MPH , Centers for Disease Control and Prevention, DHHS, Atlanta, GA, Khuanchai Suparatpinyo, MD, Chiang Mai University, Thailand, Jose Vazquez, MD, Henry Ford Health System, Detroit, MI, Murray Wittner, MD, PhD, Albert Einstein College of Medicine, Bronx, NY

Pregnancy, Leader, Heather Watts, MD, National Institutes of Health, DHHS, Rockville, MD, **Members,** Jean R. Anderson, MD, Johns Hopkins University, Baltimore, MD, Lynne Mofenson, MD, National Institutes of Health, DHHS, Rockville, MD.

Pharmacologic Issues/Tables, Leader, Alice Pau, PharmD, National Institutes of Health, DHHS, Bethesda, MD, **Members,** Ian R. McNicholl, PharmD , University of California, San Francisco, San Francisco, CA, Charles A. Peloquin, PharmD, National Jewish Medical and Research Center, Denver, CO, Paul J. Weidle, PharmD, MPH, Centers for Disease Control and Prevention, DHHS, Atlanta, GA

Immunizations, Leader, Gina Mootrey, DO, MPH, Centers for Disease Control and Prevention, DHHS, Atlanta, GA

Other Participants, Judith Aberg, MD, New York University, New York, NY, Miriam J. Alter, PhD, University of Texas Medical Branch, Galveston, TX, Roberto Badaro, MD, University of California, San Diego, La Jolla, CA, A. Cornelius Baker, Whitman-Walker Clinic, Washington, DC, John Bartlett, MD, Johns Hopkins University, Baltimore, MD, John Bennett, MD, National Institutes of Health, DHHS, Bethesda, MD, Pedro Cahn MD, PhD, Fundación Huesped, Argentina, Victoria Cargill, MD, National Institutes of Health, DHHS, Seattle, WA, Kenneth Castro, MD, Centers for Disease Control and Prevention, DHHS, Atlanta, GA, Richard E. Chaisson, MD, Johns Hopkins University, Baltimore, MD, Myron Cohen, MD, University of North Carolina, Chapel Hill, NC, Robert Eisinger, PhD, National Institutes of Health, DHHS, Bethesda, MD, Wafaa El-Sadr, MD, MPH, Harlem Hospital, New York, NY, Judith Feinberg, MD, University of Cincinnati, Cincinnati, OH, Kenneth A. Freedberg, MD, MSc, Harvard Medical School, Boston, MA, Jose M. Gatell, MD, PhD, Unidad de Enfermedades Infecciosas, Spain, Peter A. Gross, MD, Hackensack University Medical Center, Hackensack, NJ, Diane Havlir, MD, University of California, San Francisco, San Francisco, CA, Thomas M. Hooton, MD, University of Miami Miller School of Medicine, Miami, FL, Edward Janoff, MD, University of Colorado, Denver, CO, Grace John-Stewart, MD, Phd, MPH, University of Washington, Seattle, WA, Rupert Kaul, MD, PhD, University of Toronto, Canada, Mari Kitahata, MD, PhD, University of Washington, Seattle, WA, Jens Lundgren, MD, University of Copenhagen, Denmark, Scott McClelland, MD, MPH, University of Washington, Seattle, WA, Richard D. Moore, MD, MHS, Johns Hopkins University, Baltimore, MD, James Neaton, PhD, University of Minnesota, Minneapolis, MN, Benjamin J. Park, MD, Centers for Disease Control and Prevention, DHHS, Atlanta, GA, Thomas C. Quinn, MD, Johns Hopkins University, Baltimore, MD, David Rimland, MD, Veterans Administration Medical Center, Decatur, GA, Paul E. Sax, MD, Brigham and Women's Hospital, Boston, MA, Kathleen Squires, MD, Jefferson Medical College, Philadelphia, PA, Michael Tapper, MD, Lenox Hill Hospital, New York, NY, Chloe Thio, MD, Johns Hopkins University School of Medicine, Baltimore, MD, David Thomas, MD, Johns Hopkins University, Baltimore, MD, Cindy M. Weinbaum, MD, MPH, Centers for Disease Control and Prevention, DHHS, Atlanta, GA, Thomas C. Wright, Jr., MD, Columbia University Medical Center, New York, NY

The *Morbidity and Mortality Weekly Report (MMWR)* Series is prepared by the Centers for Disease Control and Prevention (CDC) and is available free of charge in electronic format. To receive an electronic copy each week, visit *MMWR*'s free subscription page at http://www.cdc.gov/mmwr/mmwrsubscribe.html. Electronic copy also is available from CDC's Internet server at *http://www.cdc.gov/mmwr* or from CDC's file transfer protocol server at *ftp://ftp.cdc.gov/pub/publications/mmwr.* Paper copy subscriptions are available through the Superintendent of Documents, U.S. Government Printing Office, Washington, DC 20402; telephone 202-512-1800.

Data in the weekly *MMWR* are provisional, based on weekly reports to CDC by state health departments. The reporting week concludes at close of business on Friday; compiled data on a national basis are officially released to the public on the following Friday. Data are compiled in the National Center for Public Health Informatics, Division of Integrated Surveillance Systems and Services. Address all inquiries about the *MMWR* Series, including material to be considered for publication, to Editor, *MMWR* Series, Mailstop E-90, CDC, 1600 Clifton Rd., N.E., Atlanta, GA 30333 or to *mmwrq@cdc.gov.*

All material in the *MMWR* Series is in the public domain and may be used and reprinted without permission; citation as to source, however, is appreciated.

Use of trade names and commercial sources is for identification only and does not imply endorsement by the U.S. Department of Health and Human Services.

References to non-CDC sites on the Internet are provided as a service to *MMWR* readers and do not constitute or imply endorsement of these organizations or their programs by CDC or the U.S. Department of Health and Human Services. CDC is not responsible for the content of these sites. URL addresses listed in *MMWR* were current as of the date of publication.

☆U.S. Government Printing Office: 2009-523-019/41162 Region IV ISSN: 1057-5987

MMWR
Morbidity and Mortality Weekly Report
www.cdc.gov/mmwr

Recommendations and Reports
April 10, 2009 / Vol. 58 / RR-4

Continuing Education Activity Sponsored by CDC

Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents

Recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America

EXPIRATION — April 10, 2012

You must complete and return the response form electronically or by mail by **April 10, 2012**, to receive continuing education credit. If you answer all of the questions, you will receive an award letter for 3.25 hours Continuing Medical Education (CME) credit; 0.3 Continuing Education Units (CEUs); 3.25 contact hours Continuing Nursing Education (CNE) credit; 3.0 contact hours Certified Health Education Specialist (CHES) credit; or 0.3 CEUs Continuing Pharmacy Education (CPE) credit. If you return the form electronically, you will receive educational credit immediately. If you mail the form, you will receive educational credit in approximately 30 days. No fees are charged for participating in this continuing education activity.

INSTRUCTIONS

By Internet

1. Read this *MMWR* (Vol. 58, RR-4), which contains the correct answers to the questions beginning on the next page.
2. Go to the *MMWR* Continuing Education Internet site at http://www.cdc.gov/mmwr/cme/conted.html.
3. Select which exam you want to take and select whether you want to register for CME, CEU, CNE, CHES, or CPE credit.
4. Fill out and submit the registration form.
5. Select exam questions. To receive continuing education credit, you must answer all of the questions. Questions with more than one correct answer will instruct you to "Indicate all that apply."
6. Submit your answers no later than **April 10, 2012**.
7. Immediately print your Certificate of Completion for your records.

By Mail or Fax

1. Read this *MMWR* (Vol. 58, RR-4), which contains the correct answers to the questions beginning on the next page.
2. Complete all registration information on the response form, including your name, mailing address, phone number, and e-mail address.
3. Indicate whether you are registering for CME, CEU, CNE, CHES, or CPE credit.
4. Select your answers to the questions, and mark the corresponding letters on the response form. To receive continuing education credit, you must answer all of the questions. Questions with more than one correct answer will instruct you to "Indicate all that apply."
5. Sign and date the response form or a photocopy of the form and send no later than **April 10, 2012**, to
   Fax: 404-498-2388
   Mail: MMWR CE Credit
   CCHIS, Centers for Disease Control and Prevention
   1600 Clifton Rd, N.E., MS E-90
   Atlanta, GA 30333
6. Your Certificate of Completion will be mailed to you within 30 days.

ACCREDITATION

Continuing Medical Education (CME). CDC is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians. CDC designates this educational activity for a maximum of 3.25 AMA PRA category 1 credits. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Continuing Nursing Education (CNE). CDC is accredited as a provider of Continuing Nursing Education by the American Nurses Credentialing Center's Commission on Accreditation. This activity provides 3.25 contact hours.

Certified Health Education Specialist (CHES). CDC is a designated provider of continuing education contact hours (CECH) in health education by the National Commission for Health Education Credentialing, Inc. This program is a designated event for the CHES to receive 3.0 Category I contact hours in health education, CDC provider number GA0082.

Continuing Pharmacy Education (CPE). CDC is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. This program is a designated event for pharmacists to receive 0.3 CEUs in pharmacy education. The Universal Activity Number is 387-000-09-002-H02-P.

Continuing Education Unit (CEU). The CDC has been approved as an Authorized Provider by the International Association for Continuing Education and Training (IACET), 1760 Old Meadow Road, Suite 500, McLean, VA 22102. CDC is authorized by IACET to offer 0.3 CEU's for this program.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTERS FOR DISEASE CONTROL AND PREVENTION

Goal and Objectives

The goal of this report is to provide guidelines for clinicians and other health-care professionals regarding prevention and management of opportunistic illnesses (OIs) among HIV-1-infected adults and adolescents, including pregnant women. Upon completion of this educational activity, the reader should be able to 1) describe medications and their dosages for primary prophylaxis of OIs by chemoprophylaxis and vaccination, 2) describe methods for chronic suppressive therapy to prevent recurrence of OIs following treatment of acute illness, 3) describe recommendations for discontinuing primary prophylaxis and chronic suppressive therapy among persons whose CD4 cell count has increased as a result of antiretroviral therapy, 4) describe first-line medications and their dosages for the treatment of HIV-related OIs among adults and adolescents, and 5) describe recommendations for screening HIV-infected adults and adolescents for opportunistic infections.

To receive continuing education credits, please answer all of the following questions.

1. Primary prophylaxis to prevent acute infection in susceptible patients is recommended for all the following except…

A. *Pneumocystis jiroveci* (formerly *carinii*) pneumonia.
B. Disseminated *Mycobacterium avium* complex.
C. Mucocutaneous candidiasis.
D. Malaria for persons traveling to areas where malaria is endemic.
E. *Toxoplasma gondii* encephalitis.

2. Which of the following treatment regimens may be stopped if the patient's CD4 cell count rises to >100 cells/μL for >3 months due to antiretroviral therapy?

A. 100 mg of dapsone taken orally each day for prevention of *Pneumocystis jiroveci* (formerly *carinii*) pneumonia
B. One double-strength tablet of trimethoprim-sulfamethoxazole taken orally each day for prevention of *Toxoplasma gondii* in seropositive persons.
C. 400 mg of fluconazole taken orally each day for prevention of mucocutaneous candidiasis.
D. 300 mg of isoniazid and 50 mg of pyridoxine taken orally each day for persons with evidence of latent *Mycobacterium tuberculosis.*
E. 1200 mg of azithromycin taken orally once weekly for prevention of disseminated *Mycobacterium avium* complex.

3. For pregnant women in the first trimester of pregnancy, the preferred initial drug treatment for moderate to severe *Pneumocystis jiroveci* (formerly *carinii*) pneumonia is…

A. Dapsone 100 mg orally daily and TMP 15mg/kg/day orally in three divided doses.
B. Trimethoprim-sulfamethoxazole (TMP-SMX) [15–20 mg TMP and 75–100 mg. SMX]/kg/day given every 6–8 hours intravenously with adjunctive corticosteroid therapy according to the severity of illness.
C. Primaquine 15–30 mg (base) orally daily plus either clindamycin 600–900 mg. intravenously every 6–8 hours or clindamycin 300–450 mg orally very 6–8 hours with adjunctive corticosteroid therapy and after assessing G6PD status.
D. Aerosolized pentamidine 300 mg daily via Respirgard II™ nebulizer.
E. Atovaquone 750 mg orally twice daily with food.

4. Each of the following vaccinations is indicated for some or all HIV-infected men and women, except which of the following:

A. Inactivated influenza vaccination.
B. Varicella vaccination.
C. Human papillomavirus vaccination.
D. Hepatitis B vaccination.
E. Pneumococcal vaccination.

5. All of the following are recommended preferred therapy for the treatment of the associated infections except…

A. Oral ciprofloxacin at 750 mg twice daily for *Salmonella* gastroenteritis.
B. Oral clarithromycin at 500mg twice daily with oral ethambutol at 15mg/kg once daily for disseminated *Mycobacterium avium* complex.
C. Oral valacyclovir at 1,000 mg three time daily for varicella.
D. Intravenous amphotericin B deoxycholate at 0.6mg/kg daily for esophageal candidiasis.
E. Intravenous amphotericin B deoxycholate at 0.7mg/kg daily plus oral flucytosine at 100mg/kg daily administered in 4 divided doses for disseminated cryptococcosis.

6. Which of the following statements regarding syphilis is true?

A. Risk reduction counseling with a recommendation to notify and test sexual partners should be performed in all persons who have syphilis diagnosed at any stage.
B. Oral azithromycin is equally effective as intramuscular benzathine penicillin for primary, secondary or early latent infection.
C. Persons with late-latent syphilis in whom neurosyphilis has been ruled out by examination of cerebrospinal fluid should receive aqueous crystalline penicillin G at 18–24 million units per day administered intravenously as 3–4 million units IV every four hours for 10–14 days.
D. Probenecid should always be administered with penicillin for neurosyphilis.
E. Rates of syphilis among HIV-infected persons in the United States have remained stable for the past decade so that routine annual screening is now optional for sexually active patients without known contact with a syphilis-infected partner.

7. Which of the following actions is recommended to prevent exposure to OIs?

A. For cryptosporidiosis, routinely check pet dogs and cats for the parasite.
B. For listeriosis, do not eat soft cheeses.
C. For hepatitis B infection, do not travel to areas where it is endemic.
D. For histoplasmosis, avoid pet retiles.
E. For coccidiomycosis, do not use chlorinated pools frequented by infants.

8. Which of the following statements regarding viral hepatitis in HIV-infected persons is false?

A. Hepatitis A vaccination should be considered for all at-risk nonimmune patients.
B. Patients who are nonimmune to hepatitis C remain at risk for the infection.
C. Patients with viral hepatitis should avoid or limit alcohol consumption.
D. Patients with CD4 cell counts <200 cells/μL can be vaccinated for hepatitis B.
E. Treatment for hepatitis C infection is not indicated in patients with CD4 cell counts <50 cells/μL.

9. Immune reconstitution inflammatory syndrome (IRIS) has been reported in association with all of the following the infections after initiation of or a change in antiretroviral therapy (ART), except…

A. Cryptosporidial diarrhea.
B. Hepatitis B infection.
C. Progressive multifocal encephalopathy.
D. Mycobacterial infections.
E. Cryptococcosis.

10. Which of the following statements regarding herpes simplex virus (HSV) infection is false?

A. Consistent use of latex condoms can reduce sexual transmission of HSV between women and men.
B. Sexual transmission of HSV can occur even when overt lesions (genital or orolabial) are not present.
C. Prevention of recurrences of genital herpes with daily anti-HSV therapy in persons who have frequent or severe recurrences is recommended.
D. A treatment of choice for acyclovir-resistant HSV is valgancicolvir.
E. Acyclovir should not be given to pregnant women with genital HSV outbreaks due to the drug's substantial teratogenicity.

11. Which best describes your professional activities?
A. Physician.
B. Nurse.
C. Health educator.
D. Office staff.
E. Other.

12. I plan to use these recommendations as the basis for… (*indicate all that apply*):
A. Health education materials.
B. Insurance reimbursement policies.
C. Local practice guidelines.
D. Public policy.
E. Other.

13. Overall, the length of the journal article was…
A. Much to long.
B. A little to long.
C. Just right.
D. A little to short.
E. Much to short.

14. After reading this report, I am confident I can describe medications and their dosages for primary prophylaxis of OIs by chemoprophylaxis and vaccination.
A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

15. After reading this report, I am confident I can describe methods for chronic suppressive therapy to prevent recurrence of OIs following treatment of acute illness.
A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

16. After reading this report, I am confident I can describe recommendations for discontinuing primary prophylaxis and chronic suppressive therapy among persons whose CD4 cell count has increased as a result of antiretroviral therapy.
A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

17. After reading this report, I am confident I can describe first line medications and their dosages for the treatment of HIV-related OIs among adults and adolescents.
A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

18. After reading this report, I am confident I can describe recommendations for screening HIV infected adults and adolescents for opportunistic infections.
A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

19. The learning outcomes (objectives) were relevant to the goal(s) of this report.
A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

20. The instructional strategies used in this report (text, figure, and tables) helped me learn the material.
A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

(Continued on pg CE-4)

Detach or photocopy.

MMWR Response Form for Continuing Education Credit
April 10, 2009/Vol. 58/No. RR-4

Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents

Recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America

To receive continuing education credit, you must
1. provide your contact information (please print or type);
2. indicate your choice of CME, CME for nonphysicians, CEU, CNE, CHES, or CPE credit;
3. answer all of the test questions;
4. sign and date this form or a photocopy;
5. submit your answer form by **April 10, 2012.**
Failure to complete these items can result in a delay or rejection of your application for continuing education credit.

Check One
☐ CME Credit
☐ CME for nonphysicians Credit
☐ CEU Credit
☐ CNE Credit
☐ CHES Credit
☐ CPE Credit

Last Name (**print or type**) First Name

Street Address or P.O. Box

Apartment or Suite

City State ZIP Code

Phone Number Fax Number

E-Mail Address

Fill in the appropriate blocks to indicate your answers. Remember, you must answer all of the questions to receive continuing education credit!

1. [ ]A [ ]B [ ]C [ ]D [ ]E	15. [ ]A [ ]B [ ]C [ ]D [ ]E	
2. [ ]A [ ]B [ ]C [ ]D [ ]E	16. [ ]A [ ]B [ ]C [ ]D [ ]E	
3. [ ]A [ ]B [ ]C [ ]D [ ]E	17. [ ]A [ ]B [ ]C [ ]D [ ]E	
4. [ ]A [ ]B [ ]C [ ]D [ ]E	18. [ ]A [ ]B [ ]C [ ]D [ ]E	
5. [ ]A [ ]B [ ]C [ ]D [ ]E	19. [ ]A [ ]B [ ]C [ ]D [ ]E	
6. [ ]A [ ]B [ ]C [ ]D [ ]E	20. [ ]A [ ]B [ ]C [ ]D [ ]E	
7. [ ]A [ ]B [ ]C [ ]D [ ]E	21. [ ]A [ ]B [ ]C [ ]D [ ]E	
8. [ ]A [ ]B [ ]C [ ]D [ ]E	22. [ ]A [ ]B [ ]C [ ]D [ ]E	
9. [ ]A [ ]B [ ]C [ ]D [ ]E	23. [ ]A [ ]B [ ]C [ ]D [ ]E	
10. [ ]A [ ]B [ ]C [ ]D [ ]E	24. [ ]A [ ]B [ ]C [ ]D [ ]E	
11. [ ]A [ ]B [ ]C [ ]D [ ]E	25. [ ]A [ ]B [ ]C [ ]D [ ]E	
12. [ ]A [ ]B [ ]C [ ]D [ ]E	26. [ ]A [ ]B [ ]C [ ]D [ ]E	
13. [ ]A [ ]B [ ]C [ ]D [ ]E	27. [ ]A [ ]B	
14. [ ]A [ ]B [ ]C [ ]D [ ]E	28. [ ]A [ ]B [ ]C [ ]D [ ]E [ ]F	

Signature ***Date I Completed Exam***

21. The content was appropriate given the stated objective(s) of the course.
A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

22. The authors demonstrated expertise in the subject matter.
A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

23. Overall, the quality of the journal article was excellent.
A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

24. The availability of CE credit influenced my decision to participate in this activity.
A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.
F. Not applicable.

25. These recommendations will improve the quality of my practice.
A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

26. The *MMWR* format was conducive to leaning this content.
A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

27. Do you feel this course was commercially biased?
(*Indicate yes or no; if yes, please explain in the space provided.*)
A. Yes.
B. No.

28. How did you learn about the continuing education activity?
A. Internet.
B. Advertisement (e.g., fact sheet, *MMWR* cover, newsletter, or journal).
C. Coworker/supervisor.
D. Conference presentation.
E. *MMWR* subscription.
F. Other.

Correct answers for questions 1–10.
1C; 2E; 3B; 4C; 5D; 6A; 7B; 8E; 9A; 10E.

Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents

January 10, 2011

Developed by the DHHS Panel on
Antiretroviral Guidelines for Adults
and Adolescents – A Working Group of the
Office of AIDS Research Advisory Council (OARAC)

How to Cite the Adult and Adolescent Guidelines:
Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. January 10, 2011; 1–166. Available at **http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf**. Accessed [insert date] [insert page number, table number, etc. if applicable]

It is emphasized that concepts relevant to HIV management evolve rapidly. The Panel has a mechanism to update recommendations on a regular basis, and the most recent information is available on the **AIDS*info* Web site** (**http://aidsinfo.nih.gov**).

What's New in the Guidelines?

Key changes made to update the December 1, 2009, version of the guidelines are summarized below. Throughout the revised guidelines, significant updates are highlighted and fully discussed.

Introduction

The Panel emphasizes its recognition of the importance of clinical research in generating evidence to address unanswered questions related to the optimal safety and efficacy of antiretroviral therapy (ART). The Panel encourages both the development of protocols and patient participation in well-designed, Institutional Review Board (IRB)-approved clinical trials.

CD4 T-cell Count

The Panel recognizes that changes in CD4 cell count are seldom used in decision for ART changes in a patient on a suppressive ART regimen whose CD4 count is well above the threshold for opportunistic infection risk. In such patients, the Panel recommends that the CD4 count may be monitored less frequently, for example every 6 to 12 months (instead of every 3 to 6 months), unless there are changes in the patient's clinical status, such as new HIV-associated clinical symptoms or initiation of treatment with interferon, corticosteroids, or anti-neoplastic agents **(CIII)**.

Viral Load Testing

The Panel recognizes that low-level positive viral load results (typically <200 copies/mL) have been commonly reported with some viral load assays. For the purpose of patient monitoring, the Panel defines virologic failure as a confirmed viral load >200 copies/mL, which eliminates most cases of viremia caused by isolated blips or assay variability.

Drug-Resistance Testing

The Panel provides more specific recommendations on when to use genotypic testing to detect resistance to integrase strand transfer inhibitors (INSTIs).

- Because standard genotypic drug-resistance testing involves testing for mutations in the reverse transcriptase (RT) and protease (PR) genes, if transmitted INSTI resistance is a concern, providers may wish to supplement standard genotypic resistance testing with genotypic testing for resistance to this class of drugs **(CIII)**.
- In persons failing INSTI-based regimens, genotypic testing for INSTI resistance should be considered to determine whether to include a drug from this class in subsequent regimens **(BIII)**.

What to Start: Initial Combination Regimens for the Antiretroviral-Naïve Patient

Changes to the "What to Start" recommendations include the following:

- A regimen consisting of maraviroc (MVC) + zidovudine/lamivudine (ZDV/3TC) is now listed as an "Acceptable Regimen" because FDA approval of MVC for use in ART-naïve patients was based on the results of a randomized controlled trial using this regimen **(CI).**
- "MVC + tenofovir/emtricitabine (TDF/FTC)" and "MVC + abacavir (ABC)/3TC" have been added as "Regimens that may be acceptable but more definitive data are needed" **(CIII).**
- In response to a recent change to the Invirase® product label based on findings from a healthy volunteer study that reported significant PR and QT interval prolongations, ritonavir-boosted saquinavir (SQV/r)-based regimens have been moved from "Alternative PI-based Regimens" to "Regimens that are Acceptable but Should be Used with Caution."

Hepatitis B (HBV)/HIV Coinfection

This section has been revised to provide more specific recommendations for management of HIV patients coinfected with HBV, including recommendations for patients with 3TC/FTC-resistant HBV infection and for patients who cannot tolerate TDF-based regimens.

Mycobacterium Tuberculosis Disease with HIV Coinfection

Based on recent randomized controlled trials showing survival and clinical benefits of starting ART earlier in treatment-naïve patients with active tuberculosis (TB) disease, the Panel provides the following recommendations on when to start ART in patients who are receiving treatment for active TB but are not yet on ART.

- All HIV-infected patients with diagnosed active TB should be treated with ART **(AI)**.
- For patients with CD4 count <200 cells/mm^3, ART should be initiated within 2–4 weeks of starting TB treatment **(AI)**.
- For patients with CD4 count 200–500 cells/mm^3, the Panel recommends initiating ART within 2–4 weeks, or at least by 8 weeks after commencement of TB therapy **(AIII)**.
- For patients with CD4 count >500 cells/mm^3, most panel members also recommend starting ART within 8 weeks of TB therapy **(BIII)**.

Adverse Effects of Antiretroviral Agents

A new table format provides clinicians with a list of the most common and/or severe known antiretroviral (ARV)-associated adverse events listed by ARV drug class.

Additional Updates

The following sections and their relevant tables have also been updated:

- Coreceptor Tropism Assays
- Treatment Goals
- Initiating Antiretroviral Therapy in Treatment-Naïve Patients
- What Not to Use
- Virologic and Immunologic Failure (previously titled “Management of Patients with Antiretroviral Treatment Failure”)
- Regimen Simplification
- Exposure-Response Relationship and Therapeutic Drug Monitoring for Antiretroviral Agents
- Acute HIV Infection
- HIV and Illicit Drug Users (with new Table)
- HIV-2 Infection
- Drug Interactions (and Tables)
- Drug Characteristics Tables (Appendices)

Table of Contents

GUIDELINES PANEL MEMBERS vii

INTRODUCTION 1
- Guidelines Development Process 1
- *Table 1. Outline of the Guidelines Development Process* 1
- *Table 2. Rating Scheme for Recommendations* 3

BASELINE EVALUATION 4

LABORATORY TESTING FOR INITIAL ASSESSMENT AND MONITORING WHILE ON ANTIRETROVIRAL THERAPY 5
- *Table 3. Laboratory Monitoring Schedule for Patients Prior to and After Initiation of Antiretroviral Therapy* 6
- CD4 T-Cell Count 7
- Plasma HIV RNA Testing 9
- Drug-Resistance Testing 11
- *Table 4. Recommendations for Using Drug-Resistance Assays* 15
- HLA-B*5701 Screening 19
- Coreceptor Tropism Assays 21

TREATMENT GOALS 24
- Strategies to Achieve Treatment Goals 24

INITIATING ANTIRETROVIRAL THERAPY IN TREATMENT-NAÏVE PATIENTS 27
- Benefits of Antiretroviral Therapy 28
- Potential Limitations of Earlier Initiation of Therapy 32
- Summary 33
- Recommendations 34
- The Need for Early Diagnosis of HIV 36
- Conclusion 36

WHAT TO START: INITIAL COMBINATION REGIMENS FOR THE ANTIRETROVIRAL-NAÏVE PATIENT 41
- Considerations When Selecting a First Antiretroviral Regimen for Antiretroviral Therapy-Naïve Patients 41
- *Table 5a. Preferred and Alternative Antiretroviral Regimens for Antiretroviral Therapy-Naïve Patients* 43
- *Table 5b. Acceptable Antiretroviral Regimens for Treatment-Naïve Patients* 44
- NNRTI–Based Regimens (1 NNRTI + 2 NRTIs) 45
- PI-Based Regimens (RTV-Boosted or Unboosted PI + 2 NRTIs) 47
- INSTI-Based Regimens (INSTI + 2 NRTIs) 50
- CCR5 Antagonist-Based Regimens (CCR5-A + 2 NRTIs) 50
- Dual-NRTI Options as Part of Initial Combination Therapy 51
- All-NRTI Regimens 53

Table 6. Advantages and Disadvantages of Antiretroviral Components Recommended as Initial Antiretroviral Therapy 55
Table 7. Antiretroviral Components Not Recommended as Initial Therapy 58

WHAT NOT TO USE 63
Antiretroviral Regimens Not Recommended 63
Antiretroviral Components Not Recommended 63
Table 8. Antiretroviral Regimens or Components That Should Not Be Offered At Any Time 65

MANAGEMENT OF THE TREATMENT-EXPERIENCED PATIENT 68
Virologic and Immunologic Failure 68
Regimen Simplification 77
Exposure-Response Relationship and Therapeutic Drug Monitoring (TDM) for Antiretroviral Agents 81
Table 9a. Trough Concentrations of Antiretroviral Drugs for Patients Who Have Drug-Susceptible Virus 83
Table 9b. Trough Concentrations of Antiretroviral Drugs for Treatment-Experienced Patients with Virologic Failure 84
Discontinuation or Interruption of Antiretroviral Therapy 85

CONSIDERATIONS FOR ANTIRETROVIRAL USE IN SPECIAL PATIENT POPULATIONS 89
Acute HIV Infection 89
Table 10. Identifying, Diagnosing, and Managing Acute HIV-1 Infection 92
HIV-Infected Adolescents and Young Adults 94
HIV and Illicit Drug Users (IDUs) 98
Table 11. Drug Interactions between Antiretroviral Agents and Drugs Used to Treat Opioid Addiction 100
HIV-Infected Women 103
HIV-2 Infection 108

CONSIDERATIONS FOR ANTIRETROVIRAL USE IN PATIENTS WITH COINFECTIONS 110
Hepatitis B (HBV)/HIV Coinfection 110
Hepatitis C (HCV)/HIV Coinfection 113
Mycobacterium Tuberculosis Disease with HIV Coinfection 116

LIMITATIONS TO TREATMENT SAFETY AND EFFICACY 121
Adherence to Antiretroviral Therapy 121
Table 12. Strategies to Improve Adherence to Antiretroviral Therapy 123
Adverse Effects of Antiretroviral Agents 125
Table 13. Antiretroviral Therapy-Associated Common and/or Severe Adverse Effects 126
Drug Interactions 130
Table 14. Drugs That Should Not Be Used with PI, NNRTI, or CCR5 Antagonist 133
Table 15a. Drug Interactions between PIs and Other Drugs 134

Table 15b. Drug Interactions between NNRTIs and Other Drugs 142
Table 15c. Drug Interactions between NRTIs and Other Drugs (Including ARV Agents) 145
Table 15d. Drug Interactions between CCR5 Antagonist and Other Drugs 146
Table 15e. Drug Interactions between Integrase Inhibitor and Other Drugs 146
Table 16a. Interactions among PIs 147
Table 16b. Interactions between NNRTIs, MVC, RAL, and PIs 148

PREVENTING SECONDARY TRANSMISSION OF HIV 150
Prevention Counseling 150
Antiretroviral Therapy as Prevention 150
Summary 151

CONCLUSION 152

LIST OF TABLES
Table 1. Outline of the Guidelines Development Process 1
Table 2. Rating Scheme for Recommendations 3
Table 3. Laboratory Monitoring Schedule for Patients Prior to and After Initiation of Antiretroviral Therapy 6
Table 4. Recommendations for Using Drug-Resistance Assays 15
Table 5a. Preferred and Alternative Antiretroviral Regimens for Antiretroviral Therapy-Naïve Patients 43
Table 5b. Acceptable Antiretroviral Regimens for Treatment-Naïve Patients 44
Table 6. Advantages and Disadvantages of Antiretroviral Components Recommended as Initial Antiretroviral Therapy 55
Table 7. Antiretroviral Components Not Recommended as Initial Therapy 58
Table 8. Antiretroviral Regimens or Components That Should Not Be Offered At Any Time 65
Table 9a. Trough Concentrations of Antiretroviral Drugs for Patients Who Have Drug-Susceptible Virus 83
Table 9b. Trough Concentrations of Antiretroviral Drugs for Treatment-Experienced Patients with Virologic Failure 84
Table 10. Identifying, Diagnosing, and Managing Acute HIV-1 Infection 92
Table 11. Drug Interactions between Antiretroviral Agents and Drugs Used to Treat Opioid Addiction 100
Table 12. Strategies to Improve Adherence to Antiretroviral Therapy 123
Table 13. Antiretroviral Therapy-Associated Common and/or Severe Adverse Effects 126
Table 14. Drugs That Should Not Be Used with PI, NNRTI, or CCR5 Antagonist 133
Table 15a. Drug Interactions between PIs and Other Drugs 134
Table 15b. Drug Interactions between NNRTIs and Other Drugs 142

Table 15c. Drug Interactions between NRTIs and Other Drugs (Including ARV Agents) 145
Table 15d. Drug Interactions between CCR5 Antagonist and Other Drugs 146
Table 15e. Drug Interactions between Integrase Inhibitor and Other Drugs 146
Table 16a. Interactions among PIs 147
Table 16b. Interactions between NNRTIs, MVC, RAL, and PIs 148

APPENDIX A: KEY TO ACRONYMS 153

APPENDIX B: DRUG CHARACTERISTICS TABLES
Appendix B, Table 1. Characteristics of NRTIs 157
Appendix B, Table 2. Characteristics of NNRTIs 159
Appendix B, Table 3. Characteristics of PIs 160
Appendix B, Table 4. Characteristics of Integrase Inhibitor 163
Appendix B, Table 5. Characteristics of Fusion Inhibitor 163
Appendix B, Table 6. Characteristics of CCR5 Antagonist 163
Appendix B, Table 7. Antiretroviral Dosing Recommendations in Patients with Renal or Hepatic Insufficiency 164

Financial Disclosures for Members of DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents available at: **http://aidsinfo.nih.gov/contentfiles/AA_FinancialDisclosures.pdf**

Guidelines Panel Members
DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents

These Guidelines were developed by the Department of Health and Human Services (DHHS) Panel on Antiretroviral Guidelines for Adults and Adolescents (a Working Group of the Office of AIDS Research Advisory Council).

Panel Co-Chairs:
John G. Bartlett, Johns Hopkins University, Baltimore, MD
H. Clifford Lane, National Institutes of Health, Bethesda, MD

Executive Secretary:
Alice K. Pau, National Institutes of Health, Bethesda, MD

Scientific Members:

Jean R. Anderson	Johns Hopkins University, Baltimore, MD
John T. Brooks	Centers for Disease Control and Prevention, Atlanta, GA
Eric Daar	University of California–Los Angeles, Harbor-UCLA Medical Center, Los Angeles, CA
Steven G. Deeks	University of California–San Francisco, San Francisco, CA
Carlos del Rio	Emory University, Atlanta, GA
Robert T. Dodge	University of North Carolina, Chapel Hill, NC
Courtney V. Fletcher	University of Nebraska Medical Center, Omaha, NE
Gerald H. Friedland	Yale University School of Medicine, New Haven, CT
Joel E. Gallant	Johns Hopkins University, Baltimore, MD
Christopher M. Gordon	National Institutes of Health, Bethesda, MD
Roy M. Gulick	Weill Medical College of Cornell University, New York, NY
W. Keith Henry	Hennepin County Medical Center & University of Minnesota, Minneapolis, MN
Martin S. Hirsch	Massachusetts General Hospital and Harvard Medical School, Boston, MA
Michael D. Hughes	Harvard School of Public Health, Boston, MA
Bill G. Kapogiannis	National Institutes of Health, Bethesda, MD
Daniel R. Kuritzkes	Brigham and Women's Hospital & Harvard Medical School, Boston, MA
James Neaton	University of Minnesota, Minneapolis, MN
Richard W. Price	University of California–San Francisco, San Francisco, CA
Michael Saag	University of Alabama at Birmingham, Birmingham, AL
Paul E. Sax	Brigham and Women's Hospital & Harvard Medical School, Boston, MA
Mark Sulkowski	Johns Hopkins University, Baltimore, MD
Zelalem Temesgen	Mayo Clinic, Rochester, MN
Paul Volberding	University of California, San Francisco & VA Medical Center, San Francisco, CA
David A. Wohl	University of North Carolina, Chapel Hill, NC

Community Members:

Lei Chou	Treatment Action Group, New York, NY
Paul Dalton	San Francisco, CA
Heidi Nass	University of Wisconsin, Madison, WI
Jeffrey Taylor	Palm Springs, CA
Nelson Vergel	Program for Wellness Restoration, Houston, TX

Representatives from Department of Health and Human Services Agencies:

Victoria Cargill	National Institutes of Health
Laura Cheever	Health Resources and Services Administration
Jonathan Kaplan	Centers for Disease Control and Prevention
Henry Masur	National Institutes of Health
Lynne Mofenson	National Institutes of Health
Jeffrey Murray	Food and Drug Administration
Kimberly Struble	Food and Drug Administration

Non-Voting Observer:

Sarita Boyd	National Institutes of Health, SAIC-Frederick, Inc., NCI-Frederick, Frederick, MD

Acknowledgement:
The Panel would also like to acknowledge *Nina H. Lin, M.D., (Massachusetts General Hospital & Harvard Medical School, Boston, MA)* for her assistance in the preparation of the Guidelines.

Updated January 10, 2011

Introduction (Updated January 10, 2011)

Antiretroviral therapy (ART) for the treatment of human immunodeficiency virus (HIV) infection has improved steadily since the advent of potent combination therapy in 1996. New drugs have been approved that offer new mechanisms of action, improvements in potency and activity even against multidrug-resistant viruses, dosing convenience, and tolerability.

The Department of Health and Human Services (DHHS) Panel on Antiretroviral Guidelines for Adults and Adolescents (the Panel) is a working group of the Office of AIDS Research Advisory Council (OARAC). The primary goal of the Panel is to provide recommendations for HIV care practitioners based on current knowledge of antiretroviral (ARV) drugs used to treat adults and adolescents with HIV infection in the United States. The Panel reviews new evidence and updates recommendations when needed. The primary areas of attention have included baseline assessment, treatment goals, indications for initiation of ART, choice of the initial regimen in ART-naïve patients, drugs or combinations to be avoided, management of adverse effects and drug interactions, management of treatment failure, and special ART-related considerations in specific patient populations.

These guidelines generally represent the state of knowledge regarding the use of ARV agents. However, because the science evolves rapidly, the availability of new agents and new clinical data may change therapeutic options and preferences. Information included in these guidelines may not be consistent with approved labeling for the particular products or indications in question, and the terms "safe" and "effective" may not be synonymous with the Food and Drug Administration (FDA)-defined legal standards for product approval. The guidelines are updated frequently by the Panel (current and archived versions of the guidelines are available on the AIDS*info* Web site at **http://www.aidsinfo.nih.gov**). However, the guidelines cannot always keep pace with the rapid evolution of new data in this field, and they cannot provide guidance for all patients. Clinicians should exercise clinical judgment in management decisions tailored to unique patient circumstances.

The Panel recognizes the importance of clinical research in generating evidence to address unanswered questions related to the optimal safety and efficacy of ART. The Panel encourages both the development of protocols and patient participation in well-designed, Institutional Review Board (IRB)-approved clinical trials.

GUIDELINES DEVELOPMENT PROCESS

Table 1 provides an outline of the composition of the Panel and guidelines process.

Table 1. Outline of the Guidelines Development Process (Updated November 3, 2008)

Page 1 of 2

Topic	Comment
Goal of the guidelines	Provide guidance to HIV care practitioners on the optimal use of ARV agents for the treatment of HIV infection in adults and adolescents in the United States.
Panel members	The Panel is composed of more than 30 voting members who have expertise in HIV care and research. The U.S. government representatives include at least 1 representative from each of the following DHHS agencies: Centers for Disease Control and Prevention (CDC), FDA, Health Resource Services Administration (HRSA), and National Institutes of Health (NIH). These members are appointed by their respective agencies. Approximately 2/3 of the Panel members are nongovernmental scientific members. There are 4–5 community members with knowledge in HIV treatment and care. Members who do not represent U.S. government agencies are selected after an open announcement to call for nominations. Each member serves on the Panel for a 4-year term, with an option to be reappointed for an additional term. A list of the current members can be found on **Page vii** of this document.

Table 1. Outline of the Guidelines Development Process
Page 2 of 2

Topic	Comment
Financial disclosure	All members of the Panel submit a written financial disclosure annually reporting any association with manufacturers of ARV drugs or diagnostics used for management of HIV infections. A list of the latest disclosures is available on the AIDS*info* Web site (**http://aidsinfo.nih.gov/contentfiles/AA_Roster.pdf**).
Users of the guidelines	HIV treatment providers
Developer	Panel on Antiretroviral Guidelines for Adults and Adolescents—a working group of the OARAC
Funding source	Office of AIDS Research, NIH
Evidence collection	The recommendations in the guidelines are generally based on studies published in peer-reviewed journals. On some occasions, particularly when new information may affect patient safety, unpublished data presented at major conferences or prepared by the FDA and/or manufacturers as warnings to the public may be used as evidence to revise the guidelines.
Recommendation grading	As described in **Table 2**
Method of synthesizing data	Each section of the guidelines is assigned to a working group of Panel members with expertise in the area of interest. The members of the working group synthesize the available data and propose recommendations to the Panel. All proposals are discussed at monthly teleconferences and then voted on by the Panel before being endorsed as official recommendations.
Other guidelines	These guidelines focus on treatment for HIV-infected adults and adolescents. Separate guidelines outline the use of ART for other populations, such as pregnant women and children. These guidelines are also available on the AIDS*info* Web site (**http://www.aidsinfo.nih.gov**). There is a brief discussion of the management of women of reproductive age and pregnant women in this document. For a more detailed and up-to-date discussion on this group of women and other special populations, the Panel defers to the designated expertise offered by panels that have developed those guidelines.
Update plan	The Panel meets monthly by teleconference to review data that may warrant modification of the guidelines. Updates may be prompted by new drug approvals (or new indications, dosing formulations, or frequency), new significant safety or efficacy data, or other information that may have a significant impact on the clinical care of patients. For cases in which significant new data become available that may affect patient safety, a warning announcement with the Panel's recommendations may be made on the AIDS*info* Web site until appropriate changes can be made in the guidelines document. Updated guidelines are available on the AIDS*info* Web site (**http://www.aidsinfo.nih.gov**).
Public comments	After release of an update on the AIDS*info* Web site, the public is given a 2-week period to submit comments to the Panel. These comments are reviewed, and a determination is made as to whether revisions are indicated. The public may also submit comments to the Panel at any time at **contactus@aidsinfo.nih.gov**.

Basis for Recommendations

Recommendations in these guidelines are based upon scientific evidence and expert opinion. Each recommended statement is rated with a letter of **A**, **B**, or **C** that represents the strength of the recommendation and with a numeral **I**, **II**, or **III** that represents the quality of the evidence. (See **Table 2**.)

Table 2. Rating Scheme for Recommendations (Updated November 3, 2008)

Strength of Recommendation	Quality of Evidence for Recommendation
A: Strong recommendation for the statement **B:** Moderate recommendation for the statement **C:** Optional recommendation for the statement	**I:** One or more randomized trials with clinical outcomes and/or validated laboratory endpoints **II:** One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes **III:** Expert opinion

HIV Expertise in Clinical Care

Multiple studies have demonstrated that better outcomes are achieved in HIV-infected outpatients cared for by a clinician with HIV expertise *[1-6]*, which reflects the complexity of HIV infection and its treatment. Thus, appropriate training and experience, as well as ongoing continuing medical education (CME), are important components for optimal care. Primary care providers without HIV experience, such as those who provide service in rural or underserved areas, should identify experts in the region who will provide consultation when needed.

References

1. Kitahata MM, Koepsell TD, Deyo RA, et al. Physicians' experience with the acquired immunodeficiency syndrome as a factor in patients' survival. *N Engl J Med.* 1996;334(11):701-706.
2. Kitahata MM, Van Rompaey SE, Shields AW. Physician experience in the care of HIV-infected persons is associated with earlier adoption of new antiretroviral therapy. *J Acquir Immune Defic Syndr.* 2000;24(2):106-114.
3. Landon BE, Wilson IB, McInnes K, et al. Physician specialization and the quality of care for human immunodeficiency virus infection. *Arch Intern Med.* 2005;165(10):1133-1139.
4. Laine C, Markson LE, McKee LJ, et al. The relationship of clinic experience with advanced HIV and survival of women with AIDS. *AIDS.* 1998;12(4):417-424.
5. Kitahata MM, Van Rompaey SE, Dillingham PW, et al. Primary care delivery is associated with greater physician experience and improved survival among persons with AIDS. *J Gen Intern Med.* 2003;18(2):95-103.
6. Delgado J, Heath KV, Yip B, et al. Highly active antiretroviral therapy: physician experience and enhanced adherence to prescription refill. *Antivir Ther.* 2003;8(5):471-478.

Baseline Evaluation (Updated January 10, 2011)

Each HIV-infected patient entering into care should have a complete medical history, physical examination, and laboratory evaluation and should be counseled regarding the implications of HIV infection. The goals of the initial evaluation are to confirm the presence of HIV infection, obtain appropriate baseline historical and laboratory data, ensure patient understanding about HIV infection and its transmission, and initiate care as recommended by established guidances such as the HIV primary care guidelines *[1]* and the guidelines for prevention and treatment of HIV-associated opportunistic infections *[2]*. Baseline information can then be used to define management goals and plans.

The following laboratory tests performed during initial patient visits can be used to stage HIV disease and to assist in the selection of antiretroviral (ARV) drug regimens:

- HIV antibody testing (if prior documentation is not available or if HIV RNA is below the assay's limit of detection) **(AI)**;
- CD4 T-cell count **(AI)**;
- Plasma HIV RNA (viral load) **(AI)**;
- Complete blood count, chemistry profile, transaminase levels, blood urea nitrogen (BUN) and creatinine, urinalysis, and serologies for hepatitis A, B, and C viruses **(AIII)**;
- Fasting blood glucose and serum lipids **(AIII)**; and
- Genotypic resistance testing at entry into care, regardless of whether ART will be initiated immediately **(AIII)**. For patients who have HIV RNA levels <500–1,000 copies/mL, amplification of virus for resistance testing may not always be successful **(BII)**.

In addition, other tests, including screening tests for sexually transmitted infections and tests for determining risk for opportunistic infections and need for prophylaxis, should be performed as recommended by HIV primary care and opportunistic infections guidelines *[1-2]*.

Patients living with HIV infection must often cope with multiple social, psychiatric, and medical issues that are best addressed through a patient-centered, multidisciplinary approach to the disease. The evaluation also must include assessment of high-risk behaviors, substance abuse, social support, mental illness, comorbidities, economic factors (e.g., unstable housing), medical insurance status and adequacy of coverage, and other factors that are known to impair adherence to treatment and to increase the risk of HIV transmission. Once evaluated, these factors should be managed accordingly.

Education about HIV risk behaviors and effective strategies to prevent HIV transmission should be provided at each patient visit. (See **Preventing Secondary Transmission of HIV**.)

References

1. Aberg JA, Kaplan JE, Libman H, et al. Primary care guidelines for the management of persons infected with human immunodeficiency virus: 2009 update by the HIV medicine Association of the Infectious Diseases Society of America. *Clin Infect Dis.* 2009;49(5):651-681.
2. Centers for Disease Control and Prevention (CDC). Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. *MMWR Recomm Rep.* 2009;58(RR-4):1-207.

Laboratory Testing for Initial Assessment and Monitoring While on Antiretroviral Therapy

(Updated January 10, 2011)

A number of laboratory tests are important for initial evaluation of HIV-infected patients upon entry into care, during follow-up if antiretroviral therapy (ART) has not been initiated, and prior to and after initiation or modification of therapy to assess virologic and immunologic efficacy of ART and to monitor for laboratory abnormalities that may be associated with antiretroviral (ARV) drugs. **Table 3** outlines the Panel's recommendations for the frequency of testing. As noted in the table, some of the tests may be repeated more frequently if clinically indicated.

Two surrogate markers are used routinely to assess the immune function and level of HIV viremia: CD4 T-cell count (CD4 count) and plasma HIV RNA (viral load). Resistance testing should be used to guide selection of an ARV regimen in both ART-naïve and ART-experienced patients; a viral tropism assay should be performed prior to initiation of a CCR5 antagonist; and HLA-B*5701 testing should be performed prior to initiation of abacavir (ABC). The rationale and utility of these laboratory tests are discussed below.

Table 3. Laboratory Monitoring Schedule for Patients Prior to and After Initiation of Antiretroviral Therapy (Updated January 10, 2011)

	Entry into care	Follow-up before ART	ART initiation or modification[1]	2–8 weeks post-ART initiation or modification	Every 3–6 months	Every 6 months	Every 12 months	Treatment failure	Clinically indicated
CD4 count	√	every 3–6 months	√		√	In clinically stable patients with suppressed viral load, CD4 count can be monitored every 6–12 months (see text)		√	√
Viral load	√	every 3–6 months	√	√[2]	√[3]			√	√
Resistance testing	√		√[4]					√	√
HLA-B*5701 testing			√ if considering ABC						
Tropism testing			√ if considering a CCR5 antagonist					√ if considering a CCR5 antagonist or for failure of CCR5 antagonist-based regimen	√
Hepatitis B serology[5]	√		√ may repeat if HBsAg (-) and HBsAb (-) at baseline						√
Basic chemistry[6]	√	every 6–12 months	√	√	√				√
ALT, AST, T. bilirubin	√	every 6–12 months	√	√	√				√
CBC with differential	√	every 3–6 months	√	√ if on ZDV	√				√
Fasting lipid profile	√	if normal, annually	√	√ consider 4–8 weeks after starting new ART		√ if abnormal at last measurement	√ if normal at last measurement		√
Fasting glucose	√	if normal, annually	√		√ if abnormal at last measurement	√ if normal at last measurement			√
Urinalysis[7]	√		√			√ if on TDF[8]	√		√
Pregnancy test			√ if starting EFV						√

[1]ARV modification may be done for treatment failure, adverse effects, or simplification.
[2]If HIV RNA is detectable at 2–8 weeks, repeat every 4–8 weeks until suppression to <200 copies/mL, then every 3–6 months.
[3]For adherent patients with suppressed viral load and stable clinical and immunologic status for >2–3 years, some experts may extend the interval for HIV RNA monitoring to every 6 months.
[4]For ART-naïve patients, if resistance testing was performed at entry into care, repeat testing is optional; for patients with viral suppression who are switching therapy for toxicity or convenience, resistance testing will not be possible and therefore is not necessary.
[5] If HBsAg is positive at baseline or prior to initiation of ART, TDF + (FTC or 3TC) should be used as part of ARV regimen to treat both HBV and HIV infections. If HBsAg and HBsAb are negative at baseline, hepatitis B vaccine series should be administered.
[6] Serum Na, K, HCO_3, Cl, BUN, creatinine, glucose (preferably fasting); some experts suggest monitoring phosphorus while on TDF; determination of renal function should include estimation of creatinine clearance using Cockcroft-Gault equation or estimation of glomerular filtration rate based on MDRD equation.
[7]For patients with renal disease, consult "Guidelines for the Management of Chronic Kidney Disease in HIV-Infected Patients: Recommendations of the HIV Medicine Association of the Infectious Diseases Society of America" *[1]*.
[8] More frequent monitoring may be indicated for patients with increased risk of renal insufficiency, such as patients with diabetes, hypertension, etc.

Acronyms: 3TC = lamivudine, ABC = abacavir, ALT = alanine aminotransferase, ART = antiretroviral therapy, AST = aspartate aminotranserase, CBC = complete blood count, EFV = efavirenz, FTC = emtricitabine, HBsAb = hepatitis B surface antibody, HBsAg = hepatitis B surface antigen, HBV = hepatitis B virus, MDRD = modification of diet in renal disease (equation), TDF = tenofovir, ZDV = zidovudine

References

1. Gupta SK, Eustace JA, Winston JA, et al. Guidelines for the management of chronic kidney disease in HIV-infected patients: recommendations of the HIV Medicine Association of the Infectious Diseases Society of America. *Clin Infect Dis.* 2005;40(11):1559-1585.

CD4 T-CELL COUNT (Updated January 10, 2011)

The CD4 count serves as the major laboratory indicator of immune function in patients who have HIV infection. It is one of the key factors in deciding whether to initiate ART and prophylaxis for opportunistic infections, and it is the strongest predictor of subsequent disease progression and survival according to clinical trials and cohort studies *[1-2]*. A significant change (2 standard deviations) between two tests is approximately a 30% change in the absolute count or an increase or decrease in CD4 percentage by 3 percentage points.

- **Use of CD4 Count for Initial Assessment**. The CD4 count is one of the most important factors in the decision to initiate ART and/or prophylaxis for opportunistic infections. All patients should have a baseline CD4 count at entry into care **(AI)**. Recommendations for initiation of ART based on CD4 count are found in the **Initiating Antiretroviral Therapy in Antiretroviral-Naïve Patients** section of these guidelines.
- **Use of CD4 Count for Monitoring Therapeutic Response**. An adequate CD4 response for most patients on therapy is defined as an increase in CD4 count in the range of 50–150 cells/mm^3 per year, generally with an accelerated response in the first 3 months. Subsequent increases in patients with good virologic control show an average increase of approximately 50–100 cells/mm^3 per year for the subsequent years until a steady state level is reached *[3]*. Patients who initiate therapy with a low CD4 count or at an older age may have a blunted increase in their count despite virologic suppression.

Frequency of CD4 Count Monitoring. In general, CD4 counts should be monitored every 3–4 months to (1) determine when to start ART in untreated patients, (2) assess immunologic response to ART, and (3) assess the need for initiation or discontinuation of prophylaxis for opportunistic infections **(AI)**.

The CD4 cell count response to ART varies widely, but a poor CD4 response is rarely an indication for modifying a virologically suppressive ARV regimen. In patients with consistently suppressed viral loads who have already experienced ART-related immune reconstitution, the CD4 cell count provides limited information, and frequent testing may cause unnecessary anxiety in patients with clinically inconsequential fluctuations. Thus, for the patient on a suppressive regimen whose CD4 cell count has increased well above the threshold for opportunistic infection risk, the CD4 count can be measured less frequently than the viral load. In such patients, CD4 count may be monitored every 6 to 12 months, unless there are changes in the patient's clinical status, such as new HIV-associated clinical symptoms or initiation of treatment with interferon, corticosteroids, or anti-neoplastic agents **(CIII)**.

Factors that affect absolute CD4 count. The absolute CD4 count is a calculated value based on the total white blood cell (WBC) count and the percentages of total and CD4+ T lymphocytes. This absolute number may fluctuate among individuals or may be influenced by factors that may affect the total WBC and lymphocyte percentages, such as use of bone marrow–suppressive medications or the presence of acute infections. Splenectomy *[4-5]* or coinfection with human T-lymphotropic virus type I (HTLV-1) *[6]* may cause misleadingly elevated absolute CD4 counts. Alpha-interferon, on the other hand, may reduce the absolute CD4 number without changing the CD4 percentage *[7]*. In all these cases, CD4 percentage remains stable and may be a more appropriate parameter to assess the patient's immune function.

References

1. Mellors JW, Munoz A, Giorgi JV, et al. Plasma viral load and CD4+ lymphocytes as prognostic markers of HIV-1 infection. *Ann Intern Med.* 1997;126(12):946-954.
2. Egger M, May M, Chene G, et al. Prognosis of HIV-1-infected patients starting highly active antiretroviral therapy: a collaborative analysis of prospective studies. *Lancet.* 2002;360(9327):119-129.
3. Kaufmann GR, Perrin L, Pantaleo G, et al. CD4 T-lymphocyte recovery in individuals with advanced HIV-1 infection receiving potent antiretroviral therapy for 4 years: the Swiss HIV Cohort Study. *Arch Intern Med.* 2003;163(18):2187-2195.
4. Zurlo JJ, Wood L, Gaglione MM, et al. Effect of splenectomy on T lymphocyte subsets in patients infected with the human immunodeficiency virus. *Clin Infect Dis.* 1995;20(4):768-771.
5. Bernard NF, Chernoff DN, Tsoukas CM. Effect of splenectomy on T-cell subsets and plasma HIV viral titers in HIV-infected patients. *J Hum Virol.* 1998;1(5):338-345.

6. Casseb J, Posada-Vergara MP, Montanheiro P, et al. T CD4+ cells count among patients co-infected with human immunodeficiency virus type 1 (HIV-1) and human T-cell leukemia virus type 1 (HTLV-1): high prevalence of tropical spastic paraparesis/HTLV-1-associated myelopathy (TSP/HAM). *Rev Inst Med Trop Sao Paulo.* 2007;49(4):231-233.
7. Berglund O, Engman K, Ehrnst A, et al. Combined treatment of symptomatic human immunodeficiency virus type 1 infection with native interferon-alpha and zidovudine. *J Infect Dis.* 1991;163(4):710-715.

PLASMA HIV RNA TESTING (Updated January 10, 2011)

Plasma HIV RNA (viral load) should be measured in all patients at baseline and on a regular basis thereafter, especially in patients who are on treatment, because viral load is the most important indicator of response to antiretroviral therapy (ART) **(AI)**. Analysis of 18 trials that included more than 5,000 participants with viral load monitoring showed a significant association between a decrease in plasma viremia and improved clinical outcome *[1]*. Thus, viral load testing serves as a surrogate marker for treatment response *[2]* and can be useful in predicting clinical progression *[3-4]*. The minimal change in viral load considered to be statistically significant (2 standard deviations) is a threefold, or a 0.5 $\log_{10}$ copies/mL change.

Optimal viral suppression is generally defined as a viral load persistently below the level of detection (<20–75 copies/mL, depending on the assay used). However, isolated "blips" (viral loads transiently detectable at low levels, typically <400 copies/mL) are not uncommon in successfully treated patients and are not thought to represent viral replication or to predict virologic failure *[5]*. In addition, low-level positive viral load results (typically <200 copies/mL) appear to be more common with some viral load assays than others, and there is no definitive evidence that patients with viral loads quantified as <200 copies/mL using these assays are at increased risk for virologic failure *[6-8]*. For the purposes of clinical trials the AIDS Clinical Trials Group (ACTG) currently defines virologic failure as a confirmed viral load >200 copies/mL, which eliminates most cases of apparent viremia caused by blips or assay variability *[9]*. This definition may also be useful in clinical practice. (See **Virologic and Immunologic Failure**.)

For most individuals who are adherent to their antiretroviral (ARV) regimens and who do not harbor resistance mutations to the prescribed drugs, viral suppression is generally achieved in 12–24 weeks, even though it may take longer in some patients. Recommendations for the frequency of viral load monitoring are summarized below.

- **At Initiation or Change in Therapy.** Plasma viral load should be measured before initiation of therapy and preferably within 2–4 weeks, and not more than 8 weeks, after treatment initiation or after treatment modification **(BI)**. Repeat viral load measurement should be performed at 4–8-week intervals until the level falls below the assay's limit of detection **(BIII)**.
- **In Patients Who Have Viral Suppression but Therapy Was Modified Due to Drug Toxicity or Regimen Simplification.** Viral load measurement should be performed within 2–8 weeks after changing therapy. The purpose of viral load monitoring at this point is to confirm potency of the new regimen **(BIII)**.
- **In Patients on a Stable ARV Regimen.** Viral load should be repeated every 3–4 months or as clinically indicated **(BII)**. Some clinicians may extend the interval to every 6 months for adherent patients who have suppressed viral loads for more than 2–3 years and whose clinical and immunologic status is stable **(BIII)**.

Monitoring in Patients with Suboptimal Response. In addition to viral load monitoring, a number of additional factors, such as adherence to prescribed medications, altered pharmacology, or drug interactions, should be assessed. Patients who fail to achieve viral suppression should undergo resistance testing to aid in the selection of an alternative regimen, as discussed in **Drug Resistance Testing** and **Virologic and Immunologic Failure** **(AI)**.

References

1. Murray JS, Elashoff MR, Iacono-Connors LC, et al. The use of plasma HIV RNA as a study endpoint in efficacy trials of antiretroviral drugs. *AIDS.* 1999;13(7):797-804.
2. Hughes MD, Johnson VA, Hirsch MS, et al. Monitoring plasma HIV-1 RNA levels in addition to CD4+ lymphocyte count improves assessment of antiretroviral therapeutic response. ACTG 241 Protocol Virology Substudy Team. *Ann Intern Med.* 1997;126(12):929-938.
3. Marschner IC, Collier AC, Coombs RW, et al. Use of changes in plasma levels of human immunodeficiency virus type 1 RNA to assess the clinical benefit of antiretroviral therapy. *J Infect Dis.* 1998;177(1):40-47.
4. Thiebaut R, Morlat P, Jacqmin-Gadda H, et al. Clinical progression of HIV-1 infection according to the viral response during the first year of antiretroviral treatment. Groupe d'Epidemiologie du SIDA en Aquitaine (GECSA). *AIDS.* 2000;14(8):971-978.
5. Havlir DV, Bassett R, Levitan D, et al. Prevalence and predictive value of intermittent viremia with combination hiv therapy. *JAMA.* 2001;286(2):171-179.
6. Damond F, Roquebert B, Benard A, et al. Human immunodeficiency virus type 1 (HIV-1) plasma load discrepancies between the Roche COBAS AMPLICOR HIV-1 MONITOR Version 1.5 and the Roche COBAS AmpliPrep/COBAS TaqMan HIV-1 assays. *J Clin Microbiol.* 2007;45(10):3436-3438.

7. Gatanaga H, Tsukada K, Honda H, et al. Detection of HIV type 1 load by the Roche Cobas TaqMan assay in patients with viral loads previously undetectable by the Roche Cobas Amplicor Monitor. *Clin Infect Dis.* 2009;48(2):260-262.
8. Willig JH, Nevin CR, Raper JL, et al. Cost ramifications of increased reporting of detectable plasma HIV-1 RNA levels by the Roche COBAS AmpliPrep/COBAS TaqMan HIV-1 version 1.0 viral load test. *J Acquir Immune Defic Syndr.* 2010;54(4):442-444.
9. Ribaudo H, Lennox J, Currier J, et al. Virologic failure endpoint definition in clinical trials: Is using HIV-1 RNA threshold <200 copies/mL better than <50 copies/mL? An analysis of ACTG studies. Paper presented at: 16th Conference on Retroviruses and Opportunistic Infections; February 8-11, 2009; Montreal, Canada. Abstract 580.

DRUG-RESISTANCE TESTING (Updated January 10, 2011)

Panel's Recommendations:

- ***HIV drug-resistance testing is recommended for persons with HIV infection when they enter into care regardless of whether antiretroviral therapy (ART) will be initiated immediately or deferred (AIII). If therapy is deferred, repeat testing at the time of ART initiation should be considered (CIII).***
- ***Genotypic testing is recommended as the preferred resistance testing to guide therapy in antiretroviral (ARV)-naïve patients (AIII).***
- ***Standard genotypic drug-resistance testing in ARV-naïve persons involves testing for mutations in the reverse transcriptase (RT) and protease (PR) genes. If transmitted integrase strand transfer inhibitor (INSTI) resistance is a concern, providers may wish to supplement standard genotypic resistance testing with genotypic testing for resistance to this class of drug (CIII).***
- ***HIV drug-resistance testing should be performed to assist in the selection of active drugs when changing ARV regimens in persons with virologic failure and HIV RNA levels >1,000 copies/mL (AI). In persons with HIV RNA levels >500 but <1,000 copies/mL, testing may be unsuccessful but should still be considered (BII).***
- ***Drug-resistance testing should also be performed when managing suboptimal viral load reduction (AII).***
- ***In persons failing INSTI-based regimens, genotypic testing for INSTI resistance should be considered to determine whether to include a drug from this class in subsequent regimens (BIII).***
- ***Drug-resistance testing in the setting of virologic failure should be performed while the person is taking prescribed ARV drugs or, if not possible, within 4 weeks after discontinuing therapy (AII).***
- ***Genotypic testing is recommended as the preferred resistance testing to guide therapy in patients with suboptimal virologic responses or virologic failure while on first or second regimens (AIII).***
- ***Addition of phenotypic to genotypic testing is generally preferred for persons with known or suspected complex drug-resistance mutation patterns, particularly to protease inhibitors (PIs) (BIII).***
- ***Genotypic resistance testing is recommended for all pregnant women prior to initiation of therapy (AIII) and for those entering pregnancy with detectable HIV RNA levels while on therapy (AI).***

Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = data from randomized controlled trials; II = data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = expert opinion

Genotypic and Phenotypic Resistance Assays

Genotypic and phenotypic resistance assays are used to assess viral strains and inform selection of treatment strategies. Standard assays provide information on resistance to nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PIs). Testing for integrase and fusion inhibitor resistance can also be ordered separately from several commercial laboratories. No genotypic assays for assessing resistance to CCR5 antagonists are currently commercially available for clinical use in the United States. (See **Coreceptor Tropism Assays**.)

Genotypic Assays

Genotypic assays detect drug-resistance mutations present in relevant viral genes. Most genotypic assays involve sequencing of the RT and PR genes to detect mutations that are known to confer drug resistance. Genotypic assays that assess mutations in the integrase and gp41 (envelope) genes are also commercially available. Genotypic assays can be performed rapidly with results available within 1–2 weeks of sample collection. Interpretation of test results requires knowledge of the mutations that different ARV drugs select for and of the potential for cross resistance to other drugs conferred by certain mutations. The International AIDS Society-USA (IAS-USA) maintains a list of updated significant resistance-associated mutations in the RT, PR, integrase, and envelope genes (see **http://www.iasusa.org/resistance_mutations**) *[1]*. The Stanford University HIV Drug Resistance Database (**http://hivdb.stanford.edu**) also provides helpful guidance for interpreting genotypic resistance test results. Various tools are now available to assist the provider in interpreting genotypic test results *[2-5]*. Clinical trials have demonstrated the benefit of consultation with specialists in HIV drug resistance in improving virologic outcomes *[6]*.

Clinicians are thus encouraged to consult a specialist to facilitate interpretation of genotypic test results and the design of an optimal new regimen.

Phenotypic Assays

Phenotypic assays measure the ability of a virus to grow in different concentrations of ARV drugs. RT and PR gene sequences and, more recently, integrase and envelope sequences derived from patient plasma HIV RNA are inserted into the backbone of a laboratory clone of HIV or used to generate pseudotyped viruses that express the patient-derived HIV genes of interest. Replication of these viruses at different drug concentrations is monitored by expression of a reporter gene and is compared with replication of a reference HIV strain. The drug concentration that inhibits viral replication by 50% (i.e., the median inhibitory concentration [$IC]_{50}$) is calculated, and the ratio of the IC_{50} of test and reference viruses is reported as the fold increase in IC_{50} (i.e., fold resistance).

Automated phenotypic assays are commercially available with results reported in 2–3 weeks. However, phenotypic assays cost more to perform than genotypic assays. In addition, interpretation of phenotypic assay results is complicated by incomplete information regarding the specific resistance level (i.e., fold increase in IC_{50}) that is associated with drug failure, although clinically significant fold increase cutoffs are now available for some drugs *[7-11]*. Again, consultation with a specialist can be helpful for interpreting test results.

Further limitations of both genotypic and phenotypic assays include lack of uniform quality assurance for all available assays, relatively high cost, and insensitivity for minor viral species. Despite being present, drug-resistant viruses constituting less than 10%–20% of the circulating virus population will probably not be detected by available assays. This limitation is important because after drugs exerting selective pressure on drug-resistant populations are discontinued, a wild-type virus often re-emerges as the predominant population in the plasma. As a consequence, the proportion of virus with resistance mutations decreases to below the 10%–20% threshold *[12-14]*. For some drugs, this reversion to predominantly wild-type virus can occur in the first 4–6 weeks after drugs are stopped. Prospective clinical studies have shown that, despite this plasma reversion, reinstitution of the same ARV agents (or those sharing similar resistance pathways) is usually associated with early drug failure, and the virus present at failure is derived from previously archived resistant virus *[15]*. Therefore, resistance testing is of greatest value when performed before or within 4 weeks after drugs are discontinued **(AII)**. Because detectable resistant virus may persist in the plasma of some patients for longer periods of time, resistance testing beyond 4 to 6 weeks after discontinuation may still reveal mutations. However, the absence of detectable resistance in such patients must be interpreted with caution in designing subsequent ARV regimens.

Use of Resistance Assays in Clinical Practice (Table 4)

No definitive prospective data exist to support using one type of resistance assay over another (i.e., genotypic vs. phenotypic) in different clinical situations. In most situations genotypic testing is preferred because of the faster turnaround time, lower cost, and enhanced sensitivity for detecting mixtures of wild-type and resistant virus. However, for patients with a complex treatment history, results derived from both assays might provide critical and complementary information to guide regimen changes.

Use of Resistance Assays in Determining Initial Treatment

Transmission of drug-resistant HIV strains is well documented and associated with suboptimal virologic response to initial ART *[16-19]*. The likelihood that a patient will acquire drug-resistant virus is related to the prevalence of drug resistance in HIV-infected persons engaging in high-risk behaviors in the community. In the United States and Europe, recent studies suggest the risk that transmitted virus will be resistant to at least one ARV drug is in the range of 6%–16% *[20-25]*, with 3%–5% of transmitted viruses exhibiting resistance to drugs from more than one class *[16, 24]*.

If the decision is made to initiate therapy in a person with acute HIV infection, resistance testing at baseline will provide guidance in selecting a regimen to optimize virologic response. Therefore, resistance testing in this situation is recommended **(AIII)** and a genotypic assay is preferred **(AIII)**. In this setting, treatment initiation should not be delayed by pending resistance testing results. Once results are obtained, the treatment regimen can be modified if warranted by the results. (See **Acute HIV Infection**.) In the absence of therapy, resistant viruses may decline over

time to less than the detection limit of standard resistance tests but may still increase the risk of treatment failure when therapy is eventually initiated *[26-28]*. Therefore, if therapy is deferred, resistance testing during acute HIV infection should still be performed **(AIII)**. In this situation, the genotypic resistance test result might be kept on record for several years before it becomes clinically useful. Because it is possible for a patient to acquire drug-resistant virus (i.e., superinfection) between entry into care and initiation of ART, repeat resistance testing at the time treatment is started should be considered **(CIII)**.

Performing drug-resistance testing before ART initiation in patients with chronic HIV infection is less straightforward. The rate at which transmitted resistance-associated mutations revert to wild-type virus has not been completely delineated, but mutations present at the time of HIV transmission are more stable than those selected under drug pressure, and it is often possible to detect resistance-associated mutations in viruses that were transmitted several years earlier *[29-31]*. No prospective trial has addressed whether drug-resistance testing prior to initiation of therapy confers benefit in this population. However, data from several, but not all, studies suggest suboptimal virologic responses in persons with baseline mutations *[16-19, 32-34]*. In addition, a cost-effectiveness analysis of early genotypic resistance testing suggests that baseline testing in this population should be performed *[35]*. Therefore, resistance testing in chronically infected persons at the time of entry into HIV care is recommended **(AIII)**. Genotypic testing is generally preferred in this situation because of lower cost, more rapid turnaround time, ability to detect mixtures of wild-type and resistant virus, and the relative ease of interpretation **(AIII)**. If therapy is deferred, repeat testing just prior to initiation of ART should be considered because the patient may have acquired drug-resistant virus (i.e., superinfection) **(CIII)**.

Standard genotypic drug-resistance testing in ARV-naïve persons involves testing for mutations in the RT and PR genes. Although transmission of INSTI-resistant virus has rarely been reported, as use of INSTIs increases, the potential for transmission of INSTI-resistant virus may also increase. Therefore, providers may wish to supplement standard baseline genotypic resistance testing with genotypic testing for resistance to this class of drugs **(CIII).**

Use of Resistance Assays in the Event of Virologic Failure

Resistance assays are useful in guiding decisions for patients experiencing virologic failure while on ART. Several prospective studies assessed the utility of resistance testing in guiding ARV drug selection in patients with virologic failure. These studies involved genotypic assays, phenotypic assays, or both *[6, 36-42]*. In general, these studies found that early virologic response to salvage regimens was improved when results of resistance testing were available to guide changes in therapy, compared with responses observed when changes in therapy were guided only by clinical judgment. Additionally, one observational study demonstrated improved survival in patients with detectable HIV plasma RNA when drug-resistance testing was performed *[43]*. Thus, resistance testing appears to be a useful tool in selecting active drugs when changing ARV regimens for virologic failure in persons with HIV RNA >1,000 copies/mL **(AI)**. (See **Virologic and Immunologic Failure**.) In persons with >500 but <1,000 copies/mL, testing may be unsuccessful but should still be considered **(BII)**. Drug-resistance testing is not usually recommended in persons with a plasma viral load <500 copies/mL because resistance assays cannot be consistently performed given low HIV RNA levels **(AIII)**.

Resistance testing also can help guide treatment decisions for patients with suboptimal viral load reduction **(AII)**. Virologic failure in the setting of combination ART is, for certain patients, associated with resistance to only one component of the regimen *[44-46]*. In that situation, substituting individual drugs in a failing regimen might be possible, although this concept will require clinical validation. (See **Virologic and Immunologic Failure**.)

Genotypic testing is generally preferred for virologic failure or suboptimal viral load reduction in persons failing their first or second ARV drug regimen because of lower cost, faster turnaround time, and greater sensitivity for detecting mixtures of wild-type and resistant virus **(AIII)**. Addition of phenotypic to genotypic testing is generally preferred for persons with known or suspected complex drug-resistance mutation patterns, particularly to PIs **(BIII)**.

In patients failing INSTI-based regimens, testing for INSTI resistance should be considered to determine whether to include drugs from this class in subsequent regimens; genotypic testing is preferred **(BIII)**. Although it is not a drug-resistance assay, a coreceptor tropism assay should be performed whenever the use of a CCR5 antagonist is being considered **(AI)**. Coreceptor tropism testing should also be considered for patients who exhibit virologic failure on a CCR5 antagonist **(CIII)**. However, such testing may be of limited value because the absence of detectable CXCR4-

using virus does not exclude the possibility that CCR5 antagonist resistance may have developed. Assays for resistance to CCR5 inhibitors are not yet commercially available *[47]*. (See **Coreceptor Tropism Assays**.)

Use of Resistance Assays in Pregnant Women

In pregnant women, the goal of ART is to maximally reduce plasma HIV RNA to provide appropriate maternal therapy and prevent mother-to-child transmission (MTCT) of HIV. Genotypic resistance testing is recommended for all pregnant women prior to initiation of therapy **(AIII)** and for those entering pregnancy with detectable HIV RNA levels while on therapy **(AI)**. Phenotypic testing may provide additional information in those found to have complex drug-resistance mutation patterns, particularly to PIs **(BIII)**. Optimal prevention of perinatal transmission may require initiation of ART while results of resistance testing are pending. Once the results are available, the ARV regimen can be changed as needed.

Table 4. Recommendations for Using Drug-Resistance Assays (Updated January 10, 2011)

Clinical Setting/Recommendation	Rationale
Drug-resistance assay recommended	
In acute HIV infection: Drug-resistance testing is recommended regardless of whether ART is initiated immediately or deferred **(AIII)**. A genotypic assay is generally preferred **(AIII)**.	If ART is to be initiated immediately, drug-resistance testing will determine whether drug-resistant virus was transmitted. Test results will help in the design of initial regimens or to modify or change regimens if results are obtained subsequent to treatment initiation. Genotypic testing is preferable to phenotypic testing because of lower cost, faster turnaround time, and greater sensitivity for detecting mixtures of wild-type and resistant virus.
If ART is deferred, repeat resistance testing should be considered at the time therapy is initiated **(CIII)**. A genotypic assay is generally preferred **(AIII)**.	If ART is deferred, testing should still be performed because of the greater likelihood that transmitted resistance-associated mutations will be detected earlier in the course of HIV infection. Results of resistance testing may be important when treatment is initiated. Repeat testing at the time ART is initiated should be considered because the patient may have acquired a drug-resistant virus (i.e., superinfection).
In ART-naïve patients with chronic HIV infection: Drug-resistance testing is recommended at the time of entry into HIV care, regardless of whether therapy is initiated immediately or deferred **(AIII)**. A genotypic assay is generally preferred **(AIII)**.	Transmitted HIV with baseline resistance to at least one drug is seen in 6%–16% of patients, and suboptimal virologic responses may be seen in patients with baseline resistant mutations. Some drug-resistance mutations can remain detectable for years in untreated chronically infected patients.
If therapy is deferred, repeat resistance testing should be considered prior to the initiation of ART **(CIII)**. A genotypic assay is generally preferred **(AIII)**.	Repeat testing prior to initiation of ART should be considered because the patient may have acquired a drug-resistant virus (i.e., a superinfection). Genotypic testing is preferable to phenotypic testing because of lower cost, faster turnaround time, and greater sensitivity for detecting mixtures of wild-type and resistant virus.
If an INSTI is considered for an ART-naïve patient and transmitted INSTI resistance is a concern, providers may wish to supplement standard resistance testing with a specific INSTI genotypic resistance assay **(CIII)**.	Standard genotypic drug-resistance assays test only for mutations in the RT and PR genes.

Table 4. Recommendations for Using Drug-Resistance Assays
Page 2 of 2

Clinical Setting/Recommendation	Rationale
In patients with virologic failure: Drug-resistance testing is recommended in persons on combination ART with HIV RNA levels >1,000 copies/mL **(AI)**. In persons with HIV RNA levels >500 but <1,000 copies/mL, testing may be unsuccessful but should still be considered **(BII)**.	Testing can help determine the role of resistance in drug failure and maximize the clinician's ability to select active drugs for the new regimen. Drug-resistance testing should be performed while the patient is taking prescribed ARV drugs or, if not possible, within 4 weeks after discontinuing therapy.
A standard genotypic resistance assay is generally preferred for those experiencing virologic failure on their first or second regimens **(AIII)**.	Genotypic testing is preferable to phenotypic testing because of lower cost, faster turnaround time, and greater sensitivity for detecting mixtures of wild-type and resistant virus.
In patients failing INSTI-based regimens, genotypic testing for INSTI resistance should be considered to determine whether to include drugs from this class in subsequent regimens **(BIII)**.	Standard genotypic drug-resistance assays test only for mutations in the RT and PR genes.
Addition of phenotypic assay to genotypic assay is generally preferred for those with known or suspected complex drug-resistance patterns, particularly to PIs **(BIII)**.	Phenotypic testing can provide useful additional information for those with complex drug-resistance mutation patterns, particularly to PIs.
In patients with suboptimal suppression of viral load: Drug-resistance testing is recommended for persons with suboptimal suppression of viral load after initiation of ART **(AII)**.	Testing can help determine the role of resistance and thus assist the clinician in identifying the number of active drugs available for a new regimen.
In HIV-infected pregnant women: Genotypic resistance testing is recommended for all pregnant women prior to initiation of ART **(AIII)** and for those entering pregnancy with detectable HIV RNA levels while on therapy **(AI)**.	The goal of ART in HIV-infected pregnant women is to achieve maximal viral suppression for treatment of maternal HIV infection and for prevention of perinatal transmission of HIV. Genotypic resistance testing will assist the clinician in selecting the optimal regimen for the patient.
Drug-resistance assay not usually recommended	
After therapy discontinued: Drug-resistance testing is not usually recommended after discontinuation (>4 weeks) of ARV drugs **(BIII)**.	Drug-resistance mutations might become minor species in the absence of selective drug pressure, and available assays might not detect minor drug-resistant species. If testing is performed in this setting, the detection of drug resistance may be of value; however, the absence of resistance does not rule out the presence of minor drug-resistant species.
In patients with low HIV RNA levels: Drug-resistance testing is not usually recommended in persons with a plasma viral load <500 copies/mL **(AIII)**.	Resistance assays cannot be consistently performed given low HIV RNA levels.

References

1. Hirsch MS, Gunthard HF, Schapiro JM, et al. Antiretroviral drug resistance testing in adult HIV-1 infection: 2008 recommendations of an International AIDS Society-USA panel. *Clin Infect Dis.* 2008;47(2):266-285.
2. Flandre P, Costagliola D. On the comparison of artificial network and interpretation systems based on genotype resistance mutations in HIV-1-infected patients. *AIDS.* 2006;20(16):2118-2120.
3. Vercauteren J, Vandamme AM. Algorithms for the interpretation of HIV-1 genotypic drug resistance information. *Antiviral Res.* 2006;71(2-3):335-342.
4. Gianotti N, Mondino V, Rossi MC, et al. Comparison of a rule-based algorithm with a phenotype-based algorithm for the interpretation of HIV genotypes in guiding salvage regimens in HIV-infected patients by a randomized clinical trial: the mutations and salvage study. *Clin Infect Dis.* 2006;42(10):1470-1480.
5. Torti C, Quiros-Roldan E, Regazzi M, et al. A randomized controlled trial to evaluate antiretroviral salvage therapy guided by rules-based or phenotype-driven HIV-1 genotypic drug-resistance interpretation with or without concentration-controlled intervention: the Resistance and Dosage Adapted Regimens (RADAR) study. *Clin Infect Dis.* 2005;40(12):1828-1836.
6. Tural C, Ruiz L, Holtzer C, et al. Clinical utility of HIV-1 genotyping and expert advice: the Havana trial. *AIDS.* 2002;16(2):209-218.
7. Lanier ER, Ait-Khaled M, Scott J, et al. Antiviral efficacy of abacavir in antiretroviral therapy-experienced adults harbouring HIV-1 with specific patterns of resistance to nucleoside reverse transcriptase inhibitors. *Antivir Ther.* 2004;9(1):37-45.
8. Miller MD, Margot N, Lu B, et al. Genotypic and phenotypic predictors of the magnitude of response to tenofovir disoproxil fumarate treatment in antiretroviral-experienced patients. *J Infect Dis.* 2004;189(5):837-846.
9. Flandre P, Chappey C, Marcelin AG, et al. Phenotypic susceptibility to didanosine is associated with antiviral activity in treatment-experienced patients with HIV-1 infection. *J Infect Dis.* 2007;195(3):392-398.
10. Naeger LK, Struble KA. Food and Drug Administration analysis of tipranavir clinical resistance in HIV-1-infected treatment-experienced patients. *AIDS.* 2007;21(2):179-185.
11. Naeger LK, Struble KA. Effect of baseline protease genotype and phenotype on HIV response to atazanavir/ritonavir in treatment-experienced patients. *AIDS.* 2006;20(6):847-853.
12. Verhofstede C, Wanzeele FV, Van Der Gucht B, et al. Interruption of reverse transcriptase inhibitors or a switch from reverse transcriptase to protease inhibitors resulted in a fast reappearance of virus strains with a reverse transcriptase inhibitor-sensitive genotype. *AIDS.* 1999;13(18):2541-2546.
13. Miller V, Sabin C, Hertogs K, et al. Virological and immunological effects of treatment interruptions in HIV-1 infected patients with treatment failure. *AIDS.* 2000;14(18):2857-2867.
14. Devereux HL, Youle M, Johnson MA, et al. Rapid decline in detectability of HIV-1 drug resistance mutations after stopping therapy. *AIDS.* 1999;13(18):F123-127.
15. Benson CA, Vaida F, Havlir DV, et al. A randomized trial of treatment interruption before optimized antiretroviral therapy for persons with drug-resistant HIV: 48-week virologic results of ACTG A5086. *J Infect Dis.* 2006;194(9):1309-1318.
16. Little SJ, Holte S, Routy JP, et al. Antiretroviral-drug resistance among patients recently infected with HIV. *N Engl J Med.* 2002;347(6):385-394.
17. Borroto-Esoda K, Waters JM, Bae AS, et al. Baseline genotype as a predictor of virological failure to emtricitabine or stavudine in combination with didanosine and efavirenz. *AIDS Res Hum Retroviruses.* 2007;23(8):988-995.
18. Pozniak AL, Gallant JE, DeJesus E, et al. Tenofovir disoproxil fumarate, emtricitabine, and efavirenz versus fixed-dose zidovudine/lamivudine and efavirenz in antiretroviral-naive patients: virologic, immunologic, and morphologic changes--a 96-week analysis. *J Acquir Immune Defic Syndr.* 2006;43(5):535-540.
19. Kuritzkes DR, Lalama CM, Ribaudo HJ, et al. Preexisting resistance to nonnucleoside reverse-transcriptase inhibitors predicts virologic failure of an efavirenz-based regimen in treatment-naive HIV-1-infected subjects. *J Infect Dis.* 2008;197(6):867-870.
20. Weinstock HS, Zaidi I, Heneine W, et al. The epidemiology of antiretroviral drug resistance among drug-naive HIV-1-infected persons in 10 US cities. *J Infect Dis.* 2004;189(12):2174-2180.
21. Wensing AM, van de Vijver DA, Angarano G, et al. Prevalence of drug-resistant HIV-1 variants in untreated individuals in Europe: implications for clinical management. *J Infect Dis.* 2005;192(6):958-966.
22. Cane P, Chrystie I, Dunn D, et al. Time trends in primary resistance to HIV drugs in the United Kingdom: multicentre observational study. *BMJ.* 2005;331(7529):1368.
23. Bennett D, McCormick L, Kline R, et al. US surveillance of HIV drug resistance at diagnosis using HIV diagnostic sera. Paper presented at: 12th Conference on Retroviruses and Opportunistic Infections; Feb 22-25, 2005; Boston, MA. Abstract 674.
24. Wheeler WH, Ziebell RA, Zabina H, et al. Prevalence of transmitted drug resistance associated mutations and HIV-1 subtypes in new HIV-1 diagnoses, U.S.-2006. *AIDS.* 2010;24(8):1203-1212.
25. Ross L, Lim ML, Liao Q, et al. Prevalence of antiretroviral drug resistance and resistance-associated mutations in antiretroviral therapy-naive HIV-infected individuals from 40 United States cities. *HIV Clin Trials.* 2007;8(1):1-8.
26. Johnson JA, Li JF, Wei X, et al. Minority HIV-1 drug resistance mutations are present in antiretroviral treatment-naive populations and associate with reduced treatment efficacy. *PLoS Med.* 2008;5(7):e158.
27. Simen BB, Simons JF, Hullsiek KH, et al. Low-abundance drug-resistant viral variants in chronically HIV-infected, antiretroviral treatment-naive patients significantly impact treatment outcomes. *J Infect Dis.* 2009;199(5):693-701.
28. Paredes R, Lalama CM, Ribaudo HJ, et al. Pre-existing minority drug-resistant HIV-1 variants, adherence, and risk of antiretroviral treatment failure. *J Infect Dis.* 2010;201(5):662-671.

29. Smith DM, Wong JK, Shao H, et al. Long-term persistence of transmitted HIV drug resistance in male genital tract secretions: implications for secondary transmission. *J Infect Dis.* 2007;196(3):356-360.
30. Novak RM, Chen L, MacArthur RD, et al. Prevalence of antiretroviral drug resistance mutations in chronically HIV-infected, treatment-naive patients: implications for routine resistance screening before initiation of antiretroviral therapy. *Clin Infect Dis.* 2005;40(3):468-474.
31. Little SJ, Frost SD, Wong JK, et al. Persistence of transmitted drug resistance among subjects with primary human immunodeficiency virus infection. *J Virol.* 2008;82(11):5510-5518.
32. Saag MS, Cahn P, Raffi F, et al. Efficacy and safety of emtricitabine vs stavudine in combination therapy in antiretroviral-naive patients: a randomized trial. *JAMA.* 2004;292(2):180-189.
33. Jourdain G, Ngo-Giang-Huong N, Le Coeur S, et al. Intrapartum exposure to nevirapine and subsequent maternal responses to nevirapine-based antiretroviral therapy. *N Engl J Med.* 2004;351(3):229-240.
34. Pillay D, Bhaskaran K, Jurriaans S, et al. The impact of transmitted drug resistance on the natural history of HIV infection and response to first-line therapy. *AIDS.* 2006;20(1):21-28.
35. Sax PE, Islam R, Walensky RP, et al. Should resistance testing be performed for treatment-naive HIV-infected patients? A cost-effectiveness analysis. *Clin Infect Dis.* 2005;41(9):1316-1323.
36. Cingolani A, Antinori A, Rizzo MG, et al. Usefulness of monitoring HIV drug resistance and adherence in individuals failing highly active antiretroviral therapy: a randomized study (ARGENTA). *AIDS.* 2002;16(3):369-379.
37. Durant J, Clevenbergh P, Halfon P, et al. Drug-resistance genotyping in HIV-1 therapy: the VIRADAPT randomised controlled trial. *Lancet.* 1999;353(9171):2195-2199.
38. Baxter JD, Mayers DL, Wentworth DN, et al. A randomized study of antiretroviral management based on plasma genotypic antiretroviral resistance testing in patients failing therapy. CPCRA 046 Study Team for the Terry Beirn Community Programs for Clinical Research on AIDS. *AIDS.* 2000;14(9):F83-93.
39. Cohen CJ, Hunt S, Sension M, et al. A randomized trial assessing the impact of phenotypic resistance testing on antiretroviral therapy. *AIDS.* 2002;16(4):579-588.
40. Meynard JL, Vray M, Morand-Joubert L, et al. Phenotypic or genotypic resistance testing for choosing antiretroviral therapy after treatment failure: a randomized trial. *AIDS.* 2002;16(5):727-736.
41. Vray M, Meynard JL, Dalban C, et al. Predictors of the virological response to a change in the antiretroviral treatment regimen in HIV-1-infected patients enrolled in a randomized trial comparing genotyping, phenotyping and standard of care (Narval trial, ANRS 088). *Antivir Ther.* 2003;8(5):427-434.
42. Wegner SA, Wallace MR, Aronson NE, et al. Long-term efficacy of routine access to antiretroviral-resistance testing in HIV type 1-infected patients: results of the clinical efficacy of resistance testing trial. *Clin Infect Dis.* 2004;38(5):723-730.
43. Palella FJ, Jr., Armon C, Buchacz K, et al. The association of HIV susceptibility testing with survival among HIV-infected patients receiving antiretroviral therapy: a cohort study. *Ann Intern Med.* 2009;151(2):73-84.
44. Havlir DV, Hellmann NS, Petropoulos CJ, et al. Drug susceptibility in HIV infection after viral rebound in patients receiving indinavir-containing regimens. *JAMA.* 2000;283(2):229-234.
45. Descamps D, Flandre P, Calvez V, et al. Mechanisms of virologic failure in previously untreated HIV-infected patients from a trial of induction-maintenance therapy. Trilege (Agence Nationale de Recherches sur le SIDA 072) Study Team). *JAMA.* 2000;283(2):205-211.
46. Machouf N, Thomas R, Nguyen VK, et al. Effects of drug resistance on viral load in patients failing antiretroviral therapy. *J Med Virol.* 2006;78(5):608-613.
47. Lewis M MJ, Simpson P, et al. Changes in V3 loop sequence associated with failure of maraviroc treatment in patients enrolled in the MOTIVATE 1 and 2 trials. Paper presented at: 15th Conference on Retroviruses and Opportunistic Infections.; February 3-6, 2008; Boston, Massachusetts. Abstract 871.

HLA-B*5701 SCREENING (Updated December 1, 2007)

Panel's Recommendations:

- ***The Panel recommends screening for HLA-B*5701 before starting patients on an abacavir (ABC)-containing regimen to reduce the risk of hypersensitivity reaction (HSR) (AI).***
- ***HLA-B*5701-positive patients should not be prescribed ABC (AI).***
- ***The positive status should be recorded as an ABC allergy in the patient's medical record (AII).***
- ***When HLA-B*5701 screening is not readily available, it remains reasonable to initiate ABC with appropriate clinical counseling and monitoring for any signs of HSR (CIII).***

Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = data from randomized controlled trials; II = data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = expert opinion

The ABC HSR is a multiorgan clinical syndrome typically seen within the initial 6 weeks of ABC treatment. This reaction has been reported in 5%–8% of patients participating in clinical trials when using clinical criteria for the diagnosis, and it is the major reason for early discontinuation of ABC. Discontinuing ABC usually promptly reverses HSR, whereas subsequent rechallenge can cause a rapid, severe, and even life-threatening recurrence *[1]*.

Studies that evaluated demographic risk factors for ABC HSR have shown racial background as a risk factor, with white patients generally having a higher risk (5%–8%) than black patients (2%–3%). Several groups reported a highly significant association between ABC HSR and the presence of the major histocompatibility complex (MHC) class I allele HLA-B*5701 *[2-3]*. Because the clinical criteria used for ABC HSR are overly sensitive and may lead to false-positive ABC HSR diagnoses, an ABC skin patch test (SPT) was developed as a research tool to immunologically confirm ABC HSR *[4]*. A positive ABC SPT is an ABC-specific delayed HSR that results in redness and swelling at the skin site of application. All ABC SPT–positive patients studied were also positive for the HLA-B*5701 allele *[5]*. The ABC SPT could be falsely negative for some patients with ABC HSR and, at this point, is not recommended for use as a clinical tool. The PREDICT-1 study randomized patients before starting ABC either to be prospectively screened for HLA-B*5701 (with HLA-B*5701–positive patients not offered ABC) or to standard of care at the time of the study (i.e., no HLA screening, with all patients receiving ABC) *[6]*. The overall HLA-B*5701 prevalence in this predominately white population was 5.6%. In this cohort, screening for HLA-B*5701 eliminated immunologic ABC HSR (defined as ABC SPT positive) compared with standard of care (0% vs. 2.7%), yielding a 100% negative predictive value with respect to SPT and significantly decreasing the rate of clinically suspected ABC HSR (3.4% vs. 7.8%). The SHAPE study corroborated the low rate of immunologically validated ABC HSR in black patients and confirmed the utility of HLA-B*5701 screening for the risk of ABC HSR (100% sensitivity in black and white populations) *[7]*.

On the basis of the results of these studies, the Panel recommends screening for HLA-B*5701 before starting patients on an ABC-containing regimen **(AI)**. HLA-B*5701–positive patients should not be prescribed ABC **(AI)**, and the positive status should be recorded as an ABC allergy in the patient's medical record **(AII)**. HLA-B*5701 testing is needed only once in a patient's lifetime; thus, efforts to carefully record and maintain the test result and to educate the patient about its implications are important. The specificity of the HLA-B*5701 test in predicting ABC HSR is lower than the sensitivity (i.e., 33%–50% of HLA-B*5701–positive patients would likely not develop confirmed ABC HSR if exposed to ABC). HLA-B*5701 should not be used as a substitute for clinical judgment or pharmacovigilance, because a negative HLA-B*5701 result does not absolutely rule out the possibility of some form of ABC HSR. When HLA-B*5701 screening is not readily available, it remains reasonable to initiate ABC with appropriate clinical counseling and monitoring for any signs of ABC HSR **(CIII)**.

References

1. Hetherington S, McGuirk S, Powell G, et al. Hypersensitivity reactions during therapy with the nucleoside reverse transcriptase inhibitor abacavir. *Clin Ther.* 2001;23(10):1603-1614.
2. Mallal S, Nolan D, Witt C, et al. Association between presence of HLA-B*5701, HLA-DR7, and HLA-DQ3 and hypersensitivity to HIV-1 reverse-transcriptase inhibitor abacavir. *Lancet.* 2002;359(9308):727-732.
3. Hetherington S, Hughes AR, Mosteller M, et al. Genetic variations in HLA-B region and hypersensitivity reactions to abacavir. *Lancet.* 2002;359(9312):1121-1122.

4. Phillips EJ, Sullivan JR, Knowles SR, et al. Utility of patch testing in patients with hypersensitivity syndromes associated with abacavir. *AIDS.* 2002;16(16):2223-2225.
5. Phillips E, Rauch A, Nolan D, et al. Pharmacogenetics and clinical characteristics of patch test confirmed patients with abacavir hypersensitivity. *Rev Antivir Ther.* 2006:3: Abstract 57.
6. Mallal S, Phillips E, Carosi G, et al. HLA-B*5701 screening for hypersensitivity to abacavir. *N Engl J Med.* 2008;358(6):568-579.
7. Saag M, Balu R, Phillips E, et al. High sensitivity of human leukocyte antigen-b*5701 as a marker for immunologically confirmed abacavir hypersensitivity in white and black patients. *Clin Infect Dis.* 2008;46(7):1111-1118.

CORECEPTOR TROPISM ASSAYS (Updated January 10, 2011)

Panel's Recommendations:

- ***Coreceptor tropism assay should be performed whenever the use of a CCR5 inhibitor is being considered (AI).***
- ***Coreceptor tropism testing might also be considered for patients who exhibit virologic failure on a CCR5 inhibitor (CIII).***

Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = data from randomized controlled trials; II = data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = expert opinion

HIV enters cells by a complex process that involves sequential attachment to the CD4 receptor followed by binding to either the CCR5 or CXCR4 molecules and fusion of the viral and cellular membranes *[1]*. CCR5 inhibitors (i.e., maraviroc [MVC]), prevent HIV entry into target cells by binding to the CCR5 receptor *[2]*. Phenotypic and, to a lesser degree, genotypic assays have been developed that can determine the coreceptor tropism (i.e., CCR5, CXCR4, or both) of the patient's dominant virus population. One assay (*Trofile*, Monogram Biosciences, Inc., South San Francisco, CA) was used to screen patients who were participating in studies that formed the basis of approval for MVC, the only CCR5 inhibitor currently available. Other assays are under development and are currently used primarily for research purposes or in clinical situations in which the *Trofile* assay is not readily available.

Background

The vast majority of patients harbor a CCR5-utilizing virus (R5 virus) during acute/recent infection, which suggests that the R5 variant is preferentially transmitted compared with the CXCR4 (X4) variant. Viruses in many untreated patients eventually exhibit a shift in coreceptor tropism from CCR5 to either CXCR4 or both CCR5 and CXCR4 (i.e., dual- or mixed-tropic; D/M-tropic). This shift is temporally associated with a more rapid decline in CD4 T-cell counts *[3-4]*, although whether this shift is a cause or a consequence of progressive immunodeficiency remains undetermined *[1]*. Antiretroviral (ARV)-treated patients who have extensive drug resistance are more likely to harbor detectable X4- or D/M-tropic variants than untreated patients who have comparable CD4 T-cell counts *[5]*. The prevalence of X4- or D/M-tropic variants increases to more than 50% in treated patients who have CD4 counts <100 cells/mm^3 *[5-6]*.

Phenotypic Assays

There are now at least two high-throughput phenotypic assays that can quantify the coreceptor characteristics of plasma-derived virus. Both involve the generation of laboratory viruses that express patient-derived envelope proteins (i.e., gp120 and gp41). These pseudoviruses are either replication competent (*Phenoscript* assay, VIRalliance, Paris, France) or replication defective (*Trofile* assay, Monogram Biosciences, Inc.) *[7-8]*. These pseudoviruses then are used to infect target cell lines that express either CCR5 or CXCR4. In the *Trofile* assay, the coreceptor tropism of the patient-derived virus is confirmed by testing the susceptibility of the virus to specific CCR5 or CXCR4 inhibitors *in vitro*. The *Trofile* assay takes about 2 weeks to perform and requires a plasma HIV RNA level ≥1,000 copies/mL.

The performance characteristics of these assays have evolved. Most, if not all, patients enrolled in premarketing clinical trials of MVC and other CCR5 inhibitors were screened with an earlier, less sensitive version of the *Trofile* assay *[7]*. This earlier assay failed to routinely detect low levels of CXCR4-utilizing variants. As a consequence, some patients enrolled in these clinical trials harbored low, undetectable levels of CXCR4-utilizing viruses at baseline and exhibited rapid virologic failure after initiation of a CCR5 inhibitor *[9]*. This assay has since been revised and is now able to detect lower levels of CXCR4-utlizing viruses. *In vitro*, the assay can detect CXCR4-utilizing clones with 100% sensitivity when those clones make up 0.3% of the population *[10]*. Although this more sensitive assay has had limited use in prospective clinical trials, it is now the only one that is commercially available. For unclear reasons, a minority of samples cannot be successfully phenotyped with either generation of the *Trofile* assay. In patients with plasma HIV-1 RNA below the limit of detection, coreceptor usage can be determined from proviral DNA obtained from peripheral blood mononuclear cells; however, the clinical utility of this assay remains to be determined *[11]*.

Genotypic Assays

Genotypic determination of HIV-1 coreceptor usage is based on sequencing the V3-coding region of HIV-1 *env*, the principal determinant of coreceptor usage. A variety of algorithms and bioinformatics programs can be used to predict coreceptor usage from the V3 sequence. When compared to the phenotypic assay, genotypic methods show high specificity (~90%) but only modest sensitivity (~50%–70%) for the presence of a CXCR4-utilizing virus. Given these performance characteristics, these assays may not be sufficiently robust to completely rule out the presence of an X4 or D/M variant *[12]*.

Recent studies in which V3 genotyping was performed on samples from patients screening for clinical trials of MVC suggest that genotyping performed as well as phenotyping in predicting the response to MVC *[13-14]*. On the basis of these data, accessibility, and cost, European guidelines currently favor genotypic testing for determining coreceptor usage. An important caveat to these results is that the majority of patients who received MVC were first shown to have R5 virus by a phenotypic assay (*Trofile*). Consequently, the opportunity to assess treatment response to MVC in patients whose virus was considered R5 by genotype but D/M or X4 by phenotype was limited to a relatively small number of patients. It is also important to note that the genotyping approaches used in these studies are not routinely available from clinical laboratories in the United States at this time.

Given the uncertainty regarding the genotypic assays and fewer logistical barriers to obtaining a phenotype in the United States than elsewhere, the Panel recommends that a phenotype be used as the preferred coreceptor tropism screening test in the United States.

Use of Coreceptor Tropism Assays in Clinical Practice

Coreceptor tropism assays should be used whenever the use of a CCR5 inhibitor is being considered **(AI)**. Coreceptor tropism testing might also be considered for patients who exhibit virologic failure on MVC (or any CCR5 inhibitor) **(CIII)**.

Other potential clinical uses for the tropism assay are for prognostic purposes or for assessment of tropism prior to starting antiretroviral therapy (ART), in case a CCR5 inhibitor is required later (e.g., in a regimen change for toxicity). Currently, sufficient data do not exist to support these uses.

References

1. Moore JP, Kitchen SG, Pugach P, et al. The CCR5 and CXCR4 coreceptors--central to understanding the transmission and pathogenesis of human immunodeficiency virus type 1 infection. *AIDS Res Hum Retroviruses.* 2004;20(1):111-126.
2. Fatkenheuer G, Pozniak AL, Johnson MA, et al. Efficacy of short-term monotherapy with maraviroc, a new CCR5 antagonist, in patients infected with HIV-1. *Nat Med.* 2005;11(11):1170-1172.
3. Connor RI, Sheridan KE, Ceradini D, et al. Change in coreceptor use correlates with disease progression in HIV-1--infected individuals. *J Exp Med.* 1997;185(4):621-628.
4. Koot M, Keet IP, Vos AH, et al. Prognostic value of HIV-1 syncytium-inducing phenotype for rate of CD4+ cell depletion and progression to AIDS. *Ann Intern Med.* 1993;118(9):681-688.
5. Hunt PW, Harrigan PR, Huang W, et al. Prevalence of CXCR4 tropism among antiretroviral-treated HIV-1-infected patients with detectable viremia. *J Infect Dis.* 2006;194(7):926-930.
6. Wilkin TJ, Su Z, Kuritzkes DR, et al. HIV type 1 chemokine coreceptor use among antiretroviral-experienced patients screened for a clinical trial of a CCR5 inhibitor: AIDS Clinical Trial Group A5211. *Clin Infect Dis.* 2007;44(4):591-595.
7. Whitcomb JM, Huang W, Fransen S, et al. Development and characterization of a novel single-cycle recombinant-virus assay to determine human immunodeficiency virus type 1 coreceptor tropism. *Antimicrob Agents Chemother.* 2007;51(2):566-575.
8. Trouplin V, Salvatori F, Cappello F, et al. Determination of coreceptor usage of human immunodeficiency virus type 1 from patient plasma samples by using a recombinant phenotypic assay. *J Virol.* 2001;75(1):251-259.
9. Westby M, Lewis M, Whitcomb J, et al. Emergence of CXCR4-using human immunodeficiency virus type 1 (HIV-1) variants in a minority of HIV-1-infected patients following treatment with the CCR5 antagonist maraviroc is from a pretreatment CXCR4-using virus reservoir. *J Virol.* 2006;80(10):4909-4920.
10. Trinh L, Han D, Huang W, et al. Technical validation of an enhanced sensitivity Trofile HIV coreceptor tropism assay for selecting patients for therapy with entry inhibitors targeting CCR5. *Antivir Ther.* 2008;13(Suppl 3):A128
11. Toma J, Frantzell A, Cook J, et al. Phenotypic determination of HIV-1 coreceptor tropism using cell-associated DNA derived from blood samples. Paper presented at: 17th Conference on Retroviruses and Opportunistic Infections; Feb 16-19, 2010, 2010; San Francisco, CA.

12. Lin NH, Kuritzkes DR. Tropism testing in the clinical management of HIV-1 infection. *Curr Opin HIV AIDS.* 2009;4(6):481-487.
13. Chapman D, Valdez H, Lewis M, et al. Clinical, virologic, and immunologic characteristics of patients with discordant phenotypic and genotypic co-receptor tropism test results. Paper presented at: 50th Interscience Conference on Antimicrobial Agents and Chemotherapy; Sep 12-15, 2010, 2010; Boston, MA.
14. McGovern RA, Thielen A, Mo T, et al. Population-based V3 genotypic tropism assay: a retrospective analysis using screening samples from the A4001029 and MOTIVATE studies. *AIDS.* 2010;24(16):2517-2525.

Treatment Goals (Updated January 10, 2011)

Eradication of HIV infection cannot be achieved with available antiretroviral (ARV) regimens even when new, potent drugs are added to a regimen already suppressing plasma viral load below the limits of detection with commercially available assays *[1]*. This is chiefly because the pool of latently infected CD4 T-cells is established during the earliest stages of acute HIV infection *[2]* and persists with a long half-life, despite prolonged suppression of plasma viremia *[3-7]*. Therefore the primary goals for initiating antiretroviral therapy (ART) are to:

- reduce HIV-associated morbidity and prolong the duration and quality of survival,
- restore and preserve immunologic function,
- maximally and durably suppress plasma HIV viral load (see **Plasma HIV RNA Testing**), and
- prevent HIV transmission.

Adoption of treatment strategies recommended in these guidelines has reduced HIV-related morbidity and mortality *[8-11]* and has reduced perinatal *[12]* and, probably, behavior-associated transmission of HIV *[13-16]*. HIV suppression with ART may also decrease inflammation and immune activation thought to contribute to higher rates of cardiovascular and other end-organ damage reported in HIV-infected cohorts. (See **Initiating Antiretroviral Therapy**.) Maximal and durable suppression of plasma viremia delays or prevents the selection of drug-resistance mutations, preserves CD4 T-cell numbers, and confers substantial clinical benefits, all of which are important treatment goals *[17-18]*.

Achieving viral suppression requires the use of ARV regimens with at least two, and preferably three, active drugs from two or more drug classes. Baseline resistance testing and patient characteristics should guide the specific regimen design. (See **What to Start: Initial Combination Regimens for the Antiretroviral-Naïve Patient**.) When initial suppression is not achieved or is lost, rapidly changing to a new regimen with at least two active drugs is required. (See **Virologic and Immunologic Failure**.) The increasing number of drugs and drug classes makes viral suppression below detection limits an appropriate goal in all patients, even those with primary or acquired drug resistance.

Viral load reduction to below limits of assay detection in an ART-naïve patient usually occurs within the first 12–24 weeks of therapy. Predictors of virologic success include:

- high potency of ARV regimen,
- excellent adherence to treatment regimen *[19]*,
- low baseline viremia *[20]*,
- higher baseline CD4 count (>200 cells/mm^3) *[21]*, and
- rapid reduction of viremia in response to treatment *[20, 22]*.

Successful outcomes are usually observed although adherence difficulties may lower the success rate in clinical practice to below the 90% rate commonly seen in clinical trials *[23]*.

STRATEGIES TO ACHIEVE TREATMENT GOALS

Achieving treatment goals requires a balance of sometimes competing considerations, outlined below. Providers and patients must work together to define individualized strategies to achieve treatment goals.

Selection of Initial Combination Regimen

Several preferred and alternative ARV regimens are recommended for use. (See **What to Start**.) Many of these regimens have comparable efficacy but vary to some degree in dosing frequency and symmetry, pill burden, drug interactions, and potential side effects. A regimen should be tailored to each patient to enhance adherence and thus improve long-term treatment success. Individual regimen choice is based on such considerations as expected side

effects, convenience, comorbidities, interactions with concomitant medications, and results of pretreatment genotypic drug-resistance testing.

Pretreatment Drug-Resistance Testing

Current studies suggest a 6%–16% prevalence of HIV drug resistance in ART-naïve patients *[24-28]*, and some studies suggest that the presence of transmitted drug-resistant viruses may lead to suboptimal virologic responses *[29]*. Therefore, pretreatment genotypic resistance testing should be used to guide selection of the most optimal initial ARV regimen. (See **Drug-Resistance Testing**.)

Improving Adherence

Suboptimal adherence may result in reduced treatment response. Incomplete adherence can result from complex medication regimens; patient factors, such as active substance abuse and depression; and health system issues, including interruptions in access to medication and inadequate treatment education and support. Conditions that promote adherence should be maximized prior to and after initiation of ART. (See **Adherence to Antiretroviral Therapy**.)

References

1. Dinoso JB, Kim SY, Wiegand AM, et al. Treatment intensification does not reduce residual HIV-1 viremia in patients on highly active antiretroviral therapy. *Proc Natl Acad Sci U S A.* 2009;106(23):9403-9408.
2. Chun TW, Engel D, Berrey MM, et al. Early establishment of a pool of latently infected, resting CD4(+) T cells during primary HIV-1 infection. *Proc Natl Acad Sci U S A.* 1998;95(15):8869-8873.
3. Chun TW, Stuyver L, Mizell SB, et al. Presence of an inducible HIV-1 latent reservoir during highly active antiretroviral therapy. *Proc Natl Acad Sci U S A.* 1997;94(24):13193-13197.
4. Finzi D, Hermankova M, Pierson T, et al. Identification of a reservoir for HIV-1 in patients on highly active antiretroviral therapy. *Science.* 1997;278(5341):1295-1300.
5. Finzi D, Blankson J, Siliciano JD, et al. Latent infection of CD4+ T cells provides a mechanism for lifelong persistence of HIV-1, even in patients on effective combination therapy. *Nat Med.* 1999;5(5):512-517.
6. Wong JK, Hezareh M, Gunthard HF, et al. Recovery of replication-competent HIV despite prolonged suppression of plasma viremia. *Science.* 1997;278(5341):1291-1295.
7. Siliciano JD, Kajdas J, Finzi D, et al. Long-term follow-up studies confirm the stability of the latent reservoir for HIV-1 in resting CD4+ T cells. *Nat Med.* 2003;9(6):727-728.
8. Mocroft A, Vella S, Benfield TL, et al. Changing patterns of mortality across Europe in patients infected with HIV-1. EuroSIDA Study Group. *Lancet.* 1998;352(9142):1725-1730.
9. Palella FJ, Jr., Delaney KM, Moorman AC, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. *N Engl J Med.* 1998;338(13):853-860.
10. Vittinghoff E, Scheer S, O'Malley P, et al. Combination antiretroviral therapy and recent declines in AIDS incidence and mortality. *J Infect Dis.* 1999;179(3):717-720.
11. ART CC AC. Life expectancy of individuals on combination antiretroviral therapy in high-income countries: a collaborative analysis of 14 cohort studies. *Lancet.* 2008;372(9635):293-299.
12. Mofenson LM, Lambert JS, Stiehm ER, et al. Risk factors for perinatal transmission of human immunodeficiency virus type 1 in women treated with zidovudine. Pediatric AIDS Clinical Trials Group Study 185 Team. *N Engl J Med.* 1999;341(6):385-393.
13. Wood E, Kerr T, Marshall BD, et al. Longitudinal community plasma HIV-1 RNA concentrations and incidence of HIV-1 among injecting drug users: prospective cohort study. *BMJ.* 2009;338:b1649.
14. Quinn TC, Wawer MJ, Sewankambo N, et al. Viral load and heterosexual transmission of human immunodeficiency virus type 1. Rakai Project Study Group. *N Engl J Med.* 2000;342(13):921-929.
15. Dieffenbach CW, Fauci AS. Universal voluntary testing and treatment for prevention of HIV transmission. *JAMA.* 2009;301(22):2380-2382.
16. Montaner JS, Hogg R, Wood E, et al. The case for expanding access to highly active antiretroviral therapy to curb the growth of the HIV epidemic. *Lancet.* 2006;368(9534):531-536.
17. O'Brien WA, Hartigan PM, Martin D, et al. Changes in plasma HIV-1 RNA and CD4+ lymphocyte counts and the risk of progression to AIDS. Veterans Affairs Cooperative Study Group on AIDS. *N Engl J Med.* 1996;334(7):426-431.
18. Garcia F, de Lazzari E, Plana M, et al. Long-term CD4+ T-cell response to highly active antiretroviral therapy according to baseline CD4+ T-cell count. *J Acquir Immune Defic Syndr.* 2004;36(2):702-713.
19. Paterson DL, Swindells S, Mohr J, et al. Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. *Ann Intern Med.* 2000;133(1):21-30.
20. Powderly WG, Saag MS, Chapman S, et al. Predictors of optimal virological response to potent antiretroviral therapy. *AIDS.* 1999;13(14):1873-1880.

21. Yamashita TE, Phair JP, Munoz A, et al. Immunologic and virologic response to highly active antiretroviral therapy in the Multicenter AIDS Cohort Study. *AIDS.* 2001;15(6):735-746.
22. Townsend D, Troya J, Maida I, et al. First HAART in HIV-infected patients with high viral load: value of HIV RNA levels at 12 weeks to predict virologic outcome. *J Int Assoc Physicians AIDS Care (Chic Ill).* 2009;8(5):314-317.
23. Moore RD, Keruly JC, Gebo KA, et al. An improvement in virologic response to highly active antiretroviral therapy in clinical practice from 1996 through 2002. *J Acquir Immune Defic Syndr.* 2005;39(2):195-198.
24. Weinstock HS, Zaidi I, Heneine W, et al. The epidemiology of antiretroviral drug resistance among drug-naive HIV-1-infected persons in 10 US cities. *J Infect Dis.* 2004;189(12):2174-2180.
25. Bennett D, McCormick L, Kline R, et al. US surveillance of HIV drug resistance at diagnosis using HIV diagnostic sera. Paper presented at: 12th Conference on Retroviruses and Opportunistic Infections; Feb 22-25, 2005; Boston, MA. Abstract 674.
26. Wheeler W, Mahle K, Bodnar U, et al. Antiretroviral drug-resistance mutations and subtypes in drug-naive persons newly diagnosed with HIV-1 infection, US, March 2003 to October 2006. Paper presented at: 14th Conference on Retroviruses and Opportunistic Infections; February 25-28, 2007; Los Angeles, CA. Abstract 648.
27. Ross L, Lim ML, Liao Q, et al. Prevalence of antiretroviral drug resistance and resistance-associated mutations in antiretroviral therapy-naive HIV-infected individuals from 40 United States cities. *HIV Clin Trials.* 2007;8(1):1-8.
28. Vercauteren J, Wensing AM, van de Vijver DA, et al. Transmission of drug-resistant HIV-1 is stabilizing in Europe. *J Infect Dis.* 2009;200(10):1503-1508.
29. Borroto-Esoda K, Waters JM, Bae AS, et al. Baseline genotype as a predictor of virological failure to emtricitabine or stavudine in combination with didanosine and efavirenz. *AIDS Res Hum Retroviruses.* 2007;23(8):988-995.

Initiating Antiretroviral Therapy in Treatment-Naïve Patients (Updated January 10, 2011)

Panel's Recommendations:

- ***Antiretroviral therapy (ART) should be initiated in all patients with a history of an AIDS-defining illness or with a CD4 count <350 cells/mm^3 (AI).***
- ***ART is also recommended for patients with CD4 counts between 350 and 500 cells/mm^3 (A/B*-II).***
- ***ART should be initiated, regardless of CD4 count, in patients with the following conditions: HIV-associated nephropathy (HIVAN) (AII) and hepatitis B virus (HBV) coinfection when treatment of HBV is indicated (AIII).***
- ***A combination antiretroviral (ARV) drug regimen is also recommended for pregnant women who do not meet criteria for treatment with the goal to prevent perinatal transmission (AI).***
- ***For patients with CD4 counts >500 cells/mm^3, Panel members are evenly divided: 50% favor starting ART at this stage of HIV disease (B); 50% view initiating therapy at this stage as optional (C) (B/C-III).***
- ***Patients initiating ART should be willing and able to commit to lifelong treatment and should understand the benefits and risks of therapy and the importance of adherence (AIII). Patients may choose to postpone therapy, and providers, on a case-by-case basis, may elect to defer therapy based on clinical and/or psychosocial factors.***

Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = data from randomized controlled trials; II = data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = expert opinion

* ***Panel members are divided on the strength of this recommendation: 55% voted for strong recommendation (A) and 45% voted for moderate recommendation (B).***

The primary goal of ART is to reduce HIV-associated morbidity and mortality. This is best accomplished by using ART to maximally inhibit HIV replication, as measured by consistent plasma HIV RNA (viral load) values below the level of detection using commercially available assays. Additional benefits of ART, supported by accumulating evidence, are reduction in HIV-associated inflammation and its associated complications and reduction in HIV transmission.

Over the past 20 years, the Panel has made several changes to the recommendations on when to start therapy based on prevailing clinical trial and cohort data and therapeutic options available at the time of each revision. The standard procedure for the Panel is to only make recommendations in agreement with two-thirds of the Panel members. This has not been possible for the ***When to Start*** recommendations in this version of the guidelines. Accordingly, the breakdown of votes is presented for recommendations supported by less than two-thirds of Panel members.

Randomized controlled trials provide evidence supporting the benefit of ART in patients with CD4 counts ≤350 cells/mm^3. However, such evidence showing benefit for patients with higher CD4 cell counts is not yet available. Based on cumulative observational cohort data demonstrating benefits of ART in reducing AIDS- and non-AIDS-associated morbidity and mortality, the Panel now recommends ART for patients with CD4 count between 350 and 500 cells/mm^3 **(A-B/II)**. For patients with CD4 count >500 cells/mm^3, Panel members are evenly divided: 50% favor starting ART at earlier stages of HIV disease **(BIII)**; 50% view initiating therapy at this stage as optional **(CIII)**.

Panel members favoring earlier initiation of therapy base their recommendation on several recent developments: (1) report from at least one recent cohort study demonstrating survival benefit with initiation of ART at CD4 count >500 cells/mm^3; (2) growing awareness that untreated HIV infection may be associated with development of many non-AIDS-defining diseases, including cardiovascular disease, kidney disease, liver disease, and malignancy; (3) availability of ARV regimens that are more effective, more convenient, and better tolerated than ARV combinations no longer in use; and (4) increasing evidence that effective ART reduces HIV transmission **(BIII)**.

The other 50% of the Panel members feel that current evidence does not definitively demonstrate clear benefit of ART in all patients with CD4 count >500 cells/mm^3. They also feel that risks of short- or long-term drug-related complications, nonadherence to lifelong therapy in asymptomatic patients, and potential for development of drug resistance may offset possible benefits of earlier initiation of therapy. Thus, pending more definitive supporting evidence, these Panel members recommend that therapy in this setting should be optional and considered on a case-by-case basis **(CIII)**.

The known benefits, risks, and limitations of ART, as well as the strength of the recommendations according to CD4 count levels, are discussed below.

BENEFITS OF ANTIRETROVIRAL THERAPY

Earlier studies definitively showed that potent combination ART improves survival and reduces AIDS-related complications in patients with advanced HIV disease. There is now increasing evidence demonstrating the benefits of viral suppression and immunologic responses on reducing mortality and non-AIDS-related complications in patients with higher pretreatment CD4 counts. The following is a focused discussion of the rationale that forms the basis for the Panel's recommendation favoring earlier treatment.

Reduction in Mortality and/or AIDS-Related Morbidity

Patients with a history of an AIDS-defining illness or CD4 count <350 cells/mm^3

HIV-infected patients with CD4 counts <200 cells/mm^3 are at higher risk of opportunistic diseases, non-AIDS morbidity, and death. Randomized controlled trials in patients with CD4 counts <200 cells/mm^3 and/or a history of an AIDS-defining condition provide strong evidence that ART improves survival and delays disease progression in these patients *[1-3]*. Long-term data from multiple observational cohort studies evaluating earlier ART (>200 cells/mm^3) compared with later treatment (<200 cells/mm^3) have also provided strong support for these findings *[4-8]*.

Few large, randomized controlled trials address when to start therapy in patients with CD4 counts >200 cells/mm^3. CIPRA HT-001 is a randomized clinical trial conducted in Haiti. Study participants were randomized to start ART at CD4 counts of 200–350 cells/mm^3 or to defer treatment until their CD4 counts dropped below 200 cells/mm^3 or they developed an AIDS-defining condition. In an interim analysis of the study, a higher mortality rate (hazard ratio [HR] = 4.0, p = 0.0011) and greater incident tuberculosis (HR = 2.0, p = 0.0125) were observed among patients who deferred therapy compared with participants who began ART with CD4 counts of 200–350 cells/mm^3 *[9]*. This evidence led to the study Data Safety Monitoring Board's recommendation to terminate the trial before completion.

The SMART study was a multinational trial enrolling more than 5,400 participants with CD4 counts >350 cells/mm^3. Participants were randomized to continuous ART or to treatment interruption until CD4 count dropped to <250 cells/mm^3. In a subgroup analysis involving the 249 study participants who were ART naïve at enrollment, a trend of lower risk of serious AIDS- and non-AIDS-related events was seen in those who initiated therapy immediately compared with those who deferred therapy until CD4 count dropped to <250 cells/mm^3 (p = 0.06) *[10]*.

Collectively, these studies support the Panel's recommendation that ART should be initiated in patients with a history of an AIDS-defining illness or with a CD4 count <350 cells/mm^3 **(AI)**.

Patients with a CD4 count between 350 and 500 cells/mm^3

There are no randomized trials using current combination regimens in patients with CD4 counts >350 cells/mm^3 to provide data that directly address the question of when to start therapy in patients with CD4 counts of 350–500 cells/mm^3. Data from the ART Cohort Collaboration (ART-CC), which included 61,798 patient-years of follow-up, showed a declining risk of AIDS or death for up to 5 years in subjects starting therapy with a CD4 count ≥350 cells/mm^3 compared with subjects starting between 200 and 349 cells/mm^3 *[11]*. A more recent rigorous analysis of this cohort found that deferring therapy until the 251 to 350 cells/mm^3 range was associated with a higher rate of

progression to AIDS and death compared with initiating therapy in the 351 to 450 cells/mm^3 range (risk ratio: 1.28, 95% confidence interval [CI]: 1.04 to 1.57) *[6]*.

In a collaboration of North American cohort studies (NA-ACCORD) that evaluated patients regardless of whether they had started therapy, the 6,278 patients who deferred therapy until CD4 counts were <350 cells/mm^3 had an increased risk of death compared with 2,084 patients who initiated therapy with CD4 counts between 351 and 500 cells/mm^3 (risk ratio: 1.69, 95% CI: 1.26 to 2.26) after adjustment for other factors that differed between these two groups *[12]*.

When interpreting both of these cohort studies it is important to note that although the relative risk of a mortality event is evident, the overall number of events was small. In these cohort studies, the relative risks determined could have been influenced by unmeasured confounders that cannot be adjusted for in the analysis. The findings from these observational cohort studies point to potential harm if therapy is deferred until CD4 count falls to <350 cells/mm^3. Based on these findings, combined with emerging biologic evidence regarding potential damage to end organs from inflammation associated with untreated HIV replication and the potential reduction in HIV transmission with treatment (see below), the Panel recommends initiation of ART in patients with CD4 counts between 350 and 500 cells/mm^3. Panel members are divided on the strength of this recommendation: 55% voted for strong recommendation (A) and 45% voted for moderate recommendation (B) **(A/B-II)**.

Patients with a CD4 count >500 cells/mm^3

The NA-ACCORD study also observed patients who started treatment at CD4 counts >500 cells/mm^3 or after CD4 counts dropped below this threshold. The adjusted mortality rates were significantly higher among the 6,935 patients who deferred therapy until CD4 count fell to <500 cells/mm^3 compared with rates in the 2,200 patients who started therapy while CD4 count was > 500 cells/mm^3 (risk ratio: 1.94, 95% CI: 1.37 to 2.79) *[12]*. Although large and generally representative of care in the United States, the study has several limitations, including the small number of deaths and the potential for unmeasured confounders that might have influenced outcomes independent of ART.

In contrast, analysis of the ART-CC cohort failed to identify a benefit for patients initiating ART with CD4 counts > 450 cells/mm^3. This analysis also did not identify a harmful effect of this strategy *[6]*. Deferral of therapy to the 351–450 cells/mm^3 range was associated with a similar rate of progression to AIDS/death compared with initiation of therapy in the 451–550 cells/mm^3 range (risk ratio: 0.99, 95% CI: 0.76 to 1.29). This study also found that the proportion of patients with CD4 counts between 451 and 550 cells/mm^3 who would progress to AIDS or death before having a CD4 count <450 cells/mm^3 was low (1.6%; 95% CI: 1.1 to 2.1%).

Based on these data, along with a better understanding of the pathogenesis of HIV infection and the growing awareness that untreated HIV infection increases the risk of many non-AIDS-defining diseases (see below), 50% of Panel members favor initiation of ART in HIV-infected persons with a CD4 count >500 cells/mm^3 **(BIII)**.

The other 50% of the Panel members are reluctant to broadly recommend starting ART at higher CD4 cell counts and consider that therapy should be optional at this stage of HIV disease **(CIII)**. In making this recommendation, the Panel members note that the amount of data supporting initiation of therapy decreases as the CD4 count increases above 350–500 cells/mm^3, and that concerns remain over the unknown overall benefit and long-term risks with earlier treatment.

When discussing starting ART at higher CD4 cell counts (>500 cells/mm^3), clinicians should inform patients that data on the clinical benefit of starting treatment at such levels is not conclusive. There is a need for further ongoing research (both with randomized clinical trials and cohort studies) to assess the short- and long-term clinical and public health benefits and cost effectiveness of starting therapy at higher CD4 counts. Such research findings will provide guidance for future recommendations by the Panel.

Effects of Antiretroviral Therapy on HIV-Related Morbidity

HIV-related morbidity and mortality derive not only from immune deficiency but also from direct effects of HIV on specific end organs and the indirect effects of HIV-associated inflammation on these organs. In general, the available data demonstrate that:

- Untreated HIV infection may have detrimental effects at all stages of infection.
- Treatment is beneficial even when initiated later in infection. However, later therapy may not repair damage associated with viral replication during early stages of infection.
- Earlier treatment may prevent the damage associated with HIV replication during early stages of infection.

Clinical studies have demonstrated that sustaining viral suppression and maintaining higher CD4 count, mostly as a result of effective combination ART, delay or prevent some non-AIDS-defining complications, such as HIV-associated kidney disease. Sustained viral suppression and immune recovery may also delay or prevent other disorders, such as liver disease, cardiovascular disease, and malignancies, as discussed below.

HIV-associated nephropathy (HIVAN)

HIVAN is the most common cause of chronic kidney disease in HIV-infected individuals that may lead to end-stage kidney disease *[13]*. HIVAN is seen almost exclusively in black patients and can occur at any CD4 count. Ongoing viral replication appears to be directly involved in renal injury *[14]*. HIVAN is extremely uncommon in virologically suppressed patients *[15]*. ART in patients with HIVAN has been associated with both preserved renal function and prolonged survival *[16-18]* and therefore should be started in these patients **(AII)**.

Coinfection with hepatitis B virus (HBV) and/or hepatitis C virus (HCV)

HIV infection is associated with more rapid progression of viral hepatitis-related liver disease, including cirrhosis, end-stage liver disease, hepatocellular carcinoma, and fatal hepatic failure *[19-20]*. Although the mechanisms of accelerated liver disease in HIV-infected patients have not been fully elucidated, HIV-related immunodeficiency and a direct interaction of HIV with hepatic stellate and Kupffer cells have been implicated *[21-24]*. ART may attenuate liver disease progression in persons coinfected with HBV and/or HCV by preserving or restoring immune function and reducing HIV-related immune activation and inflammation *[25-27]*. ARV drugs active against both HIV and HBV (e.g., tenofovir disoproxil fumarate [TDF], lamivudine [3TC], emtricitabine [FTC]) may also prevent the development of significant liver disease by directly suppressing HBV replication *[28-29]*. Although ARV drugs do not directly inhibit HCV replication, HCV treatment outcomes may be improved if HIV replication is controlled or if CD4 counts are increased *[30]*. The presence of chronic viral hepatitis increases the risk of ARV-induced liver injury; however, the majority of coinfected persons do not develop clinically significant liver injury, particularly those receiving recommended ARV regimens *[31-33]*. Some studies suggest that the rate of hepatotoxicity is greater in persons with more advanced HIV disease. Nevirapine (NVP) toxicity is a notable exception: the hypersensitivity reaction and associated hepatotoxicity to this drug are more frequent in patients with higher CD4 cell counts *[34]*. Collectively, these data suggest earlier treatment of HIV infection in persons coinfected with HBV, and possibly HCV **(CIII)**, may reduce the risk of liver disease progression. Furthermore, ART including drugs active against both HIV and HBV should be started in all patients coinfected with HBV who are also going to receive HBV treatment **(AIII)**.

Cardiovascular disease

Cardiovascular disease is a major cause of mortality among HIV-infected patients, accounting for a third of serious non-AIDS conditions and at least 10% of deaths among HIV-infected patients *[35-36]*. Studies link exposure to specific ARV drugs to a higher risk of cardiovascular disease *[37-38]*. Certain HIV treatment regimens are associated with a more atherogenic lipid profile as assessed by lipoprotein particle size analysis among HIV-infected men compared with uninfected controls *[39]*. Untreated HIV infection may also be associated with an increased risk of cardiovascular disease. In some cross-sectional studies, patients with HIV have higher levels of markers of inflammation and endothelial dysfunction than HIV-uninfected controls *[40-42]*. In two randomized trials, markers of inflammation and coagulation increased following treatment interruption *[43-44]*. One study suggests that ART may improve endothelial function *[45]*.

In the SMART study, the risk of cardiovascular events was greater in participants randomized to CD4-guided treatment interruption compared with participants who received continuous ART *[46]*. In other studies, ART resulted in marked improvement in parameters associated with cardiovascular diseases, including markers of inflammation (e.g., interleukin 6 [IL-6] and high sensitivity C-reactive protein [hsCRP]) and endothelial dysfunction *[41, 45]*. There is also a modest association between lower CD4 count while on therapy and short-term risk of cardiovascular disease

[42, 47-48]. However, in at least one of these cohorts (the CASCADE study), the link between CD4 count and fatal cardiovascular events was no longer statistically significant when adjusting for plasma HIV RNA level. Collectively, the data linking viremia and endothelial dysfunction and inflammation, the increased risk of cardiovascular events with treatment interruption, and the association between cardiovascular disease and CD4 cell depletion suggest that early control of HIV replication with ART can be used as a strategy to reduce cardiovascular disease risk **(BIII)**.

Malignancies

Several population-based analyses suggest increased incidence of non-AIDS-associated malignancies during chronic HIV infection. The incidence of non-AIDS malignancy in HIV-infected subjects is higher than in matched HIV-uninfected controls *[49]*. Large cohort studies of mostly patients receiving ART have reported a consistent link between low CD4 counts (<350–500 cells/mm^3) and the risk of AIDS- and/or non-AIDS-defining malignancy *[42, 47, 50-53]*. The ANRS C04 Study demonstrated a statistically significant relative risk of all cancers evaluated (except for anal carcinoma) in patients with CD4 counts <500 cells/mm^3 compared with patients with current CD4 counts >500 cells/mm^3 and a protective effect of ART for HIV-associated malignancies *[50]*. This potential effect of HIV-associated immunodeficiency is particularly striking with regard to cancers associated with chronic viral infections (e.g., HBV, HCV, human papilloma virus [HPV], Epstein-Barr virus [EBV], human herpes virus-8 [HHV-8]) *[54-55]*. Cumulative HIV viremia itself may also be associated with the risk of non-Hodgkin lymphoma and other AIDS-defining malignancies, independent of other factors *[53, 56]*. Together this evidence suggests that initiating ART to suppress HIV replication and maintain CD4 counts at above 350–500 cells/mm^3 may reduce the risk of both AIDS-defining and non-AIDS-defining malignancies **(CIII)**.

Neurocognitive decline

Early in the HIV epidemic, HIV was identified in brain tissue *[57]* and assumed to be the cause of AIDS dementia complex *[58]*. The improvement of AIDS dementia complex symptoms with the use of ART supported this assumption *[59-60]*. The CASCADE observational cohort reported a dramatic decline in the incidence of HIV-associated dementia from 6.49 per 1,000 person-years (before 1997) to 0.66 per 1,000 person-years (2003–2006), after the widespread use of potent ART *[61]*. In this cohort, having a current CD4 count >350 cells/mm^3 was associated with the lowest risk of developing HIV-associated dementia. HIV infection has also been associated with a number of less severe neurologic complications, including changes in neuropsychological ability, speed of processing, and everyday functioning *[62]*. Such syndromes also were predicted by a lower pretherapy CD4 nadir and/or by CD4 count while on therapy *[63-64]*. Additional clinical data are needed to determine the relative roles of ongoing HIV replication and potential neurotoxicity of ARV agents in the development of neurocognitive dysfunction. Whether early initiation of therapy will prevent HIV-associated neurocognitive dysfunction remains unclear. However, the neurological complications that may accompany uncontrolled HIV replication and CD4 depletion suggest a potential benefit of earlier initiation of ART **(CIII)**.

Age and treatment-related immune reconstitution

The CD4 cell response to ART is an important predictor of short-term and long-term morbidity and mortality. Treatment initiation at an older age is consistently associated with a less robust CD4 count response; starting therapy at a younger age may result in better immunologic and perhaps clinical outcomes *[65-67]***(CIII)**.

T-cell activation and inflammation

Early untreated HIV infection is associated with sustained high-level inflammation and T-cell activation *[68-70]*. The degree of T-cell activation during untreated HIV disease is associated with risk of subsequent disease progression, independent of other factors such as plasma HIV RNA levels and the peripheral CD4 T-cell count *[71-72]*. ART results in a rapid, but often incomplete, decrease in most markers of HIV-associated immune activation *[73-77]*. Persistent T-cell activation and/or T-cell dysfunction is particularly evident among patients who delay therapy until later stage disease (CD4 count <350 cells/mm^3) *[74, 77-78]*. The degree of persistent inflammation during treatment, as represented by the levels of IL-6, may be independently associated with risk of death *[44]*. Collectively, these observations support earlier use of ART for at least two reasons. First, treatment decreases the level of inflammation and T-cell activation, which may be associated with reduced short-term risk of AIDS- and non-AIDS-related

morbidity and mortality *[44, 79-80]*. Second, because the degree of residual inflammation and/or T-cell dysfunction during ART appears to be higher in patients with lower CD4 cell nadirs *[74, 77-78]*, earlier treatment may result in less residual immunological perturbations on therapy, and hence less risk for AIDS- and non-AIDS-related complications **(CIII)**.

Prevention of HIV Transmission

Prevention of mother-to-child transmission

Effective ART reduces transmission of HIV. The most dramatic and well-established example of this effect is the use of ART in pregnant women to prevent mother-to-child transmission (MTCT) of HIV. Effective suppression of HIV replication, as reflected in plasma HIV RNA, is a key determinant in reducing perinatal transmission. In the United States, the use of combination ART during pregnancy has reduced the HIV transmission rate from approximately 20%–30% to <2% *[81]*. Thus, use of combination ARV drug regimens is recommended for all HIV-infected pregnant women to prevent MTCT of HIV **(AI)**, even if the mother does not meet the criteria for initiation of therapy for treatment of her HIV infection. Following delivery, considerations regarding continuation of the ARV regimen for maternal therapeutic indications are the same as for other nonpregnant individuals. For detailed recommendations, see ***Perinatal Guidelines*** *[82]*.

Prevention of sexual transmission

Emerging evidence supports the concept of "treatment as prevention" of sexual transmission of HIV. Lower plasma HIV RNA levels are associated with decreases in the concentration of the virus in genital secretions *[83-84]*. Studies of HIV serodiscordant heterosexual couples have demonstrated a relationship between the level of plasma viremia and HIV transmission risk: when plasma HIV RNA levels are lower, transmission events are less common *[85-89]*. These investigations, as well as other observational studies and modeling analyses demonstrating a decreased rate of HIV transmission among serodiscordant heterosexual couples following the introduction of ART, suggest that suppression of viremia in ART-adherent patients with no concomitant sexually transmitted infections (STIs) substantially reduces the risk of HIV transmission *[88-93]*. Based on these studies, the use of effective ART regardless of CD4 count is likely to reduce transmission to the uninfected sexual partner **(BII)**.

POTENTIAL LIMITATIONS OF EARLIER INITIATION OF THERAPY

Although there are benefits associated with earlier initiation of ART, there are also potential limitations to this approach. Concerns about long-term toxicity and the development of ARV resistance have served as a rationale for the deferral of HIV therapy. Earlier initiation of ART at higher CD4 counts (e.g., >500 cells/mm^3) results in greater cumulative time on therapy. Assuming treatment for many decades after initiation, the additional therapy represents a small percentage of the total time on ART for most patients.

Although newer ARV regimens are generally better tolerated, more convenient, and more potent than older regimens, there are fewer longer term safety data for the newer agents. Analyses supporting ART initiation at CD4 counts >350 cells/mm^3 (e.g., NA-ACCORD and ART-CC) were conducted with cohorts largely treated with regimens less commonly used in clinical practice. These studies reported on clinical endpoints of death and/or AIDS disease progression but lacked information on drug toxicities, resistance, or adherence. Therefore, in considering earlier initiation of therapy, concerns for some adverse consequences of ART remain.

Antiretroviral Drug Toxicities and Quality of Life

Earlier initiation of ART extends exposure to ARV agents by several years. The D:A:D study found an increased incidence of cardiovascular disease associated with cumulative exposure to some drugs within the nucleoside reverse transcriptase inhibitor (NRTI) and protease inhibitor (PI) classes *[38, 94]*. In the SMART study, continuous exposure to ART has been associated with significantly greater loss of bone density compared with interruption or deferral of therapy *[46]*. There may be unknown complications related to cumulative use of ARV drugs for many decades. A list of known ARV-associated toxicities can be found in **Adverse Effects of Antiretroviral Agents**.

Although ART frequently improves quality of life among symptomatic patients, it may also be associated with reduced quality of life in some patients, especially those who are asymptomatic at initiation of therapy. Although better tolerated and easier to administer than older drugs, most ARV drugs now used in first-line regimens can cause side effects that may reduce quality of life. Efavirenz (EFV), for example, can cause neurocognitive or psychiatric side effects, and all the PIs have been associated with gastrointestinal side effects. Furthermore, some patients may find that the inconvenience of taking medication every day outweighs the overall benefit and might choose to delay therapy whenever possible.

Drug Resistance

Very early treatment initiation may lead to an earlier onset of drug resistance selection in nonadherent patients. The consequent harm is loss of important drugs or drug classes and risk of transmission of drug-resistant HIV. Some asymptomatic patients may be less motivated to remain adherent to their HIV treatment regimens if treatment is initiated far in advance of an immediate risk of HIV-associated morbidity and mortality. The greater convenience and potency of current ARV regimens facilitate adherence and reduce the risk of ARV resistance. One study suggests that the risk of drug resistance at the time of virologic failure is lower among patients who initiated treatment at higher CD4 counts *[95]*. Treatment adherence is key to viral suppression and should be stressed prior to initiation of therapy and during follow-up visits.

Nonadherence to Antiretroviral Therapy

At any CD4 count, adherence to therapy is essential to achieve viral suppression and prevent emergence of resistance mutations. Several behavioral and social factors associated with poor adherence, such as untreated major psychiatric disorders, active substance abuse, social circumstances, patient concerns about side effects, and poor adherence to clinic visits, have been identified. Clinicians should identify areas where additional intervention is needed to improve adherence both before and after initiation of therapy. Some strategies to improve adherence are discussed in **Adherence.**

Cost

Although ART adds to the annual cost of treatment, several modeling studies support the cost effectiveness of HIV therapy initiated soon after diagnosis *[96-98]*. Studies have reported that the annual cost of care is 2½ times higher for patients with CD4 counts <50 cells/mm^3 compared with patients with CD4 counts >350 cells/mm^3 *[99]*. A large proportion of the health care expenditure in patients with advanced infection is from non-ARV drugs and hospitalization. However, no cost comparisons have been reported between those starting ART with a CD4 count between 350 and 500 cells/mm^3 versus >500 cells/ mm^3.

SUMMARY

In earlier versions of these treatment guidelines, concerns about long-term toxicity, reduced quality of life, and the potential for drug resistance served as key reasons to defer HIV therapy for as long as possible. Inherent in this argument was the assumption that the harm associated with viral replication was less than the harm associated with the toxicities of ARV drugs in patients with higher CD4 counts. There is now more evidence that untreated HIV infection has negative consequences on health at all stages of disease. Also, the drug combinations now available are better tolerated than previous regimens, leading to greater efficacy and improved adherence *[100]*. The current guidelines therefore emphasize avoiding adverse consequences of untreated HIV infection while managing potential drug toxicity.

RECOMMENDATIONS

Based on the cumulative weight of evidence described above, the Panel recommends that:

- ART should be initiated in all patients with a history of an AIDS-defining illness or with a CD4 count of <350 cells/mm^3 **(AI)**.
- ART is also recommended for patients with CD4 counts between 350 and 500 cells/mm^3 **(A/B-II)**.*
- ART should also be initiated, regardless of CD4 count, in patients with the following conditions: HIVAN **(AII)** and HBV coinfection when treatment of HBV is indicated **(AIII)**.
- A combination ARV drug regimen is also recommended for pregnant women who do not meet criteria for treatment with the goal to prevent perinatal transmission **(AI)**.
- For patients with CD4 counts >500 cells/mm^3, 50% of the Panel members favor starting ART (B); the other 50% of members view treatment as optional (C) in this setting **(B/C-III)**.
- Patients initiating ART should be willing and able to commit to lifelong treatment and should understand the benefits and risks of therapy and the importance of adherence (**AIII**).
- Patients may choose to postpone therapy, and providers, on a case-by-case basis, may elect to defer therapy based on clinical and/or psychosocial factors.

* The Panel is divided on the strength of this recommendation: 55% of Panel members voted for strong recommendation **(A)** and 45% voted for moderate recommendation **(B)**.

Conditions Favoring More Rapid Initiation of Therapy

Deferring ART may be appropriate in some cases. However, several conditions increase the urgency for therapy, including:

- Pregnancy **(AI)** (Clinicians should refer to the ***Perinatal Guidelines*** for more detailed recommendations for the management of HIV-infected pregnant women.) *[82]*
- AIDS-defining conditions **(AI)**
- Acute opportunistic infections (see discussion below)
- Lower CD4 counts (e.g., <200 cells/mm^3) **(AI)**
- Rapidly declining CD4 counts (e.g., >100 cells/mm^3 decrease per year) **(AIII)**
- Higher viral loads (e.g., >100,000 copies/mL) **(BII)**
- HIVAN **(AII)**
- HBV coinfection when treatment for HBV is indicated **(AIII)**

Acute opportunistic infections

In patients with opportunistic conditions for which there is no effective therapy (e.g., cryptosporidiosis, microsporidiosis, progressive multifocal leukoencephalopathy) but for which ART may improve outcomes by improving immune responses, the benefits of ART outweigh any increased risk, and therefore treatment should be started as soon as possible **(AIII)**.

In the setting of opportunistic infections, such as cryptococcal meningitis or non-tuberculous mycobacterial infections, for which immediate therapy may increase the risk of immune reconstitution inflammatory syndrome (IRIS), a short delay may be warranted before initiating ART *[101-102]* **(CIII)**.

In the setting of other opportunistic infections, such as *Pneumocystis jiroveci* pneumonia (PCP), early initiation of ART is associated with increased survival, and therapy should not be delayed *[3]* **(AI)**.

In patients who have active tuberculosis, initiating ART within the first 1–2 months of treatment for tuberculosis appears to confer a significant survival advantage *[103-104]*. (See ***Mycobacterium Tuberculosis* Disease with HIV Coinfection**.)

Clinicians should refer to the ***Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents*** *[105]* for more detailed discussion on when to initiate ART in the setting of a specific opportunistic infection.

Conditions Where Deferral of Therapy Might be Considered

Some patients and their clinicians may decide to defer therapy for a period of time based on clinical or personal circumstances. The degree to which these factors might argue for deferral of therapy depends on the CD4 count and viral load. Although deferring therapy for the reasons discussed below may be reasonable for patients with high CD4 counts (e.g., >500 cells/mm^3), deferral for patients with much lower CD4 counts (e.g., <200 cells/mm^3) should be considered only in rare situations and should be undertaken with close clinical follow-up. A brief delay in initiating therapy may be considered to allow a patient more time to prepare for lifelong treatment.

When there are significant barriers to adherence

Deferring treatment for patients with higher CD4 counts who are at risk of poor adherence may be prudent while the barriers to adherence are being addressed. However, increased urgency for ART (see above) may override potential predictors of poor adherence.

Several methodologies exist to help providers assess adherence. When the most feasible measure of adherence is self-report, this assessment should be completed at each clinic visit, using one of the available reliable and valid instruments *[106-107]*. If other objective measures are available (e.g., pharmacy refill data, pill count), these methods should also be implemented as therapy begins *[108-110]*. Continuous assessment and counseling make it possible for the clinician to intervene early to address barriers to adherence occurring at any point during treatment.

Presence of comorbidities that complicate or prohibit antiretroviral therapy

Deferral of ART may be considered when either the treatment or manifestations of other medical conditions could complicate the treatment of HIV infection or vice versa. Examples include:

- Patients requiring surgery that might result in an extended interruption of ART.
- Patients taking medications that have clinically significant drug interactions with ART and for whom alternative therapy is not available.

In each of these cases, it is assumed that the situation is temporary and that ART will be initiated after the conflicting condition has resolved.

There are some less common situations in which ART may not be indicated at any time while CD4 counts remain high. In particular, such situations include patients with a poor prognosis due to a concomitant medical condition who would not be expected to gain survival or quality-of-life benefits from ART. Examples include patients with incurable non-HIV-related malignancies or end-stage liver disease who are not being considered for liver transplantation. The decision to forego ART in such patients may be easier in those with higher CD4 counts; they are likely asymptomatic for HIV, and their survival is unlikely to be prolonged by ART. However, it should be noted that ART may improve outcomes, including survival, in patients with some HIV-associated malignancies (e.g., lymphoma or Kaposi's sarcoma) and in patients with liver disease due to chronic HBV or HCV.

Elite HIV controllers or long-term nonprogressors

A small subset of ARV-untreated HIV-infected persons (~3%–5%) are able to maintain normal CD4 cell counts for many years (long-term nonprogressors), while an even smaller subset (~1%) are able to maintain suppressed viral loads for years (elite controllers). It is possible that such patients would not benefit from ART. However, some nonprogressors have high viral loads, and some elite controllers progress clinically or immunologically *[111-112]*. Although therapy may be theoretically beneficial for patients in either group, clinical data supporting therapy for nonprogressors and elite controllers are lacking.

THE NEED FOR EARLY DIAGNOSIS OF HIV

Fundamental to the earlier initiation of therapy recommended in these guidelines is the assumption that patients will be diagnosed early in the course of HIV infection, making earlier initiation of therapy an option. Unfortunately, most HIV-infected patients are not diagnosed until they are at much later stages of disease *[113-116]*. Despite the 2006 Centers for Disease Control and Prevention (CDC) recommendations for routine, opt-out HIV screening in the health care setting *[117]* regardless of perceived risk of infection, the median CD4 count for newly diagnosed patients remains in the ~200 cells/mm^3 range. (The exception is pregnant women diagnosed during prenatal care, who have a much higher median initial CD4 count.) Delay in HIV diagnosis is more often seen in nonwhites, injection drug users, and older patients; a substantial proportion of these individuals develop AIDS-defining illnesses within 1 year of diagnosis *[113-116]*. Therefore, for the current treatment guidelines to have maximum impact, routine HIV screening per current CDC recommendations is essential. It is critical that all newly diagnosed patients be educated about HIV disease and linked to care for full evaluation, follow-up, and management. Once in care, focused effort is required to retain patients in the health care system.

CONCLUSION

The current recommendations are based on increasing evidence that supports earlier initiation of ART than was advocated in previous guidelines. The strength of the recommendations varies with the quality and availability of existing evidence. Panel members are divided regarding the strength of recommendations for starting therapy in patients with higher CD4 cell counts, as discussed above. The Panel will continue to monitor and assess the results of ongoing and planned randomized clinical trials and observational studies, which will provide the Panel with additional guidance to form future recommendations.

References

1. HIV Trialists' Collaborative Group. Zidovudine, didanosine, and zalcitabine in the treatment of HIV infection: meta-analyses of the randomised evidence. *Lancet.* 1999;353(9169):2014-2025.
2. Hammer SM, Squires KE, Hughes MD, et al. A controlled trial of two nucleoside analogues plus indinavir in persons with human immunodeficiency virus infection and CD4 cell counts of 200 per cubic millimeter or less. AIDS Clinical Trials Group 320 Study Team. *N Engl J Med.* 1997;337(11):725-733.
3. Zolopa A, Andersen J, Powderly W, et al. Early antiretroviral therapy reduces AIDS progression/death in individuals with acute opportunistic infections: a multicenter randomized strategy trial. *PLoS One.* 2009;4(5):e5575.
4. Mocroft A, Vella S, Benfield TL, et al. Changing patterns of mortality across Europe in patients infected with HIV-1. EuroSIDA Study Group. *Lancet.* 1998;352(9142):1725-1730.
5. Hogg RS, Yip B, Chan KJ, et al. Rates of disease progression by baseline CD4 cell count and viral load after initiating triple-drug therapy. *JAMA.* 2001;286(20):2568-2577.
6. Sterne JA, May M, Costagliola D, et al. Timing of initiation of antiretroviral therapy in AIDS-free HIV-1-infected patients: a collaborative analysis of 18 HIV cohort studies. *Lancet.* 2009;373(9672):1352-1363.
7. Baker JV, Peng G, Rapkin J, et al. CD4+ count and risk of non-AIDS diseases following initial treatment for HIV infection. *AIDS.* 2008;22(7):841-848.
8. Palella FJ, Jr., Deloria-Knoll M, Chmiel JS, et al. Survival benefit of initiating antiretroviral therapy in HIV-infected persons in different CD4+ cell strata. *Ann Intern Med.* 2003;138(8):620-626.
9. Severe P, Juste MA, Ambroise A, et al. Early versus standard antiretroviral therapy for HIV-infected adults in Haiti. *N Engl J Med.* 2010;363(3):257-265.
10. Emery S, Neuhaus JA, Phillips AN, et al. Major clinical outcomes in antiretroviral therapy (ART)-naive participants and in those not receiving ART at baseline in the SMART study. *J Infect Dis.* 2008;197(8):1133-1144.
11. May M, Sterne JA, Sabin C, et al. Prognosis of HIV-1-infected patients up to 5 years after initiation of HAART: collaborative analysis of prospective studies. *AIDS.* 2007;21(9):1185-1197.
12. Kitahata MM, Gange SJ, Abraham AG, et al. Effect of early versus deferred antiretroviral therapy for HIV on survival. *N Engl J Med.* 2009;360(18):1815-1826.
13. Szczech LA, Gupta SK, Habash R, et al. The clinical epidemiology and course of the spectrum of renal diseases associated with HIV infection. *Kidney Int.* 2004;66(3):1145-1152.
14. Marras D, Bruggeman LA, Gao F, et al. Replication and compartmentalization of HIV-1 in kidney epithelium of patients with HIV-associated nephropathy. *Nat Med.* 2002;8(5):522-526.
15. Estrella M, Fine DM, Gallant JE, et al. HIV type 1 RNA level as a clinical indicator of renal pathology in HIV-infected patients. *Clin Infect Dis.* 2006;43(3):377-380.

16. Atta MG, Gallant JE, Rahman MH, et al. Antiretroviral therapy in the treatment of HIV-associated nephropathy. *Nephrol Dial Transplant.* 2006;21(10):2809-2813.
17. Schwartz EJ, Szczech LA, Ross MJ, et al. Highly active antiretroviral therapy and the epidemic of HIV+ end-stage renal disease. *J Am Soc Nephrol.* 2005;16(8):2412-2420.
18. Kalayjian RC, Franceschini N, Gupta SK, et al. Suppression of HIV-1 replication by antiretroviral therapy improves renal function in persons with low CD4 cell counts and chronic kidney disease. *AIDS.* 2008;22(4):481-487.
19. Thein HH, Yi Q, Dore GJ, et al. Natural history of hepatitis C virus infection in HIV-infected individuals and the impact of HIV in the era of highly active antiretroviral therapy: a meta-analysis. *AIDS.* 2008;22(15):1979-1991.
20. Thio CL, Seaberg EC, Skolasky R, Jr., et al. HIV-1, hepatitis B virus, and risk of liver-related mortality in the Multicenter Cohort Study (MACS). *Lancet.* 2002;360(9349):1921-1926.
21. Weber R, Sabin CA, Friis-Moller N, et al. Liver-related deaths in persons infected with the human immunodeficiency virus: the D:A:D study. *Arch Intern Med.* 2006;166(15):1632-1641.
22. Balagopal A, Philp FH, Astemborski J, et al. Human immunodeficiency virus-related microbial translocation and progression of hepatitis C. *Gastroenterology.* 2008;135(1):226-233.
23. Blackard JT, Kang M, St Clair JB, et al. Viral factors associated with cytokine expression during HCV/HIV co-infection. *J Interferon Cytokine Res.* 2007;27(4):263-269.
24. Hong F, Tuyama A, Lee TF, et al. Hepatic stellate cells express functional CXCR4: role in stromal cell-derived factor-1alpha-mediated stellate cell activation. *Hepatology.* 2009;49(6):2055-2067.
25. Macias J, Berenguer J, Japon MA, et al. Fast fibrosis progression between repeated liver biopsies in patients coinfected with human immunodeficiency virus/hepatitis C virus. *Hepatology.* 2009;50(4):1056-1063.
26. Verma S, Goldin RD, Main J. Hepatic steatosis in patients with HIV-Hepatitis C Virus coinfection: is it associated with antiretroviral therapy and more advanced hepatic fibrosis? *BMC Res Notes.* 2008;1:46.
27. Ragni MV, Nalesnik MA, Schillo R, et al. Highly active antiretroviral therapy improves ESLD-free survival in HIV-HCV co-infection. *Haemophilia.* 2009;15(2):552-558.
28. Matthews GV, Avihingsanon A, Lewin SR, et al. A randomized trial of combination hepatitis B therapy in HIV/HBV coinfected antiretroviral naive individuals in Thailand. *Hepatology.* 2008;48(4):1062-1069.
29. Peters MG, Andersen J, Lynch P, et al. Randomized controlled study of tenofovir and adefovir in chronic hepatitis B virus and HIV infection: ACTG A5127. *Hepatology.* 2006;44(5):1110-1116.
30. Avidan NU, Goldstein D, Rozenberg L, et al. Hepatitis C viral kinetics during treatment with peg IFN-alpha-2b in HIV/HCV coinfected patients as a function of baseline CD4+ T-cell counts. *J Acquir Immune Defic Syndr.* 2009;52(4):452-458.
31. Clotet B, Bellos N, Molina JM, et al. Efficacy and safety of darunavir-ritonavir at week 48 in treatment-experienced patients with HIV-1 infection in POWER 1 and 2: a pooled subgroup analysis of data from two randomised trials. *Lancet.* 2007;369(9568):1169-1178.
32. Steigbigel RT, Cooper DA, Kumar PN, et al. Raltegravir with optimized background therapy for resistant HIV-1 infection. *N Engl J Med.* 2008;359(4):339-354.
33. Molina JM, Andrade-Villanueva J, Echevarria J, et al. Once-daily atazanavir/ritonavir compared with twice-daily lopinavir/ritonavir, each in combination with tenofovir and emtricitabine, for management of antiretroviral-naive HIV-1-infected patients: 96-week efficacy and safety results of the CASTLE study. *J Acquir Immune Defic Syndr.* 2010;53(3):323-332.
34. van Leth F, Andrews S, Grinsztejn B, et al. The effect of baseline CD4 cell count and HIV-1 viral load on the efficacy and safety of nevirapine or efavirenz-based first-line HAART. *AIDS.* 2005;19(5):463-471.
35. Smith C. Factors associated with specific causes of death amongst HIV-positive individuals in the D:A:D Study. *AIDS.* 2010;24(10):1537-1548.
36. Mocroft A, Reiss P, Gasiorowski J, et al. Serious fatal and nonfatal non-AIDS-defining illnesses in Europe. *J Acquir Immune Defic Syndr.* 2010;55(2):262-270.
37. Sabin CA, Worm SW, Weber R, et al. Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients enrolled in the D:A:D study: a multi-cohort collaboration. *Lancet.* 2008;371(9622):1417-1426.
38. Friis-Moller N, Reiss P, Sabin CA, et al. Class of antiretroviral drugs and the risk of myocardial infarction. *N Engl J Med.* 2007;356(17):1723-1735.
39. Riddler SA, Li X, Otvos J, et al. Antiretroviral therapy is associated with an atherogenic lipoprotein phenotype among HIV-1-infected men in the Multicenter AIDS Cohort Study. *J Acquir Immune Defic Syndr.* 2008;48(3):281-288.
40. Ross AC, Armentrout R, O'Riordan MA, et al. Endothelial activation markers are linked to HIV status and are independent of antiretroviral therapy and lipoatrophy. *J Acquir Immune Defic Syndr.* 2008;49(5):499-506.
41. McComsey G, Smith K, Patel P, et al. Similar reductions in markers of inflammation and endothelial activation after initiation of abacavir/lamivudine or tenofovir/emtricitabine: The HEAT Study. Paper presented at: 16th Conference on Retroviruses and Opportunistic Infections; 2009; Montreal, Canada.
42. Baker JV, Duprez D, Rapkin J, et al. Untreated HIV infection and large and small artery elasticity. *J Acquir Immune Defic Syndr.* 2009;52(1):25-31.
43. Calmy A, Gayet-Ageron A, Montecucco F, et al. HIV increases markers of cardiovascular risk: results from a randomized, treatment interruption trial. *AIDS.* 2009;23(8):929-939.
44. Kuller LH, Tracy R, Belloso W, et al. Inflammatory and coagulation biomarkers and mortality in patients with HIV infection. *PLoS Med.* 2008;5(10):e203.
45. Torriani FJ, Komarow L, Parker RA, et al. Endothelial function in human immunodeficiency virus-infected antiretroviral-naive subjects before and after starting potent antiretroviral therapy: The ACTG (AIDS Clinical Trials Group) Study 5152s. *J Am Coll Cardiol.* 2008;52(7):569-576.

46. El-Sadr WM, Lundgren JD, Neaton JD, et al. CD4+ count-guided interruption of antiretroviral treatment. *N Engl J Med.* 2006;355(22):2283-2296.
47. Marin B, Thiebaut R, Bucher HC, et al. Non-AIDS-defining deaths and immunodeficiency in the era of combination antiretroviral therapy. *AIDS.* 2009;23(13):1743-1753.
48. Phillips AN, Neaton J, Lundgren JD. The role of HIV in serious diseases other than AIDS. *AIDS.* 2008;22(18):2409-2418.
49. Bedimo RJ, McGinnis KA, Dunlap M, et al. Incidence of non-AIDS-defining malignancies in HIV-infected versus noninfected patients in the HAART era: impact of immunosuppression. *J Acquir Immune Defic Syndr.* 2009.
50. Guiguet M, Boue F, Cadranel J, et al. Effect of immunodeficiency, HIV viral load, and antiretroviral therapy on the risk of individual malignancies (FHDH-ANRS CO4): a prospective cohort study. *Lancet Oncol.* 2009.
51. Monforte A, Abrams D, Pradier C, et al. HIV-induced immunodeficiency and mortality from AIDS-defining and non-AIDS-defining malignancies. *AIDS.* 2008;22(16):2143-2153.
52. Reekie J, Mocroft A, Engsig F, et al. Relationship between current level of immunodeficiency and non-AIDS-defining malignancies. Paper presented at: 16th Conference on Retroviruses and Opportunistic Infections; February, 2009; Montreal, Canada. Abstract 860a.
53. Bruyand M, Thiebaut R, Lawson-Ayayi S, et al. Role of uncontrolled HIV RNA level and immunodeficiency in the occurrence of malignancy in HIV-infected patients during the combination antiretroviral therapy era: Agence Nationale de Recherche sur le Sida (ANRS) CO3 Aquitaine Cohort. *Clin Infect Dis.* 2009;49(7):1109-1116.
54. Silverberg MJ, Chao C, Leyden WA, et al. HIV infection and the risk of cancers with and without a known infectious cause. *AIDS.* 2009;23(17):2337-2345.
55. Grulich AE, van Leeuwen MT, Falster MO, et al. Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis. *Lancet.* 2007;370(9581):59-67.
56. Zoufaly A, Stellbrink HJ, Heiden MA, et al. Cumulative HIV viremia during highly active antiretroviral therapy is a strong predictor of AIDS-related lymphoma. *J Infect Dis.* 2009;200(1):79-87.
57. Shaw GM, Harper ME, Hahn BH, et al. HTLV-III infection in brains of children and adults with AIDS encephalopathy. *Science.* 1985;227(4683):177-182.
58. Janssen RS, Nwanyanwu OC, Selik RM, et al. Epidemiology of human immunodeficiency virus encephalopathy in the United States. *Neurology.* 1992;42(8):1472-1476.
59. Schmitt FA, Bigley JW, McKinnis R, et al. Neuropsychological outcome of zidovudine (AZT) treatment of patients with AIDS and AIDS-related complex. *N Engl J Med.* 1988;319(24):1573-1578.
60. Robertson KR, Robertson WT, Ford S, et al. Highly active antiretroviral therapy improves neurocognitive functioning. *J Acquir Immune Defic Syndr.* 2004;36(1):562-566.
61. Bhaskaran K, Mussini C, Antinori A, et al. Changes in the incidence and predictors of human immunodeficiency virus-associated dementia in the era of highly active antiretroviral therapy. *Ann Neurol.* 2008;63(2):213-221.
62. Vance D, Wadley V, Crowe M, et al. Cognitive and everyday functioning in younger and older adults with and without HIV (in press). *Clinical Gerontologist.*
63. Robertson KR, Smurzynski M, Parsons TD, et al. The prevalence and incidence of neurocognitive impairment in the HAART era. *AIDS.* 2007;21(14):1915-1921.
64. Munoz-Moreno JA, Fumaz CR, Ferrer MJ, et al. Nadir CD4 cell count predicts neurocognitive impairment in HIV-infected patients. *AIDS Res Hum Retroviruses.* 2008;24(10):1301-1307.
65. The Collaboration of Observational HIV Epidemiological Research Europe (COHERE) study group. Response to combination antiretroviral therapy: variation by age. *AIDS.* 2008;22(12):1463-1473.
66. Nogueras M, Navarro G, Anton E, et al. Epidemiological and clinical features, response to HAART, and survival in HIV-infected patients diagnosed at the age of 50 or more. *BMC Infect Dis.* 2006;6:159.
67. Bosch RJ, Bennett K, Collier AC, et al. Pretreatment factors associated with 3-year (144-week) virologic and immunologic responses to potent antiretroviral therapy. *J Acquir Immune Defic Syndr.* 2007;44(3):268-277.
68. Fahey JL, Taylor JM, Detels R, et al. The prognostic value of cellular and serologic markers in infection with human immunodeficiency virus type 1. *N Engl J Med.* 1990;322(3):166-172.
69. Giorgi JV, Lyles RH, Matud JL, et al. Predictive value of immunologic and virologic markers after long or short duration of HIV-1 infection. *J Acquir Immune Defic Syndr.* 2002;29(4):346-355.
70. Deeks SG, Kitchen CM, Liu L, et al. Immune activation set point during early HIV infection predicts subsequent CD4+ T-cell changes independent of viral load. *Blood.* 2004;104(4):942-947.
71. Giorgi JV, Hultin LE, McKeating JA, et al. Shorter survival in advanced human immunodeficiency virus type 1 infection is more closely associated with T lymphocyte activation than with plasma virus burden or virus chemokine coreceptor usage. *J Infect Dis.* 1999;179(4):859-870.
72. Hazenberg MD, Otto SA, van Benthem BH, et al. Persistent immune activation in HIV-1 infection is associated with progression to AIDS. *AIDS.* 2003;17(13):1881-1888.
73. Gandhi RT, Spritzler J, Chan E, et al. Effect of baseline- and treatment-related factors on immunologic recovery after initiation of antiretroviral therapy in HIV-1-positive subjects: results from ACTG 384. *J Acquir Immune Defic Syndr.* 2006;42(4):426-434.
74. Hunt PW, Martin JN, Sinclair E, et al. T cell activation is associated with lower CD4+ T cell gains in human immunodeficiency virus-infected patients with sustained viral suppression during antiretroviral therapy. *J Infect Dis.* 2003;187(10):1534-1543.
75. Neuhaus J, Jacobs DR, Jr., Baker JV, et al. Markers of inflammation, coagulation, and renal function are elevated in adults with HIV infection. *J Infect Dis.* 2010;201(12):1788-1795.
76. Valdez H, Connick E, Smith KY, et al. Limited immune restoration after 3 years' suppression of HIV-1 replication in patients with moderately advanced disease. *AIDS.* 2002;16(14):1859-1866.

77. Robbins GK, Spritzler JG, Chan ES, et al. Incomplete reconstitution of T cell subsets on combination antiretroviral therapy in the AIDS Clinical Trials Group protocol 384. *Clin Infect Dis.* 2009;48(3):350-361.
78. Lange CG, Lederman MM, Medvik K, et al. Nadir CD4+ T-cell count and numbers of CD28+ CD4+ T-cells predict functional responses to immunizations in chronic HIV-1 infection. *AIDS.* 2003;17(14):2015-2023.
79. Palella FJ, Jr., Gange SJ, Benning L, et al. Inflammatory biomarkers and abacavir use in the Women's Interagency HIV Study and the Multicenter AIDS Cohort Study. *AIDS.* 2010;24(11):1657-1665.
80. Rodger AJ, Fox Z, Lundgren JD, et al. Activation and coagulation biomarkers are independent predictors of the development of opportunistic disease in patients with HIV infection. *J Infect Dis.* 2009;200(6):973-983.
81. Centers for Disease Control and Prevention (CDC). Achievements in public health. Reduction in perinatal transmission of HIV infection--United States, 1985-2005. *MMWR Morb Mortal Wkly Rep.* 2006;55(21):592-597.
82. Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission. Recommendations for use of antiretroviral drugs in pregnant HIV-1-infected women for maternal health and interventions to reduce perinatal HIV transmission in the United States. May 24, 2010:1-117. http://aidsinfo.nih.gov/contentfiles/PerinatalGL.pdf.
83. Vernazza PL, Troiani L, Flepp MJ, et al. Potent antiretroviral treatment of HIV-infection results in suppression of the seminal shedding of HIV. The Swiss HIV Cohort Study. *AIDS.* 2000;14(2):117-121.
84. Coombs RW, Reichelderfer PS, Landay AL. Recent observations on HIV type-1 infection in the genital tract of men and women. *AIDS.* 2003;17(4):455-480.
85. Quinn TC, Wawer MJ, Sewankambo N, et al. Viral load and heterosexual transmission of human immunodeficiency virus type 1. Rakai Project Study Group. *N Engl J Med.* 2000;342(13):921-929.
86. Tovanabutra S, Robison V, Wongtrakul J, et al. Male viral load and heterosexual transmission of HIV-1 subtype E in northern Thailand. *J Acquir Immune Defic Syndr.* 2002;29(3):275-283.
87. Kayitenkore K, Bekan B, Rufagari J, et al. The impact of ART on HIV transmission among HIV serodiscordant couples. Paper presented at: XVI International AIDS Conference; August 13-18, 2006; Toronto, Canada. Abstract MOKC101.
88. Reynolds S, Makumbi F, Kagaayi J, et al. ART reduced the rate of sexual transmission of HIV among HIV-discordant couples in rural Rakai, Uganda. Paper presented at: 16th Conference on Retroviruses and Opportunistic Infections; February 8-11, 2009; Montreal, Canada. Abstract 52a.
89. Sullivan P, Kayitenkore K, Chomba E, et al. Reduction of HIV transmission risk and high risk sex while prescribed ART: Results from discordant couples in Rwanda and Zambia. Paper presented at: 16th Conference on Retroviruses and Opportunistic Infections; February 8-11, 2009; Montreal, Canada. Abstract 52bLB.
90. Granich RM, Gilks CF, Dye C, et al. Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model. *Lancet.* 2009;373(9657):48-57.
91. Bunnell R, Ekwaru JP, Solberg P, et al. Changes in sexual behavior and risk of HIV transmission after antiretroviral therapy and prevention interventions in rural Uganda. *AIDS.* 2006;20(1):85-92.
92. Castilla J, Del Romero J, Hernando V, et al. Effectiveness of highly active antiretroviral therapy in reducing heterosexual transmission of HIV. *J Acquir Immune Defic Syndr.* 2005;40(1):96-101.
93. Wilson DP, Law MG, Grulich AE, et al. Relation between HIV viral load and infectiousness: a model-based analysis. *Lancet.* 2008;372(9635):314-320.
94. Worm SW, Sabin C, Weber R, et al. Risk of myocardial infarction in patients with HIV infection exposed to specific individual antiretroviral drugs from the 3 major drug classes: the data collection on adverse events of anti-HIV drugs (D:A:D) study. *J Infect Dis.* 2010;201(3):318-330.
95. Uy J, Armon C, Buchacz K, et al. Initiation of HAART at higher CD4 cell counts is associated with a lower frequency of antiretroviral drug resistance mutations at virologic failure. *J Acquir Immune Defic Syndr.* 2009;51(4):450-453.
96. Freedberg KA, Losina E, Weinstein MC, et al. The cost effectiveness of combination antiretroviral therapy for HIV disease. *N Engl J Med.* 2001;344(11):824-831.
97. Schackman BR, Goldie SJ, Weinstein MC, et al. Cost-effectiveness of earlier initiation of antiretroviral therapy for uninsured HIV-infected adults. *Am J Public Health.* 2001;91(9):1456-1463.
98. Mauskopf J, Kitahata M, Kauf T, et al. HIV antiretroviral treatment: early versus later. *J Acquir Immune Defic Syndr.* 2005;39(5):562-569.
99. Chen RY, Accortt NA, Westfall AO, et al. Distribution of health care expenditures for HIV-infected patients. *Clin Infect Dis.* 2006;42(7):1003-1010.
100. Willig JH, Abroms S, Westfall AO, et al. Increased regimen durability in the era of once-daily fixed-dose combination antiretroviral therapy. *AIDS.* 2008;22(15):1951-1960.
101. Bicanic T, Meintjes G, Rebe K, et al. Immune reconstitution inflammatory syndrome in HIV-associated cryptococcal meningitis: a prospective study. *J Acquir Immune Defic Syndr.* 2009;51(2):130-134.
102. Phillips P, Bonner S, Gataric N, et al. Nontuberculous mycobacterial immune reconstitution syndrome in HIV-infected patients: spectrum of disease and long-term follow-up. *Clin Infect Dis.* 2005;41(10):1483-1497.
103. Velasco M, Castilla V, Sanz J, et al. Effect of simultaneous use of highly active antiretroviral therapy on survival of HIV patients with tuberculosis. *J Acquir Immune Defic Syndr.* 2009;50(2):148-152.
104. Abdool Karim SS, Naidoo K, Grobler A, et al. Timing of initiation of antiretroviral drugs during tuberculosis therapy. *N Engl J Med.* 2010;362(8):697-706.
105. Kaplan JE, Benson C, Holmes KH, et al. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. *MMWR Recomm Rep.* 2009;58(RR-4):1-207.
106. Lu M, Safren SA, Skolnik PR, et al. Optimal recall period and response task for self-reported HIV medication adherence. *AIDS Behav.* 2008;12(1):86-94.

107. Simoni JM, Kurth AE, Pearson CR, et al. Self-report measures of antiretroviral therapy adherence: A review with recommendations for HIV research and clinical management. *AIDS Behav.* 2006;10(3):227-245.
108. Bisson GP, Gross R, Bellamy S, et al. Pharmacy refill adherence compared with CD4 count changes for monitoring HIV-infected adults on antiretroviral therapy. *PLoS Med.* 2008;5(5):e109.
109. Kalichman SC, Amaral CM, Cherry C, et al. Monitoring medication adherence by unannounced pill counts conducted by telephone: reliability and criterion-related validity. *HIV Clin Trials.* 2008;9(5):298-308.
110. Moss AR, Hahn JA, Perry S, et al. Adherence to highly active antiretroviral therapy in the homeless population in San Francisco: a prospective study. *Clin Infect Dis.* 2004;39(8):1190-1198.
111. Hunt PW, Brenchley J, Sinclair E, et al. Relationship between T cell activation and CD4+ T cell count in HIV-seropositive individuals with undetectable plasma HIV RNA levels in the absence of therapy. *J Infect Dis.* 2008;197(1):126-133.
112. Choudhary SK, Vrisekoop N, Jansen CA, et al. Low immune activation despite high levels of pathogenic human immunodeficiency virus type 1 results in long-term asymptomatic disease. *J Virol.* 2007;81(16):8838-8842.
113. Egger M. Outcomes of ART in resource-limited and industrialized countries. Paper presented at: 14th Conference on Retroviruses and Opportunistic Infections; 2007; Los Angeles, CA. Abstract 62.
114. Wolbers M, Bucher HC, Furrer H, et al. Delayed diagnosis of HIV infection and late initiation of antiretroviral therapy in the Swiss HIV Cohort Study. *HIV Med.* 2008;9(6):397-405.
115. Grigoryan A, Hall HI, Durant T, et al. Late HIV diagnosis and determinants of progression to AIDS or death after HIV diagnosis among injection drug users, 33 US States, 1996-2004. *PLoS One.* 2009;4(2):e4445.
116. Centers for Disease Control and Prevention (CDC). Late HIV testing - 34 states, 1996-2005. *MMWR Morb Mortal Wkly Rep.* 2009;58(24):661-665.
117. Branson BM, Handsfield HH, Lampe MA, et al. Revised recommendations for HIV testing of adults, adolescents, and pregnant women in health-care settings. *MMWR Recomm Rep.* 2006;55(RR-14):1-17.

What to Start: Initial Combination Regimens for the Antiretroviral-Naïve Patient (Updated January 10, 2011)

Panel's Recommendations:

- ***The Panel recommends the following as preferred regimens for antiretroviral (ARV)-naïve patients:***
  - ***efavirenz/tenofovir/emtricitabine (EFV/TDF/FTC) (AI)***
  - ***ritonavir-boosted atazanavir + tenofovir/emtricitabine (ATV/r + TDF/FTC) (AI)***
  - ***ritonavir-boosted darunavir + tenofovir/emtricitabine (DRV/r + TDF/FTC) (AI)***
  - ***raltegravir + tenofovir/emtricitabine (RAL + TDF/FTC) (AI)***
- ***A list of Panel-recommended alternative and acceptable regimens can be found in Table 5a and Table 5b.***
- ***Selection of a regimen should be individualized based on virologic efficacy, toxicity, pill burden, dosing frequency, drug-drug interaction potential, resistance-testing results, and comorbid conditions.***
- ***Based on individual patient characteristics and needs, in some instances, an alternative regimen may actually be a preferred regimen for a patient.***

Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = data from randomized controlled trials; II = data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = expert opinion

There are more than 20 approved ARV drugs in 6 mechanistic classes with which to design combination regimens. These 6 classes include the nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), fusion inhibitors (FIs), CCR5 antagonists, and integrase strand transfer inhibitors (INSTIs).

The Panel provides recommendations for preferred, alternative, and acceptable regimens; regimens that may be acceptable but more definitive data are needed; and regimens that may be acceptable but should be used with caution (**Tables 5a and 5b**). Potential advantages and disadvantages of the components recommended as initial therapy for ARV-naïve patients are listed in **Table 6** to guide prescribers in choosing the regimen best suited for an individual patient. A list of agents or components not recommended for initial treatment can be found in **Table 7**.

CONSIDERATIONS WHEN SELECTING A FIRST ANTIRETROVIRAL REGIMEN FOR ANTIRETROVIRAL THERAPY-NAÏVE PATIENTS

Data Used for Making Recommendations

The Panel reviews clinical trial data published in peer-reviewed journals and data prepared by manufacturers for Food and Drug Administration (FDA) review. In selected cases, data presented in abstract format in major scientific meetings also are reviewed. The first criterion for selection is published information from a randomized, prospective clinical trial with an adequate sample size that demonstrates durable viral suppression and immunologic enhancement (as evidenced by increase in CD4 count). Few of these trials include clinical endpoints, such as development of AIDS-defining illness or death. Thus, assessment of regimen efficacy and potency is primarily based on surrogate marker endpoints (HIV RNA and CD4 responses). The Panel reviewed data from randomized clinical trials to arrive at preferred, alternative, or acceptable ratings in **Tables 5a and 5b**. "Preferred regimens" are those studied in randomized controlled trials and shown to have optimal and durable virologic efficacy, favorable tolerability and toxicity profiles, and ease of use. "Alternative regimens" are those regimens that are effective but have potential disadvantages when compared to preferred regimens. On the basis of individual patient characteristics and needs, a regimen listed as an alternative may actually be the preferred regimen in certain situations. Some regimens are classified as "Acceptable Regimens" because of reduced virologic activity, lack of efficacy data from large clinical trials, or other factors (such as greater toxicities, requiring additional testing, pill burden, or drug interaction potential) compared with preferred or alternative regimens.

Lastly, the Panel classified several regimens as "regimens that are acceptable but should be used with caution" because of some safety or efficacy concerns explained in **Table 5b.**

Factors to Consider When Selecting an Initial Regimen

Regimen selection should be individualized and should be based on a number of factors, including:

- comorbid conditions (e.g., cardiovascular disease, chemical dependency, liver disease, psychiatric disease, renal diseases, or tuberculosis);
- potential adverse drug effects;
- potential drug interactions with other medications;
- pregnancy or pregnancy potential;
- results of genotypic drug-resistance testing;
- gender and pretreatment CD4 count if considering nevirapine (NVP);
- HLA-B*5701 testing if considering abacavir (ABC);
- coreceptor tropism assay if considering maraviroc (MVC);
- patient adherence potential; and
- convenience (e.g., pill burden, dosing frequency, and food and fluid considerations).

Considerations for Therapies

A listing of characteristics (i.e., dosing, pharmacokinetics, and common adverse effects) of individual ARV agents can be found in **Appendix B, Tables 1–6**. Additionally, **Appendix B, Table 7** provides clinicians with ARV dosing recommendations for patients who have renal or hepatic insufficiency.

Possible regimens include combinations of two NRTIs with an NNRTI, a PI (preferably boosted with ritonavir [RTV]), an INSTI (namely raltegravir [RAL]) or a CCR5 antagonist (namely MVC). In clinical trials, NNRTI-, PI-, INSTI-, or CCR5 antagonist-based regimens have all resulted in suppression of HIV RNA levels and CD4 cell increases in a large majority of patients *[1-7]*. Some comparative data are available. (See below.)

Tables 5a and 5b include the Panel's recommendations for initial therapy.

Table 5a. Preferred and Alternative Antiretroviral Regimens for Antiretroviral Therapy-Naïve Patients (Updated January 10, 2011)

Selection of a regimen should be individualized based on virologic efficacy, toxicity, pill burden, dosing frequency, drug-drug interaction potential, resistance testing results, and comorbid conditions. Refer to **Table 6** for a list of advantages and disadvantages and **Appendix B, Tables 1–6** for dosing information for individual ARV agents listed below. The regimens in each category are listed in alphabetical order.

Preferred Regimens (Regimens with optimal and durable efficacy, favorable tolerability and toxicity profile, and ease of use) **The preferred regimens for nonpregnant patients are arranged by order of FDA approval of components other than nucleosides, thus, by duration of clinical experience.**	
NNRTI-Based Regimen • EFV/TDF/FTC[1] **(AI)** **PI-Based Regimens** *(in alphabetical order)* • ATV/r + TDF/FTC[1] **(AI)** • DRV/r (once daily) + TDF/FTC[1] **(AI)** **INSTI-Based Regimen** • RAL + TDF/FTC[1] **(AI)** **Preferred Regimen[2] for Pregnant Women** • LPV/r (twice daily) + ZDV/3TC[1] **(AI)**	**Comments** **EFV** should not be used during the first trimester of pregnancy or in women trying to conceive or not using effective and consistent contraception. **ATV/r** should not be used in patients who require >20 mg omeprazole equivalent per day. Refer to **Table 15a** for dosing recommendations regarding interactions between ATV/r and acid-lowering agents.
Alternative Regimens (Regimens that are effective and tolerable but have potential disadvantages compared with preferred regimens. An alternative regimen may be the preferred regimen for some patients.)	
NNRTI-Based Regimens *(in alphabetical order)* • EFV + (ABC or ZDV)/3TC[1] **(BI)** • NVP + ZDV/3TC[1] **(BI)** **PI-Based Regimens** *(in alphabetical order)* • ATV/r + (ABC or ZDV)/3TC[1] **(BI)** • FPV/r (once or twice daily) + either [(ABC or ZDV)/3TC[1]] or TDF/FTC[1] **(BI)** • LPV/r (once or twice daily) + either [(ABC or ZDV)/3TC[1]] or TDF/FTC[1] **(BI)**	**Comments** **NVP** • NVP should not be used in patients with moderate to severe hepatic impairment (Child-Pugh B or C)[3] • NVP should not be used in women with pre-ARV CD4 count >250 cells/mm^3 or men with pre-ARV CD4 count >400 cells/mm^3. **ABC** • ABC should not be used in patients who test positive for HLA-B*5701. • Use ABC with caution in patients with high risk of cardiovascular disease or with pretreatment HIV RNA >100,000 copies/mL. (See text.) **Once-daily LPV/r** is not recommended in pregnant women.

[1]3TC may substitute for FTC or vice versa.
[2]For more detailed recommendations on ARV use in an HIV-infected pregnant woman, refer to the ***Perinatal Guidelines*** available at **http://aidsinfo.nih.gov/guidelines**.
[3]Refer to **Appendix B, Table 7** for the criteria for Child-Pugh classification.

The following combinations in the recommended list above are available as fixed-dose combination formulations: ABC/3TC, EFV/TDF/FTC, LPV/r, TDF/FTC, and ZDV/3TC.

Acronyms: 3TC = lamivudine, ABC = abacavir, ATV = atazanavir, ATV/r = atazanavir/ritonavir, DRV = darunavir, DRV/r = darunavir/ritonavir, EFV = efavirenz, FPV = fosamprenavir, FPV/r = fosamprenavir/ritonavir, FTC = emtricitabine, INSTI = integrase strand transfer inhibitor, LPV = lopinavir, LPV/r = lopinavir/ritonavir, NNRTI = non-nucleoside reverse transcriptase inhibitor, NRTI = nucleos(t)ide reverse transcriptase inhibitor, NVP = nevirapine, PI = protease inhibitor, RAL = raltegravir, TDF = tenofovir, ZDV = zidovudine

Table 5b. Acceptable Antiretroviral Regimens for Treatment-Naïve Patients (Updated January 10, 2011)

Acceptable Regimens (CI) (Regimens that may be selected for some patients but are less satisfactory than preferred or alternative regimens) **and Regimens that may be Acceptable but more definitive data are needed (CIII)**	
NNRTI-Based Regimen • EFV + ddI + (3TC or FTC) **(CI)** **PI-Based Regimens** • ATV + (ABC or ZDV)/3TC[1] **(CI)** • DRV/r + (ABC or ZDV)/3TC[1] **(CIII)** **INSTI-Based Regimen** • RAL + (ABC or ZDV)/3TC[1] **(CIII)** **CCR5 Antagonist-Based Regimens** • MVC + ZDV/3TC[1] **(CI)** • MVC + TDF/FTC[1] or ABC/3TC[1] **(CIII)**	**Comments** **EFV + ddI + (FTC or 3TC)** has only been studied in small clinical trials. **ATV/r** is generally preferred over ATV. Unboosted ATV may be used when RTV boosting is not possible. **MVC** Tropism testing should be performed before initiation of therapy; only patients found to have only CCR5-tropic virus are candidates for MVC.
Regimens that may be acceptable but should be used with caution (Regimens that have demonstrated virologic efficacy in some studies but have safety, resistance, or efficacy concerns. See comments below.)	
NNRTI-Based Regimens • NVP + ABC/3TC[1] **(CIII)** • NVP + TDF/FTC[1] **(CIII)** **PI-Based Regimens** • FPV + [(ABC or ZDV)/3TC[1] or TDF/FTC[1]] **(CIII)** • SQV/r + TDF/FTC[1] **(CI)** • SQV/r + (ABC or ZDV)/3TC[1] **(CIII)**	**Comments** Use **NVP** and **ABC** together with caution because both can cause HSRs within first few weeks after initiation of therapy. Early virologic failure with high rates of resistance has been reported in some patients receiving **NVP + TDF + (3TC or FTC)**. Larger clinical trials are currently in progress. **FPV/r** is generally preferred over unboosted FPV. Virologic failure with unboosted FPV-based regimen may select mutations that confer cross resistance to DRV. **SQV/r** • SQV/r was associated with PR and QT prolongation in a healthy volunteer study. • Baseline ECG is recommended before initiation of SQV/r. • SQV/r is not recommended in patients with any of the following: 1. pretreatment QT interval >450 msec 2. refractory hypokalemia or hypomagnesemia 3. concomitant therapy with other drugs that prolong QT interval 4. complete AV block without implanted pacemaker 5. risk of complete AV block

[1]3TC maybe substituted with FTC or vice versa.

Acronyms: 3TC = lamivudine, ABC = abacavir, ATV = atazanavir, ATV/r = atazanavir/ritonavir, AV = atrioventricular, ddI = didanosine, DRV = darunavir, DRV/r = darunavir/ritonavir, ECG = electrocardiogram, EFV = efavirenz, FPV = fosamprenavir, FPV/r = fosamprenavir/ritonavir, FTC = emtricitabine, HSR = hypersensitivity reaction, INSTI = integrase strand transfer inhibitor, msec = millisecond, MVC = maraviroc, NNRTI = non-nucleoside reverse transcriptase inhibitor, NVP = nevirapine, PI = protease inhibitor, RAL = raltegravir, RTV = ritonavir, SQV = saquinavir, SQV/r = saquinavir/ritonavir, TDF = tenofovir, ZDV = zidovudine

NNRTI- versus PI- versus INSTI- versus CCR5 Antagonist-Based Regimens

EFV-based regimens have been compared with a variety of other regimens in clinical trials, including boosted or unboosted PI-based, RAL-based, and MVC-based regimens *[3-9]*. No regimen has proven superior to EFV-based regimens with respect to virologic responses.

NNRTI- versus PI-Based Regimens

RTV-boosted PI-based regimens have shown good virologic and immunologic responses but are often associated with more gastrointestinal symptoms, whereas EFV-based regimens are associated with more rash and central nervous system adverse effects. Both types of regimens may be associated with hepatic transaminase elevations *[10]*.

Drug resistance to most PIs requires multiple mutations in the HIV protease gene, and it seldom develops after early virologic failure *[11]*, especially when RTV boosting is used. Resistance to EFV or NVP, however, is conferred by a single mutation in the reverse transcriptase gene, and it develops rapidly after virologic failure *[11]*. An estimated 8% of newly infected patients in the United States carry NNRTI-resistant viruses *[12]*. Because of the concern for primary resistance in the ART-naïve population, genotypic testing results should be used to guide the selection of the initial ARV regimen. (See **Drug-Resistance Testing**.) In terms of convenience, the coformulated tablet of TDF, FTC, and EFV allows for once-daily dosing with a single tablet. Most PI-based regimens include RTV, may be dosed once or twice daily, and generally require more pills in the regimen, although the pill burden associated with PI-based regimens has decreased when compared with older PIs (for example, nelfinavir [NFV]or indinavir [IDV]). Drug-drug interactions are important with both kinds of regimens, but more clinically significant interactions are seen with RTV-boosted PI regimens.

Other Treatment Options

Another option for initial therapy is the combination of TDF, FTC, and RAL *[6]*. This combination has shown similar virologic efficacy as compared with a combination of TDF, FTC, and EFV up to 96 weeks *[13]* and is generally well tolerated. There are no clinical trial data comparing INSTI-based with PI-based regimens. RAL requires twice-daily dosing, has a low genetic barrier for selection of resistance mutations, and has had relatively limited use with other dual-NRTI combinations. MVC has been approved for use in ART-naïve patients, based on data from the MERIT study comparing MVC/zidovudine (ZDV)/lamivudine (3TC) with EFV/ZDV/3TC *[7]*.

The discussions below focus on the rationale for the Panel's recommendations, based on the efficacy, safety, and other characteristics of different agents within the individual drug classes.

NNRTI-BASED REGIMENS (1 NNRTI + 2 NRTIs)

Summary: NNRTI-Based Regimens

Four NNRTIs (delavirdine [DLV], EFV, etravirine [ETR], and NVP) are currently FDA approved.

NNRTI-based regimens have demonstrated virologic potency and durability. The major disadvantages of currently available NNRTIs involve prevalence of NNRTI-resistant viral strains in ART-naïve patients *[12, 14-16]* and the low genetic barrier of NNRTIs for development of resistance. Resistance testing should be performed for ART-naïve patients to guide therapy selection. (See **Drug-Resistance Testing**.) The first three approved NNRTIs (i.e., DLV, EFV, NVP) require only a single mutation to confer resistance, and cross resistance affecting these three NNRTIs is common. ETR, an NNRTI approved for ART-experienced patients, has *in vitro* activity against some viruses with mutations that confer resistance to DLV, EFV, and NVP *[17]*.

On the basis of clinical trial results and safety data, the Panel recommends either EFV or NVP as the NNRTI for initial ART. In most instances, EFV is preferred, based on its potency and tolerability (as discussed below). EFV should not be used in pregnant women (especially during the first trimester) or in women of childbearing potential who are planning to conceive or who are sexually active with men and not using effective and consistent contraception.

NVP may be used as an alternative to EFV for the initial NNRTI-based regimen in women with pretreatment CD4 counts ≤250 cells/mm^3 or in men with pretreatment CD4 counts ≤400 cells/mm^3 **(BI)**. (See discussion below.)

Among these four agents, DLV is dosed three times daily, has the least supportive clinical trial data, and appears to have the least antiviral activity. As such, DLV is **not recommended** as part of an initial regimen **(BIII)**. ETR has not been studied in large, randomized trials in ART-naïve participants. Thus, ETR **cannot be recommended** as part of initial therapy **(BIII)**.

Following is a more detailed discussion of preferred and alternative NNRTI-based regimens for initial therapy.

EFV as Preferred NNRTI

Large randomized, controlled trials and cohort studies of ART-naïve patients have demonstrated potent viral suppression in EFV-treated patients; a substantial proportion of these patients had HIV RNA <50 copies/mL during up to 7 years of follow-up *[1-2, 18]*. Studies that compared EFV-based regimens with other regimens demonstrated the combination of EFV with two NRTIs was superior virologically to some PI-based regimens, including indinavir (IDV) *[3]*, ritonavir-boosted lopinavir (LPV/r) *[4]*, and nelfinavir (NFV) *[8]* and to triple-NRTI–based regimens of ABC, ZDV, and 3TC or ABC, TDF, and 3TC *[19-20]*. EFV-based regimens also had comparable virologic activity when compared with NVP- *[21-22]*, atazanavir (ATV)- *[5]*, RAL- *[6]*, or MVC-based *[7]* regimens.

The ACTG 5142 study randomized patients to receive two NRTIs together with either EFV or LPV/r (or an NRTI-sparing regimen of EFV and LPV/r) *[4]*. The dual-NRTI and EFV regimen was associated with a better virologic response than the dual-NRTI and LPV/r regimen at 96 weeks, whereas the dual-NRTI with LPV/r regimen was associated with a better CD4 response and less drug resistance after virologic failure.

The 2NN trial compared EFV with NVP, both given with stavudine (d4T) and 3TC, in ART-naïve patients. Virologic responses were similar for both drugs, although NVP was associated with greater toxicity and did not meet criteria for noninferiority compared with EFV *[21]*.

Two major limitations of EFV are its central nervous system adverse effects, which usually resolve over a few weeks, and its potential teratogenic effects. In animal reproductive studies, EFV caused major congenital anomalies in the central nervous system in nonhuman primates at drug exposure levels similar to those achieved in humans *[23]*. Several cases of neural tube defects in human newborns of mothers exposed to EFV during the first trimester of pregnancy have been reported *[24-25]*. Therefore, EFV is not recommended in pregnant women during the first trimester of pregnancy or in women with high pregnancy potential (women of childbearing potential who are trying to conceive or who are sexually active with men and are not using effective and consistent contraception) **(AIII)**.

Studies that use EFV and dual-NRTI combinations (ABC, didanosine [ddI], d4T, TDF, or ZDV together with FTC or 3TC) show durable virologic activity, although there may be differences among the various combinations chosen. (See **Dual-NRTI Options**.) A single tablet coformulated with TDF, FTC, and EFV provides one-tablet, once-daily dosing and is currently the preferred NNRTI-based regimen **(AI)**.

NVP as Alternative NNRTI

In the 2NN trial, 70% of participants in the EFV arm and 65.4% in the twice-daily NVP arm had virologic suppression (defined as HIV RNA <50 copies/mL) at 48 weeks. This difference did not reach criteria necessary to demonstrate noninferiority of NVP *[21]*. Two deaths were attributed to NVP use. One resulted from fulminant hepatitis and one from staphylococcal sepsis as a complication of Stevens-Johnson syndrome.

In a randomized controlled trial, NVP was found to be noninferior to boosted ATV when combined with TDF/FTC *[26]*. This study enrolled only women and men with CD4 counts <250 cells/mm^3 and <400 cells/mm^3, respectively, the threshold recommended to reduce the incidence of hepatic toxicity (see below). Three smaller studies (n <100) have suggested more virologic failures than would be expected in ART-naïve participants who receive NVP plus TDF and either 3TC or FTC *[27-29]*. Pending published results from randomized trials, clinicians should closely monitor virologic responses if using this combination **(CIII)**.

Serious hepatic events have been observed when NVP was initiated in ART-naïve patients. These events generally occur within the first few weeks of treatment. In addition to experiencing elevated serum transaminases, approximately half of the patients also develop skin rash, with or without fever or flu-like symptoms. Retrospective analysis of reported events suggests that women with higher CD4 counts appear to be at highest risk *[30-31]*. A 12-fold higher incidence of symptomatic hepatic events was seen in women (including pregnant women) with CD4 counts >250 cells/mm^3 at the time of NVP initiation compared with women with CD4 counts ≤250 cells/mm^3 (11.0% vs. 0.9%). An increased risk was also seen in men with pretreatment CD4 counts >400 cells/mm^3 compared with men with pretreatment CD4 counts ≤400 cells/mm^3 (6.3% vs. 1.2%). Most of these patients had no identifiable underlying hepatic abnormalities. In some cases, hepatic injuries continued to progress despite discontinuation of NVP *[31-32]*. In contrast, other studies have not shown an association between baseline CD4 counts and severe NVP hepatotoxicity *[33-34]*. Symptomatic hepatic events have not been reported with single-dose NVP given to mothers or infants for prevention of perinatal HIV infection.

On the basis of the earlier safety data, the Panel recommends that NVP may be considered as an alternative to EFV as initial therapy for women with pretreatment CD4 counts ≤250 cells/mm^3 or in men with CD4 counts ≤400 cells/mm^3. Patients who experience CD4 count increases to levels above these thresholds as a result of NVP-containing therapy can safely continue therapy without an increased risk of adverse hepatic events *[35]*.

At the initiation of NVP, a 14-day lead-in period at a dosage of 200 mg once daily should be instituted before increasing to the maintenance dosage of 200 mg twice daily. Some experts recommend monitoring serum transaminases at baseline, prior to and 2 weeks after dose escalation, and then monthly for the first 18 weeks. Clinical and laboratory parameters should be assessed at each visit.

PI-BASED REGIMENS (RTV-BOOSTED OR UNBOOSTED PI + 2 NRTIs)

Summary: PI-Based Regimens

PI-based regimens have demonstrated more virologic potency and durability and higher barriers to resistance than NNRTI- and INSTI-based regimens. In patients who experience virologic failure while on their first PI-based regimen, few or no PI mutations are detected at failure. Each PI has its own virologic potency, adverse effect profile, and pharmacokinetic properties. The characteristics, advantages, and disadvantages of each PI can be found in **Table 6** and **Appendix B, Table 3**. In selecting a boosted PI-based regimen for an ART-naïve patient, clinicians should consider factors such as dosing frequency, food requirements, pill burden, daily RTV dose, drug interaction potential, baseline lipid profile, toxicity profile of the individual PI, and pregnancy status. (See the ***Perinatal Guidelines*** for specific recommendations in pregnancy *[36]*.)

A number of metabolic abnormalities, including dyslipidemia and insulin resistance, have been associated with PI use. The currently available PIs differ in their propensity to cause these metabolic complications, which are also dependent on the dose of RTV used as a pharmacokinetic boosting agent. Some studies have suggested that LPV/r, IDV, fosamprenavir (FPV), or FPV/r may be associated with increased rates of myocardial infarction (MI) or stroke *[37-38]*. It should be noted that in both studies, there were too few patients receiving ATV/r or DRV/r to be included in the analysis. Ritonavir-boosted saquinavir (SQV/r) can prolong the PR and QT intervals on electrocardiogram (ECG). The degree of QT prolongation is greater than that seen with some other boosted PIs. Therefore, SQV/r should be used with caution in patients at risk of or who use concomitant drugs that may potentiate these ECG abnormalities *[39]*.

The potent inhibitory effect of RTV on the cytochrome P (CYP) 450 3A4 isoenzyme has allowed the addition of low-dose RTV to other PIs as a pharmacokinetic booster to increase drug exposure and prolong plasma half-life of the active PI. This allows for reduced dosing frequency and/or pill burden, which may improve overall adherence to the regimen. The increased trough concentration (C_{min}) may improve the ARV activity of the primary PI, which can be beneficial when the patient harbors HIV strains with reduced susceptibility to the PI *[40-42]* and also may contribute to the lower risk of resistance upon virologic failure compared with unboosted PIs. The drawbacks associated with this strategy are the potential for increased risk of hyperlipidemia and a greater potential of drug-drug interactions from the addition of RTV. In patients without pre-existing PI resistance, there is growing support for the use of once-daily

boosted PI regimens that use only 100 mg per day of RTV because they tend to cause fewer gastrointestinal side effects and less metabolic toxicity than regimens that use RTV at a dose of 200 mg per day. In the case of RTV-boosted darunavir (DRV) (800/100 mg once daily) and ATV (300/100 mg once daily), there are large head-to-head trials demonstrating noninferiority or superiority compared with LPV/r, with less gastrointestinal and lipid toxicity.

The Panel uses the following criteria to distinguish between preferred versus alternative PIs in ART-naïve patients: (1) demonstrated superior or noninferior virologic efficacy when compared with at least one other PI-based regimen, with at least published 48-week data; (2) RTV-boosted PI with no more than 100 mg of RTV per day; (3) once-daily dosing; (4) low pill count; and (5) good tolerability. Using these criteria, the Panel recommends ATV + RTV (once daily) **(AI)** and DRV + RTV (once daily) **(AI)** as preferred PIs.

Preferred PI Components (in alphabetical order, by active PI component)

RTV-Boosted ATV (ATV/r). RTV boosting of ATV, given as two pills once daily, enhances the concentrations of ATV and improves virologic activity compared with unboosted ATV in a clinical trial *[43]*.

The CASTLE study compared once-daily ATV/r with twice-daily LPV/r, each in combination with TDF/FTC, in 883 ARV-naïve participants. In this open-label, noninferiority study, analysis at 48 weeks *[44]* and at 96 weeks *[45]* showed similar virologic and CD4 responses of the two regimens. More hyperbilirubinemia and less gastrointestinal toxicity were seen in the ATV/r arm. This study supports the designation of ATV/r + TDF/FTC as a preferred regimen.

The main adverse effect associated with ATV/RTV is indirect hyperbilirubinemia, with or without jaundice or scleral icterus, but without concomitant hepatic transaminase elevations. Several cases of nephrolithiasis have also been reported in patients who received RTV-boosted or unboosted ATV *[46]*. ATV/RTV requires acidic gastric pH for dissolution. Thus, concomitant use of drugs that raise gastric pH, such as antacids, H_2 antagonists, and particularly proton pump inhibitors, may impair absorption of ATV. **Table 15a** provides recommendations for how to use RTV-boosted ATV with these agents.

RTV-Boosted DRV (DRV/r). The ARTEMIS study compared DRV/r (800/100 mg once daily, three pills per day) with LPV/r (once or twice daily), both in combination with TDF/FTC, in a randomized, open-label, noninferiority trial. The study enrolled 689 ART-naïve participants. At 48 weeks, DRV/r was noninferior to LPV/r. The virologic response rates were lower in the LPV/r arm among those participants whose baseline HIV RNA levels were >100,000 copies/mL. Grades 2 to 4 adverse events, primarily diarrhea, were seen more frequently in LPV/r recipients *[47]*. At 96 weeks, virologic response to DRV/r was superior to response with LPV/r *[48]*.

Alternative PI Components (in alphabetical order, by active PI component)

RTV-Boosted FPV (FPV/r) (once or twice daily). FPV/r is recommended as an alternative PI. The KLEAN trial compared twice-daily FPV/r with LPV/r, each in combination with ABC and 3TC, in ART-naïve patients. At Weeks 48 and 144, similar percentages of subjects achieved viral loads of <400 copies/mL *[49-50]*. Clinical and laboratory adverse events did not differ between the regimens. In this study of ART-naïve participants, twice-daily FPV/r was noninferior to twice-daily LPV/r. In the KLEAN study, the occurrence of metabolic adverse effects was similar with boosted FPV and with LPV/r. Based on the above criteria for preferred PIs that favor once-daily regimens with no more than 100 mg/day of RTV, twice-daily FPV is now considered an alternative choice.

In a study comparing once-daily FPV/r (1,400 mg with RTV 200 mg once daily) with NFV *[51]*, similar virologic efficacy was reported in both arms. A comparative trial of once-daily FPV/r (1,400/100 mg) with once-daily ATV/r, both in combination with TDF/FTC, was conducted in 106 ARV-naïve participants *[52]*. Similar virologic and CD4 benefits were seen with both regimens. The small sample size of this study precludes the assessment of superior or noninferior virologic efficacy required for a preferred PI. Collectively, FPV/r regimens, with once- or twice-daily dosing, are recommended as alternatives.

RTV-Boosted LPV (LPV/r) (coformulated) (BI). LPV/r is the only available coformulated boosted PI. It can be given once or twice daily. However, the need for 200 mg/day of RTV, and the higher rate of gastrointestinal side

effects and hyperlipidemia when compared with boosted PIs using RTV 100 mg/day, make it an alternative rather than preferred PI for ART-naïve patients. Early studies showed that LPV/r was superior to NFV in maintaining suppressed viral loads *[53]*. A 7-year follow-up study of LPV/r and two NRTIs showed sustained virologic suppression in patients who were maintained on the originally assigned regimen *[54]*. Results of clinical trials that compared LPV/r with ATV/r, DRV/r, FPV/r, or SQV/r are discussed in the respective sections of this document. The ACTG 5142 study showed that the regimen of twice-daily LPV/r plus two NRTIs had decreased virologic efficacy when compared with EFV plus two NRTIs. However, the CD4 response was greater with LPV/r, and there was less drug resistance associated with virologic failure *[4]*.

Several trials have evaluated different formulations and dosages of LPV/r administered once or twice daily *[47, 55-56]*. In the largest trial that compared once-daily with twice-daily LPV/r, both in combination with TDF/FTC, 664 ART-naïve participants were randomized to receive once- or twice-daily soft-gel capsules or once- or twice-daily tablets for 8 weeks; at Week 8, all participants received the tablet formulation and maintained their same randomized dosing schedule *[57]*. At Week 48, 77% of once-daily and 76% of twice-daily LPV/r recipients achieved viral loads <50 copies/mL. Rates of moderate to severe drug-related diarrhea were similar between the two groups. In addition to diarrhea, major adverse effects of LPV/r include insulin resistance and hyperlipidemia, especially hypertriglyceridemia; these required pharmacologic management in some patients. In the D:A:D and French observational cohorts, cumulative use of LPV/r was associated with a slightly increased risk of MI *[37-38]*. Once-daily LPV/r should not be used in patients who have HIV mutations associated with PI resistance because higher LPV trough levels may be required to suppress resistant virus. LPV/r given twice daily is the preferred PI for use in pregnant women *[36]*. Once-daily dosing should not be used in this situation, especially during the third trimester, when LPV levels are expected to decline. For more detailed information regarding ART drug choices and related issues in pregnancy, see the ***Perinatal Guidelines*** *[36]*.

Acceptable PI-Based Component

ATV. Unboosted ATV is given once daily and has fewer adverse effects on lipid profiles than other available PIs. Three studies compared ATV-based combination regimens with either NFV- or EFV-based regimens. These studies established similar virologic efficacy among ATV 400 mg once daily and both comparator treatment groups in ARV-naïve patients after 48 weeks of therapy *[5, 43, 58-59]*. The ACTG 5175 trial compared three regimens in ART-naïve patients. The Data Safety Monitoring Board for this trial recommended that participants be unblinded and switched to alternative therapy if they were randomized to ATV + enteric-coated ddI + FTC because of an inferior virologic response when compared with the other two arms—once-daily EFV plus either ZDV/3TC (twice daily) or TDF/FTC (once daily) *[60]*. If unboosted ATV is prescribed for an ART-naïve patient, clinicians should consider using a dual-NRTI backbone other than ddI + FTC (or 3TC).

Unboosted ATV may be an initial therapy for patients when a once-daily regimen without RTV is desired and for patients with underlying risk factors indicating that hyperlipidemia may be particularly undesirable. ATV should be used with RTV-boosting if TDF or EFV are used concomitantly because these two agents can lower the concentrations of ATV. ATV requires acidic gastric pH for dissolution. Thus, concomitant use of drugs that raise gastric pH, such as antacids, H_2 antagonists, and proton pump inhibitors, may significantly impair ATV absorption. Proton pump inhibitors should not be used in patients who are taking unboosted ATV. H_2 antagonists and antacids should be used with caution and with careful dose separation. (See **Tables 14 and 15a**.)

PI Components that May be Acceptable but Should be Used with Caution (in alphabetical order, by active PI component)

FPV. In a study comparing unboosted FPV given twice daily with NFV, more participants randomized to FPV achieved viral suppression at 48 weeks than participants assigned to NFV, and greater differences were seen in those who had pretreatment viral loads >100,000 copies/mL *[61]*. However, virologic failure on unboosted FPV may select for resistance mutations that confer cross resistance to DRV *[62-63]*, a PI with an important role in management of ART-experienced patients. As such, FPV/r is preferred over unboosted FPV, and the unboosted strategy should be used with caution.

RTV-Boosted SQV (SQV/r). The GEMINI study compared SQV/r (1,000/100 mg twice daily) with LPV/r, both given twice daily, in combination with TDF/FTC given once daily, in 337 ART-naïve participants who were monitored over 48 weeks. Similar levels of viral suppression and increases in CD4 counts were seen in both arms *[64]*. Triglyceride levels were higher in the LPV/r arm. The SQV/r regimen has a higher pill burden and requires twice-daily dosing and 200 mg of RTV. In a healthy volunteer study, SQV/r use was associated with increases in both QT and PR intervals. The degree of QT prolongation was greater than that seen with some other boosted PIs. Rare cases of torsades de pointes and complete heart block have been reported in post-marketing surveillance. Based on these findings, an ECG is recommended prior to initiation of SQV/r. SQV/r is not recommended for patients with any of the following conditions: documented congenital or acquired QT prolongation, pretreatment QT interval of >450 milliseconds (msec), refractory hypokalemia or hypomagnesemia, complete atrioventricular (AV) block without implanted pacemakers, at risk of complete AV block, or receiving other drugs that prolong QT interval *[39]*. Based on these restrictions and because there are several other preferred or alternative PI options, the Panel recommends that SQV/r may be acceptable but should be used with caution in selected ARV-naïve patients. (See **Table 5b** for rating.)

INSTI-BASED REGIMENS (INSTI + 2 NRTIs)

RAL. RAL is an INSTI that is approved for use in ART-naïve patients, based on results of STARTMRK, a Phase III study that compared RAL (400 mg twice daily) with EFV (600 mg once daily), each in combination with TDF/FTC, in ART-naïve subjects. This multinational double-blind, placebo-controlled study enrolled 563 subjects with plasma HIV-1 RNA levels >5,000 copies/mL. At Week 48, similar numbers of subjects achieved HIV-1 RNA levels <50 copies/mL in both groups (86.1% and 81.9% for RAL and EFV, respectively, p <0.001 for noninferiority). CD4 counts rose by 189 cells/mm^3 in the RAL group versus 163 cells/mm^3 in the EFV group. Serious adverse events occurred at a similar frequency in both groups *[6]*. At 96 weeks, virologic and immunologic responses remained similar in both groups with no new safety concerns identified *[13]*. Based on these data, the Panel recommends RAL + TDF/FTC (or 3TC) as a preferred regimen for ART-naïve patients **(AI)**.

Comparisons of RAL-based regimen with other regimens in ART-naïve subjects have not yet been reported, and there is less experience with RAL than with EFV or boosted PIs for initial therapy. In addition, RAL must be administered twice daily, a potential disadvantage when compared with some other regimens. RAL, like EFV, has a lower genetic barrier to resistance than RTV-boosted PIs, and resistance mutations were observed at approximately the same frequency in the comparative trial. RAL use with other dual NRTIs (such as ABC/3TC or ZDV/3TC) may be acceptable, but more definitive data for these regimens are needed **(CIII)**.

CCR5 ANTAGONIST-BASED REGIMENS (CCR5-A + 2 NRTIs)

The MERIT study compared the CCR5 antagonist MVC with EFV, both in combination with ZDV/3TC, in a randomized, double-blinded trial in ART-naïve participants *[7]*. Only participants who had CCR5-tropic virus and had no evidence of resistance to any drugs used in the study were enrolled (n = 721). At 48 weeks, virologic suppression (defined as HIV RNA <400 copies/mL) was seen in 70.6% of MVC recipients and in 73.1% of EFV recipients, and HIV RNA <50 copies/mL was observed in 65.3% of MVC recipients and in 69.3% of EFV recipients. The HIV RNA <50 copies/mL results did not meet the criteria set by the investigators to demonstrate noninferiority for MVC in this study. CD4 count increased by an average of 170 cells/mm^3 in the MVC arm and by 144 cells/mm^3 in the EFV arm. Through 48 weeks, more participants discontinued MVC compared with EFV because of lack of efficacy (11.9% vs. 4.2%), whereas fewer participants discontinued MVC because of toxicity (4.2% vs. 13.6%). Follow-up results at 96 weeks demonstrated durable responses *[65]*. In a post-hoc reanalysis using a more sensitive viral tropism assay, 15% of patients with non-R5 screening virus were excluded from analysis, and their retrospective exclusion resulted in similar response rates in both arms, using either the HIV RNA criteria of <400 or <50 copies/mL. Based on the results, FDA approved MVC for use in regimens for ART-naïve patients. Because MVC requires twice-daily dosing, requires an expensive tropism assay prior to use, and there is little experience with regimens other than ZDV/3TC, the Panel recommends MVC + ZDV/3TC as an acceptable regimen for use in ART-naïve patients **(CI)**. Although the MERIT trial used ZDV/3TC as its NRTI backbone, many clinicians would favor the combination of MVC with TDF/FTC or ABC/3TC pending further data **(CIII)**.

DUAL-NRTI OPTIONS AS PART OF INITIAL COMBINATION THERAPY

Summary: Dual-NRTI Components

Dual NRTIs are commonly used in combination with an NNRTI, a PI (usually boosted with RTV), an INSTI, or a CCR5 antagonist. Most dual-NRTI combinations used in clinical practice consist of a primary NRTI plus 3TC or FTC. Both 3TC and FTC have few adverse effects but may select for the M184V resistance mutation, which confers high-level resistance to both drugs; a modest decrease in susceptibility to ddI and ABC; and improved susceptibility to ZDV, d4T, and TDF *[66]*.

All NRTIs except ddI can be taken without food restrictions. Adherence may be additionally improved with once-daily dosing (available for all NRTIs except d4T and ZDV) and with fixed-dosage combinations, such as ABC/3TC, TDF/FTC (with or without EFV), or ZDV/3TC.

The Panel's recommendations on specific dual-NRTI options are made on the basis of virologic potency and durability, short- and long-term toxicities, the propensity to select for resistance mutations, and dosing convenience.

Preferred Dual-NRTI

TDF/FTC (coformulated). TDF is a nucleotide analog with potent activity against both HIV and hepatitis B virus (HBV) and with a long intracellular half-life that allows for once-daily dosing. The fixed-dose combinations of TDF/FTC and TDF/FTC/EFV are both administered as one tablet once daily and are designed to improve adherence.

TDF, when used with either 3TC or FTC as part of an EFV-based regimen in ART-naïve patients, demonstrated potent virologic suppression *[18]* and was superior to ZDV/3TC in virologic efficacy up to 144 weeks *[67]*. In the 934 study, more participants in the ZDV/3TC arm developed loss of limb fat (as assessed by dual-energy x-ray absorptiometry [DXA]) and anemia at 96 and 144 weeks compared with the TDF/FTC arm *[67]*. Emergence of the M184V mutation was less frequent than with ZDV/3TC, and no participant had developed the K65R mutation after 144 weeks of therapy, in contrast to other studies in which TDF was combined with 3TC. TDF with FTC or 3TC has been studied in combination with several boosted PIs and RAL in randomized clinical trials; all such trials demonstrate good virologic benefit *[6, 44, 47, 52, 56]*.

TDF/FTC was compared with ABC/3TC in the ACTG 5202 study *[68]* and the HEAT trial *[69]*. Inferior virologic responses were observed in participants randomized to ABC/3TC who had a pretreatment HIV RNA >100,000 copies/mL. This was not confirmed by the results from the HEAT trial. (See the ABC/3TC section below for more detailed discussion.)

One randomized controlled trial found NVP to be noninferior to boosted ATV when combined with TDF/FTC *[26]*. Three small studies (n <100) have suggested more virologic failures than would be expected in ART-naïve participants who receive NVP plus TDF and either 3TC or FTC *[27-29]*. Pending published results from randomized trials, clinicians should closely monitor virologic responses if using this combination **(CIII)**.

Renal impairment, manifested by increases in serum creatinine, glycosuria, hypophosphatemia, and acute tubular necrosis, has been reported with TDF use *[70-71]*. Risk factors may include advanced HIV disease, greater treatment experience, and pre-existing renal impairment *[72]*. Renal function, urinalysis, and electrolytes should be monitored in patients who are on TDF. In patients who have some degree of pre-existing renal insufficiency (creatinine clearance [CrCl] <50 mL/min), TDF dosage adjustment is required. (See **Appendix B, Table 7** for dosage recommendations.) However, because no safety and efficacy data that use the dosage adjustment guidelines for renal dysfunction are available, the use of alternative NRTIs (especially ABC) may be preferred over dose-adjusted TDF in this setting.

TDF concentrations can be increased by some PIs, and studies have suggested a greater risk of renal dysfunction when TDF is used in PI-based regimens *[70, 73-76]*. TDF has been used in combination with PIs without renal toxicity in several clinical trials that involved patients who had CrCl >50–60 mL/min. Furthermore, in two randomized studies comparing TDF/FTC to ABC/3TC, participants receiving TDF/FTC experienced a significantly greater decline in bone mineral density *[77-78]*.

TDF plus either FTC or 3TC is the preferred NRTI combination, especially for patients coinfected with both HIV and HBV because these drugs have activity against both viruses. The use of a single HBV-active NRTI (e.g., 3TC or FTC) can lead to HBV resistance and is not recommended. (See **Hepatitis B (HBV)/HIV Coinfection**.)

Alternative Dual NRTIs (in alphabetical order)

ABC/3TC (coformulated) for Patients Who Test Negative for HLA-B*5701. ABC has the potential for serious hypersensitivity reactions (HSRs). Clinically suspected HSRs have been observed in 5%–8% of patients who start ABC. The risk of this reaction is highly associated with the presence of the HLA-B*5701 allele *[79-80]*. (See **HLA-B*5701 Screening**.) HLA-B*5701 testing should precede the use of ABC. ABC should not be given to patients who test positive for HLA-B*5701, and based on test results, ABC hypersensitivity should be noted on the patient's allergy list. Patients who test negative are less likely to experience HSR, but they should be counseled about the symptoms of the reaction.

In a comparative trial of ABC/3TC and ZDV/3TC (both given twice daily and combined with EFV), participants from both arms achieved similar virologic responses. The ABC-treated participants experienced a greater CD4 T-cell increase at 48 weeks *[81]*. The fixed-dose combination of ABC/3TC allows for one-pill, once-daily dosing.

The ACTG 5202 study, a randomized controlled trial in more than 1,800 participants, evaluated the efficacy and safety of ABC/3TC versus TDF/FTC when used in combination with either EFV or RTV-boosted ATV. Treatment randomization was stratified based on a screening HIV RNA of <100,000 copies/mL or ≥100,000 copies/mL. An independent Data Safety Monitoring Board recommended early termination of the ≥100,000 copies/mL stratification group because of a significantly shorter time to study-defined virologic failure in the ABC/3TC arm compared with the TDF/FTC arm *[68]*. Participants who had HIV RNA levels <100,000 copies/mL at study screening remained randomized and on study; a subsequent analysis of virological responses in this lower viral load stratum showed no significant differences between ABC/3TC and TDF/FTC *[82]*. In another study (HEAT), 688 participants received ABC/3TC or TDF/FTC in combination with once-daily LPV/r. A subgroup analysis according to baseline HIV RNA of <100,000 copies/mL or ≥100,000 copies/mL yielded similar percentages of participants with HIV RNA <50 copies/mL at 96 weeks for the two regimens (63% vs. 58% for those who had <100,000 copies/mL and 56% vs. 58% for those who had ≥100,000 copies/mL, respectively) *[69]*. The ASSERT study compared open label ABC/3TC with TDF/FTC in 385 HLA-B5701-negative, ART-naïve patients; all study subjects also received EFV. At 48 weeks, a lower proportion of the ABC/3TC-treated subjects had HIV RNA <50 copies/mL (59%) compared with those receiving TDF/FTC (71%, difference 11.6%, 95% confidence interval [CI] 2.2 to 21.1) *[83]*.

An association between ABC use and MI was first reported in the D:A:D cohort. This large, multinational observational study group found that recent (within 6 months) or current use of ABC, but not TDF, predicted an increased risk of MI, particularly in participants with pre-existing cardiac risk factors *[37, 84]*. In contrast, a pooled analysis of 52 clinical trials involving more than 9,500 participants who had received ABC showed no increase in MI risk *[85]*. Several additional retrospective studies have subsequently addressed this issue, but no consensus has been reached, either on the association or a possible mechanism *[86]*.

Pending additional data, ABC/3TC should be used with caution in individuals who have plasma HIV RNA levels ≥100,000 copies/mL as well as in persons at higher risk of cardiovascular disease. However, the combination of ABC/3TC remains a good alternative dual-NRTI option for some ART-naïve patients.

ZDV/3TC (coformulated). The dual-NRTI combination of ZDV/3TC has extensive durability, safety, and tolerability experience *[3, 5, 8, 19, 87-89]*. A fixed-dose combination of ZDV/3TC is available for one-tablet, twice-daily dosing. Selection of the 3TC-associated M184V mutation has been associated with increased susceptibility to ZDV. In a comparative trial of ABC/3TC versus ZDV/3TC (both given twice daily and combined with EFV), even though virologic responses were similar in both arms, the CD4 count increase was greater in the ABC/3TC-treated patients than in the ZDV/3TC-treated patients *[81]*.

Bone marrow suppression, manifested by macrocytic anemia and/or neutropenia, is seen in some patients. ZDV also is associated with gastrointestinal toxicity, fatigue, and possibly mitochondrial toxicity, including lactic acidosis/hepatic

steatosis and lipoatrophy. In the 934 study, participants who took ZDV had less limb fat at 96 and 144 weeks than those who took TDF, and there was a significant loss of fat among ZDV recipients between 48, 96, and 144 weeks *[67]*. In ACTG 5142, limb fat was lowest in patients treated with d4T, but those treated with ZDV had less limb fat than those treated with TDF *[10]*. Primarily because of its greater toxicity compared with TDF/FTC, ZDV/3TC is now considered an alternative rather than a preferred dual-NRTI option **(BI)**.

ZDV/3TC remains the preferred option in pregnant women. This dual NRTI has the most pharmacokinetic, safety, and efficacy data for both mother and newborn. For more detailed information regarding ARV drug choices and related issues in pregnancy, see the ***Perinatal Guidelines*** *[36]*.

Acceptable Dual NRTI

ddI + (FTC or 3TC). The FTC-301A trial tested ddI + FTC with EFV in ART-naïve patients and demonstrated potent virologic suppression *[90]*. The GESIDA 3903 study compared ddI/3TC with ZDV/3TC, combined with EFV *[91]*. At 48 weeks, virologic response for ddI/3TC was noninferior to ZDV/3TC.

The ACTG 5175 trial compared three regimens in ART-naïve patients. The Data Safety Monitoring Board for this trial recommended that participants be unblinded and switched to alternative therapy if they were randomized to a regimen of ATV + enteric-coated ddI + FTC because of an inferior virologic response compared with the other two arms (once-daily EFV plus either ZDV/3TC twice daily or TDF/FTC once daily) *[60]*. Alternative PIs should be considered if ddI + (FTC or 3TC) are used. ddI use also is associated with an increased risk of pancreatitis, peripheral neuropathy, other mitochondria-associated toxicities, and possibly noncirrhotic portal hypertension *[92]*. In the D:A:D study of MI risk, the use of ddI within the previous 6 months was associated with an increased risk of MI, compared with the use of other NRTIs *[84]*. This increase in cardiovascular risk was not seen in other cohort studies *[93]*.

Based on the limited clinical trial experience with the use of ddI + 3TC (or FTC) with another ARV drug other than EFV, the unfavorable results from ACTG 5175, and the many side effects associated with ddI, the Panel considers it an acceptable but inferior option and only to be used with EFV **(CI)**.

NRTIs and Hepatitis B Virus (HBV). Three of the current NRTIs—FTC, 3TC, and TDF—have activity against HBV. Most HBV/HIV coinfected patients should use coformulated TDF/FTC (or TDF + 3TC) as their NRTI backbone to provide additional activity against HBV and to avoid selection of HBV mutation that confers resistance to 3TC/FTC. It is important to note that patients who have HBV/HIV coinfection may be at risk of acute exacerbation of hepatitis after initiation or upon discontinuation of TDF, 3TC, or FTC *[94-96]*. Thus, these patients should be monitored closely for clinical or chemical hepatitis if these drugs are initiated or discontinued. (See **Hepatitis B (HBV)/HIV Coinfection** and **Initiating Antiretroviral Therapy**.)

ALL-NRTI REGIMENS

Several clinical trials that studied triple-NRTI regimens have shown suboptimal virologic activity *[19-20, 97-100]*.

ABC/3TC/ZDV (coformulated). ABC/3TC/ZDV is the only triple-NRTI combination for which randomized, controlled trials are available. ABC/3TC/ZDV demonstrated comparable ARV activity to IDV-based *[88-89]* and NFV-based regimens *[100]* but was inferior virologically to an EFV-based regimen *[19]*. This combination is **generally not recommended (BI)** and should be used only when a preferred, an alternative, or an acceptable NNRTI-, PI-, or INSTI-based regimen is less desirable because of concerns about toxicities, drug interactions, or regimen complexity.

ZDV/3TC + TDF. The DART study demonstrated that the combination of ZDV/3TC + TDF has antiviral activity *[101]*; however, comparative data with standard regimens are not available and therefore this combination **cannot be recommended** in routine clinical practice **(BIII)**.

ZDV/3TC + ABC + TDF. A quadruple-NRTI regimen of ZDV/3TC + ABC + TDF first showed comparable virologic responses to an EFV-based regimen in a small pilot study *[102]*. A larger study randomized 322 subjects to receive TDF/FTC combined with EFV, ATV/RTV, or a quadruple-NRTI regimen with ZDV and ABC. Although the

threshold of noninferiority for the protocol-defined virologic response was satisfied by the quadruple-NRTI regimen, the proportion of patients reaching HIV RNA ≤50 copies/mL was lower with the quadruple-NRTI regimen and the rate of serious toxicity was twice as high as that observed with the EFV-based regimen *[103]*. Thus, this regimen **cannot be recommended (BI)**.

Table 6. Advantages and Disadvantages of Antiretroviral Components Recommended as Initial Antiretroviral Therapy (Updated January 10, 2011)

ARV Class	ARV Agent(s)	Advantages	Disadvantages
NNRTI (in alphabetical order)		**NNRTI Class Advantages:** • Long half-lives	**NNRTI Class Disadvantages:** • Low genetic barrier to resistance (single mutation confers resistance for EFV, NVP, and DLV); greater risk of resistance at the time of failure or treatment interruption • Potential for cross resistance • Skin rash • Potential for CYP450 drug interactions (See Tables 14, 15b, and 16b.) • Transmitted resistance to NNRTIs more common than resistance to PIs
	EFV	• Virologic responses equivalent or superior to all comparators to date • Lowest pill burden; once-daily dosing • Fixed-dose combination with TDF/FTC	• Neuropsychiatric side effects • Teratogenic in nonhuman primates, and several cases of neural tube defect reported in infants of women with first-trimester exposure. EFV is contraindicated in first trimester of pregnancy; avoid use in women with pregnancy potential. • Dyslipidemia
	NVP	• No food effect • Fewer lipid effects than EFV	• Higher incidence of rash than with other NNRTIs, including rare but serious hypersensitivity reactions (Stevens-Johnson syndrome or toxic epidermal necrolysis) • Higher incidence of hepatotoxicity than with other NNRTIs, including serious and even fatal cases of hepatic necrosis • Contraindicated in patients with moderate or severe (Child-Pugh B or C) hepatic impairment • Some data suggest that ART-naïve patients with high pre-NVP CD4 counts (>250 cells/mm^3 for females, >400 cells/mm^3 for males) are at higher risk of symptomatic hepatic events. NVP is not recommended in these patients unless benefit clearly outweighs risk. • Early virologic failure of NVP + TDF + (FTC or 3TC) in small clinical trials • Fewer clinical trial data than for EFV
PI (in alphabetical order)		**PI Class Advantages:** • Higher genetic barrier to resistance • PI resistance uncommon with failure (boosted PIs)	**PI Class Disadvantages:** • Metabolic complications (e.g., dyslipidemia, insulin resistance, hepatotoxicity) • Gastrointestinal adverse effects • CYP3A4 inhibitors and substrates: potential for drug interactions (more pronounced with RTV-based regimens) (See Tables 14 and 15a.)
	ATV	• Fewer adverse effects on lipids than other PI • Once-daily dosing • Low pill burden (two pills per day) • Good GI tolerability • Signature mutation (I50L) not associated with broad PI cross resistance	• Indirect hyperbilirubinemia sometimes leading to jaundice or scleral icterus • PR interval prolongation: generally inconsequential unless combined with another drug with similar effect • Cannot be coadministered with TDF, EFV, or NVP (See ATV/r.) • Nephrolithiasis • Skin rash • Food requirement • Absorption depends on food and low gastric pH (See Table 15a for detailed information regarding interactions with H2 antagonists, antacids, and PPIs.)
	ATV/r	• RTV boosting: higher trough ATV concentration and greater antiviral effect • Once-daily dosing • Low pill burden (two pills per day)	• More adverse effects on lipids than unboosted ATV • More hyperbilirubinemia and jaundice than unboosted ATV • Food requirement • Absorption depends on food and low gastric pH (See Table 15a for interactions with H_2 antagonists, antacids, and PPIs.) • RTV boosting required with TDF and EFV. With EFV, use ATV 400 mg and RTV 100 mg once daily (PI-naïve patients only). • Should not be coadministered with NVP

Table 6. Advantages and Disadvantages of Antiretroviral Components Recommended as Initial Antiretroviral Therapy
Page 2 of 3

ARV Class	ARV Agent(s)	Advantages	Disadvantages
	DRV/r	• Once-daily dosing	• Skin rash • Food requirement
	FPV	• No food effect	• Skin rash • Potential for PI resistance with failure, including emergence of mutations that can cause DRV cross resistance
	FPV/r	• Twice-daily dosing resulted in efficacy comparable to LPV/r • RTV boosting: higher trough APV concentration and greater antiviral effect • Once-daily dosing possible with RTV 100 mg or 200 mg daily • No food effect	• Skin rash • Hyperlipidemia • Once-daily dosing results in lower APV concentrations than twice-daily dosing • For FPV 1,400 mg + RTV 200 mg: requires 200 mg of RTV and no coformulation • Fewer data on FPV 1,400 mg + RTV 100 mg dose than on DRV/r and ATV/r
	LPV/r	• Coformulated • No food requirement • Recommended PI in pregnant women (twice daily only) • Greater CD4 count increase than with EFV-based regimens	• Requires 200 mg per day of RTV • Lower drug exposure in pregnant women—may need dose increase in third trimester • Once-daily dosing not recommended in pregnant women • Once-daily dosing: lower trough concentration than twice-daily dosing • Possible higher risk of MI associated with cumulative use of LPV/r • PR and QT interval prolongation have been reported. Use with caution in patients at risk of cardiac conduction abnormalities or receiving other drugs with similar effect.
	SQV/r	• Efficacy similar to LPV/r with less hyperlipidemia	• Highest pill burden among available PI regimens (6 pills per day) • Requires 200 mg of RTV • Food requirement • PR and/or QT interval prolongations in a healthy volunteer study • Pretreatment ECG recommended • SQV/r is not recommended for patients with any of the following conditions: (1) congenital or acquired QT prolongation; (2) pretreatment ECG >450 msec; (3) on concomitant therapy with other drugs that prolong QT interval; (4) complete AV block without implanted pacemakers; (5) risk of complete AV block.
INSTI	**RAL**	• Virologic response noninferior to EFV • Fewer drug-related adverse events and lipid changes than EFV • No food effect • Fewer drug-drug interactions than PI- or NNRTI-based regimens	• Less long-term experience in ART-naïve patients than with boosted PI- or NNRTI-based regimens • Twice-daily dosing • Lower genetic barrier to resistance than with boosted PI-based regimens • No data with NRTIs other than TDF/FTC in ART-naïve patients
CCR5 Antagonist	**MVC**	• Virologic response noninferior to EFV in post-hoc analysis of MERIT study (See text.) • Fewer adverse effects than EFV	• Requires viral tropism testing prior to initiation of therapy with additional cost and possible delay in initiation of therapy • More MVC-treated than EFV-treated patients discontinued therapy due to lack of efficacy in MERIT study • Less long-term experience in ART-naïve patients than with boosted PI- or NNRTI-based regimens • Limited experience with 2-NRTI other than ZDV/3TC • Twice-daily dosing • CYP 3A4 substrate, dosing depends on presence or absence of concomitant CYP3A4 inducer(s) or inhibitor(s)
Dual NRTIs		**Dual-NRTI Class Advantage:** Established backbone of combination ART	**Dual-NRTI Class Disadvantage:** Rare but serious cases of lactic acidosis with hepatic steatosis reported with d4T, ddI, and ZDV

Table 6. Advantages and Disadvantages of Antiretroviral Components Recommended as Initial Antiretroviral Therapy

Dual-NRTI pairs (in alphabetical order)	**ABC/3TC**	• Virologic response noninferior to ZDV/3TC • Better CD4 count response than with ZDV/3TC • Once-daily dosing • Coformulation • No food effect • No cumulative TAM-mediated resistance	• Potential for ABC HSR in patients with HLA-B*5701 • Potential for increased cardiovascular events, especially in patients with cardiovascular risk factors • Inferior virologic responses when compared with TDF/FTC in patients with baseline HIV RNA >100,000 copies/mL in ACTG 5202 study; however, this was not seen in the HEAT study.
	ddI + (3TC or FTC)	• Once-daily dosing • No cumulative TAM-mediated resistance	• Peripheral neuropathy, pancreatitis • Reports of noncirrhotic portal hypertension • Food effect; must be taken on an empty stomach • Requires dosing separation from some PIs • Increase in toxicities when used with ribavirin, TDF, d4T, or hydroxyurea • Preliminary data showed inferior virologic responses of ATV/ddI/FTC when compared with EFV/ZDV/3TC or EFV/TDF/FTC. Combination of ATV/ddI/FTC should be avoided.
	TDF/FTC or TDF + 3TC	• Better virologic responses than with ZDV/3TC • Better virologic responses than with ABC/3TC in patients with baseline HIV RNA >100,000 copies/mL in ACTG 5202 study; however, this was not seen in the HEAT study. • Active against HBV; recommended dual-NRTI for HBV/HIV coinfection • Once-daily dosing • No food effect • Coformulated (TDF/FTC) and (EFV/TDF/FTC) • No cumulative TAM-mediated resistance	• Potential for renal impairment, including rare reports of Fanconi syndrome and acute renal insufficiency • Early virologic failure of NVP + TDF + (FTC or 3TC) in small clinical trials • Potential for decrease in bone mineral density
	ZDV/3TC	• Coformulated (ZDV/3TC and ZDV/3TC/ABC) • No food effect (although better tolerated with food) • Preferred 2 NRTI in pregnant women	• Bone marrow suppression, especially anemia and neutropenia • GI intolerance, headache • Mitochondrial toxicity, including lipoatrophy, lactic acidosis, hepatic steatosis • Inferior to TDF/FTC in combination with EFV • Diminished CD4 T-cell responses compared with ABC/3TC

Acronyms: 3TC = lamivudine, ABC = abacavir, ART = antiretroviral therapy, ARV = antiretroviral, ATV = atazanavir, ATV/r = atazanavir/ritonavir, AV = atrioventricular, CYP = cytochrome P, ddI = didanosine, DLV = delavirdine, DRV/r = darunavir/ritonavir, ECG = electrocardiogram, EFV = efavirenz, FPV = fosamprenavir, FPV/r = fosamprenavir/ ritonavir, FTC = emtricitabine, GI = gastrointestinal, HBV = hepatitis B virus, HSR = hypersensitivity reaction, INSTI = integrase strand transfer inhibitor, LPV/r = lopinavir/ritonavir, MI = myocardial infarction, msec = milliseconds, MVC = maraviroc, NNRTI = non-nucleoside reverse transcriptase inhibitor, NRTI = nucleoside reverse transcriptase inhibitor, NVP = nevirapine, PI = protease inhibitor, PPI = proton pump inhibitor, SQV/r = saquinavir/ritonavir, TAM = thymidine analogue mutation, TDF = tenofovir, ZDV = zidovudine

Table 7. Antiretroviral Components Not Recommended as Initial Therapy
(Updated December 1, 2009)

ARV Drugs or Components (in alphabetical order)	**Reasons for NOT recommending as initial therapy**
ABC/3TC/ZDV (coformulated) as triple-NRTI combination regimen **(BI)**	• Inferior virologic efficacy
ABC + 3TC + ZDV + TDF as quadruple-NRTI combination **(BI)**	• Inferior virologic efficacy
ABC + ddI **(BIII)**	• Insufficient data in ART-naïve patients
ABC + TDF **(BIII)**	• Insufficient data in ART-naïve patients
DRV (unboosted)	• Use without RTV has not been studied
DLV **(BII)**	• Inferior virologic efficacy • Inconvenient (three times daily) dosing
ddI + TDF **(BII)**	• High rate of early virologic failure • Rapid selection of resistance mutations • Potential for immunologic nonresponse/CD4 T-cell decline • Increased ddI drug exposure and toxicities
T-20 **(BIII)**	• No clinical trial experience in ART-naïve patients • Requires twice-daily subcutaneous injections
ETR **(BIII)**	• Insufficient data in ART-naïve patients
IDV (unboosted) **(BIII)**	• Inconvenient dosing (three times daily with meal restrictions) • Fluid requirement
IDV (RTV-boosted) **(BIII)**	• High incidence of nephrolithiasis
NFV **(BI)**	• Inferior virologic efficacy • High incidence of diarrhea
RTV as sole PI **(BIII)**	• High pill burden • Gastrointestinal intolerance
SQV (unboosted) **(BI)**	• Inferior virologic efficacy
d4T + 3TC **(BI)**	• Significant toxicities including lipoatrophy; peripheral neuropathy; and hyperlactatemia, including symptomatic and life-threatening lactic acidosis, hepatic steatosis, and pancreatitis
TPV (ritonavir-boosted) **(BI)**	• Inferior virologic efficacy

Acronyms: 3TC = lamivudine, ABC = abacavir, ARV = antiretroviral, d4T = stavudine, ddI = didanosine, DLV = delavirdine, DRV = darunavir, ETR = etravirine; IDV = indinavir, IDV/r = ritonavir-boosted indinavir, NFV = nelfinavir, NRTI = nucleoside reverse transcriptase inhibitor, RTV = ritonavir, SQV = sacquinavir, T-20 = enfuvirtide, TDF = tenofovir, TPV = tipranavir, ZDV = zidovudine

References

1. Gulick RM, Ribaudo HJ, Shikuma CM, et al. Three- vs four-drug antiretroviral regimens for the initial treatment of HIV-1 infection: a randomized controlled trial. *JAMA.* 2006;296(7):769-781.
2. Gallant JE, Staszewski S, Pozniak AL, et al. Efficacy and safety of tenofovir DF vs stavudine in combination therapy in antiretroviral-naive patients: a 3-year randomized trial. *JAMA.* 2004;292(2):191-201.
3. Staszewski S, Morales-Ramirez J, Tashima KT, et al. Efavirenz plus zidovudine and lamivudine, efavirenz plus indinavir, and indinavir plus zidovudine and lamivudine in the treatment of HIV-1 infection in adults. Study 006 Team. *N Engl J Med.* 1999;341(25):1865-1873.
4. Riddler SA, Haubrich R, DiRienzo AG, et al. Class-sparing regimens for initial treatment of HIV-1 infection. *N Engl J Med.* 2008;358(20):2095-2106.
5. Squires K, Lazzarin A, Gatell JM, et al. Comparison of once-daily atazanavir with efavirenz, each in combination with fixed-dose zidovudine and lamivudine, as initial therapy for patients infected with HIV. *J Acquir Immune Defic Syndr.* 2004;36(5):1011-1019.
6. Lennox JL, DeJesus E, Lazzarin A, et al. Safety and efficacy of raltegravir-based versus efavirenz-based combination therapy in treatment-naive patients with HIV-1 infection: a multicentre, double-blind randomised controlled trial. *Lancet.* 2009;374(9692):796-806.
7. Cooper DA, Heera J, Goodrich J, et al. Maraviroc versus efavirenz, both in combination with zidovudine-lamivudine, for the treatment of antiretroviral-naive subjects with CCR5-tropic HIV-1 infection. *J Infect Dis.* 2010;201(6):803-813.
8. Robbins GK, De Gruttola V, Shafer RW, et al. Comparison of sequential three-drug regimens as initial therapy for HIV-1 infection. *N Engl J Med.* 2003;349(24):2293-2303.
9. Sierra Madero J, Villasis A, Mendez P, et al. A prospective, randomized, open label trial of efavirenz versus lopinavir/ritonavir based HAART among antiretroviral therapy naïve, HIV infected individuals presenting for care with CD4 cell counts <200/mm3. Paper presented at: 17th International AIDS Conference; August 3-8, 2008; Mexico City, Mexico. Abstract TUAB0104.
10. Haubrich RH, Riddler SA, DiRienzo AG, et al. Metabolic outcomes in a randomized trial of nucleoside, nonnucleoside and protease inhibitor-sparing regimens for initial HIV treatment. *AIDS.* 2009;23(9):1109-1118.
11. Hirsch MS, Gunthard HF, Schapiro JM, et al. Antiretroviral drug resistance testing in adult HIV-1 infection: 2008 recommendations of an International AIDS Society-USA panel. *Clin Infect Dis.* 2008;47(2):266-285.
12. Kim D, Wheeler W, Ziebell R, et al. Prevalence of transmitted antiretroviral drug resistance among newly-diagnosed HIV-1-infected persons, US, 2007. Paper presented at: 17th Conference on Retroviruses and Opportunistic Infections; February 16-19, 2010; San Francisco, CA. Abstract 580.
13. Lennox JL, Dejesus E, Berger DS, et al. Raltegravir versus Efavirenz regimens in treatment-naive HIV-1-infected patients: 96-week efficacy, durability, subgroup, safety, and metabolic analyses. *J Acquir Immune Defic Syndr.* 2010;55(1):39-48.
14. Novak RM, Chen L, MacArthur RD, et al. Prevalence of antiretroviral drug resistance mutations in chronically HIV-infected, treatment-naive patients: implications for routine resistance screening before initiation of antiretroviral therapy. *Clin Infect Dis.* 2005;40(3):468-474.
15. Wensing AM, van de Vijver DA, Angarano G, et al. Prevalence of drug-resistant HIV-1 variants in untreated individuals in Europe: implications for clinical management. *J Infect Dis.* 2005;192(6):958-966.
16. Weinstock HS, Zaidi I, Heneine W, et al. The epidemiology of antiretroviral drug resistance among drug-naive HIV-1-infected persons in 10 US cities. *J Infect Dis.* 2004;189(12):2174-2180.
17. Andries K, Azijn H, Thielemans T, et al. TMC125, a novel next-generation nonnucleoside reverse transcriptase inhibitor active against nonnucleoside reverse transcriptase inhibitor-resistant human immunodeficiency virus type 1. *Antimicrob Agents Chemother.* 2004;48(12):4680-4686.
18. Cassetti I, Madruga JV, Etzel A, et al. The safety and efficacy of tenofovir DF (TDF) in combination with lamivudine (3TC) and efavirenz (EFV) in antiretroviral-naïve patients through seven years. Paper presented at: 17th International AIDS Conference; August 3-8, 2008; Mexico City, Mexico. Abstract TUPE0057.
19. Gulick RM, Ribaudo HJ, Shikuma CM, et al. Triple-nucleoside regimens versus efavirenz-containing regimens for the initial treatment of HIV-1 infection. *N Engl J Med.* 2004;350(18):1850-1861.
20. Gallant JE, Rodriguez AE, Weinberg WG, et al. Early virologic nonresponse to tenofovir, abacavir, and lamivudine in HIV-infected antiretroviral-naive subjects. *J Infect Dis.* 2005;192(11):1921-1930.
21. van Leth F, Phanuphak P, Ruxrungtham K, et al. Comparison of first-line antiretroviral therapy with regimens including nevirapine, efavirenz, or both drugs, plus stavudine and lamivudine: a randomised open-label trial, the 2NN Study. *Lancet.* 2004;363(9417):1253-1263.
22. Nunez M, Soriano V, Martin-Carbonero L, et al. SENC (Spanish efavirenz vs. nevirapine comparison) trial: a randomized, open-label study in HIV-infected naive individuals. *HIV Clin Trials.* 2002;3(3):186-194.
23. Bristol Myers Squibb. Sustiva September 2009 Prescribing Information 2009; http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020972s033,021360s021lbl.pdf. Accessed Nov. 11, 2009.
24. Fundaro C, Genovese O, Rendeli C, et al. Myelomeningocele in a child with intrauterine exposure to efavirenz. *AIDS.* 2002;16(2):299-300.
25. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral Pregnancy Registry international interim report for 1 Jan 1989 - 31 January 2007. 2007; http://www.APRegistry.com.
26. Soriano V, Koppe S, Migrono H, et al. Prospective randomized comparison of nevirapine and atazanavir/ritonavir both combined with tenofovir DF/emtricitabine in treatment-naïve HIV-1 infected patients: ARTEN Study week 48 results. Paper

presented at: 5th International AIDS Society Conference on HIV Pathogenesis, Treatment, and Prevention; July 19-22, 2009; Cape Town, South Africa. Abstract LBPEB07.

27. Towner W, Kerrigan HL, LaRiviere M, et al. Efficacy of a once daily (QD) regimen of nevirapine (NVP), lamivudine (3TC) and tenofovir (TDF) in treatment-naïve HIV infected patients: A pilot study. Paper presented at: 7th International Congress on Drug Therapy in HIV Infection; November 14-17, 2004; Glasgow, Scotland. Abstract P49.
28. Rey D, Hoen B, Chavanet P, et al. High rate of early virological failure with the once-daily tenofovir/lamivudine/nevirapine combination in naive HIV-1-infected patients. *J Antimicrob Chemother.* 2009;63(2):380-388.
29. Lapadula G, Costarelli S, Quiros-Roldan E, et al. Risk of early virological failure of once-daily tenofovir-emtricitabine plus twice-daily nevirapine in antiretroviral therapy-naive HIV-infected patients. *Clin Infect Dis.* 2008;46(7):1127-1129.
30. Sanne I, Mommeja-Marin H, Hinkle J, et al. Severe hepatotoxicity associated with nevirapine use in HIV-infected subjects. *J Infect Dis.* 2005;191(6):825-829.
31. Baylor MS, Johann-Liang R. Hepatotoxicity associated with nevirapine use. *J Acquir Immune Defic Syndr.* 2004;35(5):538-539.
32. Boehringer Ingelheim. Dear Health Care Professional Letter: Clarification of risk factors for severe, life-threatening and fatal hepatotoxicity with VIRAMUNE® (nevirapine). February 2004.
33. Peters P, Stringer J, McConnell MS, et al. Nevirapine-associated hepatotoxicity was not predicted by CD4 count >/=250 cells/muL among women in Zambia, Thailand and Kenya. *HIV Med.* 2010.
34. Coffie PA, Tonwe-Gold B, Tanon AK, et al. Incidence and risk factors of severe adverse events with nevirapine-based antiretroviral therapy in HIV-infected women. MTCT-Plus program, Abidjan, Cote d'Ivoire. *BMC Infect Dis.* 2010;10:188.
35. Kesselring AM, Wit FW, Sabin CA, et al. Risk factors for treatment-limiting toxicities in patients starting nevirapine-containing antiretroviral therapy. *AIDS.* 2009;23(13):1689-1699.
36. Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission. Recommendations for use of antiretroviral drugs in pregnant HIV-1-infected women for maternal health and interventions to reduce perinatal HIV transmission in the United States. May 24, 2010:1-117. http://aidsinfo.nih.gov/contentfiles/PerinatalGL.pdf.
37. Worm SW, Sabin C, Weber R, et al. Risk of myocardial infarction in patients with HIV infection exposed to specific individual antiretroviral drugs from the 3 major drug classes: the data collection on adverse events of anti-HIV drugs (D:A:D) study. *J Infect Dis.* 2010;201(3):318-330.
38. Lang S, Mary-Krause M, Cotte L, et al. Impact of individual antiretroviral drugs on the risk of myocardial infarction in human immunodeficiency virus-infected patients: a case-control study nested within the French Hospital Database on HIV ANRS cohort CO4. *Arch Intern Med.* 2010;170(14):1228-1238.
39. Food and Drug Administration (FDA). Invirase (package insert). October 2010. http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020628s033,021785s010lbl.pdf.
40. Shulman N, Zolopa A, Havlir D, et al. Virtual inhibitory quotient predicts response to ritonavir boosting of indinavir-based therapy in human immunodeficiency virus-infected patients with ongoing viremia. *Antimicrob Agents Chemother.* 2002;46(12):3907-3916.
41. Dragsted UB, Gerstoft J, Pedersen C, et al. Randomized trial to evaluate indinavir/ritonavir versus saquinavir/ritonavir in human immunodeficiency virus type 1-infected patients: the MaxCmin1 Trial. *J Infect Dis.* 2003;188(5):635-642.
42. Dragsted UB, Gerstoft J, Youle M, et al. A randomized trial to evaluate lopinavir/ritonavir versus saquinavir/ritonavir in HIV-1-infected patients: the MaxCmin2 trial. *Antivir Ther.* 2005;10(6):735-743.
43. Malan DR, Krantz E, David N, et al. Efficacy and safety of atazanavir, with or without ritonavir, as part of once-daily highly active antiretroviral therapy regimens in antiretroviral-naive patients. *J Acquir Immune Defic Syndr.* 2008;47(2):161-167.
44. Molina JM, Andrade-Villanueva J, Echevarria J, et al. Once-daily atazanavir/ritonavir versus twice-daily lopinavir/ritonavir, each in combination with tenofovir and emtricitabine, for management of antiretroviral-naive HIV-1-infected patients: 48 week efficacy and safety results of the CASTLE study. *Lancet.* 2008;372(9639):646-655.
45. Molina JM, Andrade-Villanueva J, Echevarria J, et al. Once-daily atazanavir/ritonavir compared with twice-daily lopinavir/ritonavir, each in combination with tenofovir and emtricitabine, for management of antiretroviral-naive HIV-1-infected patients: 96-week efficacy and safety results of the CASTLE study. *J Acquir Immune Defic Syndr.* 2010;53(3):323-332.
46. Chan-Tack KM, Truffa MM, Struble KA, et al. Atazanavir-associated nephrolithiasis: cases from the US Food and Drug Administration's Adverse Event Reporting System. *AIDS.* 2007;21(9):1215-1218.
47. Ortiz R, Dejesus E, Khanlou H, et al. Efficacy and safety of once-daily darunavir/ritonavir versus lopinavir/ritonavir in treatment-naive HIV-1-infected patients at week 48. *AIDS.* 2008;22(12):1389-1397.
48. Mills AM, Nelson M, Jayaweera D, et al. Once-daily darunavir/ritonavir vs. lopinavir/ritonavir in treatment-naive, HIV-1-infected patients: 96-week analysis. *AIDS.* 2009;23(13):1679-1688.
49. Eron J, Jr., Yeni P, Gathe J, Jr., et al. The KLEAN study of fosamprenavir-ritonavir versus lopinavir-ritonavir, each in combination with abacavir-lamivudine, for initial treatment of HIV infection over 48 weeks: a randomised non-inferiority trial. *Lancet.* 2006;368(9534):476-482.
50. Pulido F, Estrada V, Baril JG, et al. Long-term efficacy and safety of fosamprenavir plus ritonavir versus lopinavir/ritonavir in combination with abacavir/lamivudine over 144 weeks. *HIV Clin Trials.* 2009;10(2):76-87.
51. Gathe JC, Jr., Ive P, Wood R, et al. SOLO: 48-week efficacy and safety comparison of once-daily fosamprenavir /ritonavir versus twice-daily nelfinavir in naive HIV-1-infected patients. *AIDS.* 2004;18(11):1529-1537.
52. Smith KY, Weinberg WG, Dejesus E, et al. Fosamprenavir or atazanavir once daily boosted with ritonavir 100 mg, plus tenofovir/emtricitabine, for the initial treatment of HIV infection: 48-week results of ALERT. *AIDS Res Ther.* 2008;5:5.
53. Walmsley S, Bernstein B, King M, et al. Lopinavir-ritonavir versus nelfinavir for the initial treatment of HIV infection. *N Engl J Med.* 2002;346(26):2039-2046.
54. Murphy RL, da Silva BA, Hicks CB, et al. Seven-year efficacy of a lopinavir/ritonavir-based regimen in antiretroviral-naive HIV-1-infected patients. *HIV Clin Trials.* 2008;9(1):1-10.

55. Eron JJ, Feinberg J, Kessler HA, et al. Once-daily versus twice-daily lopinavir/ritonavir in antiretroviral-naive HIV-positive patients: a 48-week randomized clinical trial. *J Infect Dis.* 2004;189(2):265-272.
56. Molina JM, Podsadecki TJ, Johnson MA, et al. A lopinavir/ritonavir-based once-daily regimen results in better compliance and is non-inferior to a twice-daily regimen through 96 weeks. *AIDS Res Hum Retroviruses.* 2007;23(12):1505-1514.
57. Gathe J, da Silva BA, Cohen DE, et al. A once-daily lopinavir/ritonavir-based regimen is noninferior to twice-daily dosing and results in similar safety and tolerability in antiretroviral-naive subjects through 48 weeks. *J Acquir Immune Defic Syndr.* 2009;50(5):474-481.
58. Murphy RL, Sanne I, Cahn P, et al. Dose-ranging, randomized, clinical trial of atazanavir with lamivudine and stavudine in antiretroviral-naive subjects: 48-week results. *AIDS.* 2003;17(18):2603-2614.
59. Sanne I, Piliero P, Squires K, et al. Results of a phase 2 clinical trial at 48 weeks (AI424-007): a dose-ranging, safety, and efficacy comparative trial of atazanavir at three doses in combination with didanosine and stavudine in antiretroviral-naive subjects. *J Acquir Immune Defic Syndr.* 2003;32(1):18-29.
60. Campbell T, Smeaton L, De Grutolla V, et al. PEARLS (ACTG A5175): a multinational study of didanosine-EC, emtricitabine and atazanavir vs. co-formulated zidovudine/lamivudine and efavirenz for initial treatment of HIV-1 infection. Paper presented at: 17th International AIDS Conference; 2008; Mexico City, Mexico. Abstract THAB0404.
61. Rodriguez-French A, Boghossian J, Gray GE, et al. The NEAT study: a 48-week open-label study to compare the antiviral efficacy and safety of GW433908 versus nelfinavir in antiretroviral therapy-naive HIV-1-infected patients. *J Acquir Immune Defic Syndr.* 2004;35(1):22-32.
62. Mitsuya Y, Liu TF, Rhee SY, et al. Prevalence of darunavir resistance-associated mutations: patterns of occurrence and association with past treatment. *J Infect Dis.* 2007;196(8):1177-1179.
63. Poveda E, de Mendoza C, Martin-Carbonero L, et al. Prevalence of darunavir resistance mutations in HIV-1-infected patients failing other protease inhibitors. *J Antimicrob Chemother.* 2007;60(4):885-888.
64. Walmsley S, Avihingsanon A, Slim J, et al. Gemini: a noninferiority study of saquinavir/ritonavir versus lopinavir/ritonavir as initial HIV-1 therapy in adults. *J Acquir Immune Defic Syndr.* 2009;50(4):367-374.
65. Heera J, Ive P, Botes M, et al. The MERIT study of maraviroc in antiretroviral-naïve patients with R5 HIV-1: 96-weeks results. Paper presented at: 5th International AIDS Society Conference on HIV Pathogenesis, Treatment, and Prevention; July 19-22, 2009; Cape Town, South Africa. Abstract TUAB103.
66. Ait-Khaled M, Stone C, Amphlett G, et al. M184V is associated with a low incidence of thymidine analogue mutations and low phenotypic resistance to zidovudine and stavudine. *AIDS.* 2002;16(12):1686-1689.
67. Arribas JR, Pozniak AL, Gallant JE, et al. Tenofovir disoproxil fumarate, emtricitabine, and efavirenz compared with zidovudine/lamivudine and efavirenz in treatment-naive patients: 144-week analysis. *J Acquir Immune Defic Syndr.* 2008;47(1):74-78.
68. Sax PE, Tierney C, Collier AC, et al. Abacavir-lamivudine versus tenofovir-emtricitabine for initial HIV-1 therapy. *N Engl J Med.* 2009;361(23):2230-2240.
69. Smith KY, Patel P, Fine D, et al. Randomized, double-blind, placebo-matched, multicenter trial of abacavir/lamivudine or tenofovir/emtricitabine with lopinavir/ritonavir for initial HIV treatment. *AIDS.* 2009;23(12):1547-1556.
70. Zimmermann AE, Pizzoferrato T, Bedford J, et al. Tenofovir-associated acute and chronic kidney disease: a case of multiple drug interactions. *Clin Infect Dis.* 2006;42(2):283-290.
71. Karras A, Lafaurie M, Furco A, et al. Tenofovir-related nephrotoxicity in human immunodeficiency virus-infected patients: three cases of renal failure, Fanconi syndrome, and nephrogenic diabetes insipidus. *Clin Infect Dis.* 2003;36(8):1070-1073.
72. Moore R, Keruly J, Gallant J. Tenofovir and renal dysfunction in clinical practice. Paper presented at: 14th Conference on Retrovirus and Opportunistic Infections; February 25-28, 2007; Los Angeles, CA. Abstract 832.
73. Kearney BP, Mathias A, Mittan A, et al. Pharmacokinetics and safety of tenofovir disoproxil fumarate on coadministration with lopinavir/ritonavir. *J Acquir Immune Defic Syndr.* 2006;43(3):278-283.
74. Kiser JJ, Carten ML, Aquilante CL, et al. The effect of lopinavir/ritonavir on the renal clearance of tenofovir in HIV-infected patients. *Clin Pharmacol Ther.* 2008;83(2):265-272.
75. Gallant JE, Moore RD. Renal function with use of a tenofovir-containing initial antiretroviral regimen. *AIDS.* 2009;23(15):1971-1975.
76. Goicoechea M, Liu S, Best B, et al. Greater tenofovir-associated renal function decline with protease inhibitor-based versus nonnucleoside reverse-transcriptase inhibitor-based therapy. *J Infect Dis.* 2008;197(1):102-108.
77. McComsey G, Kitch D, Daar E, et al. Bone and limb fat outcomes of ACTG A5224a, a substudy of ACTG A5202: A prospective, randomized, partially blinded Phase III trial of ABC/3TC or TDF/FTC with EFV or ATV/r for initial treatment of HIV-1 infection. Paper presented at: 17th Conference on Retroviruses and Opportunistic Infections; February 16-19, 2010; San Francisco, CA. Abstract 106LB.
78. Stellbrink HJ, Orkin C, Arribas JR, et al. Comparison of changes in bone density and turnover with abacavir-lamivudine versus tenofovir-emtricitabine in HIV-infected adults: 48-week results from the ASSERT study. *Clin Infect Dis.* 2010;51(8):963-972.
79. Mallal S, Phillips E, Carosi G, et al. HLA-B*5701 screening for hypersensitivity to abacavir. *N Engl J Med.* 2008;358(6):568-579.
80. Saag M, Balu R, Phillips E, et al. High sensitivity of human leukocyte antigen-b*5701 as a marker for immunologically confirmed abacavir hypersensitivity in white and black patients. *Clin Infect Dis.* 2008;46(7):1111-1118.
81. DeJesus E, Herrera G, Teofilo E, et al. Abacavir versus zidovudine combined with lamivudine and efavirenz, for the treatment of antiretroviral-naive HIV-infected adults. *Clin Infect Dis.* 2004;39(7):1038-1046.
82. Daar E, Tierney C, Fischl M, et al. Final results of ABC/3TC or TDF/FTC with either EFV or ATV/r in treatment-naïve HIV-infected patients. Paper presented at: 17th Conference on Retroviruses and Opportunistic Infections; February 16-19, 2010; San Francisco, CA. Abstract 59LB.

83. Post FA, Moyle GJ, Stellbrink HJ, et al. Randomized comparison of renal effects, efficacy, and safety with once-daily abacavir/lamivudine versus tenofovir/emtricitabine, administered with efavirenz, in antiretroviral-naive, HIV-1-infected adults: 48-week results from the ASSERT study. *J Acquir Immune Defic Syndr.* 2010;55(1):49-57.
84. Sabin CA, Worm SW, Weber R, et al. Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients enrolled in the D:A:D study: a multi-cohort collaboration. *Lancet.* 2008;371(9622):1417-1426.
85. Brothers CH, Hernandez JE, Cutrell AG, et al. Risk of myocardial infarction and abacavir therapy: no increased risk across 52 GlaxoSmithKline-sponsored clinical trials in adult subjects. *J Acquir Immune Defic Syndr.* 2009;51(1):20-28.
86. Behrens GM, Reiss P. Abacavir and cardiovascular risk. *Curr Opin Infect Dis.* 2010;23(1):9-14.
87. Podzamczer D, Ferrer E, Consiglio E, et al. A randomized clinical trial comparing nelfinavir or nevirapine associated to zidovudine/lamivudine in HIV-infected naive patients (the Combine Study). *Antivir Ther.* 2002;7(2):81-90.
88. Vibhagool A, Cahn P, Schechter M, et al. Triple nucleoside treatment with abacavir plus the lamivudine/zidovudine combination tablet (COM) compared to indinavir/COM in antiretroviral therapy-naive adults: results of a 48-week open-label, equivalence trial (CNA3014). *Curr Med Res Opin.* 2004;20(7):1103-1114.
89. Staszewski S, Keiser P, Montaner J, et al. Abacavir-lamivudine-zidovudine vs indinavir-lamivudine-zidovudine in antiretroviral-naive HIV-infected adults: A randomized equivalence trial. *JAMA.* 2001;285(9):1155-1163.
90. Saag MS, Cahn P, Raffi F, et al. Efficacy and safety of emtricitabine vs stavudine in combination therapy in antiretroviral-naive patients: a randomized trial. *JAMA.* 2004;292(2):180-189.
91. Berenguer J, Gonzalez J, Ribera E, et al. Didanosine, lamivudine, and efavirenz versus zidovudine, lamivudine, and efavirenz for the initial treatment of HIV type 1 infection: final analysis (48 weeks) of a prospective, randomized, noninferiority clinical trial, GESIDA 3903. *Clin Infect Dis.* 2008;47(8):1083-1092.
92. Kovari H, Ledergerber B, Peter U, et al. Association of noncirrhotic portal hypertension in HIV-infected persons and antiretroviral therapy with didanosine: a nested case-control study. *Clin Infect Dis.* 2009;49(4):626-635.
93. The SMART/INSIGHT and the D:A:D Study Groups TSIatDADSG. Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients. *AIDS.* 2008;22(14):F17-24.
94. Drake A, Mijch A, Sasadeusz J. Immune reconstitution hepatitis in HIV and hepatitis B coinfection, despite lamivudine therapy as part of HAART. *Clin Infect Dis.* 2004;39(1):129-132.
95. Bessesen M, Ives D, Condreay L, et al. Chronic active hepatitis B exacerbations in human immunodeficiency virus-infected patients following development of resistance to or withdrawal of lamivudine. *Clin Infect Dis.* 1999;28(5):1032-1035.
96. Sellier P, Clevenbergh P, Mazeron MC, et al. Fatal interruption of a 3TC-containing regimen in a HIV-infected patient due to re-activation of chronic hepatitis B virus infection. *Scand J Infect Dis.* 2004;36(6-7):533-535.
97. Barnas D, Koontz D, Bazmi H, et al. Clonal resistance analyses of HIV type-1 after failure of therapy with didanosine, lamivudine and tenofovir. *Antivir Ther.* 2010;15(3):437-441.
98. Gerstoft J, Kirk O, Obel N, et al. Low efficacy and high frequency of adverse events in a randomized trial of the triple nucleoside regimen abacavir, stavudine and didanosine. *AIDS.* 2003;17(14):2045-2052.
99. Bartlett JA, Johnson J, Herrera G, et al. Long-term results of initial therapy with abacavir and lamivudine combined with efavirenz, amprenavir/ritonavir, or stavudine. *J Acquir Immune Defic Syndr.* 2006;43(3):284-292.
100. Kumar PN, Rodriguez-French A, Thompson MA, et al. A prospective, 96-week study of the impact of Trizivir, Combivir/nelfinavir, and lamivudine/stavudine/nelfinavir on lipids, metabolic parameters and efficacy in antiretroviral-naive patients: effect of sex and ethnicity. *HIV Med.* 2006;7(2):85-98.
101. DART Virology Group and Trial Team. Virological response to a triple nucleoside/nucleotide analogue regimen over 48 weeks in HIV-1-infected adults in Africa. *AIDS.* 2006;20(10):1391-1399.
102. Moyle G, Higgs C, Teague A, et al. An open-label, randomized comparative pilot study of a single-class quadruple therapy regimen versus a 2-class triple therapy regimen for individuals initiating antiretroviral therapy. *Antivir Ther.* 2006;11(1):73-78.
103. Puls RL, Srasuebkul P, Petoumenos K, et al. Efavirenz versus boosted atazanavir or zidovudine and abacavir in antiretroviral treatment-naive, HIV-infected subjects: week 48 data from the Altair study. *Clin Infect Dis.* 2010;51(7):855-864.

What Not to Use (January 10, 2011)

Some antiretroviral (ARV) regimens or components are not generally recommended because of suboptimal antiviral potency, unacceptable toxicities, or pharmacologic concerns. These are summarized below.

ANTIRETROVIRAL REGIMENS NOT RECOMMENDED

Monotherapy with nucleoside reverse transcriptase inhibitor (NRTI). Single-NRTI therapy does not demonstrate potent and sustained antiviral activity and **should not be used (AII)**. For prevention of mother-to-child transmission (PMTCT), zidovudine (ZDV) monotherapy is not recommended but might be considered in certain unusual circumstances in women with HIV RNA <1,000 copies/mL, although the use of a potent combination regimen is preferred. (See ***Perinatal Guidelines*** *[1]*, available at **http://aidsinfo.nih.gov**.)

Single-drug treatment regimens with a ritonavir (RTV)-boosted protease inhibitor (PI), either lopinavir (LPV) *[2]*, atazanavir (ATV) *[3]*, or darunavir (DRV) *[4-5]* are under investigation with mixed results, and **cannot be recommended** outside of a clinical trial at this time.

Dual-NRTI regimens. These regimens **are not recommended** because they have not demonstrated potent and sustained antiviral activity compared with triple-drug combination regimens **(AI)** *[6]*.

Triple-NRTI regimens. In general, triple-NRTI regimens other than abacavir/lamivudine/zidovudine (ABC/3TC/ZDV) **(BI)** and possibly lamivudine/zidovudine + tenofovir (3TC/ZDV + TDF) **(BII) should not be used** because of suboptimal virologic activity *[7-9]* or lack of data **(AI)**.

ANTIRETROVIRAL COMPONENTS NOT RECOMMENDED

Atazanavir (ATV) + indinavir (IDV). Both of these PIs can cause Grade 3 to 4 hyperbilirubinemia and jaundice. Additive adverse effects may be possible when these agents are used concomitantly. Therefore, these two PIs **are not recommended** for combined use **(AIII)**.

Didanosine (ddI) + stavudine (d4T). The combined use of ddI and d4T as a dual-NRTI backbone can result in a high incidence of toxicities, particularly peripheral neuropathy, pancreatitis, and lactic acidosis *[10-13]*. This combination has been implicated in the deaths of several HIV-infected pregnant women secondary to severe lactic acidosis with or without hepatic steatosis and pancreatitis *[14]*. Therefore, the combined use of ddI and d4T **is not recommended (AII)**.

Didanosine (ddI) + tenofovir (TDF). Use of ddI + TDF may increase ddI concentrations *[15]* and serious ddI-associated toxicities including pancreatitis and lactic acidosis *[16-17]*. These toxicities may be lessened by ddI dose reduction. The use of this combination has also been associated with immunologic nonresponse or CD4 cell decline despite viral suppression *[18-19]*, high rates of early virologic failure *[20-21]*, and rapid selection of resistance mutations *[20, 22]*. Because of these adverse outcomes, this dual-NRTI combination **is not generally recommended (AII)**. Clinicians caring for patients who are clinically stable on regimens containing ddI + TDF should consider altering the NRTIs to avoid this combination.

Two-non-nucleoside reverse transcriptase inhibitor (2-NNRTI) combinations. In the 2NN trial, ARV-naïve participants were randomized to receive once- or twice-daily nevirapine (NVP) versus efavirenz (EFV) versus EFV plus NVP, all combined with d4T and 3TC *[23]*. A higher frequency of clinical adverse events that led to treatment discontinuation was reported in participants randomized to the two-NNRTI arm. Both EFV and NVP may induce metabolism of etravirine (ETR), which leads to reduction in ETR drug exposure *[24]*. Based on these findings, the Panel **does not recommend using two NNRTIs in combination in any regimen (AI)**.

Efavirenz (EFV) in first trimester of pregnancy and in women with significant childbearing potential. EFV use was associated with significant teratogenic effects in nonhuman primates at drug exposures similar to those representing human exposure. Several cases of congenital anomalies have been reported after early human gestational exposure to EFV *[25-26]*. EFV **should be avoided** in pregnancy, particularly during the first trimester, and in women of childbearing potential who are trying to conceive or who are not using effective and consistent contraception **(AIII)**. If no other ARV options are available for the woman who is pregnant or at risk of becoming pregnant, the provider should consult with a clinician who has expertise in both HIV infection and pregnancy. (See ***Perinatal Guidelines*** *[1]*, available at **http://aidsinfo.nih.gov**.)

Emtricitabine (FTC) + lamivudine (3TC). Both of these drugs have similar resistance profiles and have minimal additive antiviral activity. Inhibition of intracellular phosphorylation may occur *in vivo*, as seen with other dual-cytidine analog combinations *[27]*. These two agents **should not be used** as a dual-NRTI combination **(AIII)**.

Etravirine (ETR) + unboosted PI. ETR may induce the metabolism and significantly reduce the drug exposure of unboosted PIs. Appropriate doses of the PIs have not been established *[24]* **(AII)**.

Etravirine (ETR) + ritonavir (RTV)-boosted atazanavir (ATV) or fosamprenavir (FPV). ETR may alter the concentrations of these PIs. Appropriate doses of the PIs have not been established *[24]* **(AII)**.

Etravirine (ETR) + ritonavir (RTV)-boosted tipranavir (TPV). RTV-boosted TPV significantly reduces ETR concentrations. These drugs **should not be coadministered** *[24]* **(AII)**.

Nevirapine (NVP) initiated in ARV-naïve women with CD4 counts >250 cells/mm^3 or in ARV-naïve men with CD4 counts >400 cells/mm^3. Greater risk of symptomatic hepatic events, including serious and life-threatening events, has been observed in these patient groups. NVP **should not be initiated** in these patients **(BI)** unless the benefit clearly outweighs the risk *[28-30]*. Patients who experience CD4 count increases to levels above these thresholds as a result of antiretroviral therapy (ART) can be safely switched to NVP *[31]*.

Unboosted darunavir (DRV), saquinavir (SQV), or tipranavir (TPV). The virologic benefit of these PIs has been demonstrated only when they were used with concomitant RTV. Therefore, use of these agents as part of a combination regimen **without RTV is not recommended (AII)**.

Stavudine (d4T) + zidovudine (ZDV). These two NRTIs **should not be used** in combination because of antagonism demonstrated *in vitro [32]* and *in vivo [33]* **(AII)**.

Table 8. Antiretroviral Regimens or Components That Should Not Be Offered At Any Time
(Updated January 10, 2011)

	Rationale	Exception
Antiretroviral Regimens Not Recommended		
Monotherapy with NRTI (AII)	• Rapid development of resistance • Inferior ARV activity when compared with combination of three or more ARV agents	• No exception
Dual-NRTI regimens (AI)	• Rapid development of resistance • Inferior ARV activity when compared with combination of three or more ARV agents	• No exception
Triple-NRTI regimens (AI) except for ABC/ZDV/3TC (BI) or possibly TDF + ZDV/3TC (BII)	• High rate of early virologic nonresponse seen when triple-NRTI combinations, including ABC/TDF/3TC and TDF/ddI/3TC, were used as initial regimen in ART-naïve patients. • Other triple-NRTI regimens have not been evaluated.	• ABC/ZDV/3TC (BI) and possibly TDF + ZDV/3TC (BII) in patients in whom other combinations are not desirable
Antiretroviral Components Not Recommended as Part of an Antiretroviral Regimen		
ATV + IDV (AIII)	• Potential additive hyperbilirubinemia	• No exception
ddI + d4T (AII)	• High incidence of toxicities: peripheral neuropathy, pancreatitis, and hyperlactatemia • Reports of serious, even fatal, cases of lactic acidosis with hepatic steatosis with or without pancreatitis in pregnant women	• When no other ARV options are available and potential benefits outweigh the risks **(BIII)**
ddI + TDF (AII)	• Increased ddI concentrations and serious ddI-associated toxicities • Potential for immunologic nonresponse and/or CD4 cell count decline • High rate of early virologic failure • Rapid selection of resistance mutations at failure	• Clinicians caring for patients who are clinically stable on regimens containing TDF + ddI should consider altering the NRTIs to avoid this combination.
2-NNRTI combination (AI)	• When EFV combined with NVP, higher incidence of clinical adverse events seen when compared with either EFV- or NVP-based regimen. • Both EFV and NVP may induce metabolism and may lead to reductions in ETR exposure; thus, they should not be used in combination with ETR.	• No exception
EFV in first trimester of pregnancy or in women with significant childbearing potential (AIII)	• Teratogenic in nonhuman primates	• When no other ARV options are available and potential benefits outweigh the risks **(BIII)**
FTC + 3TC (AIII)	• Similar resistance profiles • No potential benefit	• No exception
ETR + unboosted PI (AII)	• ETR may induce metabolism of these PIs; appropriate doses not yet established	• No exception
ETR + RTV-boosted ATV or FPV (AII)	• ETR may alter the concentrations of these PIs; appropriate doses not yet established	• No exception
ETR + RTV-boosted TPV (AII)	• ETR concentration may be significantly reduced by RTV-boosted TPV	• No exception
NVP in ARV-naïve women with CD4 count >250 cells/mm^3 or men with CD4 count >400 cells/mm^3 (BI)	• High incidence of symptomatic hepatotoxicity	• If no other ARV option available; if used, patient should be closely monitored
d4T + ZDV (AII)	• Antagonistic effect on HIV-1	• No exception
Unboosted DRV, SQV, or TPV (AII)	• Inadequate bioavailability	• No exception

Acronyms:
3TC = lamivudine, ABC = abacavir, ATV = atazanavir, d4T = stavudine, ddI = didanosine, DRV = darunavir, EFV = efavirenz, ETR = etravirine, FPV = fosamprenavir, FTC = emitricitabine, IDV = indinavir, NVP = nevirapine, RTV = ritonavir, SQV = saquinavir, TDF = tenofovir, TPV = tipranavir, ZDV = zidovudine

References

1. Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission. Recommendations for use of antiretroviral drugs in pregnant HIV-1-infected women for maternal health and interventions to reduce perinatal HIV transmission in the United States. May 24, 2010:1-117. http://aidsinfo.nih.gov/contentfiles/PerinatalGL.pdf.
2. Delfraissy JF, Flandre P, Delaugerre C, et al. Lopinavir/ritonavir monotherapy or plus zidovudine and lamivudine in antiretroviral-naive HIV-infected patients. *AIDS.* 2008;22(3):385-393.
3. Swindells S, DiRienzo AG, Wilkin T, et al. Regimen simplification to atazanavir-ritonavir alone as maintenance antiretroviral therapy after sustained virologic suppression. *JAMA.* 2006;296(7):806-814.
4. Arribas JR, Horban A, Gerstoft J, et al. The MONET trial: darunavir/ritonavir with or without nucleoside analogues, for patients with HIV RNA below 50 copies/ml. *AIDS.* 2010;24(2):223-230.
5. Katlama C, Valantin MA, Algarte-Genin M, et al. Efficacy of darunavir/ritonavir maintenance monotherapy in patients with HIV-1 viral suppression: a randomized open-label, noninferiority trial, MONOI-ANRS 136. *AIDS.* 2010;24(15):2365-2374.
6. Hirsch M, Steigbigel R, Staszewski S, et al. A randomized, controlled trial of indinavir, zidovudine, and lamivudine in adults with advanced human immunodeficiency virus type 1 infection and prior antiretroviral therapy. *J Infect Dis.* 1999;180(3):659-665.
7. Gallant JE, Rodriguez AE, Weinberg WG, et al. Early virologic nonresponse to tenofovir, abacavir, and lamivudine in HIV-infected antiretroviral-naive subjects. *J Infect Dis.* 2005;192(11):1921-1930.
8. Bartlett JA, Johnson J, Herrera G, et al. Long-term results of initial therapy with abacavir and lamivudine combined with efavirenz, amprenavir/ritonavir, or stavudine. *J Acquir Immune Defic Syndr.* 2006;43(3):284-292.
9. Barnas D, Koontz D, Bazmi H, et al. Clonal resistance analyses of HIV type-1 after failure of therapy with didanosine, lamivudine and tenofovir. *Antivir Ther.* 2010;15(3):437-441.
10. Moore RD, Wong WM, Keruly JC, et al. Incidence of neuropathy in HIV-infected patients on monotherapy versus those on combination therapy with didanosine, stavudine and hydroxyurea. *AIDS.* 2000;14(3):273-278.
11. Robbins GK, De Gruttola V, Shafer RW, et al. Comparison of sequential three-drug regimens as initial therapy for HIV-1 infection. *N Engl J Med.* 2003;349(24):2293-2303.
12. Boubaker K, Flepp M, Sudre P, et al. Hyperlactatemia and antiretroviral therapy: the Swiss HIV Cohort Study. *Clin Infect Dis.* 2001;33(11):1931-1937.
13. Coghlan ME, Sommadossi JP, Jhala NC, et al. Symptomatic lactic acidosis in hospitalized antiretroviral-treated patients with human immunodeficiency virus infection: a report of 12 cases. *Clin Infect Dis.* 2001;33(11):1914-1921.
14. FDA FaDA. Caution issued for HIV combination therapy with Zerit and Videx in pregnant women. *HIV Clin.* 2001;13(2):6.
15. Kearney BP, Sayre JR, Flaherty JF, et al. Drug-drug and drug-food interactions between tenofovir disoproxil fumarate and didanosine. *J Clin Pharmacol.* 2005;45(12):1360-1367.
16. Murphy MD, O'Hearn M, Chou S. Fatal lactic acidosis and acute renal failure after addition of tenofovir to an antiretroviral regimen containing didanosine. *Clin Infect Dis.* 2003;36(8):1082-1085.
17. Martinez E, Milinkovic A, de Lazzari E, et al. Pancreatic toxic effects associated with co-administration of didanosine and tenofovir in HIV-infected adults. *Lancet.* 2004;364(9428):65-67.
18. Barrios A, Rendon A, Negredo E, et al. Paradoxical CD4+ T-cell decline in HIV-infected patients with complete virus suppression taking tenofovir and didanosine. *AIDS.* 2005;19(6):569-575.
19. Negredo E, Bonjoch A, Paredes R, et al. Compromised immunologic recovery in treatment-experienced patients with HIV infection receiving both tenofovir disoproxil fumarate and didanosine in the TORO studies. *Clin Infect Dis.* 2005;41(6):901-905.
20. Leon A, Martinez E, Mallolas J, et al. Early virological failure in treatment-naive HIV-infected adults receiving didanosine and tenofovir plus efavirenz or nevirapine. *AIDS.* 2005;19(2):213-215.
21. Maitland D, Moyle G, Hand J, et al. Early virologic failure in HIV-1 infected subjects on didanosine/tenofovir/efavirenz: 12-week results from a randomized trial. *AIDS.* 2005;19(11):1183-1188.
22. Podzamczer D, Ferrer E, Gatell JM, et al. Early virological failure with a combination of tenofovir, didanosine and efavirenz. *Antivir Ther.* 2005;10(1):171-177.
23. van Leth F, Phanuphak P, Ruxrungtham K, et al. Comparison of first-line antiretroviral therapy with regimens including nevirapine, efavirenz, or both drugs, plus stavudine and lamivudine: a randomised open-label trial, the 2NN Study. *Lancet.* 2004;363(9417):1253-1263.
24. Tibotec, Inc. Intelence (package insert) 2009.
25. Fundaro C, Genovese O, Rendeli C, et al. Myelomeningocele in a child with intrauterine exposure to efavirenz. *AIDS.* 2002;16(2):299-300.
26. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral Pregnancy Registry international interim report for 1 Jan 1989 - 31 January 2007. 2007; http://www.APRegistry.com.
27. Bethell R, Adams J, DeMuys J, et al. Pharmacological evaluation of a dual deoxycytidine analogue combination: 3TC and SPD754. Paper presented at: 11th Conference on Retroviruses and Opportunistic Infections; February 8-11, 2004; San Francisco, California. Abstract 138.
28. Baylor MS, Johann-Liang R. Hepatotoxicity associated with nevirapine use. *J Acquir Immune Defic Syndr.* 2004;35(5):538-539.
29. Sanne I, Mommeja-Marin H, Hinkle J, et al. Severe hepatotoxicity associated with nevirapine use in HIV-infected subjects. *J Infect Dis.* 2005;191(6):825-829.
30. Boehringer Ingelheim. Dear Health Care Professional Letter. *Clarification of risk factors for severe, life-threatening and fatal hepatotoxicity with VIRAMUNE® (nevirapine)*2004.

31. Kesselring AM, Wit FW, Sabin CA, et al. Risk factors for treatment-limiting toxicities in patients starting nevirapine-containing antiretroviral therapy. *AIDS.* 2009;23(13):1689-1699.
32. Hoggard PG, Kewn S, Barry MG, et al. Effects of drugs on 2',3'-dideoxy-2',3'-didehydrothymidine phosphorylation in vitro. *Antimicrob Agents Chemother.* 1997;41(6):1231-1236.
33. Havlir DV, Tierney C, Friedland GH, et al. In vivo antagonism with zidovudine plus stavudine combination therapy. *J Infect Dis.* 2000;182(1):321-325.

Management of the Treatment-Experienced Patient

VIROLOGIC AND IMMUNOLOGIC FAILURE (Updated January 10, 2011)

Panel's Recommendations:

- ***Assessing and managing an antiretroviral (ARV)-experienced patient experiencing failure of antiretroviral therapy (ART) is complex. Expert advice is critical and should be sought.***
- ***Evaluation of virologic failure should include an assessment of the severity of the patient's HIV disease, ART history, use of concomitant medications with consideration of adverse drug interactions with ARV agents, HIV RNA and CD4 T-cell count trends over time, and prior drug-resistance testing results.***
- ***Drug-resistance testing should be obtained while the patient is taking the failing ARV regimen or within 4 weeks of treatment discontinuation (AII).***
- ***The goal of treatment for ARV-experienced patients with drug resistance who are experiencing virologic failure is to re-establish virologic suppression (e.g., HIV RNA <48 copies/mL) (AI).***
- ***To design a new regimen, the patient's treatment history and past and current resistance test results should be used to identify at least two (preferably three) fully active agents to combine with an optimized background ARV regimen (AI). A fully active agent is one that is likely to have ARV activity on the basis of the patient's treatment history, drug-resistance testing, and/or a novel mechanism of action.***
- ***In general, adding a single, fully active ARV in a new regimen is not recommended because of the risk of rapid development of resistance (BII).***
- ***In patients with a high likelihood of clinical progression (e.g., CD4 count <100 cells/mm^3) and limited drug options, adding a single drug may reduce the risk of immediate clinical progression, because even transient decreases in HIV RNA and/or transient increases in CD4 cell counts have been associated with clinical benefits (CI).***
- ***For some highly ART-experienced patients, maximal virologic suppression is not possible. In this case, ART should be continued (AI) with regimens designed to minimize toxicity, preserve CD4 cell counts, and avoid clinical progression.***
- ***Discontinuing or briefly interrupting therapy in a patient with viremia may lead to a rapid increase in HIV RNA and a decrease in CD4 cell count and increases the risk of clinical progression. Therefore, this strategy is not recommended (AI).***
- ***In the setting of virologic suppression, there is no consensus on how to define or treat immunologic failure.***

Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = data from randomized controlled trials; II = data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = expert opinion

Virologic Definitions

Virologic suppression: A confirmed HIV RNA level below the limit of assay detection (e.g., <48 copies/mL).

Virologic failure: The inability to achieve or maintain suppression of viral replication (to an HIV RNA level <200 copies/mL).

Incomplete virologic response: Two consecutive plasma HIV RNA levels >200 copies/mL after 24 weeks on an ARV regimen. Baseline HIV RNA may affect the time course of response, and some regimens will take longer than others to suppress HIV RNA levels.

Virologic rebound: Confirmed detectable HIV RNA (to >200 copies/mL) after virologic suppression.

Persistent low-level viremia: Confirmed detectable HIV RNA levels that are <1,000 copies/mL.

Virologic blip: After virologic suppression, an isolated detectable HIV RNA level that is followed by a return to virologic suppression.

Causes of Virologic Failure

Virologic failure in a patient can occur for multiple reasons. Data from older patient cohorts suggested that suboptimal adherence and drug intolerance/toxicity accounted for 28%–40% of virologic failure and regimen discontinuations *[1-2]*. More recent data suggest that most virologic failure on first-line regimens occurred due to either pre-existing (transmitted) drug resistance or suboptimal adherence *[3]*. Factors associated with virologic failure include:

- Patient characteristics
  - higher pretreatment or baseline HIV RNA level (depending on the specific regimen used)
  - lower pretreatment or nadir CD4 T-cell count
  - prior AIDS diagnosis
  - comorbidities (e.g., active substance abuse, depression)
  - presence of drug-resistant virus, either transmitted or acquired
  - prior treatment failure
  - incomplete medication adherence and missed clinic appointments

- ARV regimen characteristics
  - drug side effects and toxicities
  - suboptimal pharmacokinetics (variable absorption, metabolism, or, theoretically, penetration into reservoirs)
  - food/fasting requirements
  - adverse drug-drug interactions with concomitant medications
  - suboptimal virologic potency
  - prescription errors

- Provider characteristics, such as experience in treating HIV disease

- Other or unknown reasons

Management of Patients with Virologic Failure

Assessment of Virologic Failure

If virologic failure is suspected or confirmed, a thorough work-up is indicated, addressing the following factors:
- change in HIV RNA and CD4 T-cell counts over time
- occurrence of HIV-related clinical events
- ARV treatment history
- results of prior resistance testing (if any)
- medication-taking behavior (including adherence to recommended drug doses, dosing frequency, and food/fasting requirements)
- tolerability of medications
- concomitant medications and supplements (with consideration for adverse drug-drug interactions)
- comorbidities (including substance abuse)

In many cases, the cause(s) of virologic failure will be identified. In some cases, no obvious cause(s) may be identified. It is important to distinguish among the reasons for virologic failure because the approaches to subsequent therapy differ. The following potential causes of virologic failure should be explored in depth.

- **Adherence.** Assess the patient's adherence to the regimen. For incomplete adherence, identify and address the underlying cause(s) (e.g., difficulties accessing or tolerating medications, depression, active substance abuse) and

simplify the regimen if possible (e.g., decrease pill count or dosing frequency). (See **Adherence**.)

- **Medication Intolerance.** Assess the patient's tolerance of the current regimen and the severity and duration of side effects, keeping in mind that even minor side effects can impact adherence. Management strategies for intolerance in the absence of drug resistance may include:
  - using symptomatic treatment (e.g., antiemetics, antidiarrheals)
  - changing one ARV to another within the same drug class, if needed (e.g., change to tenofovir [TDF] or abacavir [ABC] for zidovudine [ZDV]-related toxicities; change to nevirapine [NVP] or etravirine [ETR] for efavirenz [EFV]-related toxicities) *[4-5]*
  - changing from one drug class to another (e.g., from a non-nucleoside reverse transcriptase inhibitor [NNRTI] to a protease inhibitor [PI], from enfuvirtide [T-20] to raltegravir [RAL]) if necessary and no prior drug resistance is suspected

- **Pharmacokinetic Issues.** Review food/fasting requirements for each medication. Review recent history of gastrointestinal symptoms (such as vomiting or diarrhea) to assess the likelihood of short-term malabsorption. Review concomitant medications and dietary supplements for possible adverse drug-drug interactions (consult **Drug Interactions** section and tables for common interactions) and make appropriate substitutions for ARV agents and/or concomitant medications, if possible. Therapeutic drug monitoring (TDM) may be helpful if pharmacokinetic drug-drug interactions or impaired drug absorption leading to decreased ARV exposure is suspected. (See also **Exposure-Response Relationship and Therapeutic Drug Monitoring**.)

- **Suspected Drug Resistance.** Obtain resistance testing while the patient is taking the failing regimen or within 4 weeks after regimen discontinuation if the plasma HIV RNA level is >500 copies/mL **(AII)**. (See **Drug-Resistance Testing**.) Evaluate the degree of drug resistance and consider the patient's prior treatment history and prior resistance test results. Drug resistance tends to be cumulative for a given individual; thus, all prior treatment history and resistance test results should be taken into account. Routine genotypic or phenotypic testing gives information relevant for selecting nucleoside reverse transcriptase inhibitors (NRTIs), NNRTIs, and PIs. Additional drug-resistance tests for patients experiencing failure on fusion inhibitors and/or integrase strand transfer inhibitors (INSTIs) and viral tropism tests for patients experiencing failure on a CCR5 antagonist also are available. (See **Drug-Resistance Testing**.)

Changing ART

There is no consensus on the optimal time to change therapy for virologic failure. The goal of ART is to suppress HIV replication to a level where drug-resistance mutations do not emerge. However, the specific level of viral suppression needed to achieve durable virologic suppression remains unknown. Selection of drug resistance does not appear to occur in patients with persistent HIV RNA levels suppressed to <48 copies/mL *[6]*, although this remains controversial *[7]*.

The clinical implications of HIV RNA in the range of >48 to <200 copies/mL in a patient on ART are controversial. Unlike the case with higher levels of HIV RNA, most, if not all, circulating virus from individuals with this level of HIV RNA results from the release of HIV from long-lived latently infected cells and does not signify ongoing viral replication with the emergence of drug-resistant virus *[8]*. Although some studies have suggested that viremia at this low level predicts subsequent failure *[9]* and can be associated with the evolution of drug resistance *[10]*, a large retrospective analysis showed that using an HIV RNA threshold for virologic failure of <200 copies/mL had the same predictive value as using a threshold of <50 copies/mL *[11]*.

Newer technologies (e.g., Taqman assay) have made it possible to detect HIV RNA in more patients with low level viremia (<200 copies/mL) than was possible with previous assays. Use of these newer assays has resulted in more confirmatory viral load testing than may be necessary *[12-14]*.

Persistent HIV RNA levels >200 copies/mL often are associated with evidence of viral evolution and drug-resistance mutation accumulation *[15]*; this is particularly common when HIV RNA levels are >500 copies/mL *[16]*. Persistent plasma HIV RNA levels in the 200 to 1,000 copies/mL range should therefore be considered as virologic failure.

Viremia "blips" (e.g., viral suppression followed by a detectable HIV RNA level and then subsequent return to undetectable levels) usually are not associated with subsequent virologic failure *[17]*.

Management of Virologic Failure

Once virologic failure is confirmed, generally the regimen should be changed as soon as possible to avoid progressive accumulation of resistance mutations *[18]*.

Ideally, a new ARV regimen should contain at least two, and preferably three, fully active drugs on the basis of drug treatment history, resistance testing, or new mechanistic class **(AI)** *[19-27]*. Some ARV drugs (e.g., NRTIs) may contribute partial ARV activity to a regimen, despite drug resistance *[28]*, while others (e.g., T-20, NNRTIs, RAL) likely do not provide partial activity *[28-30]*. Because of the potential for drug-class cross resistance that reduces drug activity, using a "new" drug that a patient has not yet taken may not mean that the drug is fully active. In addition, archived drug-resistance mutations may not be detected by standard drug-resistance tests, emphasizing the importance of considering treatment history and prior drug-resistance tests. Drug potency and viral susceptibility are more important than the number of drugs prescribed.

Early studies of ART-experienced patients identified factors associated with better virologic responses to subsequent regimens *[31-32]*. These factors included lower HIV RNA level and/or higher CD4 cell count at the time of therapy change, using a new (i.e., not yet taken) class of ARV drugs, and using ritonavir (RTV)-boosted PIs in PI-experienced patients.

More recent clinical trials support the strategy of conducting reverse transcriptase (RT) and protease (PT) resistance testing (both genotype and phenotype) while an ART-experienced patient is taking a failing ARV regimen, designing a new regimen based on the treatment history and resistance testing results, and selecting at least two and preferably three active drugs for the new treatment regimen *[20-21, 23-24, 33]*. Higher genotypic and/or phenotypic susceptibility scores (quantitative measures of drug activity) are associated with better virologic responses *[23-24]*. Patients who receive more active drugs have a better and more prolonged virologic response than those with fewer active drugs in the regimen. Active ARV drugs include those with activity against drug-resistant viral strains, including newer members of existing classes (the NNRTI—ETR, the PIs—darunavir [DRV] and tipranavir [TPV]) and drugs with new mechanisms of action (the fusion inhibitor—T-20, the CCR5 antagonist—maraviroc [MVC] in patients with R5 but not X4 virus, and the INSTI—RAL). Drug-resistance tests for patients experiencing failure on fusion inhibitors (FIs) and/or INSTIs and viral tropism tests for patients experiencing failure on a CCR5 antagonist also are available. (See **Drug-Resistance Testing**.)

Clinical Scenarios of Virologic Failure

- ***Low-level viremia (HIV RNA <1,000 copies/mL).*** Assess adherence. Consider variability in HIV RNA assays. Patients with HIV RNA <48 copies/mL or isolated increases in HIV RNA ("blips") do not require a change in treatment *[13]* **(AII)**. There is no consensus regarding how to manage patients with HIV RNA levels >48 copies/mL and <200 copies/mL; HIV RNA levels should be followed over time to assess the need for changes (**AIII**). Patients with persistent HIV RNA levels >200 copies/mL often select out drug-resistant viral variants, particularly when HIV RNA levels are >500 copies/mL. Persistent plasma HIV RNA levels in the 200 to 1,000 copies/mL range should be considered as possible virologic failure; resistance testing should be attempted if the HIV RNA level is >500 copies/mL. For individuals with sufficient therapeutic options, consider treatment change **(BIII)**.

- ***Repeated detectable viremia (HIV RNA >1,000 copies/mL) and NO drug resistance identified.*** Consider the timing of the drug-resistance test (e.g., was the patient off ARV for >4 weeks and/or nonadherent?). Consider resuming the same regimen or starting a new regimen and then repeating genotypic testing early (e.g., in 2–4 weeks) to determine whether a resistant viral strain emerges **(CIII)**.

- ***Repeated detectable viremia (HIV RNA >1,000 copies/mL) and drug resistance identified.*** The goals in this situation are to resuppress HIV RNA levels maximally (i.e., to <48 copies/mL) and to prevent further selection of resistance mutations. With the availability of multiple new ARVs, including some with new mechanisms of action, this goal is now possible in many patients, including those with extensive treatment experience and drug resistance. With virologic failure, consider changing the treatment regimen sooner, rather than later, to minimize continued selection of resistance mutations. In a patient with ongoing viremia and evidence of resistance, some drugs in a regimen (e.g., NNRTI, T-20, RAL) should be discontinued promptly to decrease the risk of selecting additional drug-resistance mutations in order to preserve the activity of these drug classes in future regimens. A new regimen should include at least two, and preferably three, fully active agents **(AII)**.

- ***Highly drug resistant HIV.*** There is a subset of patients who have experienced toxicity and/or developed resistance to all or most currently available regimens, and designing a regimen with two or three fully active drugs is not possible. Many of these patients received suboptimal ARV regimens (i.e., did not have access to more than one or two of the drugs at the time they became available) or have been unable to adhere to any regimen. If maximal virologic suppression cannot be achieved, the goals are to preserve immunologic function and to prevent clinical progression (even with ongoing viremia). There is no consensus on how to optimize the management of these patients. It is reasonable to observe a patient on the same regimen, rather than changing the regimen, depending on the stage of HIV disease **(BII)**. Even partial virologic suppression of HIV RNA >0.5 $\log_{10}$ copies/mL from baseline correlates with clinical benefits *[34]*. There is evidence from cohort studies that continuing therapy, even in the presence of viremia and the absence of CD4 T-cell count increases, reduces the risk of disease progression *[35]*. Other cohort studies suggest continued immunologic and clinical benefits if the HIV RNA level is maintained <10,000–20,000 copies/mL *[36-37]*. However, these potential benefits all must be balanced with the ongoing risk of accumulating additional resistance mutations.

  In general, adding a single, fully active ARV in a new regimen is **not** recommended because of the risk of rapid development of resistance **(BII)**. However, in patients with a high likelihood of clinical progression (e.g., CD4 cell count <100 cells/mm^3) and limited drug options, adding a single drug may reduce the risk of immediate clinical progression, because even transient decreases in HIV RNA and/or transient increases in CD4 cell counts have been associated with clinical benefits **(CI)**. Weighing the risks (e.g., selection of drug resistance) and benefits (e.g., ARV activity) of using a single active drug in the heavily ART experienced patient is complicated, and consultation with an expert is advised.

  Patients with ongoing viremia and with an insufficient number of approved treatment options to construct a fully suppressive regimen may be candidates for research studies or expanded access programs, or single-patient access of investigational new drug(s) (IND), as specified in Food and Drug Administration (FDA) regulations: **http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm163982.htm**).

  Discontinuing or briefly interrupting therapy in a patient with viremia may lead to a rapid increase in HIV RNA and a decrease in CD4 T-cell count and increases the risk of clinical progression *[38-39]*. Therefore, this strategy is **not** recommended **(AI)**. See **Discontinuation or Interruption of Antiretroviral Therapy**.

- ***Prior treatment and suspected drug resistance, now presenting to care in need of therapy with limited information (i.e., incomplete or absence of self-reported history, medical records, or previous resistance data).*** Every effort should be made to obtain medical records and prior drug-resistance testing results; however, this is not always possible. One strategy is to restart the most recent ARV regimen and assess drug resistance in 2–4 weeks to help guide the choice of the next regimen; another strategy is to start two or three drugs known to be active based on treatment history (e.g., MVC with R5 virus, RAL if no prior INSTI).

Immunologic Failure: Definition, Causes, and Management

Immunologic failure can be defined as the failure to achieve and maintain an adequate CD4 response despite virologic suppression. Increases in CD4 counts in ARV-naïve patients with initial ARV regimens are approximately 150 cells/mm^3 over the first year *[40]*. A CD4 count plateau may occur after 4–6 years of treatment with suppressed viremia *[41-45]*.

No accepted specific definition for immunologic failure exists, although some studies have focused on patients who fail to increase CD4 counts above a specific threshold (e.g., >350 or 500 cells/mm^3) over a specific period of time (e.g., 4–7 years). Others have focused on an inability to increase CD4 counts above pretherapy levels by a certain threshold (e.g., >50 or 100 cells/mm^3) over a given time period. The former criterion may be preferable because of data linking these thresholds with the risk of non-AIDS clinical events *[46]*.

The proportion of patients experiencing immunologic failure depends on how failure is defined, the observation period, and the CD4 count when treatment was started. In the longest study conducted to date, the percentage of patients with suppressed viremia who reached a CD4 count >500 cells/mm^3 through 6 years of treatment was 42% in those starting treatment with a CD4 count <200 cells/mm^3, 66% in those starting with a CD4 count 200–350 cells/mm^3, and 85% in those starting with a CD4 count >350 cells/mm^3 *[41]*.

A persistently low CD4 count while on suppressive ART is associated with a small, but appreciable, risk of AIDS- and non-AIDS-related morbidity and mortality *[47-48]*. For example, in the FIRST study *[49]*, a low CD4 count on therapy was associated with an increased risk of AIDS-related complications (adjusted hazard ratio of 0.56 per 100 cells/mm^3 higher CD4 count). Similarly, a low CD4 count was associated with an increased risk of non-AIDS events, including cardiovascular, hepatic, and renal disease and cancer. Other studies support these associations *[50-53]*.

Factors associated with poor CD4 T-cell response:
- CD4 count <200/mm^3 when starting ART
- Older age
- Coinfection (e.g., hepatitis C virus [HCV], HIV-2, human T-cell leukemia virus type 1 [HTLV-1], HTLV-2)
- Medications, both ARVs (e.g., ZDV *[54]*, TDF + didanosine [ddI] *[55-57]*) and other medications.
- Persistent immune activation
- Loss of regenerative potential of the immune system
- Other medical conditions

Assessment of Immunologic Failure. CD4 count should be confirmed by repeat testing. Concomitant medications should be reviewed carefully, with a focus on those known to decrease white blood cells or, specifically, CD4 T-cells (e.g., cancer chemotherapy, interferon, prednisone, ZDV; combination of TDF and ddI), and consideration should be given to substituting or discontinuing these drugs, if possible. Untreated coinfections (e.g., HIV-2, HTLV-1, HTLV-2) and serious medical conditions (e.g., malignancy) also should be considered. In many cases, no obvious cause for immunologic failure can be identified.

Management of Immunologic Failure. No consensus exists on when or how to treat immunologic failure. Given the risk of clinical events, it is reasonable to focus on patients with CD4 counts <200 cells/mm^3 because patients with higher CD4 counts have a lower risk of clinical events. It is not clear that immunologic failure in the setting of virologic suppression should prompt a change in the ARV regimen. Because ongoing immune activation occurs in some patients with suppressed HIV RNA levels, some have suggested adding a drug to an existing regimen. However, this strategy does not result in clear virologic or immunologic benefit *[58]*. Others suggest changing the regimen to another regimen (e.g., from NNRTI-based to PI-based, INSTI-based, or CCR5 antagonist-based regimens), but this strategy has not shown clear benefit.

An immune-based therapy, interleukin-2, demonstrated CD4 count increases but no clinical benefit in two large randomized studies *[59]* and therefore is not recommended **(AI)**. Other immune-based therapies (e.g., gene therapies, growth hormone, cyclosporine, interleukin-7) are under investigation. Currently, immune-based therapies **should not** be used unless in the context of a clinical trial **(AIII)**.

References

1. d'Arminio Monforte A, Lepri AC, Rezza G, et al. Insights into the reasons for discontinuation of the first highly active antiretroviral therapy (HAART) regimen in a cohort of antiretroviral naive patients. I.CO.N.A. Study Group. Italian Cohort of Antiretroviral-Naive Patients. *AIDS.* 2000;14(5):499-507.
2. Mocroft A, Youle M, Moore A, et al. Reasons for modification and discontinuation of antiretrovirals: results from a single treatment centre. *AIDS.* 2001;15(2):185-194.
3. Paredes R, Lalama CM, Ribaudo HJ, et al. Pre-existing minority drug-resistant HIV-1 variants, adherence, and risk of antiretroviral treatment failure. *J Infect Dis.* 2010;201(5):662-671.
4. Schouten JT, Krambrink A, Ribaudo HJ, et al. Substitution of nevirapine because of efavirenz toxicity in AIDS clinical trials group A5095. *Clin Infect Dis.* 2010;50(5):787-791.
5. Waters L, Fisher M, Winston A, et al. A phase IV, double-blind, multicentre, randomized, placebo-controlled, pilot study to assess the feasibility of switching individuals receiving efavirenz with continuing central nervous system adverse events to etravirine. *AIDS.* 2011;25(1):65-71.
6. Kieffer TL, Finucane MM, Nettles RE, et al. Genotypic analysis of HIV-1 drug resistance at the limit of detection: virus production without evolution in treated adults with undetectable HIV loads. *J Infect Dis.* 2004;189(8):1452-1465.
7. Shiu C, Cunningham CK, Greenough T, et al. Identification of ongoing human immunodeficiency virus type 1 (HIV-1) replication in residual viremia during recombinant HIV-1 poxvirus immunizations in patients with clinically undetectable viral loads on durable suppressive highly active antiretroviral therapy. *J Virol.* 2009;83(19):9731-9742.
8. Siliciano JD, Kajdas J, Finzi D, et al. Long-term follow-up studies confirm the stability of the latent reservoir for HIV-1 in resting CD4+ T cells. *Nat Med.* 2003;9(6):727-728.
9. Eron JJ, Cooper DA, Steigbigel RT, et al. Sustained antiretroviral effect of raltegravir at week 156 in the BENCHMRK studies, and exploratory analysis of late outcomes based on early virologic responses. Paper presented at: 17th Conference on Retroviruses and Opportunistic Infections; February 16-19, 2010; San Francisco, CA. Abstract 515.
10. Taiwo B, Gallien S, Aga S, et al. HIV drug resistance evolution during persistent near-target viral suppression. *Antiviral Therapy* 2010;15:A38.
11. Ribaudo H, Lennox J, Currier J, et al. Virologic failure endpoint definition in clinical trials: Is using HIV-1 RNA threshold <200 copies/mL better than <50 copies/mL? An analysis of ACTG studies. Paper presented at: 16th Conference on Retroviruses and Opportunistic Infections; February 8-11, 2009; Montreal, Canada. Abstract 580.
12. Lima V, Harrigan R, Montaner JS. Increased reporting of detectable plasma HIV-1 RNA levels at the critical threshold of 50 copies per milliliter with the Taqman assay in comparison to the Amplicor assay. *J Acquir Immune Defic Syndr.* 2009;51(1):3-6.
13. Gatanaga H, Tsukada K, Honda H, et al. Detection of HIV type 1 load by the Roche Cobas TaqMan assay in patients with viral loads previously undetectable by the Roche Cobas Amplicor Monitor. *Clin Infect Dis.* 2009;48(2):260-262.
14. Willig JH, Nevin CR, Raper JL, et al. Cost ramifications of increased reporting of detectable plasma HIV-1 RNA levels by the Roche COBAS AmpliPrep/COBAS TaqMan HIV-1 version 1.0 viral load test. *J Acquir Immune Defic Syndr.* 2010;54(4):442-444.
15. Aleman S, Soderbarg K, Visco-Comandini U, et al. Drug resistance at low viraemia in HIV-1-infected patients with antiretroviral combination therapy. *AIDS.* 2002;16(7):1039-1044.
16. Karlsson AC, Younger SR, Martin JN, et al. Immunologic and virologic evolution during periods of intermittent and persistent low-level viremia. *AIDS.* 2004;18(7):981-989.
17. Nettles RE, Kieffer TL, Kwon P, et al. Intermittent HIV-1 viremia (Blips) and drug resistance in patients receiving HAART. *JAMA.* 2005;293(7):817-829.
18. Hosseinipour MC, van Oosterhout JJ, Weigel R, et al. The public health approach to identify antiretroviral therapy failure: high-level nucleoside reverse transcriptase inhibitor resistance among Malawians failing first-line antiretroviral therapy. *AIDS.* 2009;23(9):1127-1134.
19. Cooper DA, Steigbigel RT, Gatell JM, et al. Subgroup and resistance analyses of raltegravir for resistant HIV-1 infection. *N Engl J Med.* 2008;359(4):355-365.
20. Lazzarin A, Clotet B, Cooper D, et al. Efficacy of enfuvirtide in patients infected with drug-resistant HIV-1 in Europe and Australia. *N Engl J Med.* 2003;348(22):2186-2195.
21. Lalezari JP, Henry K, O'Hearn M, et al. Enfuvirtide, an HIV-1 fusion inhibitor, for drug-resistant HIV infection in North and South America. *N Engl J Med.* 2003;348(22):2175-2185.
22. Reynes J, Arasteh K, Clotet B, et al. TORO: ninety-six-week virologic and immunologic response and safety evaluation of enfuvirtide with an optimized background of antiretrovirals. *AIDS Patient Care STDS.* 2007;21(8):533-543.
23. Clotet B, Bellos N, Molina JM, et al. Efficacy and safety of darunavir-ritonavir at week 48 in treatment-experienced patients with HIV-1 infection in POWER 1 and 2: a pooled subgroup analysis of data from two randomised trials. *Lancet.* 2007;369(9568):1169-1178.
24. Steigbigel RT, Cooper DA, Kumar PN, et al. Raltegravir with optimized background therapy for resistant HIV-1 infection. *N Engl J Med.* 2008;359(4):339-354.
25. Katlama C, Haubrich R, Lalezari J, et al. Efficacy and safety of etravirine in treatment-experienced, HIV-1 patients: pooled 48 week analysis of two randomized, controlled trials. *AIDS.* 2009;23(17):2289-2300.
26. Gulick RM, Lalezari J, Goodrich J, et al. Maraviroc for previously treated patients with R5 HIV-1 infection. *N Engl J Med.* 2008;359(14):1429-1441.
27. Fatkenheuer G, Nelson M, Lazzarin A, et al. Subgroup analyses of maraviroc in previously treated R5 HIV-1 infection. *N Engl J Med.* 2008;359(14):1442-1455.

28. Deeks SG, Hoh R, Neilands TB, et al. Interruption of treatment with individual therapeutic drug classes in adults with multidrug-resistant HIV-1 infection. *J Infect Dis.* 2005;192(9):1537-1544.
29. Deeks SG, Lu J, Hoh R, et al. Interruption of enfuvirtide in HIV-1 infected adults with incomplete viral suppression on an enfuvirtide-based regimen. *J Infect Dis.* 2007;195(3):387-391.
30. Wirden M, Simon A, Schneider L, et al. Raltegravir has no residual antiviral activity in vivo against HIV-1 with resistance-associated mutations to this drug. *J Antimicrob Chemother.* 2009;64(5):1087-1090.
31. Gulick RM, Hu XJ, Fiscus SA, et al. Randomized study of saquinavir with ritonavir or nelfinavir together with delavirdine, adefovir, or both in human immunodeficiency virus-infected adults with virologic failure on indinavir: AIDS Clinical Trials Group Study 359. *J Infect Dis.* 2000;182(5):1375-1384.
32. Hammer SM, Vaida F, Bennett KK, et al. Dual vs single protease inhibitor therapy following antiretroviral treatment failure: a randomized trial. *JAMA.* 2002;288(2):169-180.
33. Hicks CB, Cahn P, Cooper DA, et al. Durable efficacy of tipranavir-ritonavir in combination with an optimised background regimen of antiretroviral drugs for treatment-experienced HIV-1-infected patients at 48 weeks in the Randomized Evaluation of Strategic Intervention in multi-drug reSistant patients with Tipranavir (RESIST) studies: an analysis of combined data from two randomised open-label trials. *Lancet.* 2006;368(9534):466-475.
34. Murray JS, Elashoff MR, Iacono-Connors LC, et al. The use of plasma HIV RNA as a study endpoint in efficacy trials of antiretroviral drugs. *AIDS.* 1999;13(7):797-804.
35. Miller V, Sabin C, Hertogs K, et al. Virological and immunological effects of treatment interruptions in HIV-1 infected patients with treatment failure. *AIDS.* 2000;14(18):2857-2867.
36. Ledergerber B, Lundgren JD, Walker AS, et al. Predictors of trend in CD4-positive T-cell count and mortality among HIV-1-infected individuals with virological failure to all three antiretroviral-drug classes. *Lancet.* 2004;364(9428):51-62.
37. Raffanti SP, Fusco JS, Sherrill BH, et al. Effect of persistent moderate viremia on disease progression during HIV therapy. *J Acquir Immune Defic Syndr.* 2004;37(1):1147-1154.
38. Deeks SG, Wrin T, Liegler T, et al. Virologic and immunologic consequences of discontinuing combination antiretroviral-drug therapy in HIV-infected patients with detectable viremia. *N Engl J Med.* 2001;344(7):472-480.
39. Lawrence J, Mayers DL, Hullsiek KH, et al. Structured treatment interruption in patients with multidrug-resistant human immunodeficiency virus. *N Engl J Med.* 2003;349(9):837-846.
40. Bartlett JA, DeMasi R, Quinn J, et al. Overview of the effectiveness of triple combination therapy in antiretroviral-naive HIV-1 infected adults. *AIDS.* 2001;15(11):1369-1377.
41. Moore RD, Keruly JC. CD4+ cell count 6 years after commencement of highly active antiretroviral therapy in persons with sustained virologic suppression. *Clin Infect Dis.* 2007;44(3):441-446.
42. Kaufmann GR, Perrin L, Pantaleo G, et al. CD4 T-lymphocyte recovery in individuals with advanced HIV-1 infection receiving potent antiretroviral therapy for 4 years: the Swiss HIV Cohort Study. *Arch Intern Med.* 2003;163(18):2187-2195.
43. Garcia F, de Lazzari E, Plana M, et al. Long-term CD4+ T-cell response to highly active antiretroviral therapy according to baseline CD4+ T-cell count. *J Acquir Immune Defic Syndr.* 2004;36(2):702-713.
44. Tarwater PM, Margolick JB, Jin J, et al. Increase and plateau of CD4 T-cell counts in the 3(1/2) years after initiation of potent antiretroviral therapy. *J Acquir Immune Defic Syndr.* 2001;27(2):168-175.
45. Mocroft A, Phillips AN, Ledergerber B, et al. Relationship between antiretrovirals used as part of a cART regimen and CD4 cell count increases in patients with suppressed viremia. *AIDS.* 2006;20(8):1141-1150.
46. Lau B, Gange SJ, Moore RD. Risk of non-AIDS-related mortality may exceed risk of AIDS-related mortality among individuals enrolling into care with CD4+ counts greater than 200 cells/mm3. *J Acquir Immune Defic Syndr.* 2007;44(2):179-187.
47. Loutfy MR, Walmsley SL, Mullin CM, et al. CD4(+) cell count increase predicts clinical benefits in patients with advanced HIV disease and persistent viremia after 1 year of combination antiretroviral therapy. *J Infect Dis.* 2005;192(8):1407-1411.
48. Moore DM, Hogg RS, Chan K, et al. Disease progression in patients with virological suppression in response to HAART is associated with the degree of immunological response. *AIDS.* 2006;20(3):371-377.
49. Baker JV, Peng G, Rapkin J, et al. CD4+ count and risk of non-AIDS diseases following initial treatment for HIV infection. *AIDS.* 2008;22(7):841-848.
50. Monforte A, Abrams D, Pradier C, et al. HIV-induced immunodeficiency and mortality from AIDS-defining and non-AIDS-defining malignancies. *AIDS.* 2008;22(16):2143-2153.
51. Weber R, Sabin CA, Friis-Moller N, et al. Liver-related deaths in persons infected with the human immunodeficiency virus: the D:A:D study. *Arch Intern Med.* 2006;166(15):1632-1641.
52. El-Sadr WM, Lundgren JD, Neaton JD, et al. CD4+ count-guided interruption of antiretroviral treatment. *N Engl J Med.* 2006;355(22):2283-2296.
53. Lichtenstein KA, Armon C, Buchacz K, et al. Low CD4+ T cell count is a risk factor for cardiovascular disease events in the HIV outpatient study. *Clin Infect Dis.* 2010;51(4):435-447.
54. Huttner AC, Kaufmann GR, Battegay M, et al. Treatment initiation with zidovudine-containing potent antiretroviral therapy impairs CD4 cell count recovery but not clinical efficacy. *AIDS.* 2007;21(8):939-946.
55. Barrios A, Rendon A, Negredo E, et al. Paradoxical CD4+ T-cell decline in HIV-infected patients with complete virus suppression taking tenofovir and didanosine. *AIDS.* 2005;19(6):569-575.
56. Lacombe K, Pacanowski J, Meynard JL, et al. Risk factors for CD4 lymphopenia in patients treated with a tenofovir/didanosine high dose-containing highly active antiretroviral therapy regimen. *AIDS.* 2005;19(10):1107-1108.
57. Negredo E, Bonjoch A, Paredes R, et al. Compromised immunologic recovery in treatment-experienced patients with HIV infection receiving both tenofovir disoproxil fumarate and didanosine in the TORO studies. *Clin Infect Dis.* 2005;41(6):901-905.

58. Hammer S, Bassett R, Fischl MA, et al. Randomized, placebo-controlled trial of abacavir intensification in HIV-1-infect adults with plasma HIV RNA < 500 copies/mL. Paper presented at: 11th Conference on Retroviruses and Opportunistic Infections; February 8-11, 2004; San Francisco, CA. Abstract 56.
59. Abrams D, Levy Y, Losso MH, et al. Interleukin-2 therapy in patients with HIV infection. *N Engl J Med*. 2009;361(16):1548-1559.

REGIMEN SIMPLIFICATION (Updated January 10, 2011)

Regimen simplification can be defined broadly as a change in established effective therapy to reduce pill burden and dosing frequency, to enhance tolerability, or to decrease specific food and fluid requirements. Many patients on suppressive antiretroviral therapy (ART) may be considered candidates for regimen simplification, especially if (1) they are receiving treatments that are no longer recommended as preferred or alternative choices for initial therapy; (2) they were prescribed a regimen in the setting of treatment failure at a time when there was an incomplete understanding of resistance or drug-drug interaction data; or (3) they were prescribed a regimen prior to the availability of newer options or formulations that might be easier to administer and/or more tolerable.

This section will review situations in which clinicians might consider simplifying treatment in a patient with virologic suppression. Importantly, this section will not review consideration of changes in treatment for reducing ongoing adverse effects. Regimens used in simplification strategies generally should be those that have proven high efficacy in antiretroviral (ARV)-naïve patients (see **What to Start**) or that would be predicted to be highly active for a given patient based on the individual's past treatment history and resistance profile.

Rationale

The major rationales behind regimen simplification are to improve the patient's quality of life, maintain long-term adherence, avoid toxicities that may develop with prolonged ARV use, and reduce the risk of virologic failure. Systematic reviews in the non-HIV literature have shown that adherence is inversely related to the number of daily doses *[1]*. Some prospective studies in HIV-infected individuals have shown that those on regimens with reduced dosing frequency have higher levels of adherence *[2-3]*. Patient satisfaction with regimens that contain fewer pills and reduced dosing frequency is also higher *[4]*.

Candidates for Regimen Simplification

Unlike ARV agents developed earlier in the HIV epidemic, many ARV medications approved in recent years have sufficiently long half-lives to allow for once-daily dosing, and most also do not have dietary restrictions. Patients on regimens initiated earlier in the era of potent combination ART with drugs that pose a high pill burden and/or frequent dosing requirements are often good candidates for regimen simplification.

Patients without suspected drug-resistant virus. Patients on first (or modified) treatment regimens without a history of treatment failure are ideal candidates for regimen simplification. These patients are less likely to harbor drug-resistant virus, especially if a pretreatment genotype did not detect drug resistance. Prospective clinical studies have demonstrated that the likelihood of treatment failure is relatively low in patients after simplification and, indeed, may be lower than in patients who do not simplify treatment *[5]*. However, some patients may have unrecognized drug-resistant HIV, either acquired at the time of infection or as a consequence of prior treatment, such as patients who were treated with presumably nonsuppressive mono- or dual-nucleoside reverse transcriptase inhibitor (NRTI) regimens before the widespread availability of HIV RNA monitoring and resistance testing.

Patients with documented or suspected drug resistance. Treatment simplification may also be appropriate for selected individuals who achieve viral suppression after having had documented or suspected drug resistance. Often, these patients are on regimens selected when management of drug resistance, understanding of potentially adverse drug-drug interactions, and understanding of treatment options were relatively limited. Regimen simplification may also be considered for patients on two ritonavir (RTV)-boosted protease inhibitors (PIs). Although successful in suppressing viral replication, this treatment may cause patients to be on regimens that are cumbersome, costly, and associated with potential long-term adverse events. The ability to simplify regimens in this setting often reflects the availability of recently approved agents that have activity against drug-resistant virus and are easier to take without sacrificing ARV activity. Specific situations in which drug simplification could be considered in ART-experienced patients with viral drug resistance are outlined below. Simplifying regimens in patients who have extensive prior treatment histories is complicated. In such a case, a patient's treatment history, treatment responses and tolerance, and resistance test results should be thoroughly reviewed before designing a new regimen. Expert consultation should be considered whenever possible.

Types of Treatment Simplification

Within-Class Simplifications. Within-class substitutions offer the advantage of not exposing patients to still-unused drug classes, which potentially preserves other classes for future regimens. In general, within-class substitutions use a newer agent; coformulated drugs; or a formulation that has a lower pill burden, a lower dosing frequency, or would be less likely to cause toxicity.

- ***NRTI Substitutions*** *(e.g., changing from zidovudine [ZDV] or stavudine [d4T] to tenofovir [TDF] or abacavir [ABC])**:*** This may be considered for a patient who has no history of viral resistance on an NRTI-containing regimen. Other NRTIs may be substituted to create a regimen with lower dosing frequency (e.g., once daily) that takes advantage of coformulated agents and potentially avoids some long-term toxicities (e.g., pancreatitis, peripheral neuropathy, lipoatrophy).
- ***Switching of Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)*** *(e.g., from nevirapine [NVP] to efavirenz [EFV])**:*** This may be considered to reduce dosing frequency or to take advantage of coformulated agents.
- ***Switching of PIs:*** This switch can be from one PI to another PI, to the same PI at a lower dosing frequency (such as from twice-daily to once-daily RTV-boosted lopinavir [LPV/r] or RTV-boosted darunavir [DRV/r]) or, in the case of atazanavir (ATV), to administration without RTV boosting *[6]*. (Unboosted ATV is presently not a preferred PI component and not recommended if the patient is taking TDF or if the patient has HIV with reduced susceptibility to ATV.) Such changes can reduce dosing frequency, pill count, drug-drug or drug-food interactions, or dyslipidemia or can take advantage of coformulation. These switches can be done with relative ease in patients without PI-resistant virus. However, these switches are not recommended in patients who have a history of documented or suspected PI resistance because convincing data in this setting are lacking.

Out-of-Class Substitutions. One common out-of-class substitution for regimen simplification involves a change from a PI-based to an NNRTI-based regimen. An important study in this regard was the NEFA trial, which evaluated substitution of a PI-based regimen in virologically suppressed patients with NVP, EFV, or ABC *[7]*. Although the baseline regimens in the study are no longer in widespread use, the NEFA findings are still relevant and provide information about the risks and benefits of switching treatment in patients with virologic suppression. In this study, 460 patients on stable, PI-based regimens with virologic suppression (<200 copies/mL for the previous 6 months) were switched to their randomized treatment arms. After 36 months of follow-up, virologic failure occurred more frequently in patients switched to ABC than in patients switched to EFV or NVP. The increased risk of treatment failure was particularly high in patients who had previous suboptimal treatment with mono- and dual-NRTI therapy. This emphasizes the need to consider the potential for drug-resistant virus prior to attempting simplification *[8]*.

Newer agents that target different sites in the HIV life cycle, such as the integrase strand transfer inhibitor (INSTI) raltegravir (RAL) and the CCR5 antagonist maraviroc (MVC), also offer opportunities for out-of-class substitutions, particularly in patients who have a history of virus resistant to older HIV drugs. Three randomized studies have evaluated replacing a boosted PI with RAL in virologically suppressed patients. In two of these studies *[9-10]*, the switch to RAL was associated with an increased risk of virologic failure in patients with documented or suspected pre-existing NRTI resistance; a third study did not find this higher risk, possibly due to a longer period of virologic suppression before the change *[11]*. Overall, these results suggest that in ART-experienced patients, RAL should be used with caution as a substitute for a boosted PI. This strategy should be avoided in patients with documented NRTI resistance unless there are other fully active drugs in the regimen.

Because enfuvirtide (T-20) requires twice-daily injections, causes injection-site reactions, and is more expensive than other available ARV agents, patients who are virologically suppressed on T-20-containing regimens may wish to substitute T-20 with an active oral agent. Because the majority of patients on T-20 have highly drug-resistant virus, substitution must be with another fully active agent. Data from one randomized trial and one observational study suggest that RAL can safely substitute for T-20 in patients not previously treated with INSTI *[12-13]*. Although this strategy generally maintains virologic suppression and is well tolerated, clinicians should be aware that any drug substitution may introduce unanticipated adverse effects or drug-drug interactions *[14]*.

Other newer agents that might be considered as substitutes for T-20 are etravirine (ETR) or MVC. Use of ETR in this setting would optimally be considered only when viral susceptibility to ETR can be assured from resistance testing performed prior to virologic suppression and after carefully assessing for possible deleterious drug-drug interactions

(e.g., ETR cannot be administered with several PIs [see **Table 16b**]). In the ETR early access program, switching from T-20 to ETR showed promise in maintaining viral suppression at 24 weeks, but only 37 subjects were included in this report *[15]*. MVC is only active in those with documented R5-only virus, a determination that cannot routinely be made in those with undetectable HIV RNA on a stable regimen. Although there is a commercially available proviral DNA assay to assess viral tropism in virologically suppressed patients, there are no clinical data on whether results of this test predict the successful use of MVC as a substitute for another active drug.

Reducing the number of active drugs in a regimen. This approach to treatment simplification involves switching a patient from a suppressive regimen to fewer active drugs. In early studies, this approach was associated with a higher risk of treatment failure than continuation of standard treatment with two NRTIs plus a PI *[16]*. More recently, studies have evaluated the use of an RTV-boosted PI as monotherapy after virologic suppression with a two-NRTI + boosted-PI regimen *[17-18]*. The major motivations for this approach are a reduction in NRTI-related toxicity and lower cost. In a randomized clinical trial *[18]*, low-level viremia was more common in those on maintenance LPV/r alone than on a three-drug combination regimen. Viral suppression was achieved by resuming the NRTIs. Studies of DRV/r monotherapy, both as once- or twice-daily dosing, have reported mixed results *[19-20]*. In aggregate, boosted-PI monotherapy as initial *[21]* or as simplification treatment has been somewhat less effective in achieving complete virologic suppression and avoiding resistance. Therefore, this strategy cannot be recommended outside of a clinical trial.

Monitoring After Treatment Simplification

Patients should be evaluated 2–6 weeks after treatment simplification to assess tolerance and to undergo laboratory monitoring, including HIV RNA, CD4 cell count, and markers of renal and liver function. Assessment of fasting cholesterol subsets and triglycerides should be performed within 3 months after the change in therapy. In the absence of any specific complaints, laboratory abnormalities, or viral rebound at that visit, patients may resume regularly scheduled clinical and laboratory monitoring.

References

1. Claxton AJ, Cramer J, Pierce C. A systematic review of the associations between dose regimens and medication compliance. *Clin Ther.* 2001;23(8):1296-1310.
2. Gallant JE, DeJesus E, Arribas JR, et al. Tenofovir DF, emtricitabine, and efavirenz vs. zidovudine, lamivudine, and efavirenz for HIV. *N Engl J Med.* 2006;354(3):251-260.
3. Molina JM, Podsadecki TJ, Johnson MA, et al. A lopinavir/ritonavir-based once-daily regimen results in better compliance and is non-inferior to a twice-daily regimen through 96 weeks. *AIDS Res Hum Retroviruses.* 2007;23(12):1505-1514.
4. Stone VE, Jordan J, Tolson J, et al. Perspectives on adherence and simplicity for HIV-infected patients on antiretroviral therapy: self-report of the relative importance of multiple attributes of highly active antiretroviral therapy (HAART) regimens in predicting adherence. *J Acquir Immune Defic Syndr.* 2004;36(3):808-816.
5. Gatell J, Salmon-Ceron D, Lazzarin A, et al. Efficacy and safety of atazanavir-based highly active antiretroviral therapy in patients with virologic suppression switched from a stable, boosted or unboosted protease inhibitor treatment regimen: the SWAN Study (AI424-097) 48-week results. *Clin Infect Dis.* 2007;44(11):1484-1492.
6. Squires KE, Young B, Dejesus E, et al. Similar efficacy and tolerability of atazanavir compared with atazanavir/ritonavir, each with abacavir/lamivudine after initial suppression with abacavir/lamivudine plus ritonavir-boosted atazanavir in HIV-infected patients. *AIDS.* 2010;24(13):2019-2027.
7. Martinez E. The NEFA study: results at three years. *AIDS Rev.* 2007;9(1):62.
8. Ochoa de Echaguen A, Arnedo M, Xercavins M, et al. Genotypic and phenotypic resistance patterns at virological failure in a simplification trial with nevirapine, efavirenz or abacavir. *AIDS.* 2005;19(13):1385-1391.
9. Eron JJ, Young B, Cooper DA, et al. Switch to a raltegravir-based regimen versus continuation of a lopinavir-ritonavir-based regimen in stable HIV-infected patients with suppressed viraemia (SWITCHMRK 1 and 2): two multicentre, double-blind, randomised controlled trials. *Lancet.* 2010;375(9712):396-407.
10. Vispo E, Barreiro P, Maida I, et al. Simplification From Protease Inhibitors to Once- or Twice-Daily Raltegravir: The ODIS Trial. *HIV Clin Trials.* 2010;11(4):197-204.
11. Martinez E, Larrousse M, Llibre JM, et al. Substitution of raltegravir for ritonavir-boosted protease inhibitors in HIV-infected patients: the SPIRAL study. *AIDS.* 2010;24(11):1697-1707.
12. Harris M, Larsen G, Montaner JS. Outcomes of multidrug-resistant patients switched from enfuvirtide to raltegravir within a virologically suppressive regimen. *AIDS.* 2008;22(10):1224-1226.
13. De Castro N, Braun J, Charreau I, et al. Switch from enfuvirtide to raltegravir in virologically suppressed multidrug-resistant HIV-1-infected patients: a randomized open-label trial. *Clin Infect Dis.* 2009;49(8):1259-1267.
14. Harris M, Larsen G, Montaner JS. Exacerbation of depression associated with starting raltegravir: a report of four cases. *AIDS.* 2008;22(14):1890-1892.

15. Loutfy M, Ribera E, Florence E, et al. Sustained HIV RNA suppression after switching from enfuvirtide to etravirine in the early access programme. *J Antimicrob Chemother.* 2009;64(6):1341-1344.
16. Havlir DV, Marschner IC, Hirsch MS, et al. Maintenance antiretroviral therapies in HIV infected patients with undetectable plasma HIV RNA after triple-drug therapy. AIDS Clinical Trials Group Study 343 Team. *N Engl J Med.* 1998;339(18):1261-1268.
17. Swindells S, DiRienzo AG, Wilkin T, et al. Regimen simplification to atazanavir-ritonavir alone as maintenance antiretroviral therapy after sustained virologic suppression. *JAMA.* 2006;296(7):806-814.
18. Pulido F, Arribas JR, Delgado R, et al. Lopinavir-ritonavir monotherapy versus lopinavir-ritonavir and two nucleosides for maintenance therapy of HIV. *AIDS.* 2008;22(2):F1-9.
19. Arribas JR, Horban A, Gerstoft J, et al. The MONET trial: darunavir/ritonavir with or without nucleoside analogues, for patients with HIV RNA below 50 copies/ml. *AIDS.* 2010;24(2):223-230.
20. Katlama C, Valantin MA, Algarte-Genin M, et al. Efficacy of darunavir/ritonavir maintenance monotherapy in patients with HIV-1 viral suppression: a randomized open-label, noninferiority trial, MONOI-ANRS 136. *AIDS.* 2010;24(15):2365-2374.
21. Delfraissy JF, Flandre P, Delaugerre C, et al. Lopinavir/ritonavir monotherapy or plus zidovudine and lamivudine in antiretroviral-naive HIV-infected patients. *AIDS.* 2008;22(3):385-393.

EXPOSURE-RESPONSE RELATIONSHIP AND THERAPEUTIC DRUG MONITORING (TDM) FOR ANTIRETROVIRAL AGENTS (Updated January 10, 2011)

Panel's Recommendations:

- ***Therapeutic drug monitoring (TDM) for antiretroviral (ARV) agents is not recommended for routine use in the management of the HIV-infected adult (CIII).***
- ***TDM may be considered in selected clinical scenarios, as discussed in the text below.***

Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = data from randomized controlled trials; II = data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = expert opinion

Knowledge of the relationship between systemic exposure (or concentration) and drug responses (beneficial and/or adverse) is key in selecting the dose of a drug, in understanding the variability in the response of patients to a drug, and in designing strategies to optimize response and tolerability.

TDM is a strategy applied to certain antiarrhythmics, anticonvulsants, antineoplastics, and antibiotics that utilizes measured drug concentrations to design dosing regimens to improve the likelihood of the desired therapeutic and safety outcomes. The key characteristic of a drug that is a candidate for TDM is knowledge of the exposure-response relationship and a therapeutic range of concentrations. The therapeutic range is a range of concentrations established through clinical investigations that are associated with a greater likelihood of achieving the desired therapeutic response and/or reducing the frequency of drug-associated adverse reactions.

Several ARV agents meet most of the characteristics of agents that can be considered candidates for a TDM strategy *[1]*. The rationale for TDM in managing antiretroviral therapy (ART) derives from the following:

- data showing that considerable interpatient variability in drug concentrations exists among patients who take the same dose;
- data indicating that relationships exist between the concentration of drug in the body and anti-HIV effect and, in some cases, toxicities; and
- data from small prospective studies demonstrating that TDM improved virologic response and/or decreased the incidence of concentration-related drug toxicities *[2-3]*.

TDM for ARV agents, however, is not recommended for routine use in the management of the HIV-infected adult (CIII).

Multiple factors limit the routine use of TDM in HIV-infected adults *[4-5]*. These factors include:

- lack of large prospective studies demonstrating that TDM improves clinical and virologic outcomes. (This is the most important limiting factor for the implementation of TDM at present.);
- lack of established therapeutic range of concentrations for all ARV drugs that is associated with achieving the desired therapeutic response and/or reducing the frequency of drug-associated adverse reactions;
- intrapatient variability in ARV drug concentrations;
- lack of widespread availability of clinical laboratories that perform quantitation of ARV concentrations under rigorous quality assurance/quality control standards; and
- shortage of experts to assist with interpretation of ARV concentration data and application of such data to revise patients' dosing regimens.

Exposure-Response Relationships and TDM with Different ARV Classes

Protease Inhibitors (PIs), Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs), and Integrase Inhibitors. Relationships between the systemic exposure to PIs and NNRTIs and treatment response have been reviewed in various publications *[4-7]*. Although there are limitations and unanswered questions, the consensus among clinical pharmacologists from the United States and Europe is that the data provide a framework for the potential implementation of TDM for PIs and NNRTIs. However, information on relationships between concentrations and drug-associated toxicities are sparse. Clinicians who use TDM as a strategy to manage either ARV response or toxicities should consult the most current data on the proposed therapeutic concentration range. Exposure-response data for darunavir (DRV), etravirine (ETR), and raltegravir (RAL) are accumulating but are not sufficient to recommend minimum trough concentrations. The median trough concentrations for these agents in HIV-infected persons receiving the recommended dose are included in **Table 9b**.

CCR5 Antagonists. Trough maraviroc (MVC) concentrations have been shown to be an important predictor of virologic success in studies conducted in ART-experienced persons *[8-9]*. Clinical experience in the use of TDM for MVC, however, is very limited. Nonetheless, as with PIs and NNRTIs, the exposure-response data provide a framework for TDM, and that information is presented in these guidelines (**Table 9b**).

Nucleoside Reverse Transcriptase Inhibitors (NRTIs). Relationships between plasma concentrations of NRTIs and their intracellular pharmacologically active moieties have not yet been established. Therefore, monitoring of plasma or intracellular NRTI concentrations for an individual patient largely remains a research tool. Measurement of plasma concentrations, however, is routinely used for studies of drug-drug interactions.

Scenarios for Use of TDM. Multiple scenarios exist in which both ARV concentration data and expert opinion may be useful in patient management. Consultation with a clinical pharmacologist or a clinical pharmacist with HIV expertise may be advisable in these cases. These scenarios include the following:

- **Suspect clinically significant drug-drug or drug-food interactions** that may result in reduced efficacy or increased dose-related toxicities;
- **Changes in pathophysiologic states** that may impair gastrointestinal, hepatic, or renal function, thereby potentially altering drug absorption, distribution, metabolism, or elimination;
- **Pregnant women** who may be at risk of virologic failure as a result of changes in their pharmacokinetic parameters during the later stage of pregnancy, which may result in plasma concentrations lower than those achieved in the earlier stages of pregnancy and in the nonpregnant patient;
- **Heavily pretreated patients** experiencing virologic failure and who may have viral isolates with reduced susceptibility to ARVs;
- **Use of alternative dosing regimens and ARV combinations** for which safety and efficacy have not been established in clinical trials;
- **Concentration-dependent, drug-associated toxicities**; and
- **Lack of expected virologic response** in medication-adherent persons.

TDM

- **For patients who have drug-susceptible virus**. **Table 9a** includes a synthesis of recommendations *[2-7]* for minimum target trough PI and NNRTI concentrations in persons with drug-susceptible virus.
- **For ART-experienced patients with virologic failure (see Table 9b)**. Fewer data are available to formulate suggestions for minimum target trough concentrations in ART-experienced patients who have viral isolates with reduced susceptibility to ARV agents. Concentration recommendations for tipranavir (TPV) and MVC were derived only from studies in ART-experienced persons. It is likely that use of PIs and NNRTIs in the setting of reduced viral susceptibility may require higher trough concentrations than those needed for wild-type virus. The inhibitory quotient (IQ), which is the ratio of ARV drug concentration to a measure of susceptibility (genotype or phenotype) of the patient's strain of HIV to that drug, may additionally improve prediction of virologic response—as has been shown, for example, with DRV in ART-experienced persons *[10-11]*. Exposure-response data for DRV, ETR, and RAL are accumulating but are not sufficient to recommend minimum trough concentrations. The median trough concentrations for these agents in HIV-infected persons receiving the recommended dose are included in **Table 9b**.

Using Drug Concentrations to Guide Therapy. There are several challenges and considerations for implementation of TDM in the clinical setting. Use of TDM to monitor ARV concentrations in a patient requires multiple steps:

- quantification of the concentration of the drug, usually in plasma or serum;
- determination of the patient's pharmacokinetic characteristics;
- integration of information on patient adherence;
- interpretation of the concentrations; and
- adjustment of the drug dose to achieve concentrations within the therapeutic range, if necessary.

Guidelines for the collection of blood samples and other practical suggestions can be found in a position paper by the Adult AIDS Clinical Trials Group Pharmacology Committee *[4]*.

A final caveat to the use of measured drug concentrations in patient management is a general one—drug concentration information cannot be used alone; it must be integrated with other clinical information. In addition, as knowledge of associations between ARV concentrations and virologic response continues to accumulate, clinicians who employ a TDM strategy for patient management should consult the most current literature.

Table 9a. Trough Concentrations of Antiretroviral Drugs for Patients Who Have Drug-Susceptible Virus **(Updated January 10, 2011)**

Drug	Concentration (ng/mL)
Suggested minimum target trough concentrations in patients with HIV-1 susceptible to the ARV drugs *[2-9]*	
Fosamprenavir (FPV)	400 (measured as amprenavir concentration)
Atazanavir (ATV)	150
Indinavir (IDV)	100
Lopinavir (LPV)	1,000
Nelfinavir[1] (NFV)	800
Saquinavir (SQV)	100–250
Efavirenz (EFV)	1,000
Nevirapine (NVP)	3,000

[1]Measurable active (M8) metabolite

Table 9b. Trough Concentrations of Antiretroviral Drugs for Treatment-Experienced Patients with Virologic Failure (Updated January 10, 2011)

Drug	Concentration (ng/mL)
Suggested minimum target trough concentrations for ART-experienced patients who have resistant HIV-1 strains	
Maraviroc (MVC)	>50
Tipranavir (TPV)	20,500
Median (Range) Trough Concentrations from Clinical Trials *[12-14]*	
Darunavir (DRV) (600 mg twice daily)	3,300 (1,255–7,368)
Etravirine (ETR)	275 (81–2,980)
Raltegravir (RAL)	72 (29–118)

References

1. Spector R, Park GD, Johnson GF, et al. Therapeutic drug monitoring. *Clin Pharmacol Ther.* 1988;43(4):345-353.
2. Fletcher CV, Anderson PL, Kakuda TN, et al. Concentration-controlled compared with conventional antiretroviral therapy for HIV infection. *AIDS.* 2002;16(4):551-560.
3. Fabbiani M, Di Giambenedetto S, Bracciale L, et al. Pharmacokinetic variability of antiretroviral drugs and correlation with virological outcome: 2 years of experience in routine clinical practice. *J Antimicrob Chemother.* 2009;64(1):109-117.
4. Acosta EP, Gerber JG. Position paper on therapeutic drug monitoring of antiretroviral agents. *AIDS Res Hum Retroviruses.* 2002;18(12):825-834.
5. van Luin M, Kuks PF, Burger DM. Use of therapeutic drug monitoring in HIV disease. *Curr Opin HIV AIDS.* 2008;3(3):266-271.
6. Boffito M, Acosta E, Burger D, et al. Current status and future prospects of therapeutic drug monitoring and applied clinical pharmacology in antiretroviral therapy. *Antivir Ther.* 2005;10(3):375-392.
7. LaPorte CJL, Back BJ, Blaschke T, et al. Updated guidelines to perform therapeutic drug monitoring for antiretroviral agents. *Rev Antivir Ther.* 2006;3:4-14.
8. Pfizer Inc. Selzentry (maraviroc) tablets prescribing information NY. 2007.
9. McFayden L, Jacqmin P, Wade J, et al. Maraviroc exposure response analysis: phase 3 antiviral efficacy in treatment-experienced HIV+ patients. Paper presented at: 16th Population Approach Group in Europe Meeting; June 2007, 2007; Kobenhavn, Denmark. Abstract P4-13.
10. Molto J, Santos JR, Perez-Alvarez N, et al. Darunavir inhibitory quotient predicts the 48-week virological response to darunavir-based salvage therapy in human immunodeficiency virus-infected protease inhibitor-experienced patients. *Antimicrob Agents Chemother.* 2008;52(11):3928-3932.
11. Sekar V, DeMeyer S, Vangeneugden T, et al. Pharmacokinetic/pharmacodynamic (PK/PD) analysies of TMC114 in the POWER 1 and POWER 2 trials in treatment-experienced HIV-infected patients. Paper presented at: 13th Conference on Retroviruses and Opportunistic Infections; February 5, 2006, 2006; Denver, CO. Abstract J-121.
12. Markowitz M, Morales-Ramirez JO, Nguyen BY, et al. Antiretroviral activity, pharmacokinetics, and tolerability of MK-0518, a novel inhibitor of HIV-1 integrase, dosed as monotherapy for 10 days in treatment-naive HIV-1-infected individuals. *J Acquir Immune Defic Syndr.* 2006;43(5):509-515.
13. Kakuda TN, Wade JR, Snoeck E, et al. Pharmacokinetics and pharmacodynamics of the non-nucleoside reverse-transcriptase inhibitor etravirine in treatment-experienced HIV-1-infected patients. *Clin Pharmacol Ther.* 2010;88(5):695-703.
14. Food and Drug Administration (FDA). Prezista (package insert). 2010. http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021976s016lbl.pdf.

DISCONTINUATION OR INTERRUPTION OF ANTIRETROVIRAL THERAPY

(Updated November 3, 2008)

Discontinuation of antiretroviral therapy (ART) may result in viral rebound, immune decompensation, and clinical progression. Unplanned interruption of ART may become necessary because of severe drug toxicity, intervening illness, surgery that precludes oral therapy, or unavailability of antiretroviral (ARV) medication. Some investigators have studied planned treatment discontinuation strategies in situations or for reasons that include: in patients who achieve viral suppression and wish to enhance adherence; to reduce inconvenience, long-term toxicities, and costs for patients; or in extensively treated patients who experience treatment failure due to resistant HIV, to allow reversion to wild-type virus. Potential risks and benefits of interruption vary according to a number of factors, including the clinical and immunologic status of the patient, the reason for the interruption, the type and duration of the interruption, and the presence or absence of resistant HIV at the time of interruption. Below are brief discussions on what is currently known about the risks and benefits of treatment interruption in some of these circumstances.

Short-Term Therapy Interruptions

Reasons for short-term interruption (days to weeks) of ART vary and may include drug toxicity; intercurrent illnesses that preclude oral intake, such as gastroenteritis or pancreatitis; surgical procedures; or unavailability of drugs. Stopping ARV drugs for a short time (i.e., <1 to 2 days) due to medical/surgical procedures can usually be done by holding all drugs in the regimen. Recommendations for some other scenarios are listed below:

Unanticipated Need for Short-Term Interruption

- **When a patient experiences a severe or life-threatening toxicity or unexpected inability to take oral medications**—all components of the drug regimen should be stopped simultaneously, regardless of drug half-life.

Planned Short Term Interruption (>2–3 days)

- **When all regimen components have similar half-lives and do not require food for proper absorption**—all drugs may be given with a sip of water, if allowed; otherwise, all drugs should be stopped simultaneously. All discontinued regimen components should be restarted simultaneously.
- **When all regimen components have similar half-lives and require food for adequate absorption, and the patient cannot take anything by mouth for a sustained period of time**—temporary discontinuation of all drug components is indicated. The regimen should be restarted as soon as the patient can resume oral intake.
- **When the ARV regimen contains drugs with differing half-lives**—stopping all drugs simultaneously may result in functional monotherapy with the drug with the longest half-life (typically a non-nucleoside reverse transcriptase inhibitor [NNRTI]). Options in this circumstance are discussed below. (See **Discontinuation of efavirenz, etravirine, or nevirapine**.)

Interruption of Therapy after Pregnancy

ARV drugs for prevention of perinatal transmission of HIV are recommended for all pregnant women, regardless of whether they have indications for ART for their own health. Following delivery, considerations regarding continuation of the ARV regimen for maternal therapeutic indications are the same as for other nonpregnant individuals. The decision of whether to continue therapy after delivery should take into account current recommendations for initiation of ART, current and nadir CD4 T-cell counts and trajectory, HIV RNA levels, adherence issues, and patient preference.

Planned Long-Term Therapy Interruptions

Planned therapy interruptions have been contemplated in various scenarios, listed below. Research is ongoing in several of the scenarios. Therapy interruptions **cannot be recommended** at this time outside of controlled clinical trials **(AI)**.

- **In patients who initiated therapy during acute HIV infection and achieved virologic suppression**—the optimal duration of treatment and the consequences of treatment interruption are not known at this time. (See **Acute HIV Infection**.)

- **In patients who have had exposure to multiple ARV agents, have experienced ARV treatment failure, and have few treatment options available because of extensive resistance mutations**—interruption is **not recommended** unless done in a clinical trial setting **(AI)**. Several clinical trials, largely yielding negative results, but some with conflicting results, have been conducted to better understand the role of treatment interruption in these patients *[1-4]*. The largest of these studies showed negative clinical impact of treatment interruption in these patients *[1]*. The Panel notes that partial virologic suppression from combination therapy has been associated with clinical benefit *[5]*; therefore, interruption of therapy is not recommended.
- **In patients on ART who have maintained a CD4 count above the level currently recommended for treatment initiation and irrespective of whether their baseline CD4 counts were either above or below that recommended threshold**—interruption is also **not recommended** unless done in a clinical trial setting **(BI)**. (See discussion below highlighting potential adverse outcomes seen in some treatment interruption trials.)

Temporary treatment interruption to reduce inconvenience, potential long-term toxicity, and/or overall treatment cost has been considered as a strategy for patients on ART who have maintained CD4 counts above those currently recommended for initiating therapy. Several clinical trials have been designed to determine the safety of such interruptions, in which reinitiation is triggered by predetermined CD4 count thresholds. In these trials, various CD4 count levels have been set to guide both treatment interruption and reinitiation. In the SMART study, the largest of such trials with more than 5,000 subjects, interrupting treatment with CD4 counts >350 cells/mm^3 and reinitiating when <250 cells/mm^3 was associated with an increased risk of disease progression and all cause mortality compared with the trial arm of continuous ART *[6]*. In the TRIVACAN study, the same CD4 count thresholds were used for stopping and restarting treatment *[7]*. This study also showed that interruption was an inferior strategy; the interventions in both trials were stopped early because of these findings. Data from the DART trial reported a twofold increase in rates of World Health Organization (WHO) Stage 4 events/deaths in the 12-week ART cycling group among African patients achieving a CD4 count >300/mm^3 compared with the continuous ART group *[8]*. Observational data from the EuroSIDA cohort noted a twofold increase in risk of death after a treatment interruption of ≥3 months. Factors linked to increased risk of death or progression included lower CD4 counts, higher viral loads, and a prior history of AIDS *[9]*. Other studies have reported no major safety concerns *[10-12]*, but these studies had smaller sample sizes. Results have been reported from several small observational studies evaluating treatment interruption in patients doing well with nadir CD4 counts >350/mm^3, but further studies are needed to determine the safety of treatment interruption in this population *[13-14]*. There is concern that CD4 counts <500 cells/mm^3 are associated with a range of non-AIDS clinical events (e.g., cancer and heart, liver, and kidney disease) *[6, 15-16]*.

Planned long-term therapy interruption strategies **cannot be recommended** at this time outside of controlled clinical trials **(BI)** based on available data and a range of ongoing concerns.

If therapy has to be discontinued, patients should be counseled about the need for close clinical and laboratory monitoring. They should also be aware of the risks of viral rebound, acute retroviral syndrome, increased risk of HIV transmission, decline of CD4 count, HIV disease progression or death, development of minor HIV-associated manifestations such as oral thrush, development of serious non-AIDS complications, development of drug resistance, and the need for chemoprophylaxis against opportunistic infections depending on the CD4 count. Treatment interruptions often result in rapid reductions in CD4 counts.

Prior to any planned treatment interruption, a number of ARV-specific issues should be taken into consideration. These include:

- **Discontinuation of efavirenz (EFV), etravirine (ETR), or nevirapine (NVP).** The optimal interval between stopping EFV, ETR, or NVP and other ARV drugs is not known. The duration of detectable levels of EFV or NVP after discontinuation ranges from less than 1 week to more than 3 weeks *[17-18]*. Simultaneously stopping all drugs in a regimen containing these agents may result in functional monotherapy with the NNRTIs because NNRTIs have much longer half-lives than other agents. This may increase the risk of selection of NNRTI-resistant mutations. It is further complicated by evidence that certain host genetic polymorphisms may result in slower rates of clearance. Such polymorphisms may be more common among specific ethnic groups, such as African Americans and Hispanics *[18-19]*. Some experts recommend stopping the NNRTI but continuing the other ARV drugs for a period of time. The optimal time sequence for staggered component discontinuation has not been determined. A study in South Africa demonstrated that giving 4 or 7 days of zidovudine (ZDV) + lamivudine (3TC) after a single dose of NVP reduced the risk of postnatal NVP resistance from 60% to 10%–12% *[20]*. Use of nucleoside reverse transcriptase inhibitors (NRTIs) with a longer half-life such as tenofovir (TDF) plus emtricitabine (FTC) has also been shown to decrease

NVP resistance after single-dose treatment *[21]*. The findings may, however, differ in patients on chronic NVP treatment. An alternative strategy is to substitute a protease inhibitor (PI) for the NNRTI and to continue the PI with dual NRTIs for a period of time. In a post-study analysis of the patients who interrupted therapy in the SMART trial, patients who were switched from an NNRTI- to a PI-based regimen prior to interruption had a lower rate of NNRTI-resistant mutation after interruption and a greater chance of resuppression of HIV RNA after restarting therapy than those who stopped all the drugs simultaneously or stopped the NNRTI before the 2-NRTI *[22]*. The optimal duration needed to continue the PI-based regimen after stopping the NNRTI is not known. Given the potential of prolonged detectable NNRTI concentrations for more than 3 weeks, some suggest that the PI-based regimen may need to be continued for up to 4 weeks. Further research to determine the best approach to discontinuing NNRTIs is needed. Clinical data on ETR and treatment interruption is lacking but its long half-life of approximately 40 hours suggests that stopping ETR needs to be done carefully using the same suggestions for NVP and EFV for the time being.

- **Discontinuation and reintroduction of NVP**. Because NVP is an inducer of the drug-metabolizing hepatic enzymes, administration of full therapeutic doses of NVP without a 2-week, low-dose escalation phase will result in excess plasma drug levels and potentially increase the risk of toxicity. Therefore, in a patient who has interrupted treatment with NVP for more than 2 weeks, NVP should be reintroduced with a dose escalation period of 200 mg once daily for 14 days and then a 200 mg twice-daily regimen **(AII)**.
- **Discontinuation of FTC, 3TC, or TDF in patients with hepatitis B virus (HBV) coinfection**. Patients with HBV coinfection (hepatitis B surface antigen [HbsAg] or hepatitis B e antigen [HBeAg] positive) and receiving one or a combination of these NRTIs may experience an exacerbation of hepatitis upon drug discontinuation *[23-24]*. (See **Hepatitis B (HBV)/HIV Coinfection**.)

References

1. Lawrence J, Mayers DL, Hullsiek KH, et al. Structured treatment interruption in patients with multidrug-resistant human immunodeficiency virus. *N Engl J Med.* 2003;349(9):837-846.
2. Ruiz L, Ribera E, Bonjoch A, et al. Role of structured treatment interruption before a 5-drug salvage antiretroviral regimen: the Retrogene Study. *J Infect Dis.* 2003;188(7):977-985.
3. Ghosn J, Wirden M, Ktorza N, et al. No benefit of a structured treatment interruption based on genotypic resistance in heavily pretreated HIV-infected patients. *AIDS.* 2005;19(15):1643-1647.
4. Jaafar A, Massip P, Sandres-Saune K, et al. HIV therapy after treatment interruption in patients with multiple failure and more than 200 CD4+ T lymphocyte count. *J Med Virol.* 2004;74(1):8-15.
5. Kousignian I, Abgrall S, Grabar S, et al. Maintaining antiretroviral therapy reduces the risk of AIDS-defining events in patients with uncontrolled viral replication and profound immunodeficiency. *Clin Infect Dis.* 2008;46(2):296-304.
6. El-Sadr WM, Lundgren JD, Neaton JD, et al. CD4+ count-guided interruption of antiretroviral treatment. *N Engl J Med.* 2006;355(22):2283-2296.
7. Danel C, Moh R, Minga A, et al. CD4-guided structured antiretroviral treatment interruption strategy in HIV-infected adults in west Africa (Trivacan ANRS 1269 trial): a randomised trial. *Lancet.* 2006;367(9527):1981-1989.
8. DART Trial Team DTT. Fixed duration interruptions are inferior to continuous treatment in African adults starting therapy with CD4 cell counts < 200 cells/microl. *AIDS.* 2008;22(2):237-247.
9. Holkmann Olsen C, Mocroft A, Kirk O, et al. Interruption of combination antiretroviral therapy and risk of clinical disease progression to AIDS or death. *HIV Med.* 2007;8(2):96-104.
10. Maggiolo F, Ripamonti D, Gregis G, et al. Effect of prolonged discontinuation of successful antiretroviral therapy on CD4 T cells: a controlled, prospective trial. *AIDS.* 2004;18(3):439-446.
11. Cardiello PG, Hassink E, Ananworanich J, et al. A prospective, randomized trial of structured treatment interruption for patients with chronic HIV type 1 infection. *Clin Infect Dis.* 2005;40(4):594-600.
12. Ananworanich J, Siangphoe U, Hill A, et al. Highly active antiretroviral therapy (HAART) retreatment in patients on CD4-guided therapy achieved similar virologic suppression compared with patients on continuous HAART: the HIV Netherlands Australia Thailand Research Collaboration 001.4 study. *J Acquir Immune Defic Syndr.* 2005;39(5):523-529.
13. Pogany K, van Valkengoed IG, Prins JM, et al. Effects of active treatment discontinuation in patients with a CD4+ T-cell nadir greater than 350 cells/mm3: 48-week Treatment Interruption in Early Starters Netherlands Study (TRIESTAN). *J Acquir Immune Defic Syndr.* 2007;44(4):395-400.
14. Skiest DJ, Su Z, Havlir DV, et al. Interruption of antiretroviral treatment in HIV-infected patients with preserved immune function is associated with a low rate of clinical progression: a prospective study by AIDS Clinical Trials Group 5170. *J Infect Dis.* 2007;195(10):1426-1436.
15. Monforte A, Abrams D, Pradier C, et al. HIV-induced immunodeficiency and mortality from AIDS-defining and non-AIDS-defining malignancies. *AIDS.* 2008;22(16):2143-2153.
16. Phillips AN, Neaton J, Lundgren JD. The role of HIV in serious diseases other than AIDS. *AIDS.* 2008;22(18):2409-2418.

17. Cressey TR, Jourdain G, Lallemant MJ, et al. Persistence of nevirapine exposure during the postpartum period after intrapartum single-dose nevirapine in addition to zidovudine prophylaxis for the prevention of mother-to-child transmission of HIV-1. *J Acquir Immune Defic Syndr.* 2005;38(3):283-288.
18. Ribaudo HJ, Haas DW, Tierney C, et al. Pharmacogenetics of plasma efavirenz exposure after treatment discontinuation: an Adult AIDS Clinical Trials Group Study. *Clin Infect Dis.* 2006;42(3):401-407.
19. Haas DW, Ribaudo HJ, Kim RB, et al. Pharmacogenetics of efavirenz and central nervous system side effects: an Adult AIDS Clinical Trials Group study. *AIDS.* 2004;18(18):2391-2400.
20. McIntyre JA, Hopley M, Moodley D, et al. Efficacy of short-course AZT plus 3TC to reduce nevirapine resistance in the prevention of mother-to-child HIV transmission: a randomized clinical trial. *PLoS Med.* 2009;6(10):e1000172.
21. Chi BH, Sinkala M, Mbewe F, et al. Single-dose tenofovir and emtricitabine for reduction of viral resistance to non-nucleoside reverse transcriptase inhibitor drugs in women given intrapartum nevirapine for perinatal HIV prevention: an open-label randomised trial. *Lancet.* 2007;370(9600):1698-1705.
22. Fox Z, Phillips A, Cohen C, et al. Viral resuppression and detection of drug resistance following interruption of a suppressive non-nucleoside reverse transcriptase inhibitor-based regimen. *AIDS.* 2008;22(17):2279-2289.
23. Bessesen M, Ives D, Condreay L, et al. Chronic active hepatitis B exacerbations in human immunodeficiency virus-infected patients following development of resistance to or withdrawal of lamivudine. *Clin Infect Dis.* 1999;28(5):1032-1035.
24. Sellier P, Clevenbergh P, Mazeron MC, et al. Fatal interruption of a 3TC-containing regimen in a HIV-infected patient due to re-activation of chronic hepatitis B virus infection. *Scand J Infect Dis.* 2004;36(6-7):533-535.

Considerations for Antiretroviral Use in Special Patient Populations

ACUTE HIV INFECTION (Updated January 10, 2011)

Panel's Recommendations:

- ***It is unknown if treatment of acute HIV infection results in long-term virologic, immunologic, or clinical benefit; treatment should be considered optional at this time (CIII).***
- ***Therapy should also be considered optional for patients with HIV seroconversion in the previous 6 months (CIII).***
- ***All pregnant women with acute or recent HIV infection should start a combination antiretroviral (ARV) regimen as soon as possible to prevent mother-to-child transmission (MTCT) of HIV (AI).***
- ***If the clinician and patient elect to treat acute HIV infection, treatment should be implemented with the goal of suppressing plasma HIV RNA to below detectable levels (AIII).***
- ***For patients with acute HIV infection in whom therapy is initiated, testing for plasma HIV RNA levels and CD4 count and toxicity monitoring should be performed as described for patients with established, chronic HIV infection (AII).***
- ***If the decision is made to initiate therapy in a person with acute HIV infection, genotypic resistance testing at baseline will be helpful in guiding the selection of an ARV regimen that can provide the optimal virologic response; this strategy is therefore recommended (AIII). If therapy is deferred, genotypic resistance testing should still be performed because the result may be useful in optimizing the virologic response when therapy is ultimately initiated (AIII).***
- ***Because clinically significant resistance to protease inhibitors (PIs) is less common than resistance to non-nucleoside reverse transcriptase inhibitors (NNRTIs) in antiretroviral therapy (ART)-naïve persons who harbor drug-resistant virus, a ritonavir (RTV)-boosted PI-based regimen should be used if therapy is initiated before drug-resistance test results are available (AIII).***

Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = data from randomized controlled trials; II = data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = expert opinion

An estimated 40%–90% of patients acutely infected with HIV will experience symptoms of acute retroviral syndrome characterized by fever, lymphadenopathy, pharyngitis, skin rash, myalgias/arthralgias, and other symptoms *[1-6]*. However, acute HIV infection is often not recognized by primary care clinicians because symptoms are similar to those for influenza, infectious mononucleosis, or other illnesses. Additionally, acute infection can occur asymptomatically. **Table 10** provides practitioners with guidance on the recognition, diagnosis, and management of acute HIV infection.

Diagnosis of Acute HIV Infection

Health care providers should maintain a high level of suspicion of acute HIV infection in patients who have a compatible clinical syndrome and who report recent high-risk behavior *[7]*. However, in some settings, patients may not always disclose or admit to high-risk behaviors or might not perceive their behaviors as high risk. Thus, symptoms and signs consistent with acute retroviral syndrome should motivate consideration of this diagnosis even in the absence of reported high-risk behaviors.

When acute retroviral syndrome is suspected, a plasma HIV RNA test is typically used in conjunction with an HIV antibody test to diagnose acute infection **(BII)**. Acute HIV infection is often defined by detectable HIV RNA in plasma in the setting of a negative or indeterminate HIV antibody test. A low-positive HIV RNA level (<10,000 copies/mL) may represent a false-positive test because values in acute infection are generally very high (>100,000 copies/mL) *[5-6]*. A qualitative HIV RNA test can also be used in this setting. Interest in routine screening for antibody-negative acute infection has led to select centers performing virologic testing on all antibody-negative specimens, including the use of pooled HIV RNA testing on all seronegative serum samples *[8]*. In addition, a combination HIV antigen/antibody test

(ARCHITECT), recently licensed by the Food and Drug Administration (FDA), could be used for this purpose. Patients diagnosed with acute HIV infection by a virologic test while still antibody negative or indeterminate should have confirmatory serologic testing performed over the next 3 months **(AI)**. (See **Table 10**.)

Performance of Resistance Testing

Data from the United States and Europe demonstrate that transmitted virus may be resistant to at least one ARV drug in 6%–16% of patients *[9-11]*. If the decision is made to initiate therapy in a person with acute HIV infection, genotypic resistance testing at baseline to guide the selection of an ARV regimen will likely optimize virologic response; this strategy is therefore recommended **(AIII)**. (See **Drug-Resistance Testing**.) If therapy is deferred, resistance testing should still be performed because the result may be useful in optimizing the virologic response when therapy is ultimately initiated **(AIII)**.

Treatment for Acute HIV Infection

Clinical trials information regarding treatment of acute HIV infection is limited. Ongoing trials are addressing the question of the long-term benefit of potent treatment regimens initiated during acute infection. Potential benefits and risks of treating acute infection are as follows:

- **Potential Benefits of Treating Acute Infection.** Preliminary data indicate that treatment of acute HIV infection with combination ART has a beneficial effect on laboratory markers of disease progression *[12-16]*. Theoretically, early intervention could decrease the severity of acute disease; alter the initial viral setpoint, which can affect disease progression rates; reduce the rate of viral mutation as a result of suppression of viral replication; preserve immune function; and reduce the risk of viral transmission during this highly infectious stage of disease. Additionally, although data are limited and the clinical relevance is unclear, the profound loss of gastrointestinal lymphoid tissue that occurs during the first weeks of infection may be mitigated by the early initiation of ART *[17-18]*.
- **Potential Risks of Treating Acute HIV Infection.** The potential disadvantages of initiating therapy include exposure to ART without a known clinical benefit, which could result in drug toxicities, development of drug resistance, continuous need for therapy with strict adherence, and adverse effect on quality of life.

Some of the potential benefits associated with treatment during acute infection remain uncertain and of unknown clinical relevance, while the risks are largely consistent with those for initiating therapy in chronically infected asymptomatic patients with high CD4 counts. The health care provider and the patient should be fully aware that the rationale for therapy for acute HIV infection is based on theoretical considerations, and the potential benefits should be weighed against the potential risks. For these reasons, treatment of acute HIV infection should be considered optional at this time **(CIII).** Because acute or recent HIV infection is associated with a high risk of MTCT of HIV, all HIV-infected pregnant women should start a combination ARV regimen as soon as possible to prevent perinatal transmission of HIV **(AI)** *[19]*. Following delivery, considerations regarding continuation of the ARV regimen as therapy for the mother are the same as for treatment of other nonpregnant individuals. Providers should consider enrolling patients with acute HIV infection in a clinical trial to evaluate the natural history of acute HIV and to determine the role of ART in this setting. Information regarding such trials can be obtained at **www.clinicaltrials.gov** or from local HIV treatment experts.

Treatment for Recent but Nonacute HIV Infection or Infection of Undetermined Duration

In addition to patients with acute HIV infection, some HIV clinicians also recommend consideration of therapy for patients in whom seroconversion has occurred within the previous 6 months **(CIII)**. Although the initial burst of viremia among infected adults usually resolves in 2 months, rationale for treatment during the 2- to 6-month period after infection is based on the probability that virus replication in lymphoid tissue is still not maximally contained by the immune system during this time *[20]*. In the case of pregnancy, use of a combination ARV regimen to prevent MTCT of HIV is recommended **(AI)**. For nonpregnant patients the current guidelines have provided a rationale for recommending initiation of ART in ART-naïve patients with CD4 count between 350 and 500 cells/mm^3 as well as a recommendation to consider therapy for those with CD4 count >500 cells/mm^3. (See **Initiating Antiretroviral Therapy**.) Although these recommendations are primarily based upon data from patients with chronic infection, the potential benefit of early treatment on immune recovery and on attenuation of the pathologic effects of viremia-associated inflammation and coagulation could apply to those with early HIV infection as well. Based upon all of

these considerations it is reasonable that clinicians share with patients the potential rationale for initiating ART during early HIV infection and offer treatment to those who are willing and able to commit to lifelong treatment.

Treatment Regimen for Acute or Recent HIV Infection

If the clinician and patient have made the decision to initiate ART for acute or recent HIV infection, the goal of therapy is to suppress plasma HIV RNA levels to below detectable levels **(AIII)**. Data are insufficient to draw firm conclusions regarding specific drug combinations to use in acute HIV infection. Potential combinations of agents should be those used in chronic infection. (See **What to Start**.) However, because clinically significant resistance to PIs is less common than resistance to NNRTIs in ART-naïve persons, an RTV-boosted PI-based regimen should be used if therapy is initiated before drug-resistance test results are available **(AIII)**. If resistance test results or resistance pattern of the source virus are known, this information should be used to guide the selection of the ARV regimen.

Patient Follow-up

Testing for plasma HIV RNA levels and CD4 count and toxicity monitoring should be performed as described in **Laboratory Testing for Initial Assessment and Monitoring While on Antiretroviral Therapy** (i.e., HIV RNA at initiation of therapy, after 2–8 weeks, then every 4–8 weeks until viral suppression, then every 3–4 months thereafter) **(AII)**.

Duration of Therapy for Acute or Recent HIV Infection

The optimal duration of therapy for patients with acute or recent HIV infection is unknown, but ongoing clinical trials may provide relevant data regarding these concerns. Difficulties inherent in determining the optimal duration and therapy composition for acute or recent infection (and the potential need for lifelong treatment) should be considered when counseling patients prior to initiation of therapy. Patients need to know that there are limited data regarding the benefits of stopping treatment, whereas strong data from studies in patients with chronic HIV infection show that stopping ART may be harmful *[21]*.

Table 10. Identifying, Diagnosing, and Managing Acute HIV-1 Infection (Updated January 10, 2011)

- **Suspecting acute HIV infection:** Signs or symptoms of acute HIV infection with recent (within 2–6 weeks) high risk of exposure to HIV*
  - Signs/symptoms/laboratory findings may include but are not limited to one or more of the following: fever, lymphadenopathy, skin rash, myalgia/arthralgia, headache, diarrhea, oral ulcers, leucopenia, thrombocytopenia, transaminase elevation.
  - High-risk exposures include sexual contact with a person infected with HIV or at risk of HIV, sharing of injection drug use paraphernalia, or contact of potentially infectious blood with mucous membranes or breaks in skin.*

- **Differential diagnosis:** Epstein-Barr virus (EBV)- and non-EBV (e.g., cytomegalovirus [CMV])-related infectious mononucleosis syndromes, influenza, viral hepatitis, streptococcal infection, syphilis

- **Evaluation/diagnosis of acute/primary HIV infection**
  - HIV antibody enzyme immunoassay (EIA) (rapid test if available)
    - Reactive EIA must be followed by Western blot.
    - Negative EIA or reactive EIA with negative or indeterminate Western blot should be followed by a virologic test.†
  - Positive virologic test† in this setting is consistent with acute HIV infection.
  - When acute HIV infection is diagnosed by a positive virologic test (such as HIV RNA or p24 antigen) that was preceded by a negative HIV antibody test, a confirmatory HIV antibody test should be performed over the next 3 months to confirm seroconversion.

- **Considerations for antiretroviral therapy:**
  - All pregnant women with acute or recent HIV infection should start on a combination ARV regimen as soon as possible because of the high risk of MTCT of HIV **(AI)**.
  - Treatment of acute and early HIV infection in nonpregnant persons is considered optional **(CIII)**.
  - Potentially unique benefits associated with ART during acute and early infection exist, although they remain unproven.
  - The risks of ART during acute and early infection are consistent with those for initiating ART in chronically infected asymptomatic patients with high CD4 counts.
  - If therapy is initiated, the goal should be for maintenance of maximal viral suppression.
  - Enrollment in a clinical trial should be considered.

* In some settings, behaviors conducive to acquisition of HIV infection might not be ascertained or might not be perceived as "high risk" by the health care provider or the patient or both. Thus, symptoms and signs consistent with acute retroviral syndrome should motivate consideration of this diagnosis even in the absence of reported high-risk behaviors.

† p24 antigen or HIV RNA assay. The p24 antigen is less sensitive but more specific than HIV RNA tests; HIV RNA tests are generally preferred. HIV RNA tests include quantitative branched DNA (bDNA), reverse transcriptase-polymerase chain reaction (RT-PCR), or qualitative transcription-mediated amplification (APTIMA, GenProbe).

References

1. Tindall B, Cooper DA. Primary HIV infection: host responses and intervention strategies. *AIDS.* 1991;5(1):1-14.
2. Niu MT, Stein DS, Schnittman SM. Primary human immunodeficiency virus type 1 infection: review of pathogenesis and early treatment intervention in humans and animal retrovirus infections. *J Infect Dis.* 1993;168(6):1490-1501.
3. Kinloch-de Loes S, de Saussure P, Saurat JH, et al. Symptomatic primary infection due to human immunodeficiency virus type 1: review of 31 cases. *Clin Infect Dis.* 1993;17(1):59-65.
4. Schacker T, Collier AC, Hughes J, et al. Clinical and epidemiologic features of primary HIV infection. *Ann Intern Med.* 1996;125(4):257-264.
5. Daar ES, Little S, Pitt J, et al. Diagnosis of primary HIV-1 infection. Los Angeles County Primary HIV Infection Recruitment Network. *Ann Intern Med.* 2001;134(1):25-29.
6. Hecht FM, Busch MP, Rawal B, et al. Use of laboratory tests and clinical symptoms for identification of primary HIV infection. *AIDS.* 2002;16(8):1119-1129.
7. Branson BM, Handsfield HH, Lampe MA, et al. Revised recommendations for HIV testing of adults, adolescents, and pregnant women in health-care settings. *MMWR Recomm Rep.* 2006;55(RR-14):1-17.

8. Pilcher CD, Fiscus SA, Nguyen TQ, et al. Detection of acute infections during HIV testing in North Carolina. *N Engl J Med.* 2005;352(18):1873-1883.
9. Wheeler WH, Ziebell RA, Zabina H, et al. Prevalence of transmitted drug resistance associated mutations and HIV-1 subtypes in new HIV-1 diagnoses, U.S.-2006. *AIDS.* 2010;24(8):1203-1212.
10. Kim D, Wheeler W, Ziebell R, et al. Prevalence of transmitted antiretroviral drug resistance among newly-diagnosed HIV-1-infected persons, US, 2007. Paper presented at: 17th Conference on Retroviruses and Opportunistic Infections; February 16-19, 2010; San Francisco, CA. Abstract 580.
11. Wensing AM, van de Vijver DA, Angarano G, et al. Prevalence of drug-resistant HIV-1 variants in untreated individuals in Europe: implications for clinical management. *J Infect Dis.* 2005;192(6):958-966.
12. Hoen B, Dumon B, Harzic M, et al. Highly active antiretroviral treatment initiated early in the course of symptomatic primary HIV-1 infection: results of the ANRS 053 trial. *J Infect Dis.* 1999;180(4):1342-1346.
13. Lafeuillade A, Poggi C, Tamalet C, et al. Effects of a combination of zidovudine, didanosine, and lamivudine on primary human immunodeficiency virus type 1 infection. *J Infect Dis.* 1997;175(5):1051-1055.
14. Lillo FB, Ciuffreda D, Veglia F, et al. Viral load and burden modification following early antiretroviral therapy of primary HIV-1 infection. *AIDS.* 1999;13(7):791-796.
15. Malhotra U, Berrey MM, Huang Y, et al. Effect of combination antiretroviral therapy on T-cell immunity in acute human immunodeficiency virus type 1 infection. *J Infect Dis.* 2000;181(1):121-131.
16. Smith DE, Walker BD, Cooper DA, et al. Is antiretroviral treatment of primary HIV infection clinically justified on the basis of current evidence? *AIDS.* 2004;18(5):709-718.
17. Mehandru S, Poles MA, Tenner-Racz K, et al. Primary HIV-1 infection is associated with preferential depletion of CD4+ T lymphocytes from effector sites in the gastrointestinal tract. *J Exp Med.* 2004;200(6):761-770.
18. Guadalupe M, Reay E, Sankaran S, et al. Severe CD4+ T-cell depletion in gut lymphoid tissue during primary human immunodeficiency virus type 1 infection and substantial delay in restoration following highly active antiretroviral therapy. *J Virol.* 2003;77(21):11708-11717.
19. Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission. Recommendations for use of antiretroviral drugs in pregnant HIV-1-infected women for maternal health and interventions to reduce perinatal HIV transmission in the United States. May 24, 2010:1-117. http://aidsinfo.nih.gov/contentfiles/PerinatalGL.pdf.
20. Pantaleo G, Cohen OJ, Schacker T, et al. Evolutionary pattern of human immunodeficiency virus (HIV) replication and distribution in lymph nodes following primary infection: implications for antiviral therapy. *Nat Med.* 1998;4(3):341-345.
21. El-Sadr WM, Lundgren JD, Neaton JD, et al. CD4+ count-guided interruption of antiretroviral treatment. *N Engl J Med.* 2006;355(22):2283-2296.

HIV-INFECTED ADOLESCENTS AND YOUNG ADULTS (Updated January 10, 2011)

Older children and adolescents now make up the largest percentage of HIV-infected children cared for at pediatric HIV clinics in the United States. The Centers for Disease Control and Prevention (CDC) estimates that 15% of the 35,314 new HIV diagnoses reported among the 33 states that participated in confidential, name-based HIV infection reporting in 2006 were among youth 13–24 years of age *[1]*. Recent trends in HIV prevalence reveal that the disproportionate burden of HIV/AIDS among racial minorities is even greater among youth 13–19 years of age than among young adults 20–24 years of age *[2]*. Furthermore, trends for all HIV/AIDS diagnoses in 33 states from 2001 to 2006 decreased for all transmission categories except among men who have sex with men (MSM). Notably, among all black MSM, the largest increase in HIV/AIDS diagnoses occurred among youth 13–24 years of age *[3]*. HIV-infected adolescents represent a heterogeneous group in terms of sociodemographics, mode of HIV infection, sexual and substance abuse history, clinical and immunologic status, psychosocial development, and readiness to adhere to medications. Many of these factors may influence decisions concerning when to start antiretroviral therapy (ART) and what antiretroviral (ARV) medications should be used.

Most adolescents who acquire HIV are infected through high-risk behaviors. Many of them are recently infected and unaware of their HIV infection status. Thus, many are in an early stage of HIV infection, which makes them ideal candidates for early interventions, such as prevention counseling, linkage, and engagement to care. A recent study among HIV-infected adolescents and young adults presenting for care identified primary genotypic resistance mutations to ARV medications in up to 18% of the evaluable sample of recently infected youth, as determined by the detuned antibody testing assay strategy that defined recent infection as occurring within 180 days of testing *[4]*. This transmission dynamic reflects that a substantial proportion of youth's sexual partners are likely older and may be more ART experienced; thus, awareness of the importance of baseline resistance testing among recently infected youth naïve to ART is imperative.

A limited but increasing number of HIV-infected adolescents are long-term survivors of HIV infection acquired perinatally or in infancy through blood products. Such adolescents are usually heavily ART experienced and may have a unique clinical course that differs from that of adolescents infected later in life *[5]*. If these heavily ART-experienced adolescents harbor resistant virus, optimal ARV regimens should be based on the same guiding principles as for heavily ART-experienced adults. (See **Virologic and Immunogic Failure**.)

Adolescents are developmentally at a difficult crossroad. Their needs for autonomy and independence and their evolving decisional capacity intersect and compete with concrete thinking processes, risk-taking behaviors, preoccupation with self-image, and the need to "fit in" with their peers. This makes it challenging to attract and sustain adolescents' focus on maintaining their health, particularly for those with chronic illnesses. These challenges are not specific to any particular transmission mode or stage of disease. Thus, irrespective of disease duration or mode of HIV transmission, every effort must be made to engage them in care so they can improve and maintain their health for the long term.

Antiretroviral Therapy Considerations in Adolescents

Adult guidelines for ART are usually appropriate for postpubertal adolescents, because the clinical course of HIV-infected adolescents who were infected sexually or through injection drug use during adolescence is more similar to that of adults than to that of children. Adult guidelines can also be useful for postpubertal youth who were perinatally infected because these patients often have treatment challenges associated with the use of long-term ART that mirror those of ART-experienced adults, such as extensive resistance, complex regimens, and adverse drug effects.

Dosage of medications for HIV infection and opportunistic infections should be prescribed according to Tanner staging of puberty and not solely on the basis of age *[6-7]*. Adolescents in early puberty (i.e., Tanner Stages I and II) should be administered doses on pediatric schedules, whereas those in late puberty (i.e., Tanner Stage V) should follow adult dosing schedules. However, Tanner stage and age are not necessarily directly predictive of drug pharmacokinetics. Because puberty may be delayed in children who were infected with HIV perinatally *[8]*, continued use of pediatric doses in puberty-delayed adolescents can result in medication doses that are higher than the usual adult doses. Because data are not available to predict optimal medication doses for each ARV medication for this group of children, issues such as toxicity, pill or liquid volume burden, adherence, and virologic and immunologic parameters should be considered in determining when to transition from pediatric to adult doses. Youth who are in their growth spurt period (i.e., Tanner Stage III in females and Tanner Stage IV in males) and following adult or pediatric dosing guidelines and adolescents

who have transitioned from pediatric to adult doses should be closely monitored for medication efficacy and toxicity. Therapeutic drug monitoring can be considered in selected circumstances to help guide therapy decisions in this context. Pharmacokinetic studies of drugs in youth are needed to better define appropriate dosing. For a more detailed discussion, see ***Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection*** *[9]*.

Adherence Concerns in Adolescents

HIV-infected adolescents are especially vulnerable to specific adherence problems based on their psychosocial and cognitive developmental trajectory. Comprehensive systems of care are required to serve both the medical and psychosocial needs of HIV-infected adolescents, who are frequently inexperienced with health care systems and who lack health insurance. Many HIV-infected adolescents face challenges in adhering to medical regimens for reasons that include:

- denial and fear of their HIV infection;
- misinformation;
- distrust of the medical establishment;
- fear and lack of belief in the effectiveness of medications;
- low self-esteem;
- unstructured and chaotic lifestyles;
- mood disorders and other mental illness;
- lack of familial and social support;
- absence of or inconsistent access to care or health insurance; and
- incumbent risk of inadvertent parental disclosure of the youth's HIV infection status if parental health insurance is used.

In selecting treatment regimens for adolescents, clinicians must balance the goal of prescribing a maximally potent ART regimen with realistic assessment of existing and potential support systems to facilitate adherence. Adolescents benefit from reminder systems (e.g., beepers, timers, and pill boxes) that are stylish and inconspicuous *[10]*. It is important to make medication adherence as user friendly and as little stigmatizing as possible for the older child or adolescent. The concrete thought processes of adolescents make it difficult for them to take medications when they are asymptomatic, particularly if the medications have side effects. Adherence to complex regimens is particularly challenging at a time of life when adolescents do not want to be different from their peers *[11-13]*. Directly observed therapy might be considered for selected HIV-infected adolescents such as those with mental illness *[14-18]*.

Difficult Adherence Problems

Because adolescence is characterized by rapid changes in physical maturation, cognitive processes, and life style, predicting long-term adherence in an adolescent can be very challenging. The ability of youth to adhere to therapy needs to be included as part of therapeutic decision making concerning the risks and benefits of starting treatment. Erratic adherence may result in the loss of future regimens because of the development of resistance mutations. Clinicians who care for HIV-infected adolescents frequently manage youth who, while needing therapy, pose significant concerns regarding their ability to adhere to therapy. In these cases, alternative considerations to initiation of therapy can be the following: (1) a short-term deferral of treatment until adherence is more likely or while adherence-related problems are aggressively addressed; (2) an adherence testing period in which a placebo (e.g., vitamin pill) is administered; and (3) the avoidance of any regimens with low genetic resistance barriers. Such decisions are ideally individualized to each patient and should be made carefully in context with the individual's clinical status. For a more detailed discussion on specific therapy and adherence issues for HIV-infected adolescents, see ***Guidelines for Use of Antiretroviral Agents in Pediatric HIV Infection*** *[9]*.

Special Considerations in Adolescents

Sexually transmitted infections (STIs), in particular human papilloma virus (HPV), should also be addressed in all adolescents. For a more detailed discussion on STIs, see the most recent CDC guidelines *[19]* and the pediatric opportunistic infection treatment guidelines on HPV among HIV-infected adolescents *[20]*. Family planning counseling, including a discussion of the risks of perinatal transmission of HIV and methods to reduce risks, should be provided to all youth. Providing gynecologic care for the HIV-infected female adolescent is especially important. Contraception, including the interaction of specific ARV drugs on hormonal contraceptives, and the potential for pregnancy also may alter choices of ART. As an example, efavirenz (EFV) should be used with caution in females of childbearing age and should only be prescribed after intensive counseling and education about the potential effects on the fetus, the need for close monitoring—including periodic pregnancy testing—and a commitment on the part of the teen to use effective contraception. For a more detailed discussion, see **HIV-Infected Women** and the ***Perinatal Guidelines*** *[21]*.

Transitioning Care

Given lifelong infection with HIV and the need for treatment through several stages of growth and development, HIV care programs and providers need flexibility to appropriately transition care for HIV-infected children, adolescents, and young adults. A successful transition requires an awareness of some fundamental differences between many adolescent and adult HIV care models. In most adolescent HIV clinics, care is more "teen-centered" and multidisciplinary, with primary care being highly integrated into HIV care. Teen services, such as sexual and reproductive health, substance abuse treatment, mental health, treatment education, and adherence counseling are all found in one clinic setting. In contrast, some adult HIV clinics may rely more on referral of the patient to separate subspecialty care settings, such as gynecology. Transitioning the care of an emerging young adult includes considerations of areas such as medical insurance, independence, autonomy, decisional capacity, confidentiality, and consent. Also, adult clinic settings tend to be larger and can easily intimidate younger, less motivated patients. As an additional complication to this transition, HIV-infected adolescents belong to two epidemiologically distinct subgroups: (1) those perinatally infected—who would likely have more disease burden history, complications, and chronicity; less functional autonomy; greater need for ART; and higher mortality risk; and (2) those more recently infected due to high-risk behaviors. Thus, these subgroups have unique biomedical and psychosocial considerations and needs.

To maximize the likelihood of a successful transition, facilitators to successful transitioning are best implemented early on. These include the following: (1) optimizing provider communication between adolescent and adult clinics; (2) addressing patient/family resistance caused by lack of information, stigma or disclosure concerns, and differences in practice styles; (3) preparing youth for life skills development, including counseling them on the appropriate use of a primary care provider and appointment management, the importance of prompt symptom recognition and reporting, and the importance of self-efficacy with medication management, insurance, and entitlements; (4) identifying an optimal clinic model for a given setting (i.e., simultaneous transition of mental health and/or case management versus a gradual phase-in); (5) implementing ongoing evaluation to measure the success of a selected model; (6) engaging in regular multidisciplinary case conferences between adult and adolescent care providers; (7) implementing interventions that may be associated with improved outcomes, such as support groups and mental health consultation; and (8) incorporating a family planning component into clinical care. Attention to these key areas will likely improve adherence to appointments and avert the potential for a youth to "fall through the cracks," as it is commonly referred to in adolescent medicine.

References

1. Centers for Disease Control and Prevention (CDC). HIV and AIDS in the United States: A picture of today's epidemic. 2008; http://www.cdc.gov/hiv/topics/surveillance/united_states.htm
2. Centers for Disease Control and Prevention (CDC). HIV/AIDS surveillance in adolescents and young adults (through 2007). 2009; http://www.cdc.gov/hiv/topics/surveillance/resources/slides/adolescents/index.htm.
3. MMWR. Trends in HIV/AIDS diagnoses among men who have sex with men--33 states, 2001-2006. *MMWR Morb Mortal Wkly Rep*. 2008;57(25):681-686.
4. Viani RM, Peralta L, Aldrovandi G, et al. Prevalence of primary HIV-1 drug resistance among recently infected adolescents: a multicenter adolescent medicine trials network for HIV/AIDS interventions study. *J Infect Dis.* 2006;194(11):1505-1509.
5. Grubman S, Gross E, Lerner-Weiss N, et al. Older children and adolescents living with perinatally acquired human immunodeficiency virus infection. *Pediatrics.* 1995;95(5):657-663.

6. Rogers A (ed). Pharmacokinetics and pharmacodynamics in adolescents. *J Adolesc Health.* 1994;15:605-678.
7. El-Sadar W, Oleske JM, Agins BD, et al. Evaluation and management of early HIV infection. Clinical Practice Guideline No. 7 (AHCPR Publication No. 94-0572). Rockville, MD: Agency for Health Care Policy and Research, Public Health Service, US Department of Health and Human Services, 1994.
8. Buchacz K, Rogol AD, Lindsey JC, et al. Delayed onset of pubertal development in children and adolescents with perinatally acquired HIV infection. *J Acquir Immune Defic Syndr.* 2003;33(1):56-65.
9. Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children. Guidelines for the use of antiretroviral agents in pediatric HIV infection. August 16, 2010:1-219. http://aidsinfo.nih.gov/contentfiles/PediatricGuidelines.pdf.
10. Lyon ME, Trexler C, Akpan-Townsend C, et al. A family group approach to increasing adherence to therapy in HIV-infected youths: results of a pilot project. *AIDS Patient Care STDS.* 2003;17(6):299-308.
11. Brooks-Gunn J, Graber JA. Puberty as a biological and social event: implications for research on pharmacology. *J Adolesc Health.* 1994;15(8):663-671.
12. Kyngas H, Hentinen M, Barlow JH. Adolescents' perceptions of physicians, nurses, parents and friends: help or hindrance in compliance with diabetes self-care? *J Adv Nurs.* 1998;27(4):760-769.
13. La Greca AM. Peer influences in pediatric chronic illness: an update. *J Pediatr Psychol.* 1992;17(6):775-784.
14. Murphy DA, Wilson CM, Durako SJ, et al. Antiretroviral medication adherence among the REACH HIV-infected adolescent cohort in the USA. *AIDS Care.* 2001;13(1):27-40.
15. Stenzel MS, McKenzie M, Mitty JA, et al. Enhancing adherence to HAART: a pilot program of modified directly observed therapy. *AIDS Read.* 2001;11(6):317-319, 324-318.
16. Purdy JB, Freeman AF, Martin SC, et al. Virologic response using directly observed therapy in adolescents with HIV: an adherence tool. *J Assoc Nurses AIDS Care.* 2008;19(2):158-165.
17. Garvie PA, Lawford J, Flynn PM, et al. Development of a directly observed therapy adherence intervention for adolescents with human immunodeficiency virus-1: application of focus group methodology to inform design, feasibility, and acceptability. *J Adolesc Health.* 2009;44(2):124-132.
18. Gaur A BM, Britto P, et al. Directly observed therapy for non-adherent HIV-infected adolescents - lessons learned, challenges ahead. Paper presented at: 15th Conference on Retroviruses and Opportunistic Infections. Paper presented at: 15th Conference on Retroviruses and Opportunistic Infections; 2008; Boston, MA.
19. Workowski KA, Berman SM. Sexually transmitted diseases treatment guidelines, 2006. *MMWR Recomm Rep.* 2006;55(RR-11):1-94.
20. Centers for Disease Control and Prevention (CDC). Guidelines for the Prevention and Treatment of Opportunistic Infections among HIV-exposed and HIV-infected children: recommendations from CDC, the National Institutes of Health, the HIV Medicine Association of the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the American Academy of Pediatrics. *MMWR Recomm Rep.* 2009;58(RR-11):1-166.
21. Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission. Recommendations for use of antiretroviral drugs in pregnant HIV-1-infected women for maternal health and interventions to reduce perinatal HIV transmission in the United States. May 24, 2010:1-117. http://aidsinfo.nih.gov/contentfiles/PerinatalGL.pdf.

HIV AND ILLICIT DRUG USERS (IDUs) (Updated January 10, 2011)

Treatment Challenges of HIV-Infected IDUs

Injection drug use is the second-most common mode of HIV transmission in the United States. In addition, noninjection illicit drug use may facilitate sexual transmission of HIV. Injection and noninjection illicit drugs include the following: heroin, cocaine, marijuana, and club drugs (i.e., methamphetamine, ketamine, gamma-hydroxybutyrate [GHB], and amyl nitrate). The most commonly used illicit drugs associated with HIV infection are heroin and stimulants (e.g., cocaine and amphetamines); however, the use of club drugs has increased substantially in the past several years and is common among those who have HIV infection or who are at risk of HIV infection. Methamphetamine and amyl nitrate (i.e., poppers) have been the most strongly associated with high-risk sexual behavior in men who have sex with men (MSM), and the association is less consistent with the other club drugs *[1]*.

All illicit drugs have been associated with depression and anxiety, either as part of the withdrawal process or as a consequence of repeated use. This is particularly relevant in the treatment of HIV infection because depression is one of the strongest predictors of poor adherence and poor treatment outcomes *[2]*. Although treatment of HIV disease in this population can be successful, IDUs who have HIV disease present special treatment challenges. These may include the following: (1) an array of complicating comorbid medical and mental health conditions; (2) limited access to HIV care; (3) inadequate adherence to therapy; (4) medication side effects and toxicities; (5) the need for substance abuse treatment; and (6) drug interactions that can complicate HIV treatment *[3]*.

Underlying health problems among injection and noninjection drug users result in increased morbidity and mortality, either independent of or accentuated by HIV disease. Many of these problems are the consequence of prior exposures to infectious pathogens from nonsterile needle and syringe use. Such problems can include hepatitis B or C virus infection, tuberculosis, skin and soft tissue infections, recurrent bacterial pneumonia, and endocarditis. Other morbidities such as alteration in levels of consciousness and neurologic and renal disease are not uncommon. Furthermore, these comorbidities are associated with a higher risk of drug overdoses in IDUs with HIV disease, due in part to respiratory, hepatic, and neurological impairments *[4]*. Successful HIV therapy for IDUs often rests upon acquiring familiarity with and providing care for these comorbid conditions and overdose prevention support.

IDUs have less access to HIV care and are less likely to receive antiretroviral therapy (ART) than other populations *[5-6]*. Factors associated with low rates of ART among IDUs include active drug use, younger age, female gender, suboptimal health care, recent incarceration, lack of access to rehabilitation programs, and lack of expertise among health care providers *[5-6]*. The typically unstable, chaotic life patterns of many IDUs; the powerful pull of addictive substances; and common misperceptions about the dangers, impact, and benefits of ART all contribute to decreased adherence *[7]*. The chronic and relapsing nature of substance abuse as a biologic and medical disease, compounded by the high rate of mental illness that antedates and/or is exacerbated by illicit substance use, additionally complicate the relationship between health care workers and IDUs *[8-9]*. The first step in provision of care and treatment for these individuals is to recognize the existence of a substance abuse problem. Whereas this is often open and obvious, patients may hide such behaviors from clinicians. Assessment of a patient for substance abuse should be part of routine medical history taking and should be done in a clinical, straightforward, and nonjudgmental manner.

Treatment Efficacy in HIV-Infected Illicit Drug Use Populations

Although IDUs are underrepresented in HIV therapy clinical trials, available data indicate that—when they are not actively using drugs— efficacy of ART in IDUs is similar to that seen in other populations *[10]*. Furthermore, therapeutic failure in this population generally correlates with the degree that drug use disrupts daily activities rather than with drug use *per se [11]*. Providers need to remain attentive to the possible impact these factors have upon the patient before and during prescription of ART. Although many IDUs can sufficiently control their drug use over long enough periods of time to benefit from care**,** substance abuse treatment is often necessary for successful HIV management.

Close collaboration with substance abuse treatment programs and proper support and attention to this population's special multidisciplinary needs are critical components of successful HIV treatment. Essential to this end are accommodating and flexible, community-based HIV care sites that are characterized by familiarity with and

nonjudgmental expertise in management of drug users' wide array of needs and in development of effective strategies to promote medication adherence *[9]*, including, if available, the use of adherence support mechanisms such as modified directly observed therapy, which has shown promise in this population *[12]*.

Antiretroviral Agents and Opioid Substitution Therapy

IDUs are more likely to experience an increased frequency of side effects and toxicities of ART. Although not systematically studied, this is likely because underlying hepatic, renal, neurologic, psychiatric, gastrointestinal, and hematologic disorders are highly prevalent among IDUs. Selection of ARV agents in this population should be made with consideration of these comorbid conditions. Opioid substitution therapies such as methadone and buprenorphine/naloxone and extended release naltrexone are commonly used for management of opioid dependence in HIV infected-patients.

Methadone and ART. Methadone, an orally administered, long-acting opioid agonist, is the most common pharmacologic treatment for opioid addiction. Its use is associated with decreased heroin use, decreased needle sharing, and improved quality of life. Because of its opioid-induced effects on gastric emptying and the metabolism of cytochrome P (CYP) 450 isoenzymes 2B6, 3A4, and 2D6, pharmacologic effects and interactions with ARV agents may commonly occur *[13]*. These may diminish the effectiveness of either or both therapies by causing opioid withdrawal or overdose, increased methadone toxicity, and/or decreased ARV efficacy. Efavirenz (EFV), nevirapine (NVP), and lopinavir/ritonavir (LPV/r) have been associated with significant decreases in methadone levels. It is necessary to inform patients and substance abuse treatment facilities of the likelihood of this interaction. The clinical effect is usually seen after 7 days of coadministration and may be managed by increasing the methadone dosage, usually in 5-mg to10-mg increments daily until the desired effect is achieved.

Buprenorphine and ART. Buprenorphine, a partial μ-opioid agonist, is administrated sublingually and is often coformulated with naloxone. It is being increasingly used for opioid dependence treatment. The lower risk of respiratory depression and overdose compared with methadone allows it to be prescribed by physicians in primary care for the treatment of opioid dependency. This flexible treatment setting could be of significant value to opioid-addicted HIV-infected patients who require ART because it enables one physician or program to provide both medical and substance abuse services. Limited information is currently available about interactions between buprenorphine and antiretroviral agents *[13-14]*. Findings from available studies show a more favorable drug interaction profile than that of methadone.

Naltrexone and ART. A once monthly extended-release intramuscular formulation of naltrexone was recently approved for prevention of relapse in patients who have undergone an opioid detoxification program. Naltrexone is also indicated for treatment of alcohol dependency. Naltrexone is not metabolized via the CYP 450 enzyme system and is not expected to interact with protease inhibitors (PIs) or nonnucleoside reverse transcriptase inhibitors (NNRTIs) *[15]*.

Table 11 provides the currently available pharmacokinetic interaction data that clinicians can use as a guide for managing patients receiving ART and methadone or buprenorphine. Particular attention is needed concerning communication between HIV care providers and drug treatment programs regarding additive drug toxicities and drug interactions resulting in opiate withdrawal or excess.

Methylenedioxymethamphetamine (MDMA), GHB, ketamine, and methamphetamine all have the potential to interact with ARV agents because all are metabolized, at least in part, by the CYP 450 system. Overdoses secondary to interactions between the party drugs (i.e., MDMA or GHB) and PI-based ART have been reported *[16]*.

Summary

It is usually possible over time to support most active drug users such that acceptable adherence levels with ARV agents can be achieved *[17-18]*. Providers must work to combine all available resources to stabilize an active drug user in preparation for ART. This should include identification of concurrent medical and psychiatric illnesses, drug treatment, needle and syringe exchange, reduction in high-risk sexual behavior, and harm reduction strategies. A

history of drug use alone is insufficient reason to withhold ART because individuals with a history of prior drug use have adherence rates similar to individuals who do not abuse drugs.

Important considerations in the selection of successful regimens and the provision of appropriate patient monitoring in this population include supportive clinical sites; linkage to substance abuse treatment; and awareness of the interactions between illicit drugs and ARV agents, including the increased risk of side effects and toxicities. Simple regimens should be considered to enhance medication adherence. Preference should be given to ARV agents that have a lower risk of hepatic and neuropsychiatric side effects, simple dosing schedules, and minimal interaction with methadone.

Table 11. Drug Interactions between Antiretroviral Agents and Drugs Used to Treat Opioid Addiction (January 10, 2011)

Concomitant Drug	Antiretroviral Class/Drug	Pharmacokinetic Interactions Recommendations/Clinical Comments
Buprenorphine	EFV	buprenorphine AUC ↓ 50%; norbuprenorphine* AUC ↓ 71% No withdrawal symptoms reported. No dosage adjustment recommended; however, monitor for withdrawal symptoms.
	ATV	buprenorphine AUC ↑ 93%; norbuprenorphine AUC ↑ 76%; ↓ ATV levels possible Do not coadminister buprenorphine with unboosted ATV.
	ATV/r	buprenorphine AUC ↑ 66%; norbuprenorphine AUC ↑ 105% Monitor for sedation. Buprenorphine dose reduction may be necessary.
	DRV/r	buprenorphine: no significant effect, norbuprenorphine AUC ↑ 46% and C_{min} ↑ 71% No dose adjustment necessary.
	TPV/r	buprenorphine: no significant effect; norbuprenorphine AUC, C_{max}, and C_{min} ↓ 80%; TPV Cmin ↓ 19%–40% Consider monitoring TPV level.
	3TC, ddI, TDF, ZDV, NVP, LPV/r, NFV	No significant effect No dosage adjustment necessary.
	ABC, d4T, FTC, ETR, FPV +/- RTV, IDV +/- RTV, SQV/r, RAL, MVC, T20	No data

Table 11. Drug Interactions between Antiretroviral Agents and Drugs Used to Treat Opioid Addiction

Concomitant Drug	Antiretroviral Class/Drug	Pharmacokinetic Interactions Recommendations/Clinical Comments
Methadone	ABC	methadone clearance ↑ 22% No dosage adjustment necessary.
	d4T	d4T AUC ↓ 23% and C_{max} ↓ 44% No dosage adjustment necessary.
	ZDV	ZDV AUC ↑ 29%–43% Monitor for ZDV-related adverse effects.
	EFV	methadone AUC ↓ 52% Opioid withdrawal common; increased methadone dose often necessary.
	NVP	methadone AUC ↓ 41% NVP: no significant effect Opioid withdrawal common; increased methadone dose often necessary.
	ATV/r, DRV/r, FPV/r, IDV/r, LPV/r, SQV/r, TPV/r	With ATV/r, DRV/r, FPV/r: R-methadone† AUC ↓ 16%–18%; With LPV/r: methadone AUC ↓ 26%–53%; With SQV/r 1,000/100mg BID: R-methadone AUC ↓ 19%; With TPV/r: R-methadone AUC ↓ 48% Opioid withdrawal unlikely but may occur. No adjustment in methadone usually required; however, monitor for opioid withdrawal and increase methadone dose as clinically indicated.
	FPV	No data with FPV (unboosted) With APV: R-methadone C_{min} ↓ 21%, AUC no significant change Monitor and titrate methadone as clinically indicated. The interaction with FPV is presumed to be similar.
	NFV	methadone AUC ↓ 40% Opioid withdrawal rarely occurs. Monitor and titrate dose as clinically indicated. May require increased methadone dose.
	ddI (EC capsule), 3TC, TDF, ETR, RTV, ATV, IDV, RAL	No significant effect No dosage adjustment necessary.
	FTC, MVC, T20	No data

*Norbuprenorphine is an active metabolite of buprenorphine.
† R-methadone is the active form of methadone.

Acronyms: 3TC = lamivudine, d4T = stavudine, T20 = enfuvirtide, ABC = abacavir, APV = amprenavir, ATV = atazanavir, ATV/r = atazanavir/ritonavair, ddI = didanosine, DRV/r = darunavir/ritonavir, EFV = efavirenz, ETR = etravirine, FPV = fosamprenavir, FPV/r = fosamprenavir/ritonavir, FTC = emtricitabine, IDV = indinavir, IDV/r = indinavir/ritonavir, LPV/r = lopinavir/ritonavir, MVC = maraviroc, NFV = nelfinavir, NVP = nevirapine, RAL = raltegravir, RTV = ritonavir, SQV/r = sacquinavir/ritonavir, TDF = tenofovir, TPV = tipranavir, TPV/r = tipranavir/ritonavir, ZDV = zidovudine

References

1. Colfax G, Guzman R. Club drugs and HIV infection: a review. Clin Infect Dis. May 15 2006;42(10):1463-1469.
2. Tucker JS, Burnam MA, Sherbourne CD, Kung FY, Gifford AL. Substance use and mental health correlates of nonadherence to antiretroviral medications in a sample of patients with human immunodeficiency virus infection. Am J Med. May 2003;114(7):573-580.
3. Bruce RD, Altice FL, Gourevitch MN, Friedland GH. Pharmacokinetic drug interactions between opioid agonist therapy and antiretroviral medications: implications and management for clinical practice. J Acquir Immune Defic Syndr. Apr 15 2006;41(5):563-572.
4. Wang C, Vlahov D, Galai N, et al. The effect of HIV infection on overdose mortality. AIDS. Jun 10 2005;19(9):935-942.
5. Strathdee SA, Palepu A, Cornelisse PG, et al. Barriers to use of free antiretroviral therapy in injection drug users. JAMA. Aug 12 1998;280(6):547-549.
6. Celentano DD, Vlahov D, Cohn S, Shadle VM, Obasanjo O, Moore RD. Self-reported antiretroviral therapy in injection drug users. JAMA. Aug 12 1998;280(6):544-546.
7. Altice FL, Mostashari F, Friedland GH. Trust and the acceptance of and adherence to antiretroviral therapy. J Acquir Immune Defic Syndr. Sep 1 2001;28(1):47-58.
8. Altice FL, Kamarulzaman A, Soriano VV, Schechter M, Friedland GH. Treatment of medical, psychiatric, and substance-use comorbidities in people infected with HIV who use drugs. Lancet. Jul 31 2010;376(9738):367-387.
9. Bruce RD, Altice FL, Friedland GH, Volberding P. HIV Disease Among Substance Misusers: Treatment Issues. Global AIDS/HIV Medicine. San Diego, CA: Elsevier Inc; 2007:513-526.
10. Morris JD, Golub ET, Mehta SH, Jacobson LP, Gange SJ. Injection drug use and patterns of highly active antiretroviral therapy use: an analysis of ALIVE, WIHS, and MACS cohorts. AIDS Res Ther. 2007;4:12.
11. Bouhnik AD, Chesney M, Carrieri P, et al. Nonadherence among HIV-infected injecting drug users: the impact of social instability. J Acquir Immune Defic Syndr. Dec 15 2002;31 Suppl 3:S149-153.
12. Altice FL, Maru DS, Bruce RD, Springer SA, Friedland GH. Superiority of directly administered antiretroviral therapy over self-administered therapy among HIV-infected drug users: a prospective, randomized, controlled trial. Clin Infect Dis. Sep 15 2007;45(6):770-778.
13. Gruber VA, McCance-Katz EF. Methadone, buprenorphine, and street drug interactions with antiretroviral medications. Curr HIV/AIDS Rep. Aug 2010;7(3):152-160.
14. Bruce RD, McCance-Katz E, Kharasch ED, Moody DE, Morse GD. Pharmacokinetic interactions between buprenorphine and antiretroviral medications. Clin Infect Dis. Dec 15 2006;43 Suppl 4:S216-223.
15. Food and Drug Administration (FDA). Vivitrol (package insert). October 2010. http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021897s015lbl.pdf.
16. Bruce RD AFaFG. A review of pharmacokinetic drug interactions between drugs of abuse and antiretroviral medications: Implications and management for clinical practice. Exp Rev of Clin Pharmacol. 2008;1(1):115-127.
17. Hicks PL, Mulvey KP, Chander G, et al. The impact of illicit drug use and substance abuse treatment on adherence to HAART. AIDS Care. Oct 2007;19(9):1134-1140.
18. Cofrancesco J, Jr., Scherzer R, Tien PC, et al. Illicit drug use and HIV treatment outcomes in a US cohort. AIDS. Jan 30 2008;22(3):357-365.

HIV-INFECTED WOMEN (Updated January 10, 2011)

Panel's Recommendations:

- ***The indications for initiation of antiretroviral therapy (ART) and the goals of treatment are the same for HIV-infected women as for other HIV-infected adults and adolescents (AI).***
- ***Women taking antiretroviral (ARV) drugs that have significant pharmacokinetic interactions with oral contraceptives should use an additional or alternative contraceptive method for prevention of unintended pregnancy (AIII).***
- ***In pregnant women, an additional goal of therapy is prevention of mother-to-child transmission (PMTCT), with a goal of maximal viral suppression to reduce the risk of transmission of HIV to the fetus and newborn (AI).***
- ***Genotypic resistance testing is recommended for all HIV-infected persons, including pregnant women, prior to initiation of ART (AIII) and for women entering pregnancy with detectable HIV RNA levels while on therapy (AI).***
- ***When selecting an ARV combination regimen for a pregnant woman, clinicians should consider the known safety, efficacy, and pharmacokinetic data of each agent during pregnancy (AIII).***
- ***Efavirenz (EFV) should be avoided in a pregnant woman during the first trimester or in a woman who desires to become pregnant or who does not or cannot use effective and consistent contraception (AIII).***
- ***Clinicians should consult the most current Health and Human Services (HHS) Perinatal Guidelines when designing a regimen for a pregnant woman (AIII).***

Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = data from randomized controlled trials; II = data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = expert opinion

This section provides discussion of some basic principles and unique considerations to follow when caring for HIV-infected women in general and for pregnant HIV-infected women. Clinicians who provide care for pregnant women should consult the current ***Perinatal Guidelines*** *[1]* for in-depth discussion and management assistance.

Gender Considerations in Antiretroviral Therapy

In general, studies to date have not shown differences in virologic efficacy of ART by gender *[2-4]*, although a number of studies have suggested that gender or sex may influence the frequency, presentation, and severity of selected ARV-related adverse events *[5]*. Although data are limited, there is also evidence that women may metabolize and respond to specific medications, including ARV drugs, differently than men *[6-8]*.

Adverse Effects:

- ***Nevirapine (NVP)-associated hepatotoxicity***: NVP has been associated with an increased risk of symptomatic, potentially fatal, and often rash-associated liver toxicity among ARV-naïve individuals; women with higher CD4 counts (>250 cells/mm^3) appear to be at greatest risk *[9-12]*. It is generally recommended that NVP not be prescribed to ARV-naïve women who have CD4 counts >250 cells/mm^3 unless there is no other alternative and the benefit from NVP outweighs the risk of hepatotoxicity **(AI)**.
- ***Lactic acidosis***: There appears to be a female predominance in the increased incidence of symptomatic and even fatal lactic acidosis associated with prolonged exposure to nucleoside reverse transcriptase inhibitors (NRTIs). Lactic acidosis is most common with stavudine (d4T), didanosine (ddI), and zidovudine (ZDV); however, it can occur with other NRTIs *[13]*.
- ***Metabolic complications***: A few studies have compared women to men in terms of metabolic complications associated with ARV use. HIV-infected women are more likely to experience increases in central fat with ART and are less likely to have triglyceride elevations on treatment *[14-15]*. Women have an increased risk of osteopenia/osteoporosis, particularly after menopause, and this risk may be exacerbated by HIV and ART *[16-17]*. At the present time, none of these differences requires a change in recommendations regarding treatment or monitoring.

Women of Childbearing Potential

All women of childbearing potential should be offered preconception counseling and care as a component of routine primary medical care. Discussion should include special considerations with ARV use when trying to conceive and during pregnancy. (See ***Perinatal Guidelines*** *[1]*). The most vulnerable period in fetal organogenesis is early in gestation, often before pregnancy is recognized. Sexual activity, reproductive plans, and use of effective contraception to prevent unintended pregnancy should be discussed with women. As part of the evaluation for initiating ART, women should be counseled about the potential teratogenic risk of EFV-containing regimens, should pregnancy occur. EFV-containing regimens should be avoided in women who are trying to conceive or who are sexually active and not using effective and consistent contraception.

Effective contraception should be available for women who wish to prevent pregnancy. Several protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) have drug interactions with combined oral contraceptives (COCs). Interactions include either a decrease or an increase in blood levels of ethinyl estradiol, norethindrone, or norgestimate (see **Tables 15a and b**), which potentially decrease contraceptive efficacy or increase estrogen- or progestin-related adverse effects (e.g., thromboembolic risk). In general, women who are on any of these ARV drugs should use an alternative or additional method of contraception **(AIII)**. Although there is minimal information about drug interactions with use of newer combined hormonal contraceptive methods (e.g., transdermal patch, vaginal ring), an additional or alternative contraceptive method should also be considered on the basis of established drug interactions between ARVs and COCs. Data on drug interactions between ARVs and progestin-only contraceptive methods are limited; however, recent data have found no significant changes in ARV drug concentrations of nelfinavir (NFV), NVP, or EFV when used with depot medroxyprogesterone acetate (DMPA), and there is no evidence of reduced DMPA effectiveness *[18-20]*. Intrauterine devices have been shown to be safe and effective in HIV-infected women *[21-22]*. Counseling about reproductive issues should be provided on an ongoing basis.

Pregnant Women

The use of combination ARV regimens is recommended for all HIV-infected pregnant women, regardless of virologic, immunologic, or clinical parameters, primarily for prevention of HIV transmission from mother to child and for treatment of maternal infection **(AI)**. Pregnant HIV-infected women should be counseled regarding the known benefits versus potential risks of ARV use during pregnancy to the mother, fetus, and newborn. A woman's decision regarding ARV use should be respected. Coercive and punitive policies undermine provider-patient trust and could discourage women from seeking prenatal care and adopting health care behaviors that optimize maternal, fetal, and neonatal well-being.

Prevention of Mother-to-Child Transmission (PMTCT). Both reduction of HIV RNA levels and use of ARVs appear to have an independent effect on reduction of perinatal transmission of HIV *[23-25]*. The goal of ARV use is to achieve maximal and sustained suppression of HIV RNA levels during pregnancy, but most critically by late pregnancy and the time of delivery, when most transmission occurs.

Genotypic resistance testing is recommended for all pregnant women prior to ARV initiation **(AIII)** and for women entering pregnancy with detectable HIV RNA levels while on therapy **(AI)**. Optimal prevention of perinatal transmission may require initiation of ARV before results of resistance testing are available. If results demonstrate the presence of significant mutation(s) that may confer resistance to the prescribed ARV regimen, the regimen should be modified.

Long-term follow-up is recommended for all infants born to women who have received ARVs during pregnancy, regardless of the infant's HIV status.

Regimen Considerations. Pregnancy should not preclude the use of optimal drug regimens. However, recommendations regarding the choice of ARVs for treatment of HIV-infected pregnant women are subject to unique considerations, which may result in different specific recommendations regarding timing of initiation and choice of drugs. These considerations include the following:

- potential changes in pharmacokinetics, and thus dosing requirements, which result from physiologic changes associated with pregnancy,
- potential ARV-associated adverse effects in pregnant women,
- effect on the risk of perinatal transmission of HIV, and
- potential short- and long-term effects of the ARV on the fetus and newborn, which are unknown for many drugs.

Clinicians should review the ***Perinatal Guidelines*** *[1]* for a detailed discussion of drug choices. Combination drug regimens are considered the standard of care in pregnancy, both for the treatment of HIV infection and for PMTCT. ZDV by intravenous infusion to the mother during labor and orally to the neonate for 6 weeks is recommended irrespective of antenatal regimen chosen.

There are some specific differences in treatment recommendations in pregnancy based on the above considerations.

NRTIs:

- Although no longer considered a preferred NRTI for non-pregnant adults and adolescents, ZDV is still one of the preferred NRTI drugs when used in pregnancy based on long-term effectiveness in prevention of transmission and safety data in pregnancy (for more detailed discussion, see the ***Perinatal Guidelines*** *[1]*). However, ZDV should not be included in a regimen if there is severe toxicity, documented resistance, or if the woman is also receiving d4T. Women already on a fully suppressive regimen that does not include ZDV should continue on the regimen **(AIII)**.
- The syndrome of lactic acidosis and hepatic steatosis may present with similar signs and symptoms to certain pregnancy-specific disorders (i.e., acute fatty liver of pregnancy, HELLP [hemolysis, elevated liver enzymes, low platelet count] syndrome). Given this similarity, clinicians should have a low threshold for considering lactic acidosis in the differential diagnosis and for appropriate evaluation of pregnant HIV-infected women receiving NRTIs with a consistent clinical picture, particularly if they have accompanying hepatitis or pancreatitis.

NNRTIs:

- EFV-containing regimens **should be avoided** in the first trimester, because significant teratogenic effects were seen in primate studies at drug exposures similar to those achieved during human exposure **(AIII)**. In addition, several cases of neural tube defects have now been reported after early human gestational exposure to EFV *[26-27]*. EFV may be considered for use after the first trimester if indicated because of toxicity, resistance, drug interaction issues, or other clinical concerns (e.g., adherence, presentation after first trimester on EFV-containing regimen) *[28]*.
- Although there is no evidence that pregnancy additionally increases risk of NVP toxicity over that in nonpregnant women *[29]*, NVP should not be initiated as a component of a combination regimen in ARV-naïve pregnant women who have CD4 counts >250 cells/mm^3 unless the benefit clearly outweighs the risk **(AII)**.

PIs:

- Several small studies show that optimal levels of several PIs may not be achieved in pregnancy with standard dosing, especially in the third trimester, although the clinical relevance of this is unknown *[30-32]*. For more information regarding potential dosing alterations, please refer to the ***Perinatal Guidelines*** *[1]*. Once-daily lopinavir/ritonavir (LPV/r) dosing is not recommended in pregnancy, because there are no data to address adequacy of blood levels with this dosing regimen **(BII)**.

Minimal data exist on the use of newer agents, including entry inhibitors and integrase inhibitors, in pregnancy.

Clinicians who are treating HIV-infected pregnant women are strongly encouraged to report cases of prenatal exposure to ARVs (either administered alone or in combinations) to the Antiretroviral Pregnancy Registry (**http://www.apregistry.com**). The registry collects observational data regarding exposure to FDA-approved ARV drugs during pregnancy for the purpose of assessing potential teratogenicity. For more information regarding selection and use of ART during pregnancy, refer to the ***Perinatal Guidelines*** *[1]*. Lastly, women should be counseled regarding the avoidance of breastfeeding. Continued clinical, immunologic, and virologic follow-up should be done as recommended for non-pregnant adults and adolescents.

Discontinuation of Antiretroviral Therapy Postpartum

Following delivery, considerations regarding continuation of ART for maternal therapeutic indications are the same as for other non-pregnant individuals. The decision of whether to continue therapy after delivery should take into account current recommendations for initiation of ART, current and nadir CD4 T-cell counts and trajectory, HIV RNA levels, adherence issues, and patient preference. A study from the Women and Infants Transmission Study (WITS) of women who were ARV naïve prior to pregnancy and had CD4 counts >350/mm^3 *[33]* found no significant differences in CD4 count, viral load, or disease progression among those who did or did not continue ART after delivery through 12 months postpartum. In most cases, when drugs are discontinued postnatally, all drugs should be stopped simultaneously. However, if therapy includes an NNRTI, stopping all regimen components simultaneously may result in functional monotherapy because of the long half-life of the NNRTI, which may increase risk of resistance. In one study, NVP resistance was identified in 16% of women on an NVP-containing regimen despite continuation of the NRTI backbone for 5 days after stopping NVP *[34]*. For women whose antepartum regimen included an NNRTI and who plan to stop ARV prophylaxis after delivery, consideration should be given to stopping the NNRTI and continuing the other ARV or switching from an NNRTI to a PI prior to interruption and continuing the PI with the other ARV for a period of time before electively stopping ART. The optimal interval between stopping an NNRTI and the other ARV is not known; at least 7 days is recommended but some experts recommend continuing the other ARV or substituting a PI plus two other agents for up to 30 days. Additional research is needed to assess appropriate strategies for stopping NNRTI-containing combination regimens after delivery in situations when ongoing maternal treatment is not indicated and to assess the effect of limited-duration, fully suppressive ARV prophylaxis in pregnancy on future treatment efficacy. (See **Discontinuation or Interruption of Antiretroviral Therapy**.)

In HIV and hepatitis B virus (HBV) co-infected pregnant women who are receiving ART only for perinatal prophylaxis and who are stopping therapy after delivery, careful clinical and laboratory monitoring for HBV flare should be performed postpartum when ARVs active against HBV are discontinued. However, if treatment for HBV is indicated, a full combination regimen for both HIV and HBV infection should be continued. (See **Initiating Antiretroviral Therapy**.)

References

1. Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission. Recommendations for use of antiretroviral drugs in pregnant HIV-1-infected women for maternal health and interventions to reduce perinatal HIV transmission in the United States. May 24, 2010:1-117. http://aidsinfo.nih.gov/contentfiles/PerinatalGL.pdf.
2. Collazos J, Asensi V, Carton JA. Sex differences in the clinical, immunological and virological parameters of HIV-infected patients treated with HAART. *AIDS.* 2007;21(7):835-843.
3. Fardet L, Mary-Krause M, Heard I, et al. Influence of gender and HIV transmission group on initial highly active antiretroviral therapy prescription and treatment response. *HIV Med.* 2006;7(8):520-529.
4. Currier J, Averitt Bridge D, Hagins D, et al. Sex-based outcomes of darunavir-ritonavir therapy: a single-group trial. *Ann Intern Med.* 2010;153(6):349-357.
5. Clark RA, Squires KE. Gender-specific considerations in the antiretroviral management of HIV-infected women. *Expert Rev Anti Infect Ther.* 2005;3(2):213-227.
6. Gandhi M, Aweeka F, Greenblatt RM, et al. Sex differences in pharmacokinetics and pharmacodynamics. *Annu Rev Pharmacol Toxicol.* 2004;44:499-523.
7. Floridia M, Giuliano M, Palmisano L, et al. Gender differences in the treatment of HIV infection. *Pharmacol Res.* 2008;58(3-4):173-182.
8. Ofotokun I, Chuck SK, Hitti JE. Antiretroviral pharmacokinetic profile: a review of sex differences. *Gend Med.* 2007;4(2):106-119.
9. Baylor MS, Johann-Liang R. Hepatotoxicity associated with nevirapine use. *J Acquir Immune Defic Syndr.* 2004;35(5):538-539.
10. Wit FW, Kesselring AM, Gras L, et al. Discontinuation of nevirapine because of hypersensitivity reactions in patients with prior treatment experience, compared with treatment-naive patients: the ATHENA cohort study. *Clin Infect Dis.* 2008;46(6):933-940.
11. Dieterich DT, Robinson PA, Love J, et al. Drug-induced liver injury associated with the use of nonnucleoside reverse-transcriptase inhibitors. *Clin Infect Dis.* 2004;38 Suppl 2:S80-89.
12. Leith J, Piliero P, Storfer S, et al. Appropriate use of nevirapine for long-term therapy. *J Infect Dis.* 2005;192(3):545-546; author reply 546.
13. Lactic Acidosis International Study Group LAISG. Risk factors for lactic acidosis and severe hyperlactataemia in HIV-1-infected adults exposed to antiretroviral therapy. *AIDS.* 2007;21(18):2455-2464.
14. Thiebaut R, Dequae-Merchadou L, Ekouevi DK, et al. Incidence and risk factors of severe hypertriglyceridaemia in the era of highly active antiretroviral therapy: the Aquitaine Cohort, France, 1996-99. *HIV Med.* 2001;2(2):84-88.

15. Galli M, Veglia F, Angarano G, et al. Gender differences in antiretroviral drug-related adipose tissue alterations. Women are at higher risk than men and develop particular lipodystrophy patterns. *J Acquir Immune Defic Syndr.* 2003;34(1):58-61.
16. Yin M, Dobkin J, Brudney K, et al. Bone mass and mineral metabolism in HIV+ postmenopausal women. *Osteoporos Int.* 2005;16(11):1345-1352.
17. Brown TT, Qaqish RB. Response to Berg et al. 'Antiretroviral therapy and the prevalence of osteopenia and osteoporosis: a meta-analytic review'. *AIDS.* 2007;21(13):1830-1831.
18. Watts DH, Park JG, Cohn SE, et al. Safety and tolerability of depot medroxyprogesterone acetate among HIV-infected women on antiretroviral therapy: ACTG A5093. *Contraception.* 2008;77(2):84-90.
19. Cohn SE, Park JG, Watts DH, et al. Depo-medroxyprogesterone in women on antiretroviral therapy: effective contraception and lack of clinically significant interactions. *Clin Pharmacol Ther.* 2007;81(2):222-227.
20. Nanda K, Amaral E, Hays M, et al. Pharmacokinetic interactions between depot medroxyprogesterone acetate and combination antiretroviral therapy. *Fertil Steril.* 2008;90(4):965-971.
21. Stringer EM, Kaseba C, Levy J, et al. A randomized trial of the intrauterine contraceptive device vs hormonal contraception in women who are infected with the human immunodeficiency virus. *Am J Obstet Gynecol.* 2007;197(2):144 e141-148.
22. Curtis KM, Nanda K, Kapp N. Safety of hormonal and intrauterine methods of contraception for women with HIV/AIDS: a systematic review. *AIDS.* 2009;23 Suppl 1:S55-67.
23. Ioannidis JP, Abrams EJ, Ammann A, et al. Perinatal transmission of human immunodeficiency virus type 1 by pregnant women with RNA virus loads <1000 copies/ml. *J Infect Dis.* 2001;183(4):539-545.
24. Mofenson LM, Lambert JS, Stiehm ER, et al. Risk factors for perinatal transmission of human immunodeficiency virus type 1 in women treated with zidovudine. Pediatric AIDS Clinical Trials Group Study 185 Team. *N Engl J Med.* 1999;341(6):385-393.
25. Garcia PM, Kalish LA, Pitt J, et al. Maternal levels of plasma human immunodeficiency virus type 1 RNA and the risk of perinatal transmission. Women and Infants Transmission Study Group. *N Engl J Med.* 1999;341(6):394-402.
26. Fundaro C, Genovese O, Rendeli C, et al. Myelomeningocele in a child with intrauterine exposure to efavirenz. *AIDS.* 2002;16(2):299-300.
27. Saitoh A, Hull AD, Franklin P, et al. Myelomeningocele in an infant with intrauterine exposure to efavirenz. *J Perinatol.* 2005;25(8):555-556.
28. Ford N, Mofenson L, Kranzer K, et al. Safety of efavirenz in first-trimester of pregnancy: a systematic review and meta-analysis of outcomes from observational cohorts. *AIDS.* 2010;24(10):1461-1470.
29. Ouyang DW, Brogly SB, Lu M, et al. Lack of increased hepatotoxicity in HIV-infected pregnant women receiving nevirapine compared with other antiretrovirals. *AIDS.* 2010;24(1):109-114.
30. Stek AM, Mirochnick M, Capparelli E, et al. Reduced lopinavir exposure during pregnancy. *AIDS.* 2006;20(15):1931-1939.
31. Bryson YJ, Mirochnick M, Stek A, et al. Pharmacokinetics and safety of nelfinavir when used in combination with zidovudine and lamivudine in HIV-infected pregnant women: Pediatric AIDS Clinical Trials Group (PACTG) Protocol 353. *HIV Clin Trials.* 2008;9(2):115-125.
32. Unadkat JD, Wara DW, Hughes MD, et al. Pharmacokinetics and safety of indinavir in human immunodeficiency virus-infected pregnant women. *Antimicrob Agents Chemother.* 2007;51(2):783-786.
33. Watts DH, Lu M, Thompson B, et al. Treatment interruption after pregnancy: effects on disease progression and laboratory findings. *Infect Dis Obstet Gynecol.* 2009;2009:456717.
34. Lyons FE, Coughlan S, Byrne CM, et al. Emergence of antiretroviral resistance in HIV-positive women receiving combination antiretroviral therapy in pregnancy. *AIDS.* 2005;19(1):63-67.

HIV-2 INFECTION (Updated January 10, 2011)

HIV-2 infection is endemic in West Africa. Although HIV-2 has had only limited spread outside this area, it should be considered in persons of West African origin or those who have had sexual contact or shared needles with persons of West African origin. The prevalence of HIV-2 infection is also disproportionately high in countries with strong socioeconomic ties to West Africa (e.g., France; Spain; Portugal; and former Portuguese colonies such as Brazil, Angola, Mozambique, and parts of India near Goa).

The clinical course of HIV-2 infection is generally characterized by a longer asymptomatic stage, lower plasma HIV-2 viral loads, and lower mortality rates compared with HIV-1 infection *[1-2]*. However, HIV-2 infection can progress to AIDS, and thus antiretroviral therapy (ART) may become necessary during the course of infection. Concomitant HIV-1 and HIV-2 infection may occur and should be considered in patients from an area with high prevalence of HIV-2. In the appropriate epidemiologic setting, HIV-2 infection should be suspected in patients with clinical conditions suggestive of HIV infection but with atypical serologic results (e.g., a positive screening assay with an indeterminate HIV-1 Western blot) *[3]*. The possibility of HIV-2 infection should also be considered in the appropriate epidemiologic setting in patients with serologically confirmed HIV infection but low or undetectable viral loads or in those with declining CD4 counts despite apparent virologic suppression on ART.

The Multispot HIV-1/HIV-2 Rapid Test (Bio-Rad Laboratories) is Food and Drug Administration (FDA) approved for differentiating HIV-1 from HIV-2 infection. Commercially available HIV-1 viral load assays do not reliably detect or quantify HIV-2, and no HIV-2 commercial viral load assays are currently available *[4-5]*. Most studies reporting HIV-2 viral loads use "in-house" assays that are not widely available, making it difficult to monitor virologic response in the clinical setting. In addition, no validated HIV-2 genotypic or phenotypic antiretroviral (ARV) resistance assays are available.

To date, there have been no randomized trials addressing the question of when to start ART or the choice of initial or second-line therapy for HIV-2 infection *[6]*; thus, the optimal treatment strategy has not been defined. HIV-2 appears intrinsically resistant to non-nucleoside reverse transcriptase inhibitors (NNRTIs) *[7]* and to enfuvirtide *[8]*. *In vitro* data suggest HIV-2 is sensitive to the currently available nucleoside reverse transcriptase inhibitors (NRTIs), although with a lower barrier to resistance than HIV-1 *[9-10]*. Variable sensitivity among protease inhibitors (PIs) has been reported; lopinavir (LPV), saquinavir (SQV), and darunavir (DRV) are more active against HIV-2 than other approved PIs *[11-14]*. The integrase inhibitor, raltegravir (RAL) *[15]*, and the CCR5 antagonist, maraviroc (MVC), appear active against some HIV-2 isolates, although no approved assays to determine HIV-2 coreceptor tropism exist and HIV-2 is known to utilize multiple minor coreceptors in addition to CCR5 and CXCR4 *[16]*. Several small studies suggest poor responses among HIV-2 infected individuals treated with some ARV regimens, including dual-NRTI regimens, regimens containing two NRTIs + NNRTI, and some unboosted PI-based regimens including nelfinavir (NFV) or indinavir (IDV) plus zidovudine (ZDV) and lamivudine(3TC) *[6, 17-19]*. Clinical data on the utility of triple-NRTI regimens are conflicting *[20-21]*. In general, boosted PI-containing regimens have resulted in more favorable virologic and immunologic responses *[21]*. One small study suggested satisfactory responses to lopinavir/ritonavir (LPV/r)-containing regimens in 17 of 29 (59%) of ARV-naïve subjects *[22]*.

Resistance-associated mutations develop commonly in HIV-2 patients on therapy *[17, 21, 23]*. Genotypic algorithms used to predict drug resistance in HIV-1 may not be applicable to HIV-2, because pathways and mutational patterns leading to resistance may differ *[10, 21, 24]*. CD4 cell recovery on therapy may be poor *[25]*, suggesting that more reliable methods for monitoring disease progression and treatment efficacy in HIV-2 infection are needed.

Some groups have recommended specific preferred and alternative regimens for initial therapy of HIV-2 infection *[24]*, though as yet there are no controlled trial data to reliably predict their success. Until more definitive data are available in an ART-naïve patient with HIV-2 mono-infection or with HIV-1/HIV-2 dual infection who requires treatment, clinicians should initiate a regimen containing two NRTIs and a boosted PI. Monitoring of virologic response in such patients is problematic because of the lack of a commercially available HIV-2 viral load assay; however, clinical and CD4 count improvement can be used to assess treatment response.

References

1. Matheron S, Pueyo S, Damond F, et al. Factors associated with clinical progression in HIV-2 infected-patients: the French ANRS cohort. *AIDS.* 2003;17(18):2593-2601.
2. Marlink R, Kanki P, Thior I, et al. Reduced rate of disease development after HIV-2 infection as compared to HIV-1. *Science.* 1994;265(5178):1587-1590.
3. O'Brien TR, George JR, Epstein JS, et al. Testing for antibodies to human immunodeficiency virus type 2 in the United States. *MMWR Recomm Rep.* 1992;41(RR-12):1-9.
4. Chan PA, Wakeman SE, Flanigan T, et al. HIV-2 diagnosis and quantification in high-risk patients. *AIDS Res Ther.* 2008;5:18.
5. Damond F, Benard A, Ruelle J, et al. Quality control assessment of human immunodeficiency virus type 2 (HIV-2) viral load quantification assays: results from an international collaboration on HIV-2 infection in 2006. *J Clin Microbiol.* 2008;46(6):2088-2091.
6. Gottlieb GS, Eholie SP, Nkengasong JN, et al. A call for randomized controlled trials of antiretroviral therapy for HIV-2 infection in West Africa. *AIDS.* 2008;22(16):2069-2072; discussion 2073-2064.
7. Tuaillon E, Gueudin M, Lemee V, et al. Phenotypic susceptibility to nonnucleoside inhibitors of virion-associated reverse transcriptase from different HIV types and groups. *J Acquir Immune Defic Syndr.* 2004;37(5):1543-1549.
8. Poveda E, Rodes B, Toro C, et al. Are fusion inhibitors active against all HIV variants? *AIDS Res Hum Retroviruses.* 2004;20(3):347-348.
9. Boyer PL, Sarafianos SG, Clark PK, et al. Why do HIV-1 and HIV-2 use different pathways to develop AZT resistance? *PLoS Pathog.* 2006;2(2):e10.
10. Smith RA, Anderson DJ, Pyrak CL, et al. Antiretroviral drug resistance in HIV-2: three amino acid changes are sufficient for classwide nucleoside analogue resistance. *J Infect Dis.* 2009;199(9):1323-1326.
11. Parkin NT, Schapiro JM. Antiretroviral drug resistance in non-subtype B HIV-1, HIV-2 and SIV. *Antivir Ther.* 2004;9(1):3-12.
12. Desbois D, Roquebert B, Peytavin G, et al. In vitro phenotypic susceptibility of human immunodeficiency virus type 2 clinical isolates to protease inhibitors. *Antimicrob Agents Chemother.* 2008;52(4):1545-1548.
13. Brower ET, Bacha UM, Kawasaki Y, et al. Inhibition of HIV-2 protease by HIV-1 protease inhibitors in clinical use. *Chem Biol Drug Des.* 2008;71(4):298-305.
14. Rodes B, Sheldon J, Toro C, et al. Susceptibility to protease inhibitors in HIV-2 primary isolates from patients failing antiretroviral therapy. *J Antimicrob Chemother.* 2006;57(4):709-713.
15. Roquebert B, Damond F, Collin G, et al. HIV-2 integrase gene polymorphism and phenotypic susceptibility of HIV-2 clinical isolates to the integrase inhibitors raltegravir and elvitegravir in vitro. *J Antimicrob Chemother.* 2008;62(5):914-920.
16. Owen SM, Ellenberger D, Rayfield M, et al. Genetically divergent strains of human immunodeficiency virus type 2 use multiple coreceptors for viral entry. *J Virol.* 1998;72(7):5425-5432.
17. Gottlieb GS, Badiane NM, Hawes SE, et al. Emergence of multiclass drug-resistance in HIV-2 in antiretroviral-treated individuals in Senegal: implications for HIV-2 treatment in resouce-limited West Africa. *Clin Infect Dis.* 2009;48(4):476-483.
18. Jallow S, Kaye S, Alabi A, et al. Virological and immunological response to Combivir and emergence of drug resistance mutations in a cohort of HIV-2 patients in The Gambia. *AIDS.* 2006;20(10):1455-1458.
19. Adje-Toure CA, Cheingsong R, Garcia-Lerma JG, et al. Antiretroviral therapy in HIV-2-infected patients: changes in plasma viral load, CD4+ cell counts, and drug resistance profiles of patients treated in Abidjan, Cote d'Ivoire. *AIDS.* 2003;17 Suppl 3:S49-54.
20. Matheron S, Damond F, Benard A, et al. CD4 cell recovery in treated HIV-2-infected adults is lower than expected: results from the French ANRS CO5 HIV-2 cohort. *AIDS.* 2006;20(3):459-462.
21. Ruelle J, Roman F, Vandenbroucke AT, et al. Transmitted drug resistance, selection of resistance mutations and moderate antiretroviral efficacy in HIV-2: analysis of the HIV-2 Belgium and Luxembourg database. *BMC Infect Dis.* 2008;8:21.
22. Benard A, Damond F, Campa P, et al. Good response to lopinavir/ritonavir-containing antiretroviral regimens in antiretroviral-naive HIV-2-infected patients. *AIDS.* 2009;23(9):1171-1173.
23. Damond F, Matheron S, Peytavin G, et al. Selection of K65R mutation in HIV-2-infected patients receiving tenofovir-containing regimen. *Antivir Ther.* 2004;9(4):635-636.
24. Gilleece Y, Chadwick DR, Breuer J, et al. British HIV Association guidelines for antiretroviral treatment of HIV-2-positive individuals 2010. *HIV Med.* 2010;11(10):611-619.
25. Drylewicz J, Matheron S, Lazaro E, et al. Comparison of viro-immunological marker changes between HIV-1 and HIV-2-infected patients in France. *AIDS.* 2008;22(4):457-468.

Considerations for Antiretroviral Use in Patients with Coinfections

HEPATITIS B (HBV)/HIV COINFECTION (January 10, 2011)

Panel's Recommendations:

- ***Prior to intiation of antiretroviral therapy (ART), all patients who test positive for hepatitis B surface antigen (HBsAg) should be tested for hepatitis B virus (HBV) DNA using a quantitative assay to determine the level of HBV replication (AIII).***
- ***Because emtricitabine (FTC), lamivudine (3TC), and tenofovir (TDF) have activity against both HIV and HBV, if HBV or HIV treatment is needed, ART should be initiated with the combination of TDF + FTC or TDF + 3TC as the nucleoside reverse transcriptase inhibitor (NRTI) backbone of a fully suppressive antiretroviral (ARV) regimen (AI).***
- ***If HBV treatment is needed and TDF cannot safely be used, the alternative recommended HBV therapy is entecavir in addition to a fully suppressive ARV regimen (BI). Other HBV treatment regimens include peginterferon alfa monotherapy or adefovir in combination with 3TC or FTC or telbivudine in addition to a fully suppressive ARV regimen (BII).***
- ***Entecavir has activity against HIV; its use for HBV treatment without ART in patients with dual infection may result in the selection of the M184V mutation that confers HIV resistance to 3TC and FTC. Therefore, entecavir must be used in addition to a fully suppressive ARV regimen when used in HIV/HBV-coinfected patients (AII).***
- ***Discontinuation of agents with anti-HBV activity may cause serious hepatocellular damage resulting from reactivation of HBV; patients should be advised against self-discontinuation and carefully monitored during interruptions in HBV treatment (AII).***
- ***If ART needs to be modified due to HIV virologic failure and the patient has adequate HBV suppression, the ARV drugs active against HBV should be continued for HBV treatment in combination with other suitable ARV agents to achieve HIV suppression (AIII).***

Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = data from randomized controlled trials; II = data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = expert opinion

Approximately 5%–10% of HIV-infected persons also have chronic HBV infection, defined as testing positive for HBsAg for more than 6 months *[1]*. The progression of chronic HBV to cirrhosis, end-stage liver disease, and/or hepatocellular carcinoma is more rapid in HIV-infected persons than in persons with chronic HBV alone *[2]*. Conversely, chronic HBV does not substantially alter the progression of HIV infection and does not influence HIV suppression or CD4 cell responses following ART initiation *[3-4]*. However, several liver-associated complications that are ascribed to flares in HBV activity, discontinuation of dually active ARVs, or toxicity of ARVs can affect the treatment of HIV in patients with HBV coinfection *[5-7]*. These include the following:

- FTC, 3TC, and TDF are approved ARVs that also have antiviral activity against HBV. Discontinuation of these drugs may potentially cause serious hepatocellular damage resulting from reactivation of HBV *[8]*.
- Entecavir has activity against HIV; its use for HBV treatment without ART in patients with dual infection may result in the selection of the M184V mutation that confers HIV resistance to 3TC and FTC. Therefore, entecavir must be used in addition to a fully suppressive ARV regimen when used in HIV/HBV-coinfected patients **(AII)** *[9]*.
- 3TC-resistant HBV is observed in approximately 40% of patients after 2 years on 3TC for chronic HBV and in approximately 90% of patients after 4 years when 3TC is used as the only active drug for HBV in coinfected patients. Therefore, 3TC or FTC should be used in combination with other anti-HBV drugs **(AII)** *[10]*.
- Immune reconstitution after initiation of treatment for HIV and/or HBV can be associated with elevation in transaminases, possibly because HBV is primarily an immune-mediated disease *[11]*.
- Some ARV agents can cause increases in transaminase levels. The rate and magnitude of these increases are higher with HBV coinfection *[12-13]*. The etiology and consequences of these changes in liver function tests are unclear

because continuation of ART may be accompanied by resolution of the changes. Nevertheless, some experts suspend the implicated agent(s) when the serum alanine transferase (ALT) level is increased to 5–10 times the upper limit of normal. However, in HIV/HBV-coinfected persons, increases in transaminase levels can herald hepatitis B e antigen (HBeAg) seroconversion due to immune reconstitution, so the cause of the elevations should be investigated prior to the decision to discontinue medications. In persons with transaminase increases, HBeAg seroconversion should be evaluated by testing for HBeAg and anti-HBe as well as HBV DNA levels.

Recommendations for HBV/HIV-Coinfected Patients

- All patients with chronic HBV should be advised to abstain from alcohol, assessed for immunity to hepatitis A virus (HAV) infection (anti-HAV antibody total) and vaccinated if nonimmune, advised on methods to prevent HBV transmission (methods that do not differ from those to prevent HIV transmission), and evaluated for the severity of HBV infection as outlined in the ***Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents*** *[14]*.

- Prior to intiation of ART, all persons who test positive for HBsAg should be tested for HBV DNA using a quantitative assay to determine the level of HBV replication **(AIII)**. Persons with chronic HBV infection already receiving ART active against HBV should undergo quantitative HBV DNA testing every 6–12 months to determine the effectiveness of therapy in suppressing HBV replication. The goal of HBV therapy with NRTIs is to prevent liver disease complications by sustained suppression of HBV replication to the lowest achievable level.

- **If not yet on therapy and HBV or HIV treatment is needed:** In persons without HIV infection, the recommended anti-HBV drugs for the treatment of persons naïve to HBV therapy are TDF and entecavir *[15-16]*. In HIV-infected patients, however, only TDF can be considered part of the ARV regimen; entecavir has weak anti-HIV activity and must not be considered part of an ARV regimen. In addition, only TDF is fully active for the treatment of persons with known or suspected 3TC-resistant HBV infection. To avoid selection of HBV-resistant variants, when possible, these agents should not be used as the only agent with anti-HBV activity in an ARV regimen **(AIII)**.

  Preferred regimen. The combination of TDF + FTC or TDF + 3TC should be used as the NRTI backbone of a fully suppressive ARV regimen and for the treatment of HBV infection *[17-19]* **(AII)**.

  Alternative regimens. If TDF cannot safely be used**,** entecavir should be used in addition to a fully suppressive ARV regimen **(AII)**; importantly, entecavir should not be considered to be a part of the ARV regimen *[20]* **(BII)**. Due to a partially overlapping HBV-resistance pathway, it is not known if the combination of entectavir + 3TC or FTC will provide additional virologic or clinical benefit compared with entecavir alone. In persons with known or suspected 3TC-resistant HBV infection, the entecavir dose should be increased from 0.5 mg/day to 1 mg/day. However, entecavir resistance may emerge rapidly in patients with 3TC-resistant HBV infection. Therefore, entecavir should be used with caution in such patients with frequent monitoring (~ every 3 months) of the HBV DNA level to detect viral breakthrough. Other HBV treatment regimens include peginterferon alfa monotherapy or adefovir in combination with 3TC or FTC or telbivudine in addition to a fully suppressive ARV regimen *[17, 21-22]*; however, data on these regimens in persons with HIV/HBV coinfection are limited **(BII)**. Due to safety concerns, peginterferon alfa should not be used in HIV/HBV-coinfected persons with cirrhosis.

- **Need to discontinue medications active against HBV:** The patient's clinical course should be monitored with frequent liver function tests. The use of adefovir dipivoxil, entecavir, or telbivudine to prevent flares, especially in patients with marginal hepatic reserve such as persons with compensated or decompensated cirrhosis, can be considered *[8]*. These alternative HBV regimens should only be used in addition to a fully suppressive ARV regimen.

- **Need to change ART because of HIV resistance:** If the patient has adequate HBV suppression, the ARV drugs active against HBV should be continued for HBV treatment in combination with other suitable ARV agents to achieve HIV suppression **(AIII)**.

References

1. Spradling PR, Richardson JT, Buchacz K, et al. Prevalence of chronic hepatitis B virus infection among patients in the HIV Outpatient Study, 1996-2007. *J Viral Hepat.* 2010.
2. Thio CL, Seaberg EC, Skolasky R, Jr., et al. HIV-1, hepatitis B virus, and risk of liver-related mortality in the Multicenter Cohort Study (MACS). *Lancet.* 2002;360(9349):1921-1926.
3. Konopnicki D, Mocroft A, de Wit S, et al. Hepatitis B and HIV: prevalence, AIDS progression, response to highly active antiretroviral therapy and increased mortality in the EuroSIDA cohort. *AIDS.* 2005;19(6):593-601.
4. Hoffmann CJ, Seaberg EC, Young S, et al. Hepatitis B and long-term HIV outcomes in coinfected HAART recipients. *AIDS.* 2009;23(14):1881-1889.
5. Bellini C, Keiser O, Chave JP, et al. Liver enzyme elevation after lamivudine withdrawal in HIV-hepatitis B virus co-infected patients: the Swiss HIV Cohort Study. *HIV Med.* 2009;10(1):12-18.
6. Law WP, Dore GJ, Duncombe CJ, et al. Risk of severe hepatotoxicity associated with antiretroviral therapy in the HIV-NAT Cohort, Thailand, 1996-2001. *AIDS.* 2003;17(15):2191-2199.
7. Wit FW, Weverling GJ, Weel J, et al. Incidence of and risk factors for severe hepatotoxicity associated with antiretroviral combination therapy. *J Infect Dis.* 2002;186(1):23-31.
8. Dore GJ, Soriano V, Rockstroh J, et al. Frequent hepatitis B virus rebound among HIV-hepatitis B virus-coinfected patients following antiretroviral therapy interruption. *AIDS.* 2010;24(6):857-865.
9. McMahon MA, Jilek BL, Brennan TP, et al. The HBV drug entecavir - effects on HIV-1 replication and resistance. *N Engl J Med.* 2007;356(25):2614-2621.
10. Benhamou Y, Bochet M, Thibault V, et al. Long-term incidence of hepatitis B virus resistance to lamivudine in human immunodeficiency virus-infected patients. *Hepatology.* 1999;30(5):1302-1306.
11. Manegold C, Hannoun C, Wywiol A, et al. Reactivation of hepatitis B virus replication accompanied by acute hepatitis in patients receiving highly active antiretroviral therapy. *Clin Infect Dis.* 2001;32(1):144-148.
12. Sulkowski MS, Thomas DL, Chaisson RE, et al. Hepatotoxicity associated with antiretroviral therapy in adults infected with human immunodeficiency virus and the role of hepatitis C or B virus infection. *JAMA.* 2000;283(1):74-80.
13. den Brinker M, Wit FW, Wertheim-van Dillen PM, et al. Hepatitis B and C virus co-infection and the risk for hepatotoxicity of highly active antiretroviral therapy in HIV-1 infection. *AIDS.* 2000;14(18):2895-2902.
14. Centers for Disease Control and Prevention (CDC). Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. *MMWR Recomm Rep.* 2009;58(RR-4):1-207.
15. Lok AS, McMahon BJ. Chronic hepatitis B: update 2009. *Hepatology.* 2009;50(3):661-662.
16. Woo G, Tomlinson G, Nishikawa Y, et al. Tenofovir and entecavir are the most effective antiviral agents for chronic hepatitis B: a systematic review and Bayesian meta-analyses. *Gastroenterology.* 2010;139(4):1218-1229.
17. Peters MG, Andersen J, Lynch P, et al. Randomized controlled study of tenofovir and adefovir in chronic hepatitis B virus and HIV infection: ACTG A5127. *Hepatology.* 2006;44(5):1110-1116.
18. Matthews GV, Seaberg E, Dore GJ, et al. Combination HBV therapy is linked to greater HBV DNA suppression in a cohort of lamivudine-experienced HIV/HBV coinfected individuals. *AIDS.* 2009;23(13):1707-1715.
19. de Vries-Sluijs TE, Reijnders JG, Hansen BE, et al. Long-Term Therapy with Tenofovir is Effective for Patients Co-Infected with HIV and HBV. *Gastroenterology.* 2010.
20. Pessoa MG, Gazzard B, Huang AK, et al. Efficacy and safety of entecavir for chronic HBV in HIV/HBV coinfected patients receiving lamivudine as part of antiretroviral therapy. *AIDS.* 2008;22(14):1779-1787.
21. Benhamou Y, Bochet M, Thibault V, et al. Safety and efficacy of adefovir dipivoxil in patients co-infected with HIV-1 and lamivudine-resistant hepatitis B virus: an open-label pilot study. *Lancet.* 2001;358(9283):718-723.
22. Ingiliz P, Valantin MA, Thibault V, et al. Efficacy and safety of adefovir dipivoxil plus pegylated interferon-alpha2a for the treatment of lamivudine-resistant hepatitis B virus infection in HIV-infected patients. *Antivir Ther.* 2008;13(7):895-900.

HEPATITIS C (HCV)/HIV COINFECTION (Updated December 1, 2009)

Long-term studies of patients with chronic hepatitis C virus (HCV) infection show that approximately 33% of the patients progress to cirrhosis at a median time of less than 20 years *[1-2]*. This rate of progression increases with older age, alcoholism, male sex, and HIV infection *[3-6]*. A meta-analysis demonstrated that the rate of progression to cirrhosis for persons coinfected with HCV/HIV was about three times higher than the rate for HCV mono-infected patients *[5]*. This accelerated rate is magnified in patients with low CD4 counts. Chronic HCV infection also complicates HIV treatment due to the increased frequency of antiretroviral (ARV)-associated hepatotoxicity *[7-8]*. Multiple studies have shown poor prognosis for HCV/HIV coinfection in the era of combination antiretroviral therapy (ART). It is unclear if HCV infection accelerates the rate of HIV progression *[9]* or if the accelerated rate primarily reflects the impact of injection drug use, which is strongly linked to HCV infection *[10-11]*. Although whether ART reduces the attributable morbidity/mortality from untreated HCV is unknown, the presence of chronic HCV infection influences the treatment of HIV with ARV as discussed below.

Assessment of HCV/HIV Coinfection Prior to Antiretroviral Therapy

- Prior to initiation of ART, HIV-infected patients should be screened for HCV infection with sensitive immunoassays licensed for detection of antibody to HCV in blood. To confirm the presence of chronic infection, HCV-seropositive persons should be tested for HCV RNA using a qualitative or quantitative assay *[12]*.
- Patients with HCV/HIV coinfection should be advised to avoid alcohol consumption, use appropriate precautions to prevent transmission of both viruses to others, and receive hepatitis A (HAV) and hepatitis B (HBV) vaccines if susceptible.
- All patients with HCV/HIV coinfection should be evaluated for HCV therapy. HCV treatment is recommended according to standard guidelines with strong preference for treating patients with higher CD4 counts. For patients with lower CD4 counts (<200 cells/mm^3), it may be preferable to initiate ART and delay HCV therapy until CD4 counts increase as a result of HIV treatment *[12-15]*.
- Concurrent treatment of both HIV and HCV is feasible but may be complicated by pill burden, drug toxicities, and drug interactions. Some notable considerations include:
    - Didanosine (ddI) should not be given with ribavirin because of the potential for drug-drug interactions leading to life-threatening ddI-associated mitochondrial toxicity including hepatomegaly/steatosis, pancreatitis, and lactic acidosis *[16]*.
    - Zidovudine (ZDV) combined with ribavirin should be avoided when possible because the higher rates of anemia associated with the combination make ribavirin dose reduction necessary *[17]*.
    - Abacavir (ABC) has been associated with decreased response to peginterferon plus ribavirin in some, but not all, retrospective studies; current evidence is insufficient to recommend avoiding this combination *[18-20]*.
    - Growth factors (e.g., filgrastim and erythropoietin) may be required to manage interferon-associated neutropenia and ribavirin-associated anemia; ZDV may increase the need for adjuvant growth factors due to increased bone marrow suppression *[17]*.

Antiretroviral Therapy in HCV/HIV Coinfection

- Hepatotoxicity: Drug-induced liver injury (DILI) following ART is more common in HIV/HCV coinfection. The greatest risk of DILI may be observed in coinfected persons with advanced liver disease (e.g., cirrhosis or end-stage liver disease) *[21]*. Eradication of HCV infection may decrease the likelihood of ARV-associated DILI *[22]*.
    - Given the substantial heterogeneity in patient populations and drug regimens, comparison of DILI incidence rates for individual ARV agents across clinical trials is difficult. In such studies, the highest incidence rates of Grade 3 or 4 elevations in liver enzyme levels have been observed during therapy with ARV drugs that are no longer commonly used in clinical practice and that include stavudine (d4T) (with or without ddI), nevirapine (NVP), full-dose ritonavir (RTV) (600 mg twice daily), or tipranavir (TPV) (boosted by low-dose RTV) *[23]*. Also, due to the potential for concurrent fatty liver disease (steatosis), the use of d4T or ddI should be limited *[24]*.
    - Patients should be monitored by following alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels at 1 month and then every 3 months after initiation of ART. Mild to moderate fluctuations in ALT and/or AST are typical in persons with chronic HCV infection. In the

absence of signs and/or symptoms of liver disease these fluctuations do not require interruption of ART. Significant ALT and/or AST elevation (>5 times the upper limit of the laboratory reference range) should prompt careful evaluation for signs and symptoms of liver insufficiency and for alternative causes of liver injury (e.g., acute HAV or HBV infection, hepatobiliary disease, or alcoholic hepatitis); short-term interruption of ART may be required *[25]*.

- When to start ART: The rate of liver disease (fibrosis) progression is accelerated by HIV/HCV coinfection, particularly in persons with low CD4 counts (≤350 cells/mm^3). Data derived largely from retrospective cohort studies regarding the effect of ART on the natural history of HCV disease are inconsistent *[6, 26-27]*. However, ART may slow the progression of liver disease by preserving or restoring immune function and reducing HIV-related immune activation and inflammation *[28-30]*. Thus, for most coinfected patients including those with cirrhosis, the potential benefits of ART outweigh concerns regarding DILI.
    - ART should be started in HCV/HIV-coinfected persons in accordance with the Panel's recommendation for initiating ART in ART-naïve patients.

- What to start and what not to use: Initial combination regimens for the ARV-naïve patient with HCV/HIV are the same as for persons without HCV infection. HCV infection does not significantly alter the virologic or immunologic response to effective ART *[31]*. Special considerations for ART in persons with HCV/HIV coinfection include:
    - Patients receiving or considering therapy with ribavirin should avoid ddI, d4T, and ZDV.
    - ARV agents with the greatest risk of DILI should be used with caution.
    - Cirrhotic patients should be carefully assessed for signs of liver decompensation according to the Child-Turcotte-Pugh classification system because hepatically metabolized ARV drugs may require dose modification or avoidance in patients with Child-Pugh class B and C disease. (See **Appendix B, Table 7**.)

References

1. Alter MJ, Margolis HS, Krawczynski K, et al. The natural history of community-acquired hepatitis C in the United States. The Sentinel Counties Chronic non-A, non-B Hepatitis Study Team. *N Engl J Med.* 1992;327(27):1899-1905.
2. Thomas DL, Astemborski J, Rai RM, et al. The natural history of hepatitis C virus infection: host, viral, and environmental factors. *JAMA.* 2000;284(4):450-456.
3. Poynard T, Bedossa P, Opolon P. Natural history of liver fibrosis progression in patients with chronic hepatitis C. The OBSVIRC, METAVIR, CLINIVIR, and DOSVIRC groups. *Lancet.* 1997;349(9055):825-832.
4. Wiley TE, McCarthy M, Breidi L, et al. Impact of alcohol on the histological and clinical progression of hepatitis C infection. *Hepatology.* 1998;28(3):805-809.
5. Graham CS, Baden LR, Yu E, et al. Influence of human immunodeficiency virus infection on the course of hepatitis C virus infection: a meta-analysis. *Clin Infect Dis.* 2001;33(4):562-569.
6. Thein HH, Yi Q, Dore GJ, et al. Natural history of hepatitis C virus infection in HIV-infected individuals and the impact of HIV in the era of highly active antiretroviral therapy: a meta-analysis. *AIDS.* 2008;22(15):1979-1991.
7. Sulkowski MS, Thomas DL, Chaisson RE, et al. Hepatotoxicity associated with antiretroviral therapy in adults infected with human immunodeficiency virus and the role of hepatitis C or B virus infection. *JAMA.* 2000;283(1):74-80.
8. Sulkowski MS, Thomas DL, Mehta SH, et al. Hepatotoxicity associated with nevirapine or efavirenz-containing antiretroviral therapy: role of hepatitis C and B infections. *Hepatology.* 2002;35(1):182-189.
9. Greub G, Ledergerber B, Battegay M, et al. Clinical progression, survival, and immune recovery during antiretroviral therapy in patients with HIV-1 and hepatitis C virus coinfection: the Swiss HIV Cohort Study. *Lancet.* 2000;356(9244):1800-1805.
10. Vlahov D, Graham N, Hoover D, et al. Prognostic indicators for AIDS and infectious disease death in HIV-infected injection drug users: plasma viral load and CD4+ cell count. *JAMA.* 1998;279(1):35-40.
11. Celentano DD, Vlahov D, Cohn S, et al. Self-reported antiretroviral therapy in injection drug users. *JAMA.* 1998;280(6):544-546.
12. Ghany MG, Strader DB, Thomas DL, et al. Diagnosis, management, and treatment of hepatitis C: an update. *Hepatology.* 2009;49(4):1335-1374.
13. Soriano V, Puoti M, Sulkowski M, et al. Care of patients coinfected with HIV and hepatitis C virus: 2007 updated recommendations from the HCV-HIV International Panel. *AIDS.* 2007;21(9):1073-1089.
14. Tien PC. Management and treatment of hepatitis C virus infection in HIV-infected adults: recommendations from the Veterans Affairs Hepatitis C Resource Center Program and National Hepatitis C Program Office. *Am J Gastroenterol.* 2005;100(10):2338-2354.
15. Avidan NU, Goldstein D, Rozenberg L, et al. Hepatitis C Viral Kinetics During Treatment With Peg IFN-alpha-2b in HIV/HCV Coinfected Patients as a Function of Baseline CD4+ T-Cell Counts. *J Acquir Immune Defic Syndr.* 2009.

16. Fleischer R, Boxwell D, Sherman KE. Nucleoside analogues and mitochondrial toxicity. *Clin Infect Dis.* 2004;38(8):e79-80.
17. Alvarez D, Dieterich DT, Brau N, et al. Zidovudine use but not weight-based ribavirin dosing impacts anaemia during HCV treatment in HIV-infected persons. *J Viral Hepat.* 2006;13(10):683-689.
18. Vispo E, Barreiro P, Pineda JA, et al. Low response to pegylated interferon plus ribavirin in HIV-infected patients with chronic hepatitis C treated with abacavir. *Antivir Ther.* 2008;13(3):429-437.
19. Laufer N, Laguno M, Perez I, et al. Abacavir does not influence the rate of virological response in HIV-HCV-coinfected patients treated with pegylated interferon and weight-adjusted ribavirin. *Antivir Ther.* 2008;13(7):953-957.
20. Mira JA, Lopez-Cortes LF, Barreiro P, et al. Efficacy of pegylated interferon plus ribavirin treatment in HIV/hepatitis C virus co-infected patients receiving abacavir plus lamivudine or tenofovir plus either lamivudine or emtricitabine as nucleoside analogue backbone. *J Antimicrob Chemother.* 2008;62(6):1365-1373.
21. Aranzabal L, Casado JL, Moya J, et al. Influence of liver fibrosis on highly active antiretroviral therapy-associated hepatotoxicity in patients with HIV and hepatitis C virus coinfection. *Clin Infect Dis.* 2005;40(4):588-593.
22. Labarga P, Soriano V, Vispo ME, et al. Hepatotoxicity of antiretroviral drugs is reduced after successful treatment of chronic hepatitis C in HIV-infected patients. *J Infect Dis.* 2007;196(5):670-676.
23. Nunez M. Hepatotoxicity of antiretrovirals: incidence, mechanisms and management. *J Hepatol.* 2006;44(1 Suppl):S132-139.
24. McGovern BH, Ditelberg JS, Taylor LE, et al. Hepatic steatosis is associated with fibrosis, nucleoside analogue use, and hepatitis C virus genotype 3 infection in HIV-seropositive patients. *Clin Infect Dis.* 2006;43(3):365-372.
25. Sulkowski MS, Thomas DL. Hepatitis C in the HIV-infected patient. *Clin Liver Dis.* 2003;7(1):179-194.
26. Sulkowski MS, Mehta SH, Torbenson MS, et al. Rapid fibrosis progression among HIV/hepatitis C virus-co-infected adults. *AIDS.* 2007;21(16):2209-2216.
27. Brau N, Salvatore M, Rios-Bedoya CF, et al. Slower fibrosis progression in HIV/HCV-coinfected patients with successful HIV suppression using antiretroviral therapy. *J Hepatol.* 2006;44(1):47-55.
28. Macias J, Berenguer J, Japon MA, et al. Fast fibrosis progression between repeated liver biopsies in patients coinfected with human immunodeficiency virus/hepatitis C virus. *Hepatology.* 2009;50(4):1056-1063.
29. Verma S, Goldin RD, Main J. Hepatic steatosis in patients with HIV-Hepatitis C Virus coinfection: is it associated with antiretroviral therapy and more advanced hepatic fibrosis? *BMC Res Notes.* 2008;1:46.
30. Ragni MV, Nalesnik MA, Schillo R, et al. Highly active antiretroviral therapy improves ESLD-free survival in HIV-HCV co-infection. *Haemophilia.* 2009;15(2):552-558.
31. Miller MF, Haley C, Koziel MJ, et al. Impact of hepatitis C virus on immune restoration in HIV-infected patients who start highly active antiretroviral therapy: a meta-analysis. *Clin Infect Dis.* 2005;41(5):713-720.

MYCOBACTERIUM TUBERCULOSIS DISEASE WITH HIV COINFECTION

(Updated January 10, 2011)

Panel's Recommendations:

- ***The treatment of active tuberculosis (TB) disease in patients with HIV infection should follow the same principles for persons without HIV infection (AI).***
- ***All HIV-infected patients with diagnosed active TB should be started on TB treatment immediately (AI).***
- ***All HIV-infected patients with diagnosed active TB should be treated with antiretroviral therapy (ART) (AI).***
- ***For patients with CD4 count <200 cells/mm^3, ART should be initiated within 2–4 weeks of starting TB treatment (AI).***
- ***For patients with CD4 count 200–500 cells/mm^3, the Panel recommends initiation of ART within 2–4 weeks, or at least by 8 weeks after commencement of TB therapy (AIII).***
- ***For patients with CD4 count >500 cells/mm^3, most Panel members also recommend starting ART within 8 weeks of TB therapy (BIII).***
- ***Despite pharmacokinetic drug interactions, a rifamycin should be included in regimens for patients receiving ART, with dosage adjustment if necessary (AII).***
- ***If a protease inhibitor (PI)-based regimen is used, rifabutin is the preferred rifamycin in HIV-infected patients with active TB disease due to its lower risk of substantial interactions with PIs (AII). Coadministration of rifampin and PIs (with or without ritonavir [RTV] boosting) is not recommended (AII).***
- ***Immune reconstitution inflammatory syndrome (IRIS) may occur after initiation of ART. Both ART and TB treatment should be continued while managing IRIS (AIII).***
- ***Treatment support, including directly observed therapy (DOT) of TB treatment, is strongly recommended for HIV-infected patients with active TB disease (AII).***

Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = data from randomized controlled trials; II = data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = expert opinion

Terminology: In this section, the terms "HIV-infected with active TB disease" and "HIV/TB disease" are used synonymously to designate HIV-infected patients with active TB disease in need of TB treatment. "HIV/TB coinfection" is not used because the term can refer to either active TB or latent TB infection (LTBI) in the presence of HIV infection and may cause confusion.

Treatment of Active TB in HIV Patients

HIV infection significantly increases the risk of progression from latent to active TB disease. The CD4 cell count influences both the frequency and severity of active TB disease *[1-2]*. Active TB also negatively affects HIV disease. It may be associated with a higher HIV viral load and more rapid progression of HIV disease *[2-3]*.

Active pulmonary or extrapulmonary TB disease requires prompt initiation of TB treatment. The treatment of active TB disease in HIV-infected patients should follow the general principles for persons without HIV (**AI**). Treatment of drug-susceptible TB disease should include a standard regimen that consists of isoniazid (INH) + a rifamycin (rifampin or rifabutin) + pyrazinamide + ethambutol given for 2 months, followed by INH + a rifamycin for 4 to 7 months *[4]*. A more complete discussion of the diagnosis and treatment of TB disease and LTBI in HIV patients is available in the ***Guidelines for Preventing and Treating Opportunistic Infections in HIV-Infected Adults and Adolescents*** *[4]*.

All patients with HIV/TB disease should be treated with ART **(AI)**. Important issues related to the use of ART in patients with active TB disease include: (1) when to start ART, (2) significant pharmacokinetic drug interactions with rifamycins, (3) the additive toxicities associated with ARV and TB drugs, (4) the development of IRIS with TB after

ART initiation, and (5) the need for treatment support including DOT and the integration of HIV and TB care and treatment.

When to Start Antiretroviral Therapy

Patients Diagnosed with TB While Receiving ART

At the time TB treatment is initiated in patients receiving ART, the patient's ARV regimen should be assessed with particular attention to potential pharmacokinetic interactions with rifamycins (discussed below). The patient's regimen may need to be modified to permit use of the optimal TB treatment regimen.

Patients Receiving Treatment for Active TB but Not Yet on ART

When to initiate ART in patients with active TB has been the subject of differing recommendations based upon observational studies and expert opinion *[4-6]*. Two randomized controlled trials now provide some additional evidence regarding this issue. In these studies, concomitant administration of therapy for both TB disease and HIV infection resulted in significant reduction in HIV/TB disease mortality *[7-8]*. The results of an ACTG trial will soon be available and may provide further guidance or support for recommendations concerning when to start ART in patients with active TB.

In the SAPIT study from South Africa, HIV-infected patients with smear-positive TB and CD4 counts <500 cells/mm^3 were randomized to one of three treatment arms: integrated therapy with ART initiated either during the first 4 weeks of TB therapy or after the second month (i.e., during the continuation phase of TB therapy) or sequential therapy with ART initiated after the conclusion of standard TB therapy. The sequential arm was stopped when an early analysis demonstrated a 55% reduction in mortality in the combined two integrated arms compared with the sequential therapy arm *[7]*. In the CAMELIA study from Cambodia *[8]*, patients with CD4 counts <200 cells/mm^3 were randomized to initiate ART at 2 weeks or at 8 weeks of TB treatment. A 34% reduction in mortality was seen with ART initiation at 2 weeks compared with initiation at 8 weeks ($p = 0.002$). The populations in these two studies differed: the median CD4 count among SAPIT participants was 140–150 cells/mm^3; in the CAMELIA trial, the median CD4 count at entry was 25 cells/mm^3. Low CD4 count at study baseline predicted poorer survival in both studies. Both studies demonstrated excellent ART response: 90% and >95% of participants achieved suppressed HIV RNA (<400 copies/mL) at 12 months in the SAPIT study and CAMELIA trial, respectively. Although in both studies IRIS was more common in patients initiating ART earlier, the syndrome was not associated with mortality.

Based on the available data and the potential benefits of ART in patients with active TB, the Panel recommends the following:

- ***For patients with CD4 count <200 cells/mm^3, ART should be initiated within 2–4 weeks of starting TB treatment (AI).***
- ***For patients with CD4 count 200–500 cells/mm^3, the Panel recommends initiation of ART within 2–4 weeks, or at least by 8 weeks after commencement of TB therapy (AIII).***
- ***For patients with CD4 count >500 cells/mm^3, most Panel members also recommend starting ART within 8 weeks of TB therapy (BIII).***

ART should be started as early as feasible for all HIV-infected pregnant women with active TB, both for maternal health and for prevention of mother-to-child transmission (PMTCT) of HIV **(AIII)**. An augmented immune or inflammatory response in patients with some manifestations of TB, such as meningitis, pericarditis, or respiratory failure, might be life threatening. In these circumstances, delaying initiation of ART briefly beyond recommended intervals may be appropriate **(CIII)**.

Drug Interaction Considerations

A rifamycin is a crucial component for the treatment of drug-sensitive TB. However, both rifampin and rifabutin are inducers of the hepatic cytochrome P (CYP) 450 and uridine diphosphate gluconyltransferase (UGT) 1A1 enzymes and are associated with interactions with most ARV agents including all PIs, non-nucleoside reverse transcriptase

inhibitors (NNRTIs), maraviroc (MVC), and raltegravir (RAL). Rifampin is a strong enzyme inducer, leading to enhanced drug clearance and greater reduction in ARV drug exposure. Rifabutin, a weaker enzyme inducer, is an alternative to rifampin. Because rifabutin is a substrate of the CYP 450 enzyme system, its metabolism may be affected by the NNRTI or PI as discussed below. **Tables 15a and 15b** outline the magnitude of these interactions and provide dosing recommendations when rifamycins and selected ARV drugs are used concomitantly. After determining the drugs and doses to use, patients should be closely monitored to assure good control of both TB and HIV. Suboptimal HIV suppression or suboptimal response to TB treatment should prompt assessment of drug adherence, subtherapeutic drug levels (consider therapeutic drug monitoring [TDM]), and acquired drug resistance.

Rifamycins and NNRTIs

Rifampin induces metabolism of both nevirapine (NVP) *[9]* and efavirenz (EFV) *[10]* leading to reduced NNRTI drug exposure. The extent of induction is less pronounced with EFV than with NVP. Despite the interactions, some observational studies suggest that good virologic, immunologic, and clinical outcomes may be achieved with standard doses of either EFV *[11-12]* or NVP *[13-14]* when combined with rifampin.

Rifabutin does not significantly affect EFV and NVP drug exposure. Because both EFV and NVP can induce rifabutin metabolism, an increased rifabutin dose is recommended. Few data exist on the use of rifampin and etravirine (ETR); however, because rifampin is expected to induce ETR metabolism, concomitant use is not recommended. Rifabutin is recommended in this situation.

Rifamycins and PIs

Rifampin can significantly decrease PI drug exposure, despite ritonavir (RTV) boosting, with resultant risk of ART failure *[15-16]*. Some investigators had explored the use of an additional RTV dose or doubling PI doses in attempt to overcome rifampin's induction effect. However, a high rate of serious hepatotoxicity and significant gastrointestinal intolerance resulted in terminations of these studies *[15, 17-18]*. Therefore, coadministration of rifampin and PIs is **not recommended** (**AII**).

Because rifabutin has a less significant impact on the pharmacokinetics of RTV-boosted PIs, it is the preferred rifamycin to use with PI-based regimens **(AII)**. Both RTV-boosted and -unboosted PIs can inhibit rifabutin metabolism and the optimal dose of rifabutin is yet to be defined. Most PI manufacturers suggest rifabutin 150 mg every other day (instead of normal doses of 300 mg once daily). Lower than expected drug exposure *[19-20]* and acquired rifamycin resistance have been reported in HIV-infected patients who received PI-based regimens and intermittent doses of rifabutin *[19, 21]*. If available, TDM can be helpful in assessing the adequacy of rifabutin drug exposure.

Rifamycins and MVC or RAL

MVC is a substrate of CYP3A4 and rifampin can significantly reduce MVC concentration. If concomitant use is necessary, the MVC dose should be increased. Rifabutin may be an alternative rifamycin. (See **Table 15d** for recommended doses of MVC used with rifamycins.)

Rifampin, a strong UGT1A1 enzyme inducer, significantly accelerates the metabolism of RAL *[22]*. When used in combination with rifampin, the RAL dose should be increased to 800 mg twice daily. Rifabutin has minimal effect on RAL metabolism and may be more appropriate in this situation.

Anti-TB/ARV Toxicities

ARV agents and TB drugs, particularly INH, rifamycin, and pyrazinamide, can cause drug-induced hepatitis. These first-line TB drugs should still be used for treatment of active TB disease, even with coadministration of other potentially hepatotoxic drugs or in the presence of baseline liver disease **(AIII)**. Patients receiving drugs with potential hepatotoxicity should have frequent monitoring for clinical symptoms and signs of hepatitis and laboratory monitoring for hepatotoxicity. Peripheral neuropathy can occur with INH, didanosine (ddI), or stavudine (d4T) or may be a manifestation of HIV. All patients receiving INH should also receive supplemental pyridoxine to reduce peripheral

neuropathy. Patients should be monitored closely for signs of drug-related toxicities and receive alternatives to ddI or d4T.

IRIS with TB and ARV Agents

IRIS occurs in two forms, "unmasking" and "paradoxical." The mechanism is the same for both forms of IRIS: restoration of immune competence by administration of ARV agents, resulting in an exuberant host response to TB bacilli and/or antigens. Unmasking IRIS refers to the initial clinical expression of active TB occurring soon after ARV agents are started. Paradoxical IRIS refers to the worsening of TB clinical manifestations after ARV agents are started in patients who are receiving TB treatment. Severity of IRIS ranges from mild to severe to life threatening. IRIS has been reported in 8% to greater than 40% of patients starting ART after TB is diagnosed, although the incidence depends on the definition of IRIS and the intensity of monitoring *[23-24]*.

Predictors of IRIS include CD4 count <50 cells/mm^3, higher on-ART CD4 counts, high pre-ART and lower on-ART HIV viral loads, severity of TB disease, especially high pathogen burden, and less than 30-day interval between initiation of TB and HIV treatments. *[5, 25-29]*. Most IRIS in HIV/TB disease occurs within 3 months of the start of TB treatment. Delaying the start of ART for 2–8 weeks may reduce the incidence and severity of IRIS but must be weighed against the potential benefit of earlier ART in improving immune function and preventing progression of HIV disease and mortality.

Milder or moderately severe cases of IRIS can be managed symptomatically or treated with nonsteroidal inflammatory agents. More severe cases can be successfully treated with corticosteroids. A recent randomized, placebo-controlled trial demonstrated benefit of corticosteroid treatment as measured by decreasing days of hospitalization and Karnofsky performance score without adverse consequences *[30]*. In the presence of IRIS, neither TB therapy nor ART should be stopped because both therapies are necessary for the long-term health of the patient **(AIII)**.

Immune Reconstitution with ART: Conversion to Positive Tuberculin Skin Test (TST) and Interferon-Gamma (IFN-γ) Release Assay (IGRA)

Immune reconstitution with ART may result in unmasking LTBI (i.e., conversion of a previously negative TST to a positive TST or a positive IGRA for *Mycobacterium tuberculosis*-specific proteins). A positive IGRA, similar to a positive TST, is indicative of LTBI in the absence of evidence of active TB disease *[31]*. Because treatment for LTBI is indicated in the absence of evidence of active TB disease, clinicians should be aware of this phenomenon. Patients with a negative TST or IGRA and advanced HIV disease (i.e., CD4 count <200 cells/mm^3) should have a repeat TST or IGRA after initiation of ART and CD4 count increase to >200 cells/mm^3 *[32]* **(BII)**.

Caring for Patients with HIV and TB

Integration of diagnosis and treatment and/or close collaboration between TB and HIV clinicians, health care institutions, and public health programs are necessary in order to improve medication adherence and TB treatment completion rates, reduce toxicities, and maximize HIV outcomes in HIV-infected patients with active TB disease *[4]*. These patients should receive treatment support, including adherence counseling and DOT, corresponding to their needs **(AII)**. ART simplification or use of coformulated fixed-dose combinations may also be helpful to improve drug adherence.

References

1. Jones BE, Young SM, Antoniskis D, et al. Relationship of the manifestations of tuberculosis to CD4 cell counts in patients with human immunodeficiency virus infection. *Am Rev Respir Dis.* 1993;148(5):1292-1297.
2. Perlman DC, el-Sadr WM, Nelson ET, et al. Variation of chest radiographic patterns in pulmonary tuberculosis by degree of human immunodeficiency virus-related immunosuppression. The Terry Beirn Community Programs for Clinical Research on AIDS (CPCRA). The AIDS Clinical Trials Group (ACTG). *Clin Infect Dis.* 1997;25(2):242-246.
3. Whalen C, Horsburgh CR, Hom D, et al. Accelerated course of human immunodeficiency virus infection after tuberculosis. *Am J Respir Crit Care Med.* 1995;151(1):129-135.

4. Kaplan JE, Benson C, Holmes KH, et al. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. *MMWR Recomm Rep.* 2009;58(RR-4):1-207; quiz CE201-204.
5. French MA. Disorders of immune reconstitution in patients with HIV infection responding to antiretroviral therapy. *Curr HIV/AIDS Rep.* 2007;4(1):16-21.
6. Schiffer JT, Sterling TR. Timing of antiretroviral therapy initiation in tuberculosis patients with AIDS: a decision analysis. *J Acquir Immune Defic Syndr.* 2007;44(2):229-234.
7. Abdool Karim SS, Naidoo K, Grobler A, et al. Timing of initiation of antiretroviral drugs during tuberculosis therapy. *N Engl J Med.* 2010;362(8):697-706.
8. Blanc FX, Sok T, Laureillard D, et al. Significant enhancement in survival with early (2 weeks) vs. late (8 weeks) initiation of highly active antiretroviral treatment (HAART) in severely immunosuppressed HIV-infected adults with newly diagnosed tuberculosis. Paper presented at: XVIII International AIDS Conference; July 18-23, 2010; Vienna, Austria. Abstract THLBB106.
9. Cohen K, van Cutsem G, Boulle A, et al. Effect of rifampicin-based antitubercular therapy on nevirapine plasma concentrations in South African adults with HIV-associated tuberculosis. *J Antimicrob Chemother.* 2008;61(2):389-393.
10. Lopez-Cortes LF, Ruiz-Valderas R, Viciana P, et al. Pharmacokinetic interactions between efavirenz and rifampicin in HIV-infected patients with tuberculosis. *Clin Pharmacokinet.* 2002;41(9):681-690.
11. Friedland G, Khoo S, Jack C, et al. Administration of efavirenz (600 mg/day) with rifampicin results in highly variable levels but excellent clinical outcomes in patients treated for tuberculosis and HIV. *J Antimicrob Chemother.* 2006;58(6):1299-1302.
12. Manosuthi W, Kiertiburanakul S, Sungkanuparph S, et al. Efavirenz 600 mg/day versus efavirenz 800 mg/day in HIV-infected patients with tuberculosis receiving rifampicin: 48 weeks results. *AIDS.* 2006;20(1):131-132.
13. Shipton LK, Wester CW, Stock S, et al. Safety and efficacy of nevirapine- and efavirenz-based antiretroviral treatment in adults treated for TB-HIV co-infection in Botswana. *Int J Tuberc Lung Dis.* 2009;13(3):360-366.
14. Moses M, Zachariah R, Tayler-Smith K, et al. Outcomes and safety of concomitant nevirapine and rifampicin treatment under programme conditions in Malawi. *Int J Tuberc Lung Dis.* 2010;14(2):197-202.
15. L'Homme R F, Nijland HM, Gras L, et al. Clinical experience with the combined use of lopinavir/ritonavir and rifampicin. *AIDS.* 2009;23(7):863-865.
16. Mallolas J, Sarasa M, Nomdedeu M, et al. Pharmacokinetic interaction between rifampicin and ritonavir-boosted atazanavir in HIV-infected patients. *HIV Med.* 2007;8(2):131-134.
17. Gray A, Abdool Karim SS, Gengiah TN. Ritonavir/saquinavir safety concerns curtail antiretroviral therapy options for tuberculosis-HIV-co-infected patients in resource-constrained settings. *AIDS.* 2006;20(2):302-303.
18. Haas DW, Koletar SL, Laughlin L, et al. Hepatotoxicity and gastrointestinal intolerance when healthy volunteers taking rifampin add twice-daily atazanavir and ritonavir. *J Acquir Immune Defic Syndr.* 2009;50(3):290-293.
19. Weiner M, Benator D, Burman W, et al. Association between acquired rifamycin resistance and the pharmacokinetics of rifabutin and isoniazid among patients with HIV and tuberculosis. *Clin Infect Dis.* 2005;40(10):1481-1491.
20. Boulanger C, Hollender E, Farrell K, et al. Pharmacokinetic evaluation of rifabutin in combination with lopinavir-ritonavir in patients with HIV infection and active tuberculosis. *Clin Infect Dis.* 2009;49(9):1305-1311.
21. Jenny-Avital ER, Joseph K. Rifamycin-resistant Mycobacterium tuberculosis in the highly active antiretroviral therapy era: a report of 3 relapses with acquired rifampin resistance following alternate-day rifabutin and boosted protease inhibitor therapy. *Clin Infect Dis.* 2009;48(10):1471-1474.
22. Wenning LA, Hanley WD, Brainard DM, et al. Effect of rifampin, a potent inducer of drug-metabolizing enzymes, on the pharmacokinetics of raltegravir. *Antimicrob Agents Chemother.* 2009;53(7):2852-2856.
23. Haddow LJ, Moosa MY, Easterbrook PJ. Validation of a published case definition for tuberculosis-associated immune reconstitution inflammatory syndrome. *AIDS.* 2010;24(1):103-108.
24. Meintjes G, Lawn SD, Scano F, et al. Tuberculosis-associated immune reconstitution inflammatory syndrome: case definitions for use in resource-limited settings. *Lancet Infect Dis.* 2008;8(8):516-523.
25. Manosuthi W, Kiertiburanakul S, Phoorisri T, et al. Immune reconstitution inflammatory syndrome of tuberculosis among HIV-infected patients receiving antituberculous and antiretroviral therapy. *J Infect.* 2006;53(6):357-363.
26. French MA, Price P, Stone SF. Immune restoration disease after antiretroviral therapy. *AIDS.* 2004;18(12):1615-1627.
27. Colebunders R, John L, Huyst V, et al. Tuberculosis immune reconstitution inflammatory syndrome in countries with limited resources. *Int J Tuberc Lung Dis.* 2006;10(9):946-953.
28. Michailidis C, Pozniak AL, Mandalia S, et al. Clinical characteristics of IRIS syndrome in patients with HIV and tuberculosis. *Antivir Ther.* 2005;10(3):417-422.
29. Lawn SD, Myer L, Bekker LG, et al. Tuberculosis-associated immune reconstitution disease: incidence, risk factors and impact in an antiretroviral treatment service in South Africa. *AIDS.* 2007;21(3):335-341.
30. Meintjes G, Wilkinson RJ, Morroni C, et al. Randomized placebo-controlled trial of prednisone for paradoxical tuberculosis-associated immune reconstitution inflammatory syndrome. *AIDS.* 2010;24(15):2381-2390.
31. Menzies D, Pai M, Comstock G. Meta-analysis: new tests for the diagnosis of latent tuberculosis infection: areas of uncertainty and recommendations for research. *Ann Intern Med.* 2007;146(5):340-354.
32. Girardi E, Palmieri F, Zaccarelli M, et al. High incidence of tuberculin skin test conversion among HIV-infected individuals who have a favourable immunological response to highly active antiretroviral therapy. *AIDS.* 2002;16(14):1976-1979.

Limitations to Treatment Safety and Efficacy

ADHERENCE TO ANTIRETROVIRAL THERAPY (Updated November 3, 2008)

Adherence to antiretroviral therapy (ART) has been strongly correlated with HIV viral suppression, reduced rates of resistance, an increase in survival, *and* improved quality of life *[1-2]*. Because HIV treatment is a lifelong endeavor, and because many patients will initiate therapy when they are generally in good health, feel well, and demonstrate no obvious signs or symptoms of HIV disease, adherence poses a special challenge and requires commitment from the patient and the health care team. This section of the guidelines provides clinicians with a basis to approach the challenging and complicated topic of adherence.

Predictors of Adherence

Adherence is related to characteristics of the patient, the regimen, the clinical setting, and the relationship of the provider and the patient *[3]*. To assure adherence, it is critical that the patient receive and understand information about HIV disease and the specific regimen prescribed. A number of factors have been associated with poor adherence, including the following:

- low levels of literacy *[4]*;
- certain age-related challenges (e.g., vision loss, cognitive impairment) *[5]*;
- psychosocial issues (e.g., depression, homelessness, inadequate social support, stressful life events, dementia, or psychosis) *[6]*;
- active (but not history of) substance abuse, particularly for patients who have experienced recent relapse;
- stigma *[7];*
- difficulty taking medication (e.g., trouble swallowing pills, daily schedule issues);
- complex regimens (e.g., pill burden, dosing frequency, food requirements);
- adverse drug effects; and
- treatment fatigue.

Adherence studies in the early era of combination ART with unboosted protease inhibitors (PIs) found that taking 95% or more of doses was required for full viral suppression *[8]*. More recent adherence studies that utilized boosted PIs and non-nucleoside reverse transcriptase inhibitors (NNRTIs) suggest that boosted PIs and efavirenz (EFV) may be more forgiving of lapses in adherence because of their longer half-lives *[9-10]*. Nonetheless, clinicians should encourage patients to adhere as closely as possible to the prescribed doses for all antiretroviral (ARV) regimens.

Measurement of Adherence

There is no gold standard for the assessment of adherence *[1]*, but there are many validated tools and strategies to choose from. Although patient self-report of adherence predictably overestimates adherence by as much as 20% *[11]*, this measure still is associated with viral load responses *[12]*. Thus, a patient's report of suboptimal adherence is a strong indicator of nonadherence and should be taken seriously.

When ascertained in a simple, nonjudgmental, routine, and structured format that normalizes less-than-perfect adherence and minimizes socially desirable responses, patient self-report remains the most useful method for the assessment and longitudinal monitoring of a patient's adherence in the clinical setting. A survey of all doses during the past 3 days or the past week accurately reflects longitudinal adherence and is the most practical and readily available tool for adherence assessments in clinical trials and in clinical practice *[1]*. Other strategies may also be effective. One study found that asking patients to rate their adherence on a six-point scale during 1 month was more accurate than asking them how often they miss doses or asking about the percentage of doses taken during the previous 3 or 7 days *[13]*. Pharmacy records and pill counts also can be used as an adjunct to simply asking the patient *[14]*. Other methods of assessing adherence include the use of electronic measurement devices (e.g., bottle caps, dispensing systems). However, these methods may not be feasible in some clinical settings.

Interventions to Improve Adherence

Prior to writing the first prescriptions, the clinician should assess the patient's readiness to take medication, factors that might limit adherence (psychiatric illness, active drug use, etc.) that may require additional support, understanding of the disease and the regimen, social support, housing, work and home situation, and daily schedules. Patients should understand that the first regimen is usually the best chance for a simple regimen with long-term treatment success and prevention of drug resistance. Resources individualized to each patient's schedule, competing psychosocial needs, learning needs, and literacy level should be identified to foster adherence.

Individualizing treatment with involvement of the patient in decision making is the cornerstone of any treatment plan *[14]*. The first principle of successful treatment is negotiation of an understandable plan to which the patient can commit *[15-16]*. Establishing a trusting relationship over time and maintaining good communication will help to improve adherence and long-term outcomes. With the patient who is not critically ill, several office visits and the patience of clinicians are generally required before therapy can be started.

A growing menu of possible interventions has demonstrated efficacy in improving adherence toART. For example, a meta-analysis of 19 randomized controlled trials of ARV adherence interventions found that intervention participants were 1.5 times as likely to report 95% adherence and 1.25 times as likely to achieve an undetectable viral load compared with participants in comparison conditions *[17]*. Interventions that have been successful include those focused on the patient and those that work to improve the tolerability of the regimen. Successful support interventions of different modalities have included the following: adherence support groups, peer adherence counselors, behavioral interventions, cognitive-behavioral and reminder strategies, and use of community-based case managers and peer educators. Health care team members, such as nurses, nurse practitioners, pharmacists, medication managers, and social workers, have integral roles in successful adherence programs *[18-21]*. It is also important to address the competing needs of a patient, including active substance use, depression, and housing issues, to reduce the risk of nonadherence.

A number of advances during the past several years have dramatically simplified many regimens, particularly for ART-naïve patients. Prescribing regimens that are simple to take, have a low pill burden and frequency of dosing, have no food requirements, and have low incidence and severity of adverse effects will facilitate adherence. Current treatment recommendations take regimen simplicity as well as efficacy into account.

Adherence assessment and counseling should be done at each clinical encounter and should be the responsibility of the entire health care team. Directly observed therapy (DOT) has been shown to be effective in provision of ART to active drug users *[22]*. In resource-limited settings, the use of community-based DOT has been very successful, and programs have replicated this intervention with success in the United States *[23]*. Although DOT is labor intensive and programmatically complex, modification of traditional DOT methodologies may be feasible and can be adapted in a variety of clinical settings, in which DOT is given a few days each week *[24]*.

Conclusion

Significant progress has been made regarding determinants, measurements, and interventions to improve adherence to ART. Given the various assessment strategies and potential interventions available, the challenge for the treatment team is to select the techniques that provide the best fit for their treatment setting, resources, and patient population. The complexity of this topic and the importance of adherence encourage clinicians to continue to seek novel, patient-centered ways to prevent nonadherence and to tailor adherence interventions. Early detection of nonadherence and prompt intervention can greatly reduce the development of viral resistance and the likelihood of virologic failure.

Table 12. Strategies to Improve Adherence to Antiretroviral Therapy

Strategies	Examples
Use a multidisciplinary team approach Provide an accessible, trusting health care team	• Nurses, social workers, pharmacists, and medication managers
Establish a trusting relationship with the patient	
Establish readiness to start ART	
Identify potential barriers to adherence prior to starting ART	• Psychosocial issues • Active substance abuse or at high risk of relapse • Low literacy level • Busy daily schedule and/or travel away from home • Lack of disclosure of HIV diagnosis • Skepticism about ART • Lack of prescription drug coverage
Provide resources for the patient	• Referrals for mental health and/or substance abuse treatment • Resources to obtain prescription drug coverage • Pillboxes
Involve the patient in antiretroviral (ARV) regimen selection	• For each option, review potential side effects, dosing frequency, pill burden, storage requirements, food requirements, and consequences of nonadherence
Assess adherence at every clinic visit	• Use a simple checklist the patient can complete in the waiting room • Have other members of the health care team also assess adherance • Ask the patient open-ended questions (e.g., *In the last 3 days, please tell me how you took your medicines.*)
Identify the type of nonadherence	• Failure to fill the prescription(s) • Failure to take the right dose(s) at the right time(s) • Nonadherence to food requirements
Identify reasons for nonadherence	• Adverse effects from medications • Complexity of regimen (pill burden, dosing frequency, etc.) • Difficulty swallowing large pills • Forgetfulness • Failure to understand dosing instructions • Inadequate understanding of drug resistance and its relationship to adherence • Pill fatigue • Other potential barriers (see list above)
Assess and simplify regimen, if possible	

References

1. Chesney MA. The elusive gold standard. Future perspectives for HIV adherence assessment and intervention. *J Acquir Immune Defic Syndr.* 2006;43(Suppl 1):S149-155.
2. World Heath Organization (WHO). Adherence to long term therapies – evidence for action. 2003. http://www.who.int/chp/knowledge/publications/adherence_full_report.pdf.
3. Schneider J, Kaplan SH, Greenfield S, et al. Better physician-patient relationships are associated with higher reported adherence to antiretroviral therapy in patients with HIV infection. *J Gen Intern Med.* 2004;19(11):1096-1103.
4. Marcus EN. The silent epidemic--the health effects of illiteracy. *N Engl J Med.* 2006;355(4):339-341.
5. van Eijken M, Tsang S, Wensing M, et al. Interventions to improve medication compliance in older patients living in the community: a systematic review of the literature. *Drugs Aging.* 2003;20(3):229-240.
6. Halkitis PN, Shrem MT, Zade DD, et al. The physical, emotional and interpersonal impact of HAART: exploring the realities of HIV seropositive individuals on combination therapy. *J Health Psychol.* 2005;10(3):345-358.
7. Carr RL, Gramling LF. Stigma: a health barrier for women with HIV/AIDS. *J Assoc Nurses AIDS Care.* 2004;15(5):30-39.
8. Paterson DL, Swindells S, Mohr J, et al. Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. *Ann Intern Med.* 2000;133(1):21-30.
9. Bangsberg DR. Less than 95% adherence to nonnucleoside reverse-transcriptase inhibitor therapy can lead to viral suppression. *Clin Infect Dis.* 2006;43(7):939-941.
10. Raffa JD, Tossonian HK, Grebely J, et al. Intermediate highly active antiretroviral therapy adherence thresholds and empirical models for the development of drug resistance mutations. *J Acquir Immune Defic Syndr.* 2008;47(3):397-399.
11. Arnsten JH, Demas PA, Farzadegan H, et al. Antiretroviral therapy adherence and viral suppression in HIV-infected drug users: comparison of self-report and electronic monitoring. *Clin Infect Dis.* 2001;33(8):1417-1423.
12. Simoni JM, Kurth AE, Pearson CR, et al. Self-report measures of antiretroviral therapy adherence: A review with recommendations for HIV research and clinical management. *AIDS Behav.* 2006;10(3):227-245.
13. Lu M, Safren SA, Skolnik PR, et al. Optimal recall period and response task for self-reported HIV medication adherence. *AIDS Behav.* 2008;12(1):86-94.
14. Bieszk N, Patel R, Heaberlin A, et al. Detection of medication nonadherence through review of pharmacy claims data. *Am J Health Syst Pharm.* 2003;60(4):360-366.
15. Vermeire E, Hearnshaw H, Van Royen P, et al. Patient adherence to treatment: three decades of research. A comprehensive review. *J Clin Pharm Ther.* 2001;26(5):331-342.
16. Williams A, Friedland G. Adherence, compliance, and HAART. *AIDS Clin Care.* 1997;9(7):51-54, 58.
17. Simoni JM, Pearson CR, Pantalone DW, et al. Efficacy of interventions in improving highly active antiretroviral therapy adherence and HIV-1 RNA viral load. A meta-analytic review of randomized controlled trials. *J Acquir Immune Defic Syndr.* 2006;43(Suppl 1):S23-35.
18. McPherson-Baker S, Malow RM, Penedo F, et al. Enhancing adherence to combination antiretroviral therapy in non-adherent HIV-positive men. *AIDS Care.* 2000;12(4):399-404.
19. Kalichman SC, Cherry J, Cain D. Nurse-delivered antiretroviral treatment adherence intervention for people with low literacy skills and living with HIV/AIDS. *J Assoc Nurses AIDS Care.* 2005;16(5):3-15.
20. Remien RH, Stirratt MJ, Dognin J, et al. Moving from theory to research to practice. Implementing an effective dyadic intervention to improve antiretroviral adherence for clinic patients. *J Acquir Immune Defic Syndr.* 2006;43(Suppl 1):S69-78.
21. Mannheimer SB, Morse E, Matts JP, et al. Sustained benefit from a long-term antiretroviral adherence intervention. Results of a large randomized clinical trial. *J Acquir Immune Defic Syndr.* 2006;43(Suppl 1):S41-47.
22. Altice FL, Maru DS, Bruce RD, et al. Superiority of directly administered antiretroviral therapy over self-administered therapy among HIV-infected drug users: a prospective, randomized, controlled trial. *Clin Infect Dis.* 2007;45(6):770-778.
23. Behforouz HL, Kalmus A, Scherz CS, et al. Directly observed therapy for HIV antiretroviral therapy in an urban US setting. *J Acquir Immune Defic Syndr.* 2004;36(1):642-645.
24. Goggin K, Liston RJ, Mitty JA. Modified directly observed therapy for antiretroviral therapy: a primer from the field. *Public Health Rep.* 2007;122(4):472-481.

ADVERSE EFFECTS OF ANTIRETROVIRAL AGENTS (Updated January 10, 2011)

Adverse effects have been reported with all antiretroviral (ARV) drugs and are among the most common reasons for switching or discontinuing therapy as well as for medication nonadherence *[1]*. Rates of treatment-limiting adverse events in antiretroviral therapy (ART)-naïve patients enrolled in randomized trials appear to be declining with newer ARV regimens and are generally now less than 10%. However, most clinical trials have a relatively short follow-up duration and can underestimate longer term complications of therapy. In the Swiss Cohort study, the presence of laboratory adverse events was associated with higher rates of mortality during 6 years of follow-up, highlighting the importance of adverse events in overall patient management *[2]*.

Several factors may predispose individuals to adverse effects of ARV medications. For example, women seem to have a higher propensity of developing Stevens-Johnson syndrome, rashes, and hepatotoxicity from nevirapine (NVP) (ART-naïve women with CD4 counts >250 cells/mm^3) *[3-5]* as well as higher rates of lactic acidosis from nucleoside reverse transcriptase inhibitors (NRTIs) *[6-8]*. Other factors may also contribute to the development of adverse events: concomitant use of medications with overlapping and additive toxicities; comorbid conditions that may increase the risk of or exacerbate adverse effects (e.g., alcoholism *[9]* or coinfection with viral hepatitis, which may increase risk of hepatotoxicity *[10-12]*); drug-drug interactions that may lead to an increase in dose-related toxicities (e.g., concomitant use of ribavirin with didanosine [ddI], which may increase ddI-associated toxicities) *[13-15]*); or genetic factors predisposing patients to abacavir (ABC) hypersensitivity reaction *[16-17]*.

Although the therapeutic goals of ART include achieving and maintaining viral suppression and improving patient immune function, an overarching goal should be to select a regimen that not is only effective but also is safe. This requires consideration of not only the toxicity potential of an ARV regimen but also an individual patient's underlying conditions, concomitant medications, and history of drug intolerance.

Information on adverse events is outlined in multiple tables in the guidelines:

Table 13 provides clinicians with a list of the most common and/or severe known ARV-associated adverse events listed by drug class. **Appendix B, Tables 1–6** summarize the most common adverse effects of individual ARV agents. Some approaches to the management of complications of ART have been published and will not be discussed in these tables *[18-21]*.

Table 13. Antiretroviral Therapy-Associated Common and/or Severe Adverse Effects (January 10, 2011)

(See Appendix B for additional information listed by drug.)

Adverse Effects	NRTIs	NNRTIs	PIs	INSTI	EI
Bleeding events			**All PIs:** ↑ spontaneous bleeding, hematuria in hemophilia **TPV:** Reports of intracranial hemorrhage. Risks include CNS lesions; trauma; surgery; hypertension; alcohol abuse; coagulopathy, anti-coagulant, or anti-platelet agents including vitamin E		
Bone marrow suppression	**ZDV:** Anemia, neutropenia				
Cardiovascular disease (CVD)	**ABC** and **ddI:** Associated with myocardial infarction (MI) in some but not all cohort studies. Risk greatest among those with traditional CVD risk factors.		**PIs:** Associated with MI and stroke in some cohort studies. Risk greatest among those with traditional CVD risk factors. Limited data on newer PIs (ATV, DRV, TPV). **SQV/r**, **ATV/r,** and **LPV/r:** PR interval prolongation. Risks include structural heart disease, conduction system abnormalities, cardiomyopathy, ischemic heart disease, and coadministration with drugs that prolong PR interval. **SQV/r:** QT interval prolongation in a healthy volunteer study. Risks include underlying heart conditions, pre-existing prolonged QT or arrhythmia, or use with other QT-prolonging drugs. ECG prior to SQV initiation is recommended and should be considered during therapy.		
Central nervous system (CNS) effects	**d4T:** Associated with rapidly progressive ascending neuromuscular weakness resembling Guillain-Barré syndrome (rare)	**EFV:** Somnolence, insomnia, abnormal dreams, dizziness, impaired concentration, depression, psychosis, suicidal ideation. Most symptoms subside or diminish after 2–4 weeks. Bedtime dosing may reduce symptoms. Risks include history of psychiatric illness, concomitant use of agents with neuropsychiatric effects, and ↑ plasma EFV concentrations due to genetic factors or absorption (i.e., with food).			
Diabetes mellitus (DM)/insulin resistance	**ZDV, d4T,** and **ddI**		• Reported for some **PIs (IDV, LPV/r)**, but not all PIs studied • **ATV** +/- **RTV** not found to alter insulin sensitivity		
Dyslipidemia	**d4T > ZDV > ABC:** •↑ LDL and TG	**EFV** •↑TG •↑LDL •↑HDL	↑LDL, ↑TG, ↑HDL: **all RTV-boosted PIs** ↑TG: **LPV/r** = **FPV/r** and **LPV/r** > **DRV/r** and **ATV/r**		
Gastrointestinal (GI)	Nausea and vomiting: **ddI** and **ZDV** > other **NRTIs** Pancreatitis: **ddI**		GI intolerance (diarrhea, nausea, vomiting) Diarrhea: common with **NFV**. **LPV/r** > **DRV/r** and **ATV/r**		

Adverse Effects	NRTIs	NNRTIs	PIs	INSTI	EI
Hepatic effects	Reported for most **NRTIs** **ddI:** prolonged exposure linked to noncirrhotic portal hypertension, some cases with esophageal varicees Steatosis: most commonly seen with **ZDV**, **d4T**, or **ddI** Flares: hepatitis B virus (HBV)-coinfected patients may develop severe hepatic flare when **TDF**, **3TC**, and **FTC** are withdrawn or when HBV resistance develops.	**NVP > other NNRTIs** **NVP:** • Severe hepatic toxicity with **NVP** is often associated with skin rash or symptoms of hypersensitivity. • For ARV-naïve patients, risk is greater for women with pre-**NVP** CD4 count >250 cells/mm^3 and men with pre-**NVP** CD4 count >400 cells/mm^3. Risk is higher for women. • 2-week dose escalation of **NVP** reduces risk of rash and possibly hepatotoxicity if related to hypersensitivity. • Given high risk in those with competent immune systems, **NVP** should never be used for post-exposure prophylaxis in HIV-uninfected individuals. • **NVP** is contraindicated in patients with Child-Pugh classification B or C.	**All PIs:** Drug-induced hepatitis and hepatic decompensation (and rare cases of fatalities) have been reported with all PIs to varying degrees. **TPV/r** has a higher frequency of hepatic events than other PIs. **IDV, ATV**: jaundice due to indirect hyperbilirubinemia **TPV/r:** Contraindicated in patients with moderate to severe hepatic insufficiency (Child-Pugh classification B or C)		
Hypersensitivity reaction (HSR) (excluding rash alone or Stevens Johnson syndrome[SJS])	**ABC**: • HLA-B*5701 screening prior to initiation of **ABC**. Should not be started if HLA-B*5701 is positive. • Symptoms of HSR include (in descending frequency): fever, skin rash, malaise, nausea, headache, myalgia, chills, diarrhea, vomiting, abdominal pain, dyspnea, arthralgia, respiratory symptoms • Worsen with continuation of **ABC** • Median onset 9 days; ~ 90% of reactions within first 6 weeks • Onset of rechallenge reactions is within hours of rechallenge dose	**NVP**: • Hypersensitivity syndrome of hepatic toxicity and rash that may be accompanied by fever, general malaise, fatigue, myalgias, arthralgias, blisters, oral lesions, conjunctivitis, facial edema, eosinophilia, granulocytopenia, lymphadenopathy, or renal dysfunction. • For ARV-naïve patients, risk is greater for women with pre-**NVP** CD4 count >250 cells/mm^3 and men with pre-**NVP** CD4 count >400 cells/mm^3. Risk is higher for women. • 2-week dose escalation of **NVP** reduces risk.			
Lactic acidosis	**NRTIs,** especially **d4T, ZDV,** and **ddI** • Insidious onset with GI prodrome, weight loss, and fatigue. May be rapidly progressive, with tachycardia, tachypnea, jaundice, muscular weakness, mental status changes, respiratory distress, pancreatitis, and organ failure. • Mortality up to 50% in some case series, especially in patients with serum lactate >10 mmol/L • Increased risk: female sex, obesity Laboratory findings: • ↑ lactate (often >5 mmol/L), anion gap, AST, ALT, PT, bilirubin • ↑ amylase and lipase in patients with pancreatitis • ↓ arterial pH, serum bicarbonate, serum albumin				

Adverse Effects	NRTIs	NNRTIs	PIs	INSTI	EI
Lipodystrophy	Lipoatrophy: **Thymidine analogs (d4T > ZDV).** May be more likely when combined with **EFV** vs. **boosted PI**.	Lipohypertophy: Trunk fat increase observed with **EFV**-, **PI**-, and **RAL**-containing regimens; however, causal relationship has not been established.			
Myopathy/elevated CPK	**ZDV:** myopathy			**RAL:** ↑ CPK. muscle weakness and rhabdomyolysis	
Nephrotoxicity/ urolithiasis	**TDF:** ↑ serum creatinine, proteinuria, hypophosphatemia, urinary phosphate wasting, glycosuria, hypokalemia, non-anion gap metabolic acidosis Concurrent use of **PI** may increase risk.		**IDV**: ↑ serum creatinine, pyuria; hydronephrosis or renal atrophy **IDV, ATV**: Stone, crystal formation; adequate hydration may reduce risk.		
Osteopenia/ osteoporosis	**TDF:** Associated with greater loss of bone mineral density (BMD) compared with **ZDV, d4T,** and **ABC.**	Decreases in BMD observed in studies of regimens containing different **NRTIs** combined with either **NNRTIs** or **PIs**.			
Peripheral neuropathy	Peripheral neuropathy (pain and/or paresthesias, lower extremities > upper extremities): **d4T > ddI** and **ddC** (can be irreversible) **d4T:** Associated with rapidly progressive ascending neuromuscular weakness resembling Guillain-Barré syndrome (rare)				
Rash		**All NNRTIs**	**ATV, DRV, FPV**		**MVC**
Stevens-Johnson syndrome (SJS/toxic epidermal necrosis (TEN)	**ddI, ZDV:** Reported cases	**NVP > DLV, EFV, ETR** For **NVP** risks include: •Female sex •Black, Asian, Hispanic race/ethnicity	**FPV, DRV, IDV, LPV/r, ATV:** Reported cases		

Acronyms:
Drug Classes: EI = entry inhibitor; INSTI = integrase strand transfer inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PIs = protease inhibitor
Antiretroviral Drugs: 3TC = lamivudine; ABC = abacavir; ATV = atazanavir; ATV/r = atazanavir + ritonavir; d4T = stavudine; ddC = zalcitabine; ddI = didanosine; DLV = delaviridine; DRV = darunavir; DRV/r = darunavir + ritonavir; EFV = efavirenz; ETR = etravirine; FPV = fosamprenavir; FPV/r = fosamprenavir + ritonavir; FTC = emtricitabine; IDV = indinavir; LPV/r = lopinavir + ritonavir; MVC = maraviroc; NFV = nelfinavir; NVP = nevirapine; RAL = raltegravir; RTV = ritonavir; SQV/r = saquinavir + ritonavir; TDF = tenofovir; TPV = tipranavir; ZDV = zidovudine
Other: ALT = alanine aminotransferase; ARV = antiretroviral; AST = aspartate aminotransferase; BMD = bone mineral density; CNS = central nervous system; CPK = creatine phosphokinase; CVD = cardiovascular disease; DM = diabetes mellitus; ECG = electrocardiogram; GI = gastrointestinal; HBV = hepatitis B virus; HDL = high-density lipoprotein; HSR = hypersensitivity reaction; LDL = low-density lipoprotein; MI = myocardial infarction; PT = prothrombin time; SJS = Stevens-Johnson syndrome; TEN = toxic epidermal necrosis; TG = triglyceride

References

1. O'Brien ME, Clark RA, Besch CL, et al. Patterns and correlates of discontinuation of the initial HAART regimen in an urban outpatient cohort. *J Acquir Immune Defic Syndr.* 2003;34(4):407-414.
2. Keiser O, Fellay J, Opravil M, et al. Adverse events to antiretrovirals in the Swiss HIV Cohort Study: effect on mortality and treatment modification. *Antivir Ther.* 2007;12(8):1157-1164.
3. Baylor MS, Johann-Liang R. Hepatotoxicity associated with nevirapine use. *J Acquir Immune Defic Syndr.* 2004;35(5):538-539.
4. Bersoff-Matcha SJ, Miller WC, Aberg JA, et al. Sex differences in nevirapine rash. *Clin Infect Dis.* 2001;32(1):124-129.
5. Fagot JP, Mockenhaupt M, Bouwes-Bavinck J-N, for the EuroSCAR study group. Nevirapine and the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis. *AIDS.* 2001;15(14):1843-1848.
6. Moyle GJ, Datta D, Mandalia S, et al. Hyperlactataemia and lactic acidosis during antiretroviral therapy: relevance, reproducibility and possible risk factors. *AIDS.* 2002;16(10):1341-1349.
7. Bolhaar MG, Karstaedt AS. A high incidence of lactic acidosis and symptomatic hyperlactatemia in women receiving highly active antiretroviral therapy in Soweto, South Africa. *Clin Infect Dis.* 2007;45(2):254-260.
8. Geddes R, Knight S, Moosa MY, et al. A high incidence of nucleoside reverse transcriptase inhibitor (NRTI)-induced lactic acidosis in HIV-infected patients in a South African context. *S Afr Med J.* 2006;96(8):722-724.
9. Dieterich DT, Robinson PA, Love J, Stern JO. Drug-induced liver injury associated with the use of nonnucleoside reverse-transcriptase inhibitors. *Clin Infect Dis.* 2004;38(Suppl 2):S80-89.
10. denBrinker M, Wit FW, Wertheim-van Dillen PM, et al. Hepatitis B and C virus co-infection and the risk for hepatotoxicity of highly active antiretroviral therapy in HIV-1 infection. *AIDS.* 2000;14(18):2895-2902.
11. Sulkowski MS, Thomas DL, Chaisson RE, Moore RD. Hepatotoxicity associated with antiretroviral therapy in adults infected with human immunodeficiency virus and the role of hepatitis C or B virus infection. *JAMA.* 2000;283(1):74-80.
12. Saves M, Raffi F, Clevenbergh P, et al. and the APROCO Study Group. Hepatitis B or hepatitis C virus infection is a risk factor for severe hepatic cytolysis after initiation of a protease inhibitor-containing antiretroviral regimen in human immunodeficiency virus-infected patients. *Antimicrob Agents Chemother.* 2000;44(12):3451-3455.
13. Lafeuillade A, Hittinger G, Chadapaud S. Increased mitochondrial toxicity with ribavirin in HIV/HCV coinfection. *Lancet.* 2001;357(9252):280-281.
14. Guyader D, Poinsignon Y, Cano Y, Saout L. Fatal lactic acidosis in a HIV-positive patient treated with interferon and ribavirin for chronic hepatitis C. *J Hepatol.* 2002;37(2):289-291.
15. Fleischer R, Boxwell D, Sherman KE. Nucleoside analogues and mitochondrial toxicity. *Clin Infect Dis.* 2004;38(8):e79-80.
16. Mallal S, Phillips E, Carosi G, et al. HLA-B*5701 screening for hypersensitivity to abacavir. *N Engl J Med.* 2008;358(6):568-579.
17. Saag M, Balu R, Phillips E, et al. High sensitivity of human leukocyte antigen-b*5701 as a marker for immunologically confirmed abacavir hypersensitivity in white and black patients. *Clin Infect Dis.* 2008;46(7):1111-1118.
18. European AIDS Clinical Society. Prevention and Management of Non-Infectious Co-Morbidities in HIV. November 1, 2009; http://www.europeanaidsclinicalsociety.org/guidelinespdf/2_Non_Infectious_Co_Morbidities_in_HIV.pdf.
19. Wohl DA, McComsey G, Tebas P, et al. Current concepts in the diagnosis and management of metabolic complications of HIV infection and its therapy. *Clin Infect Dis.* 2006;43(5):645-653.
20. Dube MP, Stein JH, Aberg JA, et al. Guidelines for the evaluation and management of dyslipidemia in human immunodeficiency virus (HIV)-infected adults receiving antiretroviral therapy: recommendations of the HIV Medical Association of the Infectious Disease Society of America and the Adult AIDS Clinical Trials Group. *Clin Infect Dis.* 2003;37(5):613-627.
21. Schambelan M, Benson CA, Carr A, et al. Management of metabolic complications associated with antiretroviral therapy for HIV-1 infection: recommendations of an International AIDS Society-USA panel. *J Acquir Immune Defic Syndr.* 2002;31(3):257-275.

DRUG INTERACTIONS (Updated January 10, 2011)

Potential drug-drug and/or drug-food interactions should be taken into consideration when selecting an antiretroviral (ARV) regimen. A thorough review of current medications can help in designing a regimen that minimizes undesirable interactions. In addition, the potential for drug interactions should be assessed when any new drug, including over-the-counter agents, is added to an existing ARV combination. **Tables 14–16b** list significant drug interactions with different ARV agents and suggested recommendations on contraindications, dose modifications, and alternative agents.

Protease Inhibitors (PIs) and Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

Most drug interactions with ARV drugs are mediated through inhibition or induction of hepatic drug metabolism *[1]*. All PIs and NNRTIs are metabolized in the liver by the cytochrome P (CYP) 450 system, particularly by the CYP3A4 isoenzyme. The list of drugs that may have significant interactions with PIs or NNRTIs is extensive and is continuously expanding. Some examples of these drugs include medications that are commonly prescribed in HIV-infected patients for non-HIV medical conditions, such as lipid-lowering agents (e.g., statins), benzodiazepines, calcium channel blockers, immunosuppressants (e.g., cyclosporine and tacrolimus), anticonvulsants, rifamycins, erectile dysfunction agents (e.g., sildenafil), ergot derivatives, azole antifungals, macrolides, oral contraceptives, and methadone. Herbal products, such as St. John's wort, can also cause interactions that risk adverse clinical effects.

All PIs are substrates of CYP3A4, so their metabolic rates may be altered in the presence of CYP inducers or inhibitors. Some PIs may also be inducers or inhibitors of other CYP isoenzymes and of P-glycoprotein or other transporters in the gut and elsewhere. Tipranavir (TPV), for example, is a potent inducer of CYP3A4 and P-glycoprotein. The net effect of tipranavir/ritonavir (TPV/r) on CYP3A *in vivo* appears to be enzyme inhibition. Thus, concentrations of drugs that are substrates for only CYP3A are likely to be increased if given with TPV/r. The net effect of TPV/r on a drug that is a substrate for both CYP3A and P-glycoprotein cannot be confidently predicted; significant decreases in saquinavir (SQV), amprenavir (APV), and lopinavir (LPV) concentrations have been observed *in vivo* when given with TPV/r.

The NNRTIs are also substrates of CYP3A4 and can act as an inducer (nevirapine [NVP]), an inhibitor (delavirdine [DLV]), or a mixed inducer and inhibitor (efavirenz [EFV]). Etravirine (ETR) is a substrate of CYPs 3A4, 2C9, and 2C19. It is also an inducer of CYP3A4 and an inhibitor of CYPs 2C9 and 2C19. Thus, these ARV agents can interact with each other in multiple ways and with other drugs commonly prescribed for other concomitant diseases.

The use of a CYP3A4 substrate that has a narrow margin of safety in the presence of a potent CYP3A4 inhibitor may lead to markedly prolonged elimination half-life ($t_{1/2}$) and toxic drug accumulation. Avoidance of concomitant use or dose reduction of the affected drug, with close monitoring for dose-related toxicities, may be warranted.

The inhibitory effect of ritonavir (RTV), however, can be beneficial when added to a PI, such as atazanavir (ATV), fosamprenavir (FPV), or indinavir (IDV) *[2]*. The PIs darunavir (DRV), LPV, SQV, and TPV require coadministration with RTV. Lower than therapeutic doses of RTV (100 to 400 mg per day) are commonly used in clinical practice as a pharmacokinetic enhancer to increase the trough concentration (C_{min}) and prolong the half-life of the active PIs *[3]*. The higher C_{min} allows for a greater C_{min}: inhibitory concentration (IC_{50}) ratio, which reduces the chance for development of drug resistance as a result of suboptimal drug exposure; the longer half-life allows for less frequent dosing, which may enhance medication adherence.

Coadministration of PIs or NNRTIs with a potent CYP3A4 inducer, on the other hand, may lead to suboptimal drug concentrations and reduced therapeutic effects of the ARV agents. These drug combinations should be avoided if alternative agents can be used. If this is not possible, close monitoring of plasma HIV RNA, with or without ARV dosage adjustment and therapeutic drug monitoring (TDM), may be warranted. For example, the rifamycins (i.e., rifampin and, to a lesser extent, rifabutin) are CYP3A4 inducers that can significantly reduce plasma concentrations of most PIs and NNRTIs *[4-5]*. Because rifabutin is a less potent inducer, it is generally considered a reasonable alternative to rifampin for the treatment of tuberculosis (TB) when it is used with a PI-based regimen, despite wider experience with rifampin use *[6]*. **Tables 15a and 15b** list dosage recommendations for concomitant use of rifamycins and other CYP3A4 inducers with PIs and NNRTIs.

Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

Unlike PIs and NNRTIs, NRTIs do not undergo hepatic transformation through the CYP metabolic pathway. Some, however, do have other routes of hepatic metabolism. Significant pharmacodynamic interactions of NRTIs and other drugs have been reported. They include increases in intracellular drug levels and toxicities when didanosine (ddI) is used in combination with hydroxyurea *[7-8]* or ribavirin *[9]*, additive bone marrow suppressive effects of zidovudine (ZDV) and ganciclovir *[10]*, and antagonism of intracellular phosphorylation with the combination of ZDV and stavudine (d4T) *[11]*. Pharmacokinetic interactions have also been reported. However, the mechanisms of some of these interactions are still unclear. Examples of such interactions include increases of ddI concentration in the presence of tenofovir (TDF) *[12]* and decreases in ATV concentration when ATV is coadministered with TDF *[13]*. **Table 15c** lists significant interactions with NRTIs.

CCR5 Antagonist

Maraviroc (MVC), the first Food and Drug Administration (FDA)-approved CCR5 antagonist, is a substrate of CYP3A enzymes and P-glycoprotein. As a consequence, the concentrations of MVC can be significantly increased in the presence of strong CYP3A inhibitors (such as RTV and other PIs, except for TPV/r) and are reduced when used with CYP3A inducers (such as EFV or rifampin). Dose adjustment is necessary when MVC is used in combination with these agents. (See **Table 16b** or **Appendix B, Table 6** for dosage recommendations.) MVC is neither an inducer nor an inhibitor of the CYP3A system and does not alter the pharmacokinetics of the drugs evaluated in interaction studies to date.

Integrase Inhibitor

Raltegravir (RAL), an HIV integrase strand transfer inhibitor, is primarily eliminated by glucuronidation that is mediated by the uridine diphosphate (UDP)-glucuronosyltransferase (UGT) 1A1 enzymes. Strong inducers of UGT1A1 enzymes (e.g., rifampin) can significantly reduce the concentration of RAL *[14]*. (See **Table 15e** for dosage recommendations.) Other inducers of UGT1A1, such as EFV and TPV/r, can also reduce RAL concentration. A pharmacokinetic interaction should be considered if optimal virologic response is not achieved when these drugs are used in combination.

Fusion Inhibitor

The fusion inhibitor enfuvirtide (T-20) is a 36–amino acid peptide that does not enter human cells. It is expected to undergo catabolism to its constituent amino acids with subsequent recycling of the amino acids in the body pool. No clinically significant drug-drug interaction has been identified with T-20 to date.

References

1. Piscitelli SC, Gallicano KD. Interactions among drugs for HIV and opportunistic infections. *N Engl J Med.* 2001;344(13):984-996.
2. Acosta EP. Pharmacokinetic enhancement of protease inhibitors. *J Acquir Immune Defic Syndr.* 2002;29 Suppl 1:S11-18.
3. Kempf DJ, Marsh KC, Kumar G, et al. Pharmacokinetic enhancement of inhibitors of the human immunodeficiency virus protease by coadministration with ritonavir. *Antimicrob Agents Chemother.* 1997;41(3):654-660.
4. Baciewicz AM, Chrisman CR, Finch CK, et al. Update on rifampin and rifabutin drug interactions. *Am J Med Sci.* 2008;335(2):126-136.
5. Spradling P, Drociuk D, McLaughlin S, et al. Drug-drug interactions in inmates treated for human immunodeficiency virus and Mycobacterium tuberculosis infection or disease: an institutional tuberculosis outbreak. *Clin Infect Dis.* 2002;35(9):1106-1112.
6. Blumberg HM, Burman WJ, Chaisson RE, et al. American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America: treatment of tuberculosis. *Am J Respir Crit Care Med.* 2003;167(4):603-662.
7. Havlir DV, Gilbert PB, Bennett K, et al. Effects of treatment intensification with hydroxyurea in HIV-infected patients with virologic suppression. *AIDS.* 2001;15(11):1379-1388.
8. Zala C, Salomon H, Ochoa C, et al. Higher rate of toxicity with no increased efficacy when hydroxyurea is added to a regimen of stavudine plus didanosine and nevirapine in primary HIV infection. *J Acquir Immune Defic Syndr.* 2002;29(4):368-373.
9. Fleischer R, Boxwell D, Sherman KE. Nucleoside analogues and mitochondrial toxicity. *Clin Infect Dis.* 2004;38(8):e79-80.
10. Hochster H, Dieterich D, Bozzette S, et al. Toxicity of combined ganciclovir and zidovudine for cytomegalovirus disease associated with AIDS. An AIDS Clinical Trials Group Study. *Ann Intern Med.* 1990;113(2):111-117.

11. Hoggard PG, Kewn S, Barry MG, et al. Effects of drugs on 2',3'-dideoxy-2',3'-didehydrothymidine phosphorylation in vitro. *Antimicrob Agents Chemother*. 1997;41(6):1231-1236.
12. Kearney BP, Sayre JR, Flaherty JF, et al. Drug-drug and drug-food interactions between tenofovir disoproxil fumarate and didanosine. *J Clin Pharmacol*. 2005;45(12):1360-1367.
13. Taburet AM, Piketty C, Chazallon C, et al. Interactions between atazanavir-ritonavir and tenofovir in heavily pretreated human immunodeficiency virus-infected patients. *Antimicrob Agents Chemother*. 2004;48(6):2091-2096.
14. Wenning LA, Hanley WD, Brainard DM, et al. Effect of rifampin, a potent inducer of drug-metabolizing enzymes, on the pharmacokinetics of raltegravir. *Antimicrob Agents Chemother*. 2009;53(7):2852-2856.

Table 14. Drugs That Should Not Be Used With PI, NNRTI, or CCR5 Antagonist
(Updated January 10, 2011)

This table lists only drugs that should not be coadministered at any dose and regardless of RTV boosting. See **Tables 15 and 16** for more detailed pharmacokinetic interaction data and dosage adjustments.

Drug Categories										
Antiretroviral Agents[1, 2]	**Cardiac Agents**	**Lipid-lowering Agents**	**Antimyco-bacterials**	**Gastro-intestinal Drugs**	**Neuro-leptics**	**Psycho-tropics**	**Ergot Derivatives (vasoconstrictors)**	**Herbs**	**Antiretroviral Agents**	**Others**
ATV +/− RTV	none	lovastatin pitavastatin simvastatin	rifampin rifapentine[3]	cisapride[5]	pimozide	midazolam[6] triazolam	dihydroergotamine ergonovine ergotamine methylergonovine	St. John's wort	ETR NVP	alfuzosin irinotecan salmeterol sildenafil for PAH
DRV/r	none	lovastatin pitavastatin simvastatin	rifampin rifapentine[3]	cisapride[5]	pimozide	midazolam[6] triazolam	dihydroergotamine ergonovine ergotamine methylergonovine	St. John's wort	none	alfuzosin salmeterol sildenafil for PAH
FPV +/− RTV	flecainide propafenone	lovastatin pitavastatin simvastatin	rifampin rifapentine[3]	cisapride[5]	pimozide	midazolam[6] triazolam	dihydroergotamine ergonovine ergotamine methylergonovine	St. John's wort	ETR	alfuzosin salmeterol sildenafil for PAH
LPV/r	none	lovastatin pitavastatin simvastatin	rifampin[4] rifapentine[3]	cisapride[5]	pimozide	midazolam[6] triazolam	dihydroergotamine ergonovine ergotamine methylergonovine	St. John's wort	none	alfuzosin salmeterol sildenafil for PAH
RTV	amiodarone flecainide propafenone quinidine	lovastatin pitavastatin simvastatin	rifapentine[3]	cisapride[5]	pimozide	midazolam[6] triazolam	dihydroergotamine ergonovine ergotamine methylergonovine	St. John's wort	none	alfuzosin sildenafil for PAH
SQV/r	amiodarone dofetilide flecainide lidocaine propafenone quinidine	lovastatin pitavastatin simvastatin	rifampin[4] rifapentine	cisapride[5]	pimozide	midazolam[6] triazolam trazodone	dihydroergotamine ergonovine ergotamine methylergonovine	St. John's wort garlic supplements	none	alfuzosin salmeterol sildenafil for PAH
TPV/r	amiodarone flecainide propafenone quinidine	lovastatin pitavastatin simvastatin	rifampin rifapentine[3]	cisapride[5]	pimozide	midazolam[6] triazolam	dihydroergotamine ergonovine ergotamine methylergonovine	St. John's wort	ETR	alfuzosin salmeterol sildenafil for PAH
EFV	none	none	rifapentine[3]	cisapride[5]	pimozide	midazolam[6] triazolam	dihydroergotamine ergonovine ergotamine methylergonovine	St. John's wort	other NNRTIs	none
ETR	none	none	rifampin rifapentine[3]	none	none	none	none	St John's wort	unboosted PIs ATV/r, FPV/r, or TPV/r other NNRTIs	carbamazepine phenobarbital phenytoin clopidogrel
NVP	none	none	rifapentine[3]	none	none	none	none	St. John's wort	ATV +/− RTV other NNRTIs	ketoconazole
MVC	none	none	rifapentine[3]	none	none	none	none	St. John's wort	none	none

1 DLV, IDV, and NFV are not included in this table. Refer to the FDA package insert for information regarding DLV-, IDV-, and NFV-related drug interactions.
2 Certain listed drugs are contraindicated based on theoretical considerations. Thus, drugs with narrow therapeutic indices and suspected metabolic involvement with CYP450 3A, 2D6, or unknown pathways are included in this table. Actual interactions may or may not occur in patients.
3 HIV-infected patients treated with rifapentine have a higher rate of TB relapse than those treated with other rifamycin-based regimens; an alternative agent is recommended.
4 A high rate of Grade 4 serum transaminase elevation was seen when a higher dose of RTV was added to LPV/r or SQV or when double-dose LPV/r was used with rifampin to compensate for rifampin's induction effect, so these dosing strategies should not be used.
5 The manufacturer of cisapride has a limited-access protocol for patients who meet specific clinical eligibility criteria.
6 Use of oral midazolam is contraindicated. Parenteral midazolam can be used with caution as a single dose and can be given in a monitored situation for procedural sedation.

Suggested alternatives to:
Lovastatin, simvastatin: Pravastatin and fluvastatin have the least potential for drug-drug interactions (except for pravastatin with DRV/r, see **Table 15a**). Use atorvastatin and rosuvastatin with caution; start with the lowest possible dose and titrate based on tolerance and lipid-lowering efficacy.
Rifampin: Rifabutin (with dosage adjustment – see **Tables 15a and 15b**)
Midazolam, triazolam: temazepam, lorazepam, oxazepam

Acronyms: ATV +/- RTV = atazanavir +/- ritonavir, DLV = delavirdine, DRV/r = darunavir/ritonavir, EFV = efavirenz, ETV = etravirine, FDA = Food and Drug Administration, FPV +/- RTV = fosamprenavir +/- ritonavir, HIV = human immunodeficiency virus, IDV = indinavir, LPV/r = lopinavir/ritonavir, MVC = maraviroc, NFV = nelfinavir, NNRTI = non-nucleoside reverse transcriptase inhibitor, NVP = nevirapine, PAH = pulmonary arterial hypertension, PI = protease inhibitor, RTV = ritonavir, SQV/r = saquinavir/ritonavir, TPV/r = tipranavir/ritonavir

Table 15a. Drug Interactions between PIs* and Other Drugs (Updated January 10, 2011)

*NFV and IDV are not included in this table. Please refer to the FDA package insert for information regarding NFV and IDV drug interactions.

This table provides information relating to pharmacokinetic interactions between PIs and non-ARV drugs. When information is available, interactions with boosted and unboosted PIs are listed separately. For interactions among ARV agents and for dosing recommendations, refer to **Table 16a**.

Concomitant Drug	PI	Effect on PI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Acid Reducers			
Antacids	ATV +/– RTV	↓ ATV expected when given simultaneously	Give ATV at least 2 hours before or 1 hour after antacids or buffered medications.
	FPV	APV AUC ↓ 18%; no significant change in APV C_{min}	Give FPV simultaneously with or at least 2 hours before or 1 hour after antacids.
	TPV/r	TPV AUC ↓ 27%	Give TPV at least 2 hours before or 1 hour after antacids.
H_2 receptor antagonists	**RTV-boosted PIs**		
	ATV/r	↓ ATV	H_2 receptor antagonist dose should not exceed a dose equivalent to famotidine 40 mg BID in ART-naïve patients or 20 mg BID in ART-experienced patients. Give ATV 300 mg + RTV 100 mg simultaneously with and/or ≥10 hours after the H_2 receptor antagonist. If using TDF and H_2 receptor antagonist in ART-experienced patients, use ATV 400 mg + RTV 100 mg.
	DRV/r, LPV/r	No significant effect	
	PIs without RTV		
	ATV	↓ ATV	H_2 receptor antagonist single dose should not exceed a dose equivalent of famotidine 20 mg or total daily dose equivalent of famotidine 20 mg BID in ART-naïve patients. Give ATV at least 2 hours before and at least 10 hours after the H_2 receptor antagonist.
	FPV	APV AUC ↓ 30%; no significant change in APV C_{min}	Give FPV at least 2 hours before H_2 receptor antagonist if concomitant use is necessary. Consider boosting with RTV.
Proton pump inhibitors (PPIs)	ATV	↓ ATV	**PPIs are not recommended in patients receiving unboosted ATV.** In these patients, consider alternative acid-reducing agents, RTV boosting, or alternative PIs.
	ATV/r	↓ ATV	PPIs should not exceed a dose equivalent to omeprazole 20 mg daily in PI-naïve patients. PPIs should be administered at least 12 hours prior to ATV/r. **PPIs are not recommended in PI-experienced patients**.
	DRV/r, TPV/r	↓ omeprazole PI: no significant effect	May need to increase omeprazole dose with TPV/r.
	FPV +/– RTV, LPV/r	No significant effect	
	SQV/r	SQV AUC ↑ 82%	Monitor for SQV toxicities.
Anticoagulants			
Warfarin	ATV +/- RTV, DRV/r, FPV +/- RTV, LPV/r, SQV/r, TPV/r	↑ or ↓ warfarin possible DRV/r ↓ S-warfarin AUC 21%	Monitor INR closely when stopping or starting PI and adjust warfarin dose accordingly.

Table 15a. Drug Interactions between PIs and Other Drugs

Concomitant Drug	PI	Effect on PI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Anticonvulsants			
Carbamazepine	**RTV-boosted PIs**		
	ATV/r, FPV/r, LPV/r, SQV/r, TPV/r	↑ carbamazepine possible TPV/r ↑ carbamazepine AUC 26% May ↓ PI levels substantially	Consider alternative anticonvulsant or monitor levels of both drugs and assess virologic response. **Do not coadminister with LPV/r once daily.**
	DRV/r	carbamazepine AUC ↑ 45% DRV: no significant change	Monitor anticonvulsant level and adjust dose accordingly.
	PIs without RTV		
	ATV, FPV	May ↓ PI levels substantially	Monitor anticonvulsant level and virologic response. Consider alternative anticonvulsant; RTV boosting for ATV and FPV; and/or monitoring PI level.
Lamotrigine	LPV/r	lamotrigine AUC ↓ 50% LPV: no significant change	Titrate lamotrigine dose to effect. A similar interaction is possible with other RTV-boosted PIs.
Phenobarbital	All PIs	May ↓ PI levels substantially	Consider alternative anticonvulsant or monitor levels of both drugs and assess virologic response. **Do not coadminister with LPV/r once daily.**
Phenytoin	**RTV-boosted PIs**		
	ATV/r, DRV/r, SQV/r, TPV/r	↓ phenytoin possible ↓ PI possible	Consider alternative anticonvulsant or monitor levels of both drugs and assess virologic response.
	FPV/r	phenytoin AUC ↓ 22% APV AUC ↑ 20%	Monitor phenytoin level and adjust dose accordingly. No change in FPV/r dose recommended.
	LPV/r	phenytoin AUC ↓ 31% LPV/r AUC ↓ 33%	Consider alternative anticonvulsant or monitor levels of both drugs and assess virologic response. **Do not coadminister with LPV/r once daily.**
	PIs without RTV		
	ATV, FPV	May ↓ PI levels substantially	Consider alternative anticonvulsant; RTV boosting for ATV and FPV; and/or monitoring PI level. Monitor anticonvulsant level and virologic response.
Valproic acid (VPA)	LPV/r	↓VPA possible LPV AUC ↑ 75%	Monitor VPA levels and response. Monitor for LPV-related toxicities.
Antidepressants			
Bupropion	LPV/r	bupropion AUC ↓ 57%	Titrate bupropion dose based on clinical response.
	TPV/r	bupropion AUC ↓ 46%	
Paroxetine	DRV/r	paroxetine AUC ↓ 39%	Titrate paroxetine dose based on clinical response.
	FPV/r	paroxetine AUC ↓ 58%	
Sertraline	DRV/r	sertraline AUC ↓ 49%	Titrate sertraline dose based on clinical response.
Trazodone	ATV +/- RTV, DRV/r, FPV +/- RTV, LPV/r, TPV/r	RTV 200 mg BID (for 2 days) ↑ trazodone AUC 240%	Use lowest dose of trazodone and monitor for CNS and cardiovascular adverse effects.
	SQV/r	↑ trazodone expected	**Contraindicated. Do not coadminister.**
Tricyclic antidepressants (TCAs) (amitriptyline, desipramine, imipramine, nortriptyline)	All RTV-boosted PIs	↑ TCA expected	Use lowest possible TCA dose and titrate based on clinical assessment and/or drug levels.

Concomitant Drug	PI	Effect on PI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antifungals			
Fluconazole	**RTV-boosted PIs**		
	ATV/r	No significant effect	
	SQV/r	No data with RTV boosting SQV (1,200mg TID) AUC ↑ 50%	
	TPV/r	TPV AUC ↑ 50%	Fluconazole >200 mg daily is not recommended. If high-dose fluconazole is indicated, consider alternative PI or another class of ARV drug.
Itraconazole	**RTV-boosted PIs**		
	ATV/r, DRV/r, FPV/r, TPV/r	↑ itraconazole possible ↑ PI possible	Consider monitoring itraconazole level to guide dosage adjustments. High doses (>200 mg/day) are not recommended unless dosing is guided by drug levels.
	LPV/r	↑ itraconazole	Consider not exceeding 200 mg itraconazole daily or monitor itraconazole level.
	SQV/r	Bidirectional interaction has been observed	Dose not established, but decreased itraconazole dosage may be warranted. Consider monitoring itraconazole level.
	PIs without RTV		
	ATV, FPV	↑ itraconazole possible ↑ PI possible	Consider monitoring itraconazole level to guide dosage adjustments.
Posaconazole	ATV/r	ATV AUC ↑ 146%	Monitor for adverse effects of ATV.
	ATV	ATV AUC ↑ 268%	Monitor for adverse effects of ATV.
Voriconazole	**RTV-boosted PIs**		
	ATV/r, DRV/r, FPV/r, LPV/r, SQV/r, TPV/r	RTV 400 mg BID ↓ voriconazole AUC 82% RTV 100 mg BID ↓ voriconazole AUC 39%	**Do not coadminister** voriconazole and RTV unless benefit outweighs risk. If administered, consider monitoring voriconazole level.
	PIs without RTV		
	ATV, FPV	↑ voriconazole possible ↑ PI possible	Monitor for toxicities.
Anti-mycobacterials			
Clarithromycin	ATV +/− RTV	clarithromycin AUC ↑ 94%	May cause QTc prolongation. Reduce clarithromycin dose by 50%. Consider alternative therapy.
	DRV/r, FPV/r, LPV/r, SQV/r, TPV/r	DRV/r ↑ clarithromycin AUC 57% FPV/r ↑ clarithromycin possible LPV/r ↑ clarithromycin expected RTV 500 mg BID ↑ clarithromycin 77% SQV unboosted ↑ clarithromycin 45% TPV/r ↑ clarithromycin 19% and ↓ active metabolite 97% clarithromycin ↑ unboosted SQV 177% clarithromycin ↑ TPV 66%	Monitor for clarithromycin-related toxicities. Reduce clarithromycin dose by 50% in patients with CrCl 30–60 mL/min. Reduce clarithromycin dose by 75% in patients with CrCl <30 mL/min.
	FPV	APV AUC ↑ 18%	No dose adjustment

Concomitant Drug	PI	Effect on PI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Rifabutin	**RTV-boosted PIs**		
	ATV +/– RTV	rifabutin (150 mg once daily) AUC ↑ 110% and metabolite AUC ↑ 2,101% compared with rifabutin 300 mg daily alone	Rifabutin 150 mg every other day or three times a week. Some experts recommend rifabutin 150 mg daily or 300 mg three times a week. Monitor for antimycobacterial activity. Therapeutic drug monitoring for rifabutin is recommended. Rifabutin 150 mg three times a week in combination with LPV/r has resulted in inadequate rifabutin levels and has led to acquired rifamycin resistance in patients with HIV-associated TB. Pharmacokinetic data reported in this table are results from healthy volunteer studies.
	DRV/r	rifabutin (150 mg every other day) and metabolite AUC ↑ 55% compared with rifabutin 300 mg once daily alone	
	FPV/r	rifabutin (150 mg every other day) and metabolite AUC ↑ 64% compared with rifabutin 300 mg once daily alone	
	LPV/r	rifabutin (150mg once daily) and metabolite AUC ↑ 473% compared with rifabutin 300 mg daily alone	
	SQV/r	↑ rifabutin with unboosted SQV	
	TPV/r	rifabutin (150 mg x 1 dose) and metabolite AUC ↑ 333%	
	PIs without RTV		
	FPV	↑ rifabutin AUC expected	Rifabutin 150 mg daily or 300 mg three times a week
Rifampin	All PIs	↓ PI >75% approximately	**Do not coadminister rifampin and PIs.** Additional RTV does not overcome this interaction and increases hepatotoxicity.
Benzodiazepines			
Alprazolam **Diazepam**	All PIs	↑ benzodiazepine possible RTV 200 mg BID for two days ↑ alprazolam half-life 222% and AUC 248%	Consider alternative benzodiazepines such as lorazepam, oxazepam, or temazepam.
Lorazepam **Oxazepam** **Temazepam**	All PIs	No data	Metabolism of these benzodiazepines via non-CYP450 pathways decreases interaction potential compared with other benzodiazepines.
Midazolam	All PIs	↑ midazolam expected SQV/r ↑ midazolam (oral) AUC 1,144% and C_{max} 327%	**Do not coadminister oral midazolam and PIs.** Parenteral midazolam can be used with caution as a single dose and can be given in a monitored situation for procedural sedation.
Triazolam	All PIs	↑ triazolam expected RTV 200 mg BID ↑ triazolam half-life 1,200% and AUC 2,000%	**Do not coadminister triazolam and PIs.**
Cardiac Medications			
Bosentan	All PIs	LPV/r ↑ bosentan 48-fold (Day 4) and 5-fold (Day 10) ↓ ATV expected	**Do not coadminister bosentan and ATV without RTV.** In patients on a PI (other than unboosted ATV) >10 days: start bosentan at 62.5 mg once daily or every other day. In patients on bosentan who require a PI (other than unboosted ATV): stop bosentan ≥36 hours prior to PI initiation and restart 10 days after PI initiation at 62.5 mg once daily or every other day.

Concomitant Drug	PI	Effect on PI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Digoxin	RTV, SQV/r	RTV 200 mg BID ↑ digoxin AUC 29% and half-life 43% SQV/r ↑ digoxin AUC 49%	Use with caution. Monitor digoxin levels. Digoxin dose may need to be decreased.
Dihydropyridine calcium channel blockers (CCBs)	All PIs	↑ dihydropyridine possible	Use with caution. Titrate CCB dose and monitor closely. ECG monitoring is recommended when used with ATV.
Diltiazem	ATV +/– RTV	diltiazem AUC ↑ 125%	Decrease diltiazem dose by 50%. ECG monitoring is recommended.
	DRV/r, FPV +/– RTV, LPV/r, SQV/r, TPV/r	↑ diltiazem possible	Use with caution. Adjust diltiazem according to clinical response and toxicities.
Corticosteroids			
Dexamethasone	All PIs	↓ PI levels possible	Use systemic dexamethasone with caution or consider alternative corticosteroid for long-term use.
Fluticasone (inhaled or intranasal)	All RTV-boosted PIs	RTV 100 mg BID ↑ fluticasone AUC 350-fold and ↑ C_{max} 25-fold	Coadministration can result in adrenal insufficiency, including Cushing's syndrome. **Do not coadminister unless potential benefit outweighs risk of systemic corticosteroid adverse effects.**
Prednisone	LPV/r	↑ prednisolone AUC 31%	No dosage adjustment necessary.
Herbal Products			
St. John's wort	All PIs	↓ PI expected	**Do not coadminister.**
Hormonal Contraceptives			
Hormonal contraceptives	**RTV-boosted PIs**		
	ATV/r	↓ ethinyl estradiol ↑ norgestimate	Oral contraceptive should contain at least 35 mcg of ethinyl estradiol. Oral contraceptives containing progestins other than norethindrone or norgestimate have not been studied.
	DRV/r	ethinyl estradiol AUC ↓ 44% norethindrone AUC ↓ 14%	Use alternative or additional method.
	FPV/r	ethinyl estradiol AUC ↓ 37% norethindrone AUC ↓ 34%	Use alternative or additional method.
	LPV/r	ethinyl estradiol AUC↓ 42% norethindrone AUC ↓ 17%	Use alternative or additional method.
	SQV/r	↓ ethinyl estradiol	Use alternative or additional method.
	TPV/r	ethinyl estradiol AUC ↓ 48% norethindrone: no significant change	Use alternative or additional method.
	PIs without RTV		
	ATV	ethinyl estradiol AUC ↑ 48% norethindrone AUC ↑ 110%	Oral contraceptive should contain no more than 30 mcg of ethinyl estradiol or use alternate method. Oral contraceptives containing less than 25 mcg of ethinyl estradiol or progestins other than norethindrone or norgestimate have not been studied.
	FPV	With APV: ↑ ethinyl estradiol and ↑ norethindrone; ↓ APV 20%	Use alternative method.

Concomitant Drug	PI	Effect on PI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
HMG-CoA Reductase Inhibitors			
Atorvastatin	All PIs	DRV/r + atorvastatin 10 mg similar to atorvastatin 40 mg alone; FPV +/– RTV ↑ atorvastatin AUC 130%–153%; LPV/r ↑ atorvastatin AUC 488%; SQV/r ↑ atorvastatin AUC 79%; TPV/r ↑ atorvastatin AUC 836%	Use lowest possible starting dose with careful monitoring for toxicities or consider other HMG-CoA reductase inhibitors with less potential for interaction.
Lovastatin	All PIs	Significant ↑ lovastatin expected	**Contraindicated. Do not coadminister.**
Pitavastatin	ATV	pitavastatin AUC ↑ 31%; C_{max} ↑ 60% ATV: no significant effect	No dosage adjustment needed for ATV without RTV.
	All RTV-boosted PIs	↑ pitavastatin possible	**Do not coadminister** due to possible increase in pitavastatin concentration and increased risk of rhabdomyolitis.
Pravastatin	DRV/r	pravastatin AUC ↑ 81%	Use lowest possible starting dose with careful monitoring.
	LPV/r	pravastatin AUC ↑ 33%	No dose adjustment necessary
	SQV/r	pravastatin AUC ↓ 47%–50%	No dose adjustment necessary
Rosuvastatin	ATV/r	rosuvastatin AUC ↑ 213% and C_{max} ↑ 600%	Use lowest possible starting dose with careful monitoring or consider other HMG-CoA reductase inhibitors with less potential for interaction.
	DRV/r, FPV +/- RTV, SQV/r	↑ rosuvastatin possible	
	LPV/r	rosuvastatin AUC ↑ 108% and C_{max} ↑ 366%	
	TPV/r	rosuvastatin AUC ↑ 26% and C_{max} ↑ 123%	
Simvastatin	All PIs	Significant ↑ simvastatin level; SQV/r 400 mg/400 mg BID ↑ simvastatin AUC 3,059%	**Contraindicated. Do not coadminister**.
Narcotics/Treatment for Opioid Dependence			
Buprenorphine	ATV	buprenorphine AUC ↑ 93% norbuprenorphine AUC ↑ 76% ↓ ATV possible	**Do not coadminister buprenorphine with unboosted ATV.** Norbuprenorphine is an active metabolite of buprenorphine.
	ATV/r	buprenorphine AUC ↑ 66% norbuprenorphine AUC ↑ 105%	Monitor for sedation. Buprenorphine dose reduction may be necessary. Norbuprenorphine is an active metabolite of buprenorphine.
	DRV/r	buprenorphine: no significant effect norbuprenorphine AUC ↑ 46% and C_{min} ↑ 71%	No dose adjustment necessary. Clinical monitoring is recommended. Norbuprenorphine is an active metabolite of buprenorphine.
	LPV/r	No significant effect	No dose adjustment necessary
	TPV/r	buprenorphine: no significant effect norbuprenorphine AUC, C_{max}, and C_{min} ↓ 80% TPV C_{min} ↓ 19–40%	Consider monitoring TPV level. Norbuprenorphine is an active metabolite of buprenorphine.
Methadone	**RTV-boosted PIs**		
	ATV/r, DRV/r, FPV/r, LPV/r, SQV/r, TPV/r	ATV/r, DRV/r, FPV/r ↓ R-methadone AUC 16%–18%; LPV/r ↓ methadone AUC 26%–53%; SQV/r 1,000/100mg BID ↓ R-methadone AUC 19%; TPV/r ↓ R-methadone AUC 48%	Opioid withdrawal unlikely but may occur. No adjustment in methadone usually required but monitor for opioid withdrawal and increase methadone dose as clinically indicated. (R-methadone is the active form of methadone.)

Table 15a. Drug Interactions between PIs and Other Drugs

Concomitant Drug	PI	Effect on PI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Methadone (continued)	**PIs without RTV**		
	ATV	No significant effect	No dosage adjustment necessary.
	FPV	No data with unboosted FPV APV ↓ R-methadone C_{min} 21%, AUC no significant change	Monitor and titrate methadone as clinically indicated. The interaction with FPV is presumed to be similar. (R-methadone is the active form of methadone.)
Phosphodiesterase Type 5 (PDE5) Inhibitors			
Sildenafil	All PIs	DRV/r + sildenafil 25mg similar to sildenafil 100mg alone; RTV 500 mg BID ↑ sildenafil AUC 1,000%; SQV unboosted ↑ sildenafil AUC 210%	For treatment of erectile dysfunction Start with sildenafil 25 mg every 48 hours and monitor for adverse effects of sildenafil. For treatment of pulmonary arterial hypertension **Contraindicated**
Tadalafil	All PIs	RTV 200 mg BID ↑ tadalafil AUC 124%; TPV/r (1st dose) ↑ tadalafil AUC 133%; TPV/r steady state: no significant effect	For treatment of erectile dysfunction Start with tadalafil 5 mg dose and do not exceed a single dose of 10 mg every 72 hours. Monitor for adverse effects of tadalafil. For treatment of pulmonary arterial hypertension *In patients on a PI >7 days*: Start with tadalafil 20 mg once daily and increase to 40 mg once daily based on tolerability. *In patients on tadalafil who require a PI*: Stop tadalafil ≥24 hours prior to PI initiation, restart 7 days after PI initiation at 20 mg once daily, and increase to 40 mg once daily based on tolerability.
Vardenafil	All PIs	RTV 600 mg BID ↑ vardenafil AUC 49-fold	Start with vardenafil 2.5 mg every 72 hours and monitor for adverse effects of vardenafil.
Miscellaneous Interactions			
All PIs	Colchicine	All PIs	For treatment of gout flares Colchicine 0.6 mg x 1 dose, followed by 0.3 mg 1 hour later. Do not repeat dose for at least 3 days. *With FPV without RTV*: 1.2 mg x 1 dose and no repeat dose for at least 3 days For prophylaxis of gout flares Colchicine 0.3 mg once daily or every other day *With FPV without RTV*: colchicine 0.3 mg BID or 0.6 mg once daily or 0.3 mg once daily For treatment of familial Mediterranean fever Do not exceed colchicine 0.6 mg once daily or 0.3 mg BID. *With FPV without RTV*: Do not exceed 1.2 mg once daily or 0.6 mg BID. **Do not coadminister in patients with hepatic or renal impairment.**
	Salmeterol	↑ salmeterol possible	**Do not coadminister** because of potential increased risk of salmeterol-associated cardiovascular events, including QT prolongation, palpitations, and sinus tachycardia.
ATV/r LPV/r	Atovaquone/proguanil	ATV/r ↓ atovaquone AUC 46% and ↓ proguanil AUC 41% LPV/r ↓ atovaquone AUC 74% and ↓ proguanil AUC 38%	No dosage recommendation. Consider alternative drug for malaria prophylaxis, if possible.

Acronyms: APV = amprenavir, ARV = antiretroviral, ATV = atazanavir, ATV/r = atazanavir + ritonavir, AUC = area under the curve, BID = twice daily, CCB = calcium channel blocker, C_{max} = maximum plasma concentration, C_{min} = minimum plasma concentration, CNS = central nervous system, CrCl = creatinine clearance, CYP = cytochrome P, DRV/r = darunavir + ritonavir, ECG = electrocardiogram, FDA = Food and Drug Administration, FPV = fosamprenavir (FPV is a prodrug of APV), FPV/r = fosamprenavir + ritonavir, IDV = indinavir, IDV/r = indinavir + ritonavir, INR = international normalized ratio, LPV = lopinavir, LPV/r = lopinavir + ritonavir, NFV = nelfinavir, PDE5 = phosphodiesterase type 5, PI = protease inhibitor, PPI = proton pump inhibitor, RTV = ritonavir, SQV = saquinavir, SQV/r = saquinavir + ritonavir, TB = tuberculosis, TCA = tricyclic antidepressant, TID = three times a day, TPV = tipranavir, TPV/r = tipranavir + ritonavir, VPA = valproic acid.

Table 15b. Drug Interactions between NNRTIs* and Other Drugs (Updated January 10, 2011)

*DLV is not included in this table. Please refer to the FDA package insert for information regarding DLV drug interactions.

This table provides information relating to pharmacokinetic interactions between NNRTIs and non-ARV drugs. For interactions among ARV agents and for dosing recommendations, refer to **Table 16b**.

Concomitant Drug Class/Name	NNRTI	Effect on NNRTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Anticoagulants/Antiplatelets			
Warfarin	EFV, NVP	↑ or ↓ warfarin possible	Monitor INR and adjust warfarin dose accordingly.
	ETR	↑ warfarin possible	Monitor INR and adjust warfarin dose accordingly.
Clopidogrel	ETR	↓ activation of clopidogrel possible	ETR may prevent metabolism of clopidogrel (inactive) to its active metabolite. Avoid coadministration, if possible.
Anticonvulsants			
Carbamazepine **Phenobarbital** **Phenytoin**	EFV	carbamazepine + EFV: carbamazepine AUC ↓ 27% and EFV AUC ↓ 36% phenytoin + EFV: ↓ EFV and ↓ phenytoin possible	Monitor anticonvulsant and EFV levels or, if possible, use alternative anticonvulsant.
	ETR	↓ anticonvulsant and ETR possible	**Do not coadminister.** Consider alternative anticonvulsants.
	NVP	↓ anticonvulsant and NVP possible	Monitor anticonvulsant and NVP levels and virologic responses.
Antidepressants			
Bupropion	EFV	bupropion AUC ↓ 55%	Titrate bupropion dose based on clinical response.
Paroxetine	ETR	No significant effect	No dosage adjustment necessary.
Sertraline	EFV	sertraline AUC ↓ 39%	Titrate sertraline dose based on clinical response.
Antifungals			
Fluconazole	EFV	No significant effect	
	ETR	ETR AUC ↑ 86%	No dosage adjustment. Use with caution.
	NVP	NVP AUC ↑ 110%	Increased risk of hepatotoxicity possible with this combination Monitor NVP toxicity or use alternative antiretroviral agent.
Itraconazole	EFV	itraconazole and OH-itraconazole AUC, C_{max}, and C_{min} ↓ 35%–44%	Dose adjustments for itraconazole may be necessary. Monitor itraconazole level and antifungal response.
	ETR	↓ itraconazole possible ↑ ETR possible	Dose adjustments for itraconazole may be necessary. Monitor itraconazole level and antifungal response.
	NVP	↓ itraconazole possible ↑ NVP possible	Consider monitoring NNRTI and itraconazole levels and antifungal response.
Posaconazole	EFV	posaconazole AUC ↓ 50% ↔ EFV	Consider alternative antifungal if possible or consider monitoring posaconazole level if available.
	ETR	↑ ETR possible	No dosage adjustment necessary
Voriconazole	EFV	voriconazole AUC ↓ 77% EFV AUC ↑ 44%	**Contraindicated at standard doses**. Dose: voriconazole 400 mg BID, EFV 300 mg daily
	ETR	voriconazole AUC ↑ 14% ETR AUC ↑ 36%	No dosage adjustment; use with caution. Consider monitoring voriconazole level.
	NVP	↓ voriconazole possible ↑ NVP possible	Monitor for toxicity and antifungal response and/or voriconazole level.
Antimycobacterials			
Clarithromycin	EFV	clarithromycin AUC ↓ 39%	Monitor for efficacy or consider alternative agent, such as azithromycin, for MAC prophylaxis and treatment.
	ETR	clarithromycin AUC ↓ 39% OH-clarithromycin AUC ↑ 21% ETR AUC ↑ 42%	Consider alternative agent, such as azithromycin, for MAC prophylaxis and treatment.
	NVP	clarithromycin AUC ↓ 31% OH-clarithromycin AUC ↑ 42%	Monitor for efficacy or use alternative agent, such as azithromycin, for MAC prophylaxis and treatment.

Table 15b. Drug Interactions between NNRTIs* and Other Drugs
Page 2 of 3

Concomitant Drug Class/Name	NNRTI	Effect on NNRTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antimycobacterials (continued)			
Rifabutin	EFV	rifabutin ↓ 38%	Dose: rifabutin 450–600 mg once daily or 600 mg three times a week if EFV is not coadministered with a PI.
	ETR	rifabutin and metabolite AUC ↓ 17% ETR AUC ↓ 37%	**If ETR is used with an RTV-boosted PI, rifabutin should not be coadministered.** Dose: rifabutin 300 mg once daily **if** ETR is not coadministered with an RTV-boosted PI.
	NVP	rifabutin AUC ↑ 17% and metabolite AUC ↑ 24% NVP C_{min} ↓ 16%	No dosage adjustment necessary. Use with caution.
Rifampin	EFV	EFV AUC ↓ 26%	Maintain EFV dose at 600 mg once daily and monitor for virologic response. Some clinicians suggest EFV 800 mg dose in patients >60kg.
	ETR	Significant ↓ ETR possible	**Do not coadminister.**
	NVP	NVP ↓ 20%–58%	**Do not coadminister.**
Benzodiazepines			
Alprazolam	EFV, ETR, NVP	No data	Monitor for therapeutic efficacy of alprazolam.
Diazepam	ETR	↑ diazepam possible	Decreased dose of diazepam may be necessary.
Lorazepam	EFV	lorazepam C_{max} ↑ 16%, AUC no significant effect	No dosage adjustment necessary
Midazolam	EFV	Significant↑ midazolam expected	**Do not coadminister with oral midazolam.** Parenteral midazolam can be used with caution as a single dose and can be given in a monitored situation for procedural sedation.
Triazolam	EFV	Significant ↑ triazolam expected	**Do not coadminister.**
Cardiac Medications			
Dihydropyridine calcium channel blockers (CCBs)	EFV, NVP	↓ CCBs possible	Titrate CCB dose based on clinical response.
Diltiazem	EFV	diltiazem AUC ↓ 69%	Titrate diltiazem dose based on clinical response.
	NVP	↓ diltiazem possible	
Corticosteroids			
Dexamethasone	ETR*	↓ ETR possible	Use systemic dexamethasone with caution or consider alternative corticosteroid for long-term use.
Herbal Products			
St. John's wort	EFV, ETR, NVP	↓ NNRTI	**Do not coadminister.**
Hormonal Contraceptives			
Hormonal contraceptives	EFV	ethinyl estradiol ↔ levonorgestrel AUC ↓ 83% norelgestromin AUC ↓ 64%	Use alternative or additional methods. Norelgestromin and levonorgestrel are active metabolites of norgestimate.
	ETR	ethinyl estradiol AUC ↑ 22% norethindrone: no significant effect	No dosage adjustment necessary.
	NVP	ethinyl estradiol AUC ↓ 20% norethindrone AUC ↓ 19%	Use alternative or additional methods.
		depomedroxyprogesterone acetate: no significant change	No dosage adjustment necessary
Levonorgestrel	EFV	levonorgestrel AUC ↓ 58%	Effectiveness of emergency postcoital contraception may be diminished.
HMG-CoA Reductase Inhibitors			
Atorvastatin	EFV, ETR, NVP	atorvastatin AUC ↓ 32%–43% with EFV, ETR	Adjust atorvastatin according to lipid responses, not to exceed the maximum recommended dose.
Fluvastatin	ETR	↑ fluvastatin possible	Dose adjustments for fluvastatin may be necessary.

** Error corrected January 18, 2011*

Table 15b. Drug Interactions between NNRTIs* and Other Drugs
Page 3 of 3

Concomitant Drug Class/Name	NNRTI	Effect on NNRTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
HMG-CoA Reductase Inhibitors (continued)			
Lovastatin **Simvastatin**	EFV	simvastatin AUC ↓ 68%	Adjust simvastatin dose according to lipid responses, not to exceed the maximum recommended dose. If used with RTV-boosted PI, simvastatin and lovastatin should be avoided.
	ETR, NVP	↓ lovastatin possible ↓ simvastatin possible	Adjust lovastatin or simvastatin dose according to lipid responses, not to exceed the maximum recommended dose. If used with RTV-boosted PI, simvastatin and lovastatin should be avoided.
Pitavastatin	EFV, ETR, NVP	No data	No dosage recommendation
Pravastatin **Rosuvastatin**	EFV	pravastatin AUC ↓ 44% rosuvatatin: no data	Adjust statin dose according to lipid responses, not to exceed the maximum recommended dose.
	ETR	No significant effect expected with either pravastatin or rosuvastatin	No dosage adjustment necessary
Narcotics/Treatment for Opioid Dependence			
Buprenorphine	EFV	buprenorphine AUC ↓ 50% norbuprenorphine AUC ↓ 71%	No withdrawal symptoms reported. No dosage adjustment recommended, but monitor for withdrawal symptoms.
	NVP	No significant effect	No dosage adjustment necessary
Methadone	EFV	methadone AUC ↓ 52%	Opioid withdrawal common; increased methadone dose often necessary.
	ETR	No significant effect	No dosage adjustment necessary
	NVP	methadone AUC ↓ 41% NVP: no significant effect	Opioid withdrawal common; increased methadone dose often necessary.
Phosphodiesterase Type 5 (PDE5) Inhibitors			
Sildenafil	ETR	sildenafil AUC ↓ 57%	May need to increase sildenafil dose based on clinical effect.
Tadalafil	ETR	↓ tadalafil possible	May need to increase tadalafil dose based on clinical effect.
Vardenafil	ETR	↓ vardenafil possible	May need to increase vardenafil dose based on clinical effect.
Miscellaneous Interactions			
Atovaquone/proguanil	EFV	↓ atovaquone AUC 75% ↓ progaunil AUC 43%	No dosage recommendation. Consider alternative drug for malaria prophylaxis, if possible.

Acronyms: ARV = antiretroviral, AUC = area under the curve, CCB = calcium channel blocker, C_{max} = maximum plasma concentration, C_{min} = minimum plasma concentration, DLV = delavirdine, EFV = efavirenz, ETR = etravirine, FDA = Food and Drug Administration, INR = international normalized ratio, MAC = *Mycobacterium avium* complex, NNRTI = non-nucleoside reverse transcriptase inhibitor, NVP = nevirapine, OH-clarithromycin = active metabolite of clarithromycin, PDE5 = phosphodiesterase type 5, PI = protease inhibitor

Table 15c. Drug Interactions between NRTIs and Other Drugs (Including ARV Agents)
(Updated January 10, 2011)

Concomitant Drug Class/Name	NRTI	Effect on NRTI or Concomitant Drug Concentrations	Dosage Recommendations and Clinical Comments
Antivirals			
Ganciclovir Valganciclovir	TDF	No data	Serum concentrations of these drugs and/or TDF may be increased. Monitor for dose-related toxicities.
	ZDV	No significant pharmacokinetic effects	Potential increase in hematologic toxicities
Ribavirin	ddI	↑ intracellular ddI	**Contraindicated. Do not coadminister.** Fatal hepatic failure and other ddI-related toxicities have been reported with coadministration.
	ZDV	Ribavirin inhibits phosphorylation of ZDV.	Avoid coadministration if possible or closely monitor virologic response and hematologic toxicities.
Integrase Inhibitor			
RAL	TDF	RAL AUC ↑ 49%, C_{max} ↑ 64%	No dosage adjustment necessary
Narcotics/Treatment for Opioid Dependence			
Buprenorphine	3TC, ddI, TDF, ZDV	No significant effect	No dosage adjustment necessary
Methadone	ABC	methadone clearance ↑ 22%	No dosage adjustment necessary
	d4T	d4T AUC ↓ 23% and C_{max} ↓ 44%	No dosage adjustment necessary
	ZDV	ZDV AUC ↑ 29%–43%	Monitor for ZDV-related adverse effects.
NRTIs			
ddI	d4T	No significant PK interaction	**Avoid coadministration**. Additive toxicities of peripheral neuropathy, lactic acidosis, and pancreatitis seen with this combination.
	TDF	ddI-EC AUC and C_{max} ↑ 48%–60%	**Avoid coadministration**.
Other			
Allopurinol	ddI	ddI AUC ↑ 113% ddI AUC ↑ 312% with renal impairment	**Contraindicated. Do not coadminister.** Potential for increased ddI-associated toxicities.
PIs			
ATV	ddI	With ddI-EC + ATV (with food): ddI AUC ↓ 34%; ATV no change	Administer ATV with food 2 hours before or 1 hour after didanosine.
	TDF	ATV AUC↓ 25% and C_{min} ↓ 23%–40% (higher C_{min} with RTV than without) TDF AUC ↑ 24%–37%	Dose: ATV/r 300/100 mg daily coadministered with TDF 300 mg daily. Avoid concomitant use without RTV. If using TDF and H_2 receptor antagonist in ART-experienced patients, use ATV/r 400 mg/100 mg daily. Monitor for TDF-associated toxicity.
	ZDV	ZDV C_{min} ↓ 30%, no change in AUC	Clinical significance unknown.
DRV/r	TDF	TDF AUC↑ 22%, C_{max} ↑ 24% and C_{min} ↑ 37%	Clinical significance unknown. Monitor for TDF toxicity.
LPV/r	TDF	LPV/r AUC ↓ 15% TDF AUC ↑ 34%	Clinical significance unknown. Monitor for TDF toxicity.
TPV/r	ABC	ABC ↓ 35%–44% with TPV/r 1,250/100 mg BID	Appropriate doses for this combination have not been established.
	ddI	ddI-EC ↓ 10% and TPV C_{min} ↓34% with TPV/r 1,250/100 mg BID	Separate doses by at least 2 hours.
	ZDV	ZDV AUC ↓ 31%–43% and C_{max} ↓ 46%–51% with TPV/r 1,250/100 mg BID	Appropriate doses for this combination have not been established.

Acronyms: 3TC = lamivudine, ABC = abacavir, ARV = antiretroviral, ATV = atazanavir, AUC = area under the curve, BID = twice daily, C_{max} = maximum plasma concentration, C_{min} = minimum plasma concentration, d4T = stavudine, ddI = didanosine, DRV/r = darunavir/ritonavir, EC = enteric coated, LPV/r = lopinavir/ritonavir, NRTI = nucleoside reverse transcriptase inhibitor, PI = protease inhibitor, PK = pharmacokinetic, RAL = raltegravir, TDF = tenofovir, TPV/r = tipranavir/ritonavir, ZDV = zidovudine.

Table 15d. Drug Interactions between CCR5 Antagonist and Other Drugs (Updated January 10, 2011)

This table provides information relating to pharmacokinetic interactions between MVC and non-ARV drugs. For interactions among ARV agents and for dosing recommendations, please refer to **Table 16b**.

Concomitant Drug Class/Name	CCR5 Antagonist	Effect on CCR5 Antagonist or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Anticonvulsants			
Carbamazepine Phenobarbital Phenytoin	MVC	↓ MVC possible	If used without a strong CYP3A inhibitor, use MVC 600 mg BID or an alternative antiepileptic agent.
Antifungal			
Itraconazole	MVC	↑ MVC possible	Dose: MVC 150 mg BID
Ketoconazole	MVC	MVC AUC ↑ 400%	Dose: MVC 150 mg BID
Voriconazole	MVC	↑ MVC possible	Consider dose reduction to MVC 150 mg BID
Antimycobacterials			
Clarithromycin	MVC	↑ MVC possible	Dose: MVC 150 mg BID
Rifabutin	MVC	↓ MVC possible	If used without a strong CYP3A inducer or inhibitor, use MVC 300 mg BID. If used with a strong CYP3A inhibitor, use MVC 150 mg BID.
Rifampin	MVC	MVC AUC ↓ 64%	Coadministration is not recommended. If coadministration is necessary use MVC 600 mg BID. If coadministered with a strong CYP3A inhibitor, use MVC 300 mg BID.
Herbal Products			
St. John's wort	MVC	↓ MVC possible	Coadministration is not recommended.
Hormonal Contraceptives			
Hormonal contraceptives	MVC	No significant effect on ethinyl estradiol or levonorgestrel	Safe to use in combination
Narcotics/Treatment for Opioid Dependence			
Methadone	MVC	No data	

Acronyms: ARV = antiretroviral, AUC = area under the curve, BID = twice daily, CYP = cytochrome P, MVC = maraviroc

Table 15e. Drug Interactions between Integrase Inhibitor and Other Drugs (Updated January 10, 2011)

Concomitant Drug Class/Name	Integrase Inhibitor	Effect on Integrase Inhibitor or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Acid Reducers			
Omeprazole	RAL	RAL AUC ↑ 212%, C_{max} ↑ 315%, and C_{min} ↑ 46%	No dosage adjustment recommended
Antimycobacterials			
Rifabutin	RAL	RAL AUC ↑ 19%, C_{max} ↑ 39%, and C_{min} ↓ 20%	No dosage adjustment recommended
Rifampin	RAL	RAL AUC ↓ 40% and C_{min} ↓ 61% with RAL 400 mg Rifampin with RAL 800 mg BID compared with RAL 400 mg BID alone: RAL AUC ↑ 27% and C_{min} ↓ 53%	Dose: RAL 800 mg BID Monitor closely for virologic response.
Hormonal Contraceptives			
Hormonal contraceptives	RAL	No clinically significant effect	Safe to use in combination
Narcotics/Treatment for Opioid Dependence			
Methadone	RAL	No significant effect	No dosage adjustment necessary

Acronyms: AUC = area under the curve, BID = twice daily, C_{max} = maximum plasma concentration, C_{min} = minimum plasma concentration, RAL = raltegravir

Table 16a. Interactions Among PIs* (Updated January 10, 2011)

*NFV and IDV are not included in this table. Please refer to the FDA package insert for information regarding NFV and IDV drug interactions.

Drug Affected	ATV	FPV	LPV/r	RTV	SQV	TPV
DRV	Dose: ATV 300 mg once daily + DRV 600 mg BID + RTV 100 mg BID	No data	**Should not be coadministered because doses are not established**	Dose: (DRV 600 mg + RTV 100 mg) BID or (DRV 800 mg + RTV 100 mg) once daily	**Should not be coadministered because doses are not established**	No data
FPV	Dose: Insufficient data	•	**Should not be coadministered because doses are not established**	Dose: (FPV 1,400 mg + RTV 100 mg or 200 mg) once daily; or (FPV 700 mg + RTV 100 mg) BID	Dose: Insufficient data	**Should not be coadministered because doses are not established**
LPV/r	Dose: ATV 300 mg once daily + LPV/r 400/100 mg BID	See LPV/r + FPV cell	•	LPV is coformulated with RTV as Kaletra.	See LPV/r + SQV cell	**Should not be coadministered because doses are not established**
RTV	Dose: (ATV 300mg + RTV 100mg) once daily	See RTV + FPV cell	LPV is coformulated with RTV as Kaletra.	•	Dose: (SQV 1,000 mg + RTV 100 mg) BID	Dose: (TPV 500 mg + RTV 200 mg) BID
SQV	Dose: Insufficient data	Dose: Insufficient data	Dose: SQV 1,000 mg BID + LPV/r 400/100 mg BID	See SQV + RTV cell	•	**Should not be coadministered because doses are not established**

Acronyms: ATV = atazanavir, BID = twice daily, DRV = darunavir, FDA = Food and Drug Administration, FPV = fosamprenavir, IDV = indinavir, LPV/r = lopinavir/ritonavir, NFV = nelfinavir, PI = protease inhibitor, RTV = ritonavir, SQV = saquinavir, TPV = tipranavir

Table 16b. Interactions between NNRTIs*, MVC, RAL, and PIs* (Updated January 10, 2011)

*DLV, IDV, and NFV are not included in this table. Refer to the FDA package insert for information regarding DLV, IDV, and NFV drug interactions.

		EFV	ETR	NVP	MVC	RAL
ATV	**PK data**	With unboosted ATV ATV: AUC ↓ 74% EFV: no significant change With (ATV 300 mg + RTV 100 mg) once daily with food ATV concentrations similar to unboosted ATV without EFV	With unboosted ATV ETR: AUC ↑ 50%, C_{max} ↑ 47%, and C_{min} ↑ 58% ATV: AUC ↓ 17% and C_{min} ↓ 47% With (ATV 300 mg + RTV 100 mg) once daily ETR: AUC, C_{max}, and C_{min} ↑ approximately 30% ATV: AUC ↓ 14% and C_{min} ↓ 38%	With (ATV 300 mg + RTV 100 mg) once daily ATV: AUC ↓ 42% and C_{min} ↓ 72% NVP: AUC ↑ 25%	With unboosted ATV MVC: AUC ↑ 257% With (ATV 300 mg + RTV 100 mg) once daily MVC: AUC ↑ 388%	With unboosted ATV RAL: AUC ↑ 72% With (ATV 300 mg + RTV 100 mg) once daily RAL: AUC ↑ 41%
	Dose	**Do not coadminister with unboosted ATV.** In ART-naïve patients (ATV 400 mg + RTV 100 mg) once daily **Do not coadminister in ART-experienced patients.**	**Do not coadminister with ATV +/− RTV.**	**Do not coadminister with ATV +/− RTV.**	MVC 150 mg BID with ATV +/− RTV	Standard
DRV – always use with RTV	**PK data**	With (DRV 300 mg + RTV 100 mg) BID DRV: AUC ↓ 13%, C_{min} ↓ 31% EFV: AUC ↑ 21%	ETR 100 mg BID with (DRV 600 mg + RTV 100 mg) BID DRV: no significant change ETR: AUC ↓ 37%, C_{min} ↓ 49%	With (DRV 400 mg + RTV 100 mg BID) DRV: AUC ↑ 24%† NVP: AUC ↑ 27% and C_{min} ↑ 47%	With (DRV 600 mg + RTV 100 mg) BID MVC: AUC ↑ 305% With (DRV 600 mg + RTV 100 mg) BID + ETR MVC: AUC ↑ 210%	With (DRV 600 mg + RTV 100 mg) BID RAL: AUC ↓ 29% and C_{min} ↑ 38%
	Dose	Clinical significance unknown. Use standard doses and monitor closely. Consider monitoring levels.	Standard (ETR 200 mg BID) Despite decreased ETR, safety and efficacy established with this combination in a clinical trial	Standard	MVC 150 mg BID	Standard
EFV	**PK data**	•	↓ ETR possible	NVP: no significant change EFV: AUC ↓ 22%	MVC: AUC ↓ 45%	EFV: AUC ↓ 36%
	Dose		**Do not coadminister.**	**Do not coadminister.**	MVC: 600 mg BID	Standard
ETR	**PK data**	↓ ETR possible	•	↓ ETR possible	MVC: AUC ↓ 53%, C_{max} ↓ 60%	ETR: C_{min} ↓ 17% RAL: C_{min} ↓ 34%
	Dose	**Do not coadminister.**		**Do not coadminister**.	MVC 600 mg BID	Standard
FPV	**PK data**	With (FPV 1,400 mg + RTV 200 mg) once daily APV: C_{min} ↓ 36%	With (FPV 700 mg + RTV 100 mg) BID APV: AUC ↑ 69%, C_{min} ↑ 77%	With unboosted FPV 1,400 mg BID APV: AUC ↓ 33% NVP: AUC ↑ 29% With (FPV 1,400 mg + RTV 100 mg) BID NVP: C_{min} ↑ 19%	Unknown; ↑ MVC possible	No data
	Dose	(FPV 1,400 mg + RTV 300 mg) once daily; or (FPV 700 mg + RTV 100 mg) BID EFV standard	**Do not coadminister with FPV +/− RTV.**	(FPV 700 mg + RTV 100 mg) BID NVP standard	MVC 150 mg BID	Standard
LPV/r	**PK data**	With LPV/r tablets 500/125 mg BID‡ + EFV 600 mg LPV levels similar to LPV/r 400/100 mg BID without EFV	With LPV/r tablets ETR: levels ↓ 30%–45% (comparable to the decrease with DRV/r) LPV: levels ↓ 13%–20%.	With LPV/r capsules LPV: AUC ↓ 27% and C_{min} ↓51%	MVC: AUC ↑ 295% With LPV/r + EFV MVC: AUC ↑153%	↓ RAL ↔ LPV/r
	Dose	LPV/r tablets 500/125 mg‡ BID; LPV/r oral solution 533/133 mg BID EFV standard	Standard	LPV/r tablets 500/125 mg‡ BID; LPV/r oral solution 533/133 mg BID NVP standard	MVC 150 mg BID	Standard

		EFV	ETR	NVP	MVC	RAL
NVP	**PK data**	NVP: no significant change EFV: AUC ↓ 22%	↓ ETR possible	•	No significant change	No data
	Dose	**Do not coadminister.**	**Do not coadminister.**		Without PI MVC 300 mg BID With PI (except TPV/r) MVC 150 mg BID	Standard
RAL	**PK data**	RAL: AUC ↓ 36%	ETR: C_{min} ↑ 17% RAL: C_{min} ↓ 34%	No data	RAL: AUC ↓ 37% MVC: AUC ↓ 21%	•
	Dose	Standard	Standard	No data	Standard	
RTV	**PK data**	Refer to information for boosted PI	Refer to information for boosted PI	Refer to information for boosted PI	With RTV 100 mg BID MVC: AUC ↑ 161%	With RTV 100 mg BID RAL: AUC ↓ 16%
	Dose				MVC 150 mg BID	Standard
SQV - always use with RTV	**PK data**	With SQV 1,200 mg TID SQV: AUC ↓ 62% EFV: AUC ↓ 12%	With (SQV 1,000 mg + RTV 100 mg) BID SQV: AUC unchanged ETR: AUC ↓ 33%, C_{min} ↓ 29% Reduced ETR levels similar to reduction with DRV/r	With SQV 600 mg TID SQV: AUC ↓ 38% NVP: no significant change	With (SQV 1,000 mg + RTV 100 mg) BID MVC: AUC ↑ 877% With (SQV 1,000 mg + RTV 100 mg) BID + EFV MVC: AUC ↑ 400%	No data
	Dose	(SQV 1,000 mg + RTV 100 mg) BID	(SQV 1,000 mg + RTV 100 mg) BID	(SQV 1,000 mg + RTV 100mg) BID	MVC 150 mg BID	Standard
TPV – always use with RTV	**PK data**	With (TPV 500 mg + RTV 100 mg) BID TPV: AUC ↓ 31%, C_{min} ↓ 42% EFV: no significant change With (TPV 750 mg + RTV 200 mg) BID TPV: no significant change EFV: no significant change	With (TPV 500 mg + RTV 200 mg) BID ETR: AUC ↓ 76%, C_{min} ↓ 82% TPV: AUC ↑ 18%, C_{min} ↑ 24%	With (TPV 250 mg + RTV 200 mg) BID and with (TPV 750 mg + RTV 100 mg) BID NVP: no significant change TPV: no data	With (TPV 500 mg + RTV 200 mg) BID MVC: no significant change in AUC TPV: no data	With (TPV 500 mg + RTV 200 mg) BID RAL: AUC ↓ 24%
	Dose	Standard	**Do not coadminister.**	Standard	MVC 300 mg BID	Standard

† Based on between-study comparison.

‡Use a combination of two LPV/r 200 mg/50 mg tablets + one LPV/r 100 mg/25 mg tablet to make a total dose of LPV/r 500 mg/125* mg. *(* Error corrected January 18, 2011)*

Acronyms: AUC = area under the curve, ATV = atazanavir, BID = twice daily, C_{max} = maximum plasma concentration, C_{min} = minimum plasma concentration, DLV = delavirdine, DRV = darunavir, EFV = efavirenz, ETR = etravirine, FDA = Food and Drug Administration, FPV = fosamprenavir, IDV = indinavir, LPV/r = lopinavir/ritonavir, MVC = maraviroc, NFV = nelfinavir, NNRTI = non-nucleoside reverse transcriptase inhibitor, NVP = nevirapine, PI = protease inhibitor, PK = pharmacokinetic, RAL = raltegravir, RTV = ritonavir, SQV = saquinavir, TID = three times a day, TPV = tipranavir

Preventing Secondary Transmission of HIV

(Updated December 1, 2009)

PREVENTION COUNSELING

Interventions to prevent transmission of HIV are key components of the management of HIV infection, yet multiple studies show that prevention is frequently neglected in clinical practice. Each patient encounter provides opportunities to reinforce HIV prevention messages—messages that patients often look to their providers to deliver but may fail to receive *[1-2]*. Despite the challenges to providing effective prevention interventions in a busy practice setting, multiple approaches are available, including formal guidance from the Centers for Disease Control and Prevention (CDC) for incorporating HIV prevention into medical care settings *[3]*. Such interventions have been demonstrated to be effective in changing sexual risk behavior *[4-6]*and can reinforce self-directed behavior change early in diagnosis *[7]*.

The CDC has identified prevention interventions for HIV-infected people that meet stringent criteria for efficacy and scientific rigor *[8]* and three that demonstrated efficacy in treatment settings (Options, Partnership for Health, and Positive Choices). The interventions are available through CDC trainings and materials, delivered as brief messages by providers or via laptop computer, and are readily implemented into busy clinics (**http://www.cdc.gov/hiv/topics/research/prs/index.htm**).

Evidence also exists regarding the efficacy of interventions to reduce injection drug use risk behavior. These include both behavioral interventions *[9-11]* and opiate substitution treatment with methadone *[12-13]*.

There is evidence of increases in HIV risk behaviors among infected persons coinciding with the availability of potent combination antiretroviral therapy (ART). In some cohorts the rate of reported risk behaviors almost doubled compared with rates in the era prior to such therapies *[7]*. A meta-analysis of studies of HIV risk behaviors demonstrates that the prevalence of unprotected sex acts increased in those who believed that receiving ART or having a suppressed viral load protects against transmitting HIV *[14]*. Attitudinal shifts away from safer sexual practices since the availability of potent ART underscore the role for provider-initiated HIV prevention counseling. With wider recognition of the concept that effective treatment may decrease the probability of transmission, it is particularly important for providers to help patients understand that a sustained viral load below the limits of detection will dramatically reduce but does not absolutely assure the absence of virus in the genital and blood compartments, and hence the inability to transmit virus to others *[14-15]*.

Additionally, given the role of sexually transmitted infections (STIs) as facilitators of HIV transmission, an essential adjunct to prevention counseling is the routine screening and symptom-directed testing for STIs, as recommended by CDC *[3]*.

ANTIRETROVIRAL THERAPY AS PREVENTION

ART does have a role in preventing HIV transmission. Lower levels of plasma RNA have been associated with decreases in the concentration of virus in genital secretions *[16-17]*. Observational studies have demonstrated a decreased rate of HIV transmission among serodiscordant heterosexual couples following antiretroviral (ARV)-induced viral suppression in the absence of concomitant STIs. Multiple studies have demonstrated a direct correlation between HIV inoculum size (i.e., viral load) and probability of transmission *[18-19]*. Although some data suggest that the risk of heterosexual HIV transmission is low when an individual's viral load is <40 copies/mL, these data are contingent upon several assumptions, including: (1) completely suppressed viremia; (2) complete adherence to an effective ARV regimen; and (3) the absence of a concomitant STI. Detection of HIV RNA in the genital secretions has been documented in individuals with controlled plasma HIV RNA *[20-21]*. Moreover, it is critical that any biological reduction in infectivity not be offset by increases in risk behavior (i.e., risk compensation).

SUMMARY

In summary, consistent and effective use of ART resulting in a sustained reduction in viral load, in conjunction with consistent condom usage, safer sexual and drug use practices, and detection and treatment of STIs are essential tools for prevention of sexual and blood-borne transmission of HIV. Given these important considerations, medical visits provide a vital opportunity to reinforce HIV prevention messages, discuss sexual- and drug-related risk behaviors, diagnose and treat intercurrent STIs, and develop open communication between provider and patient.

References

1. Morin SF, Koester KA, Steward WT, et al. Missed opportunities: prevention with HIV-infected patients in clinical care settings. *J Acquir Immune Defic Syndr.* 2004;36(4):960-966.
2. Mayer KH, Safren SA, Gordon CM. HIV care providers and prevention: opportunities and challenges. *J Acquir Immune Defic Syndr.* 2004;37 Suppl 2:S130-132.
3. Centers for Disease Control and Prevention (CDC). Incorporating HIV prevention into the medical care of persons living with HIV. Recommendations of CDC, the Health Resources and Services Administration, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. *MMWR Recomm Rep.* 2003;52(RR-12):1-24.
4. Metsch LR, McCoy CB, Miles CC, et al. Prevention myths and HIV risk reduction by active drug users. *AIDS Educ Prev.* 2004;16(2):150-159.
5. Johnson WD, Diaz RM, Flanders WD, et al. Behavioral interventions to reduce risk for sexual transmission of HIV among men who have sex with men. *Cochrane Database Syst Rev.* 2008(3):CD001230.
6. Centers for Disease Control and Prevention (CDC). Evolution of HIV/AIDS prevention programs--United States, 1981-2006. *MMWR Morb Mortal Wkly Rep.* 2006;55(21):597-603.
7. Gorbach PM, Drumright LN, Daar ES, et al. Transmission behaviors of recently HIV-infected men who have sex with men. *J Acquir Immune Defic Syndr.* 2006;42(1):80-85.
8. Centers for Disease Control and Prevention (CDC). HIV/AIDS Prevention Research Synthesis Project. 2009; http://www.cdc.gov/hiv/topics/research/prs/index.htm.
9. Sterk CE, Theall KP, Elifson KW. Who's getting the message? Intervention response rates among women who inject drugs and/or smoke crack cocaine. *Prev Med.* 2003;37(2):119-128.
10. Sterk CE, Theall KP, Elifson KW, et al. HIV risk reduction among African-American women who inject drugs: a randomized controlled trial. *AIDS Behav.* 2003;7(1):73-86.
11. Copenhaver MM, Johnson BT, Lee IC, et al. Behavioral HIV risk reduction among people who inject drugs: meta-analytic evidence of efficacy. *J Subst Abuse Treat.* 2006;31(2):163-171.
12. Hartel DM, Schoenbaum EE. Methadone treatment protects against HIV infection: two decades of experience in the Bronx, New York City. *Public Health Rep.* 1998;113 Suppl 1:107-115.
13. Metzger DS, Navaline H, Woody GE. Drug abuse treatment as AIDS prevention. *Public Health Rep.* 1998;113 Suppl 1:97-106.
14. Crepaz N, Hart TA, Marks G. Highly active antiretroviral therapy and sexual risk behavior: a meta-analytic review. *JAMA.* 2004;292(2):224-236.
15. Rice E, Batterham P, Rotheram-Borus MJ. Unprotected sex among youth living with HIV before and after the advent of highly active antiretroviral therapy. *Perspect Sex Reprod Health.* 2006;38(3):162-167.
16. Vernazza PL, Troiani L, Flepp MJ, et al. Potent antiretroviral treatment of HIV-infection results in suppression of the seminal shedding of HIV. The Swiss HIV Cohort Study. *AIDS.* 2000;14(2):117-121.
17. Graham SM, Holte SE, Peshu NM, et al. Initiation of antiretroviral therapy leads to a rapid decline in cervical and vaginal HIV-1 shedding. *AIDS.* 2007;21(4):501-507.
18. Sheth PM, Kovacs C, Kemal KS, et al. Persistent HIV RNA shedding in semen despite effective antiretroviral therapy. *AIDS.* 2009;23(15):2050-2054.
19. Quinn TC, Wawer MJ, Sewankambo N, et al. Viral load and heterosexual transmission of human immunodeficiency virus type 1. Rakai Project Study Group. *N Engl J Med.* 2000;342(13):921-929.
20. Marcelin AG, Tubiana R, Lambert-Niclot S, et al. Detection of HIV-1 RNA in seminal plasma samples from treated patients with undetectable HIV-1 RNA in blood plasma. *AIDS.* 2008;22(13):1677-1679.
21. Neely MN, Benning L, Xu J, et al. Cervical shedding of HIV-1 RNA among women with low levels of viremia while receiving highly active antiretroviral therapy. *J Acquir Immune Defic Syndr.* 2007;44(1):38-42.

Conclusion

The Panel has carefully reviewed recent results from clinical trials in HIV therapy and considered how they inform appropriate care guidelines. The Panel appreciates that HIV care is highly complex and rapidly evolving. Guidelines are never fixed and must always be individualized. Where possible, the Panel has based recommendations on the best evidence from prospective trials with defined endpoints. When such evidence does not yet exist, the Panel attempted to reflect reasonable options in its conclusions.

HIV care requires, as always, partnerships and open communication. The provider can make recommendations most likely to lead to positive outcomes only if the patient's own point of view and social context are well known. Guidelines are only a starting point for medical decision making. They can identify some of the boundaries of high-quality care but cannot substitute for sound judgment.

As further research is conducted and reported, guidelines will be modified. The Panel anticipates continued progress in the simplicity of regimens, improved potency and barrier to resistance, and reduced toxicity. The Panel hopes the guidelines are useful and is committed to their continued adjustment and improvement.

Appendix A: Key to Acronyms

3TC	lamivudine
3TC/ZDV	lamivudine + zidovudine
ABC	abacavir
ABC/3TC	abacavir + lamivudine
ABC/3TC/ZDV	abacavir + lamivudine + zidovudine
ACTG	AIDS Clinical Trials Group
AIDS	acquired immune deficiency syndrome
ALT	alanine aminotransferase
APV	amprenavir
ART	antiretroviral therapy
ART-CC	ART Cohort Collaboration
ARV	antiretroviral
AST	aspartate aminotransferase
ATV	atazanavir
ATV/r	atazanavir/ritonavir or ritonavir-boosted atazanavir
AUC	area under the curve
AV	atrioventricular
bDNA	branched DNA
BID	twice a day
BMD	bone mineral density
BUN	blood urea nitrogen
CAPD	chronic ambulatory peritoneal dialysis
CBC	complete blood count
CCB	calcium channel blocker
CDC	Centers for Disease Control and Prevention
CI	confidence interval
C_{max}	maximum concentration or peak concentration
CME	continuing medical education
C_{min}	minimum concentration or trough concentration
CMV	cytomegalovirus
CNS	central nervous system
CPK	creatine phosphokinase
CrCl	creatinine clearance
CVD	cardiovascular disease
CYP	cytochrome P
d4T	stavudine
D:A:D	Data Collection on Adverse Events of Anti-HIV Drugs Study
ddC	zalcitabine
ddI	didanosine
DHHS	Department of Health and Human Services
DILI	drug-induced liver injury
DLV	delavirdine
DM	diabetes mellitus
D/M	dual or mixed (tropic)
DMPA	depot medroxyprogesterone
DOT	directly observed therapy
DRV	darunavir
DRV/r	darunavir/ritonavir or ritonavir-boosted darunavir

DXA	dual-energy x-ray absorptiometry
EBV	Epstein-Barr virus
EC	enteric coated
ECG	electrocardiogram
EFV	efavirenz
EFV/FTC/TDF	efavirenz + emtricitabine + tenofovir disoproxil fumarate
EIA	enzyme immunoassay
ETR	etravirine
FDA	Food and Drug Administration
FI	fusion inhibitor
FPV	fosamprenavir
FPV/r	fosamprenavir/ritonavir or ritonavir-boosted fosamprenavir
FTC	emtricitabine
FTC/TDF	emtricitabine + tenofovir disoproxil fumarate
GAZT	AZT glucuronide
GHB	gamma hydroxybutyrate
GI	gastrointestinal
HAV	hepatitis A virus
HBeAg	hepatitis B e antigen
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HD	hemodialysis
HDL	high-density lipoprotein
HELLP	hemolysis, elevated liver enzymes, low platelet count (syndrome)
HHS	Health and Human Services
HHV	human herpes virus
HHV-8	human herpes virus 8
HIV	human immunodeficiency virus
HIV-1	human immunodeficiency virus type 1
HIV-2	human immunodeficiency virus type 2
HIVAN	HIV-associated nephropathy
HPV	human papilloma virus
HR	hazard ratio
HRSA	Health Resource Services Administration
hsCRP	high sensitivity C-reactive protein
HSR	hypersensitivity reaction
HTLV	human T-cell leukemia virus
HTLV-1	human T-cell leukemia virus type 1
HTLV-2	human T-cell leukemia virus type 2
IAS-USA	International AIDS Society-USA
IC	inhibitory concentration
IDU	illicit drug user
IDV	indinavir
IDV/r	indinavir/ritonavir or ritonavir-boosted indinavir
IFN-γ	interferon-gamma
IGRA	interferon-gamma release assay
IL-2	interleukin-2
IL-6	interleukin-6
IL-7	interleukin-7
IND	investigational new drug

INH	isoniazid
INR	international normalized ratio
INSTI	integrase strand transfer inhibitor
IQ	inhibitory quotient
IRB	Institutional Review Board
IRIS	immune reconstitution inflammatory syndrome
LDL	low-density lipoprotein
LPV	lopinavir
LPV/r	lopinavir/ritonavir or ritonavir-boosted lopinavir
LTBI	latent tuberculosis infection
MAC	*Mycobacterium avium* complex
MDMA	methylenedioxymethamphetamine
MDRD	modification of diet in renal disease (equation)
MHC	major histocompatability complex
MI	myocardial infarction
msec	milliseconds
MSM	men who have sex with men
MTB	*Mycobacterium tuberculosis*
MTCT	mother-to-child transmission
MVC	maraviroc
NA-ACCORD	The North American AIDS Cohort Collaboration on Research and Design
NFV	nelfinavir
NIH	National Institutes of Health
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
NVP	nevirapine
OAR	Office of AIDS Research
OARAC	Office of AIDS Research Advisory Council
PAH	pulmonary arterial hypertension
PCP	*Pneumocystis jirocevi* pneumonia
PDE5	phosphodiesterase type 5
PI	protease inhibitor
PK	pharmacokinetic
PMTCT	prevention of mother-to-child transmission
PO	by mouth
PPI	proton pump inhibitor
PR	protease (gene)
PT	prothrombin time
RAL	raltegravir
RT	reverse transcriptase (gene)
RT-PCR	reverse transcriptase-polymerase chain reaction
RTV	ritonavir
SJS	Stevens-Johnson syndrome
SPT	skin patch test
SQV	saquinavir
SQV/r	saquinavir/ritonavir or ritonavir-boosted saquinavir
STI	sexually transmitted infection
$t_{½}$	half-life

T-20	enfuvirtide
TAM	thymidine analogue mutation
TB	tuberculosis
TCA	tricyclic antidepressant
TDF	tenofovir disoproxil fumarate or tenofovir
TDM	therapeutic drug monitoring
TEN	toxic epidermal necrosis
TG	triglyceride
TID	three times a day
TPV	tipranavir
TPV/r	tipranavir/ritonavir or ritonavir-boosted tipranavir
TST	tuberculin skin test
UDP	uridine diphosphate
UGT1A1	uridine diphosphate glucuronosyltransferase 1A1
VPA	valproic acid
WBC	white blood cell
WHO	World Health Organization
WITS	Women and Infants Transmission Study
ZDV	zidovudine

Appendix B, Table 1. Characteristics of Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

(Updated January 10, 2011)

Generic Name (abbreviation)/ Trade Name	Formulations	Dosing Recommendations (For dosage adjustment in renal or hepatic insufficiency, see Appendix B, Table 7.)	Elimination	Serum/ Intracellular Half-lives	Adverse Events (Also see Table 13)
Abacavir (ABC)/ Ziagen **Also available as**:	Ziagen - 300-mg tablets - 20-mg/mL oral solution	Ziagen 300 mg BID or 600 mg once daily Take without regard to meals	Metabolized by alcohol dehydrogenase and glucuronyl transferase Renal excretion of metabolites 82% Dosage adjustment for ABC recommended in patients with hepatic insufficiency (See **Appendix B, Table 7**.)	1.5 hrs/ 12–26 hrs	• *Hypersensitivity reactions (HSR)*: Patients positive for HLA-B*5701 are at highest risk. HLA screening should be done prior to initiation of ABC. Rechallenge is not recommended. • Symptoms of HSR may include fever, rash, nausea, vomiting, diarrhea, abdominal pain, malaise, or fatigue or respiratory symptoms such as sore throat, cough, or shortness of breath. • Some cohort studies suggest increased risk of myocardial infarction (MI) with recent or current use of ABC, but this risk is not substantiated in other studies.
Trizivir ABC with ZDV+3TC	Trizivir ABC 300 mg + ZDV 300 mg + 3TC 150 mg	Trizivir 1 tablet BID			
Epzicom ABC with 3TC	Epzicom ABC 600 mg + 3TC 300 mg	Epzicom 1 tablet once daily			
Didanosine (ddI)/ Videx EC (generic available; dose same as Videx EC)	Videx EC 125-, 200-, 250-, 400-mg capsules Buffered tablets (non-EC) no longer available Videx 10-mg/mL oral solution	**Body weight ≥60kg**: 400 mg once daily* *With TDF*: 250 mg once daily **Body weight <60kg**: 250 mg once daily* *With TDF*: 200 mg once daily Take 1/2 hour before or 2 hours after a meal *Preferred dosing with oral solution is BID (total daily dose divided into 2 doses)	Renal excretion 50% Dosage adjustment in renal insufficiency recommended (See **Appendix B, Table 7**.)	1.5 hrs/ >20 hrs	• Pancreatitis • Peripheral neuropathy • Retinal changes, optic neuritis • Lactic acidosis with hepatic steatosis +/- pancreatitis (rare but potentially life-threatening toxicity) • Nausea, vomiting • Potential association with noncirrhotic portal hypertension, some cases presented with esophageal varices • One cohort study suggested increased risk of MI with recent or current use of ddI, but this risk is not substantiated in other studies. • Insulin resistance/diabetes mellitus
Emtricitabine (FTC)/ Emtriva **Also available as:**	Emtriva - 200-mg hard gelatin capsule - 10-mg/mL oral solution	Emtriva *Capsule*: 200 mg once daily *Oral solution*: 240 mg (24 mL) once daily Take without regard to meals	Renal excretion 86% Dosage adjustment in renal insufficiency recommended (See **Appendix B, Table 7**.)	10 hrs/ >20 hrs	• Minimal toxicity • Hyperpigmentation/skin discoloration • Severe acute exacerbation of hepatitis may occur in HBV-coinfected patients who discontinue FTC.
Atripla FTC with EFV+TDF	Atripla FTC 200 mg + EFV 600 mg + TDF 300 mg	Atripla 1 tablet at or before bedtime Take on an empty stomach to reduce side effects			
Truvada FTC with TDF	Truvada FTC 200 mg + TDF 300 mg	Truvada 1 tablet once daily			

Appendix B, Table 1. Characteristics of Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

Generic Name (abbreviation)/ Trade Name	Formulations	Dosing Recommendations (For dosage adjustment in renal or hepatic insufficiency, see Appendix B, Table 7.)	Elimination	Serum/ Intracellular Half-lives	Adverse Events (Also see Table 13)
Lamivudine (3TC)/ Epivir **Also available as:**	Epivir • 150-, 300-mg tablets • 10-mg/mL oral solution	Epivir 150 mg BID or 300 mg once daily Take without regard to meals	Renal excretion 70% Dosage adjustment in renal insufficiency recommended (See Appendix B, Table 7.)	5–7 hrs/ 18–22 hrs	• Minimal toxicity • Severe acute exacerbation of hepatitis may occur in HBV-coinfected patients who discontinue 3TC.
Combivir 3TC with ZDV	Combivir 3TC 150 mg + ZDV 300 mg	Combivir 1 tablet BID			
Epzicom 3TC with ABC	Epzicom 3TC 300 mg + ABC 600 mg	Epzicom 1 tablet once daily			
Trizivir 3TC with ZDV+ABC	Trizivir 3TC 150 mg + ZDV 300 mg + ABC 300 mg	Trizivir 1 tablet BID			
Stavudine (d4T)/ Zerit	Zerit • 15-, 20-, 30-, 40-mg capsules • 1-mg/mL oral solution	**Body weight ≥60 kg**: 40 mg BID **Body weight <60 kg**: 30 mg BID* Take without regard to meals *WHO recommends 30 mg BID dosing regardless of body weight.	Renal excretion 50% Dosage adjustment in renal insufficiency recommended (See Appendix B, Table 7.)	1 hr/ 7.5 hrs	• Peripheral neuropathy • Lipoatrophy • Pancreatitis • Lactic acidosis/severe hepatomegaly with hepatic steatosis (rare but potentially life-threatening toxicity) • Hyperlipidemia • Insulin resistance/diabetes mellitus • Rapidly progressive ascending neuromuscular weakness (rare)
Tenofovir Disoproxil Fumarate (TDF)/ Viread **Also available as:**	Viread 300-mg tablet	Viread 1 tablet once daily Take without regard to meals	Renal excretion Dosage adjustment in renal insufficiency recommended (See Appendix B, Table 7.)	17 hrs/ >60 hrs	• Renal insufficiency, Fanconi syndrome • Osteomalacia • Potential decrease in bone mineral density • Severe acute exacerbation of hepatitis may occur in HBV-coinfected patients who discontinue TDF. • Asthenia, headache, diarrhea, nausea, vomiting, and flatulence
Atripla TDF with EFV+FTC	Atripla TDF 300 mg + EFV 600 mg + FTC 200 mg	Atripla 1 tablet at or before bedtime Take on an empty stomach to reduce side effects			
Truvada TDF with FTC	Truvada TDF 300 mg + FTC 200 mg	Truvada 1 tablet once daily Take without regard to meals			
Zidovudine (ZDV)/ Retrovir (generic available; dose same as retrovir) **Also available as:**	Retrovir • 100-mg capsules • 300-mg tablets • 10-mg/mL intravenous solution • 10-mg/mL oral solution	Retrovir 300 mg BID or 200 mg TID Take without regard to meals	Metabolized to GAZT Renal excretion of GAZT Dosage adjustment in renal insufficiency recommended (See Appendix B, Table 7.)	1.1 hrs/ 7 hrs	• Bone marrow suppression: macrocytic anemia or neutropenia • Nausea, vomiting, headache, insomnia, asthenia • Nail pigmentation • Lactic acidosis/severe hepatomegaly with hepatic steatosis (rare but potentially life-threatening toxicity) • Hyperlipidemia • Insulin resistance/diabetes mellitus • Lipoatrophy • Myopathy
Combivir ZDV with 3TC	Combivir ZDV 300 mg + 3TC 150 mg	Combivir 1 tablet BID			
Trizivir ZDV with 3TC+ABC	Trizivir ZDV 300 mg + 3TC 150 mg + ABC 300 mg	Trizivir 1 tablet BID			

Appendix B, Table 2. Characteristics of Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) (Updated January 10, 2011)

Generic Name (abbreviation)/ Trade Name	Formulations	Dosing Recommendations (For dosage adjustment in renal or hepatic insufficiency, see Appendix B, Table 7.)	Elimination	Serum Half-life	Adverse Events (Also see Table 13)
Delavirdine (DLV)/ Rescriptor	100-, 200-mg tablets	400 mg TID (Four 100-mg tablets can be dispersed in >3 oz. of water to produce a slurry; 200-mg tablets should be taken as intact tablets.) Take without regard to meals Separate dose from antacids by 1 hour	CYP3A4 substrate and inhibitor; 51% excreted in urine (<5% unchanged) and 44% in feces	5.8 hrs	• Rash* • Increased transaminase levels • Nausea, headache
Efavirenz (EFV)/ Sustiva **Also available as**: Atripla EFV with FTC + TDF	• 50-, 200-mg capsules • 600-mg tablets Atripla EFV 600 mg + FTC 200 mg + TDF 300 mg	600 mg once daily at or before bedtime Take on an empty stomach to reduce side effects Atripla 1 tablet once daily at or before bedtime	Metabolized by CYPs 2B6 and 3A4 CYP3A4 mixed inducer/ inhibitor (more an inducer than an inhibitor)	40–55 hrs	• Rash* • Neuropsychiatric symptoms† • Increased transaminase levels • Hyperlipidemia • False-positive results reported with some cannabinoid and benzodiazepine screening assays • Teratogenic in nonhuman primates and potentially teratogenic in humans
Etravirine (ETR)/ Intelence	• 100-, 200-mg tablets	200 mg BID Take following a meal	CYP3A4, 2C9, and 2C19 substrate 3A4 inducer; 2C9 and 2C19 inhibitor	41 +/– 20 hrs	• Rash, including Stevens-Johnson syndrome* • Hypersensitivity reactions (HSRs) have been reported, characterized by rash, constitutional findings, and sometimes organ dysfunction, including hepatic failure • Nausea
Nevirapine (NVP)/ Viramune	• 200-mg tablets • 50-mg/5-mL oral suspension	200 mg once daily for 14 days (lead-in period); thereafter, 200 mg BID Take without regard to meals Repeat lead-in period if therapy is discontinued for >7 days In patients who develop mild to moderate rash without constitutional symptoms, continue lead-in period until rash resolves but no longer than 28 days total.	CYP450 substrate, inducer of 3A4 and 2B6; 80% excreted in urine (glucuronidated metabolites, <5% unchanged); 10% in feces	25–30 hrs	• Rash, including Stevens-Johnson syndrome* • Symptomatic hepatitis, including fatal hepatic necrosis, has been reported‡

* During clinical trials, NNRTI was discontinued because of rash among 7% of NVP-treated, 4.3% of DLV-treated, 1.7% of EFV-treated, and 2% of ETR-treated patients. Rare cases of Stevens-Johnson syndrome have been reported with all NNRTIs; the highest incidence was seen with NVP.

† Adverse events can include dizziness, somnolence, insomnia, abnormal dreams, confusion, abnormal thinking, impaired concentration, amnesia, agitation, depersonalization, hallucinations, and euphoria. Approximately 50% of patients receiving EFV may experience any of these symptoms. Symptoms usually subside spontaneously after 2–4 weeks, but may necessitate discontinuation of EFV in a small percentage of patients.

‡ Symptomatic, sometimes serious, and even fatal hepatic events (accompanied by rash in approximately 50% of cases) occur at significantly higher frequency in ARV-naïve female patients with pre-NVP CD4 counts >250 cells/mm^3 or in ARV-naïve male patients with pre-NVP CD4 counts >400 cells/mm^3. NVP should not be initiated in these patients unless the benefit clearly outweighs the risk. This toxicity has not been observed when NVP is given as single doses to mothers or infants for prevention of mother-to-child transmission of HIV.

Appendix B, Table 3. Characteristics of Protease Inhibitors (PIs) (Updated January 10, 2011)

Generic Name (abbreviation)/ Trade Name	Formulations	Dosing Recommendations (For dosage adjustment in hepatic insufficiency, see Appendix B, Table 7)	Elimination	Serum Half-life	Storage	Adverse Events (Also see Table 13)
Atazanavir (ATV)/ Reyataz	100-, 150-, 200-, 300-mg capsules	ARV-naïve patients: 400 mg once daily or (ATV 300 mg + RTV 100 mg) once daily With TDF or for ARV-experienced patients: (ATV 300 mg + RTV 100 mg) once daily With EFV in ARV-naïve patients: (ATV 400 mg + RTV 100 mg) once daily (For dosing recommendations with H_2 antagonists and proton pump inhibitor (PPIs), refer to Table 16a) Take with food	CYP3A4 inhibitor and substrate Dosage adjustment in hepatic insufficiency recommended (See Appendix B, Table 7.)	7 hrs	Room temperature (up to 25ºC or 77ºF)	• Indirect hyperbilirubinemia • PR interval prolongation: First degree symptomatic atrioventricular (AV) block reported. Use with caution in patients with underlying conduction defects or on concomitant medications that can cause PR prolongation. • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in patients with hemophilia • Nephrolithiasis • Skin rash (20%) • Serum transaminase elevations • Hyperlipidemia (especially with RTV boosting)
Darunavir (DRV)/ Prezista	75-, 150-, 300-, 400-, 600-mg tablets	ARV-naïve patients or ARV-experienced patients with no DRV mutations: (DRV 800 mg + RTV 100 mg) once daily ARV-experienced patients with at least one DRV mutation: (DRV 600 mg + RTV 100 mg) BID Unboosted DRV is **not** recommended Take with food	CYP3A4 inhibitor and substrate	15 hrs (when combined with RTV)	Room temperature (up to 25ºC or 77ºF)	• Skin rash (10%): DRV has a sulfonamide moiety; Stevens-Johnson syndrome and erythrema multiforme have been reported. • Hepatotoxicity • Diarrhea, nausea • Headache • Hyperlipidemia • Serum transaminase elevation • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in patients with hemophilia
Fosamprenavir (FPV)/ Lexiva (a prodrug of amprenavir [APV])	• 700-mg tablet • 50-mg/mL oral suspension	ARV-naïve patients: • FPV 1,400 mg BID or • (FPV 1,400 mg + RTV 100–200 mg) once daily or • (FPV 700 mg + RTV 100 mg) BID PI-experienced patients (once-daily dosing **not** recommended): • (FPV 700 mg + RTV 100 mg) BID With EFV: • (FPV 700 mg + RTV 100 mg) BID or • (FPV 1,400 mg + RTV 300 mg) once daily *Tablet*: Take without regard to meals (if not boosted with RTV tablet) *Suspension*: Take without food *FPV w/RTV tablet*: Take with meals	APV is a CYP3A4 substrate, inhibitor, and inducer Dosage adjustment in hepatic insufficiency recommended (See Appendix B, Table 7.)	7.7 hrs (APV)	Room temperature (up to 25ºC or 77ºF)	• Skin rash (12%–19%) – FPV has a sulfonamide moiety • Diarrhea, nausea, vomiting • Headache • Hyperlipidemia • Serum transaminase elevation • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in patients with hemophilia • Nephrolithiasis

Appendix B, Table 3. Characteristics of Protease Inhibitors (PIs)
Page 2 of 3

Generic Name (abbreviation)/ Trade Name	Formulations	Dosing Recommendations (For dosage adjustment in hepatic insufficiency, see Appendix B, Table 7)	Elimination	Serum Half-life	Storage	Adverse Events (Also see Table 13)
Indinavir (IDV)/ Crixivan	100-, 200-, 400-mg capsules	800 mg every 8 hrs Take 1 hour before or 2 hours after meals; may take with skim milk or low-fat meal With RTV: (IDV 800 mg + RTV 100–200 mg) BID Take without regard to meals	CYP3A4 inhibitor and substrate Dosage adjustment in hepatic insufficiency recommended (See Appendix B, Table 7.)	1.5–2 hrs	Room temperature (15º–30ºC/ 59º–86ºF) Protect from moisture	• Nephrolithiasis • GI intolerance, nausea • Hepatitis • Indirect hyperbilirubinemia • Hyperlipidemia • Headache, asthenia, blurred vision, dizziness, rash, metallic taste, thrombocytopenia, alopecia, and hemolytic anemia • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in patients with hemophilia
Lopinavir + Ritonavir (LPV/r)/ Kaletra	Tablets: (LPV 200 mg + RTV 50 mg) or (LPV 100 mg + RTV 25 mg) Oral solution: Each 5 mL contains (LPV 400 mg + RTV 100 mg) Oral solution contains 42% alcohol	LPV/r 400-mg/100-mg BID or LPV/r 800-mg/200-mg once daily Once-daily dosing is not recommended for patients with ≥3 LPV-associated mutations, pregnant women, or patients receiving EFV, NVP, FPV, NFV, carbamazepine, phenytoin, or phenobarbital. With EFV or NVP (PI-naïve or PI-experienced patients): LPV/r 500-mg/125-mg tablets BID (Use a combination of two LPV/r 200-mg/50-mg tablets + one LPV/r 100-mg/25-mg tablet to make a total dose of LPV/r 500 mg/125 mg.) or LPV/r 533-mg/133-mg oral solution BID *Tablet*: Take without regard to meals *Oral solution*: Take with food	CYP3A4 inhibitor and substrate	5–6 hrs	Oral tablet is stable at room temperature. Oral solution is stable at 2°–8°C (36°–46°F) until date on label and is stable when stored at room temperature (up to 25ºC or 77ºF) for 2 months.	• GI intolerance, nausea, vomiting, diarrhea • Pancreatitis • Asthenia • Hyperlipidemia (especially hypertriglyceridemia) • Serum transaminase elevation • Hyperglycemia • Insulin resistance/diabetes mellitus • Fat maldistribution • Possible increased bleeding episodes in patients with hemophilia • PR interval prolongation • QT interval prolongation and torsades de pointes have been reported; however, causality could not be established.
Nelfinavir (NFV)/ Viracept	• 250-, 625-mg tablets • 50-mg/g oral powder	1,250 mg BID or 750 mg TID May dissolve tablets in a small amount of water; once dissolved, patients should mix the cloudy liquid well and consume it immediately. Take with food	CYP2C19 and 3A4 substrate—metabolized to active M8 metabolite; CYP 3A4 inhibitor	3.5–5 hrs	Room temperature (15º–30ºC/ 59º–86ºF)	• Diarrhea • Hyperlipidemia • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in patients with hemophilia • Serum transaminase elevation

Appendix B, Table 3. Characteristics of Protease Inhibitors (PIs)
Page 3 of 3

Generic Name (abbreviation)/ Trade Name	Formulations	Dosing Recommendations (For dosage adjustment in hepatic insufficiency, see Appendix B, Table 7)	Elimination	Serum Half-life	Storage	Adverse Events (Also see Table 13)
Ritonavir (RTV)/ Norvir	• 100-mg soft gel capsules • 100-mg tablets • 80-mg/mL oral solution Oral solution contains 43% alcohol	As pharmacokinetic booster for other PIs: 100–400 mg per day in 1–2 divided doses (refer to other PIs for specific dosing recommendations) *Tablet*: Take with food *Capsule and oral solution*: Take with food, if possible, to improve tolerability.	CYP3A4 >2D6 substrate; potent 3A4, 2D6 inhibitor	3–5 hrs	Refrigerate capsules Capsules can be left at room temperature (up to 25ºC or 77ºF) for up to 30 days. Tablets do not require refrigeration. Oral solution should **not** be refrigerated; store at room temperature 20º–25ºC (68º–77ºF).	• GI intolerance, nausea, vomiting, diarrhea • Paresthesias—circumoral and extremities • Hyperlipidemia (especially hypertriglyceridemia) • Hepatitis • Asthenia • Taste perversion • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in patients with hemophilia
Saquinavir tablets and hard gel capsules (SQV)/ Invirase	• 500-mg tablets • 200-mg hard gel capsules	(SQV 1,000 mg + RTV 100 mg) BID Unboosted SQV is **not** recommended. Take with meals or within 2 hours after a meal	CYP3A4 inhibitor and substrate	1–2 hrs	Room temperature (15º–30ºC/ 59º–86ºF)	• GI intolerance, nausea, and diarrhea • Headache • Serum transaminase elevation • Hyperlipidemia • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in patients with hemophilia • PR interval prolongation • QT interval prolongation, torsades de pointes have been reported. Patients with pre-SQV QT interval >450 msec should not receive SQV (See Table 5b.).
Tipranavir (TPV)/ Aptivus	• 250-mg capsules • 100-mg/mL oral solution	(TPV 500 mg + RTV 200 mg) BID Unboosted TPV is **not** recommended. *TPV taken with RTV **tablets**:* Take with meals *TPV taken with RTV **capsules** or **solution**:* Take without regard to meals	Cytochrome P450 3A4 inducer and substrate Net effect when combined with RTV (CYP 3A4, 2D6 inhibitor)	6 hrs after single dose of TPV/r	Refrigerate capsules. Capsules can be stored at room temperature (25ºC or 77ºF) for up to 60 days. Oral solution should **not** be refrigerated or frozen and should be used within 60 days after opening the bottle.	• Hepatotoxicity: Clinical hepatitis (including hepatic decompensation and hepatitis-associated fatalities) has been reported; monitor closely, especially in patients with underlying liver diseases. • Skin rash (3%–21%): TPV has a sulfonamide moiety; use with caution in patients with known sulfonamide allergy. • Rare cases of fatal and nonfatal intracranial hemorrhages have been reported. Risks include brain lesion, head trauma, recent neurosurgery, coagulopathy, hypertension, alcoholism,, use of anti-coagulant or anti-platelet agents including vitamin E. • Hyperlipidemia • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in patients with hemophilia

Appendix B, Table 4. Characteristics of Integrase Inhibitor (Updated January 10, 2011)

Generic Name (abbreviation)/ Trade Name	Formulations	Dosing Recommendations (For dosage adjustment in hepatic insufficiency, see Appendix B, Table 7.)	Serum half-life	Route of Metabolism	Adverse Events (Also see Table 13)
Raltegravir (RAL)/ Isentress	400 mg tablets	400 mg BID With rifampin: 800 mg BID Take without regard to meals	~9 hrs	UGT1A1-mediated glucuronidation	• Nausea • Headache • Diarrhea • Pyrexia • CPK elevation, muscle weakness and rhabdomyolysis

Appendix B, Table 5. Characteristics of Fusion Inhibitor (Updated January 29, 2008)

Generic Name (abbreviation)/ Trade Name	Formulations	Dosing Recommendation	Serum half-life	Elimination	Storage	Adverse Events (Also see Table 13)
Enfuvirtide (T20)/ Fuzeon	• Injectable—supplied as lyophilized powder • Each vial contains 108 mg of T20; reconstitute with 1.1mL of sterile water for injection for delivery of approximately 90mg/1mL.	90 mg (1mL) subcutaneously BID	3.8 hrs	Expected to undergo catabolism to its constituent amino acids, with subsequent recycling of the amino acids in the body pool	Store at room temperature (up to 25ºC or 77ºF). Reconsti-tuted solution should be refrigerated at 2ºC–8ºC (36ºF–46Fº) and used within 24 hours.	• Local injection site reactions in almost 100% of patients (pain, erythema, induration, nodules and cysts, pruritus, ecchymosis) • Increased bacterial pneumonia • Hypersensitivity reaction (<1%): Symptoms may include rash, fever, nausea, vomiting, chills, rigors, hypotension, or elevated serum transaminases. Rechallenge is not recommended.

Appendix B, Table 6. Characteristics of CCR5 Antagonist (Updated January 29, 2008)

Generic Name (abbreviation)/ Trade Name	Formulation	Dosing Recommendations (For dosage adjustment in hepatic insufficiency, see Appendix B, Table 7.)	Serum Half-life	Elimination	Adverse Events (Also see Table 13)
Maraviroc (MVC)/ Selzentry	150-, 300-mg tablets	• **150 mg BID** when given with strong CYP3A inhibitors (with or without CYP3A inducers) including PIs (except TPV/r) • **300 mg BID** when given with NRTIs, T-20, TPV/r, NVP, RAL, and other drugs that are not strong CYP3A inhibitors or inducers • **600 mg BID** when given with CYP3A inducers, including EFV, ETR, etc. (without a CYP3A inhibitor) Take without regard to meals	14–18 hrs	CYP3A4 substrate	• Abdominal pain • Cough • Dizziness • Musculoskeletal symptoms • Pyrexia • Rash • Upper respiratory tract infections • Hepatotoxicity • Orthostatic hypotension

Appendix B, Table 7. Antiretroviral Dosing Recommendations in Patients with Renal or Hepatic Insufficiency (Updated January 10, 2011)

See reference section following tables for creatinine clearance (CrCl) calculation formulas and criteria for Child-Pugh classification.

Antiretrovirals Generic Name (abbreviation)/Trade Name	Usual Daily Dose (Refer to Appendix B Tables 1-6 for additional dosing information)	Dosing in Renal Insufficiency (Including with chronic ambulatory peritoneal dialysis [CAPD] and hemodialysis [HD])	Dosing in Hepatic Impairment
Nucleoside Reverse Transcriptase Inhibitors **Use of fixed-dose combination NRTI (+/- NNRTI) of Atripla, Combivir, Trizivir, or Epzicom is not recommended in patients with CrCl <50 mL/min. Use of Truvada is not recommended in patients with CrCl <30 mL/min.**			
Abacavir (ABC)/ Ziagen	300 mg PO BID	No dosage adjustment necessary	**Child-Pugh Score** — **Dose** 5–6 — 200 mg BID (use oral solution) > 6 — Contraindicated
Didanosine enteric coated (ddI)/ Videx EC	**Body weight ≥60 kg**: 400 mg PO once daily **Body weight <60 kg**: 250 mg PO once daily	**Dose (once daily)** **CrCl (mL/min)** — **≥60 kg** — **<60 kg** 30–59 — 200 mg — 125 mg 10–29 — 125 mg — 125 mg <10, HD, CAPD — 125 mg — use oral solution	No dosage adjustment necessary
Didanosine oral solution (ddI)/ Videx	**Body weight ≥60 kg**: 200 mg PO BID or 400 mg PO once daily **Body weight <60 kg**: 250 mg PO once daily or 125 mg PO BID	**Dose (once daily)** **CrCl (mL/min)** — **≥60 kg** — **<60 kg** 30–59 — 200 mg — 150 mg 10–29 — 150 mg — 100 mg <10, HD, CAPD — 100 mg — 75 mg	No dosage adjustment necessary
Emtricitabine (FTC)/ Emtriva	200mg oral capsule PO once daily; or 240 mg (24 mL) oral solution PO once daily	**Dose** **CrCl (mL/min)** — **Capsule** — **Solution** 30–49 — 200 mg q48h — 120 mg q24h 15–29 — 200 mg q72h — 80 mg q24h <15 or HD — 200 mg q96h — 60 mg q24h Take dose after HD session on dialysis days	No dosage recommendation
Lamivudine (3TC)/ Epivir	300 mg PO once daily; or 150 mg PO BID	**CrCl (mL/min)** — **Dose** 30–49 — 150 mg q24h 15–29 — 1 x 150 mg, then 100 mg q24h 5–14 — 1 x 150 mg, then 50 mg q24h <5 or HD — 1 x 50 mg, then 25 mg q24h Take dose after HD session on dialysis days	No dosage adjustment necessary
Stavudine (D4T)/ Zerit	**Body weight ≥60 kg**: 40 mg PO BID **Body weight <60 kg**: 30 mg PO BID	**Dose** **CrCl (mL/min)** — **≥60 kg** — **<60 kg** 26–50 — 20 mg q12h — 15 mg q12h 10–25 or HD — 20 mg q24h — 15 mg q24h Take dose after HD session on dialysis days	No dosage recommendation
Tenofovir (TDF)/ Viread	300 mg PO once daily	**CrCl (mL/min)** — **Dose** 30–49 — 300 mg q48h 10–29 — 300 mg twice weekly <10 not on HD — no recommendation HD — 300 mg q7d Take dose after HD session on dialysis days	No dosage adjustment necessary
Emtricitabine (FTC) + **Tenofovir** (TDF)/ Truvada	1 tablet PO once daily	**CrCl (mL/min)** — **Dose** 30–49 — 1 tablet q48h <30 or HD — not recommended	No dosage recommendation
Zidovudine (AZT, ZDV)/ Retrovir	300 mg PO BID	**CrCl (mL/min)** — **Dose** < 15 or HD — 100 mg TID or 300 mg once daily	No dosage recommendation

Appendix B, Table 7. Antiretroviral Dosing Recommendations in Patients with Renal or Hepatic Insufficiency

Antiretrovirals Generic Name (abbreviation)/ Trade Name	Daily Dose	Dosing in Renal Insufficiency (Including with chronic ambulatory peritoneal dialysis [CAPD] and hemodialysis [HD])	Dosing in Hepatic Impairment
Non-Nucleoside Reverse Transcriptase Inhibitors			
Delavirdine (DLV)/ Rescriptor	400 mg PO TID	No dosage adjustment necessary	No dosage recommendation; use with caution in patients with hepatic impairment
Efavirenz (EFV)/ Sustiva	600 mg PO at or before bedtime	No dosage adjustment necessary	No dosage recommendation; use with caution in patients with hepatic impairment
Efavirenz (EFV) + **Emtricitabine** (FTC) + **Tenofovir** (TDF)/ Atripla	1 tablet PO once daily	Atripla not recommended if CrCl <50 mL/min	
Etravirine (ETR)/ Intelence	200 mg PO BID	No dosage adjustment necessary	Child-Pugh Class A or B: no dosage adjustment Child-Pugh Class C: no dosage recommendation
Nevirapine (NVP)/ Viramune	200 mg PO BID	HD patients: limited data; no dosage recommendation	Child-Pugh Class B or C: contraindicated
Protease Inhibitors			
Atazanavir (ATV)/ Reyataz	400 mg PO once daily or (ATV 300 mg + RTV 100 mg) PO once daily	No dosage adjustment for patients with renal dysfunction not requiring HD ARV-naïve patients on HD: (ATV 300 mg + RTV 100 mg) once daily ARV-experienced patients on HD: ATV or RTV-boosted ATV not recommended	**Child-Pugh Score** **Dose** 7–9 300 mg once daily >9 not recommended RTV boosting is **not** recommended in patients with hepatic impairment (Child-Pugh Score ≥7).
Darunavir (DRV)/ Prezista	(DRV 800 mg + RTV 100 mg) PO once daily (ARV-naïve patients) or (DRV 600 mg + RTV 100 mg) PO BID	No dosage adjustment necessary	Mild to moderate hepatic impairment: no dosage adjustment Severe hepatic impairment: not recommended
Fosamprenavir (FPV)/ Lexiva	1,400 mg PO BID or (FPV 1,400 mg + RTV 100–200 mg) PO once daily or (FPV 700 mg + RTV 100 mg) PO BID	No dosage adjustment necessary	**Child-Pugh Score** **Dose** PI-naïve patients only: 5–9 700 mg BID 10–15 350 mg BID PI-naïve or PI-experienced patients: 5–6 700 mg BID + RTV 100 mg once daily 7–9 450 mg BID + RTV 100 mg once daily 10–15 300 mg BID + RTV 100 mg once daily
Indinavir (IDV)/ Crixivan	800 mg PO q8h	No dosage adjustment necessary	Mild to moderate hepatic insufficiency because of cirrhosis: 600 mg q8h
Lopinavir/ritonavir (LPV/r) Kaletra	400/100 mg PO BID or 800/200 mg PO once daily	Avoid once daily dosing in patients on HD	No dosage recommendation; use with caution in patients with hepatic impairment
Nelfinavir (NFV)/ Viracept	1,250 mg PO BID	No dosage adjustment necessary	Mild hepatic impairment: no dosage adjustment Moderate to severe hepatic impairment: do not use
Ritonavir (RTV)/ Norvir	As a PI-boosting agent: 100–400 mg per day	No dosage adjustment necessary	Refer to recommendations for the primary PI
Saquinavir (SQV)/ Invirase	(SQV 1,000 mg + RTV 100 mg) PO BID	No dosage adjustment necessary	Mild to moderate hepatic impairment: use with caution Severe hepatic impairment: contraindicated
Tipranavir (TPV)/ Aptivus	(TPV 500 mg + RTV 200 mg) PO BID	No dosage adjustment necessary	Child-Pugh Class A: use with caution Child-Pugh Class B or C: contraindicated

Appendix B, Table 7. Antiretroviral Dosing Recommendations in Patients with Renal or Hepatic Insufficiency

Antiretrovirals Generic Name (abbreviation)/ Trade Name	Daily Dose	Dosing in Renal Insufficiency	Dosing in Hepatic Impairment
Fusion Inhibitor			
Enfuvirtide (T20)/ Fuzeon	90 mg subcutaneous BID	No dosage adjustment necessary	No dosage adjustment necessary
CCR5 Antagonist			
Maraviroc (MVC)/ Selzentry	The recommended dose differs based on concomitant medications because of drug interactions. See **Appendix B, Table 6** for detailed dosing information.	**CrCl <30 mL/min or HD** Without potent CYP3A inhibitors or inducers: 300 mg BID; reduce to 150 mg BID if postural hypotension occurs With potent CYP3A inducers or inhibitors: not recommended	No dosage recommendations. Concentrations will likely be increased in patients with hepatic impairment.
Integrase Inhibitor			
Raltegravir (RAL)/ Isentress	400 mg BID	No dosage adjustment necessary	Mild to moderate hepatic insufficiency: no dosage adjustment necessary Severe hepatic insufficiency: no recommendation

Creatinine Clearance Calculation	
Male: $\frac{(140 - \text{age in years}) \times \text{weight (kg)}}{72 \times \text{Serum Creatinine}}$	Female: $\frac{(140 - \text{age in years}) \times \text{weight (kg)} \times 0.85}{72 \times \text{Serum Creatinine}}$

Child-Pugh Score			
Component	**Points Scored**		
	1	**2**	**3**
Encephalopathy*	None	Grade 1–2	Grade 3–4
Ascites	None	Mild or controlled by diuretics	Moderate or refractory despite diuretics
Albumin	>3.5 g/dL	2.8–3.5 g/dL	<2.8 g/dL
Total bilirubin or	<2 mg/dL (<34 μmol/L)	2–3 mg/dL (34 μmol/L to 50 μmol/L)	>3 mg/dL (>50 μmol/L)
Modified total bilirubin†	<4 mg/dL	4–7 mg/dL	>7 mg/dL
Prothrombin time (seconds prolonged) or	<4	4–6	>6
International normalized ratio (INR)	<1.7	1.7–2.3	>2.3

* Encephalopathy Grades
Grade 1: Mild confusion, anxiety, restlessness, fine tremor, slowed coordination
Grade 2: Drowsiness, disorientation, asterixis
Grade 3: Somnolent but rousable, marked confusion, incomprehensible speech, incontinence, hyperventilation
Grade 4: Coma, decerebrate posturing, flaccidity
† Modified total bilirubin used to score patients who have Gilbert's syndrome or who are taking indinavir or atazanavir

Child-Pugh Classification	Total Score*
Class A	5–6 points
Class B	7–9 points
Class C	>9 points

* Sum of points for each component

Draft United Kingdom National Guideline for the Diagnosis and Treatment of Gonorrhoea in Adults 2010 *v*5

Clinical Effectiveness Group, British Association of Sexual Health and HIV

Author and centre Chris Bignell, Consultant in Genitourinary Medicine, Nottingham University Hospitals NHS Trust

Editor Mark FitzGerald

Review Date 2015

Changes since 2005 Guideline

- Nucleic Acid amplification tests (NAATs) can be used for genital specimens but require supplementary testing if used in low prevalence areas.
- Dual testing for gonorrhoea and Chlamydia can be done using NAATs
- NAATs are more sensitive than culture in the rectum and pharynx but should be confirmed by a supplementary test
- Quinolones are no longer routinely recommended for treatment
- Indications for test of cure are clarified

DRAFT

Introduction

The main purpose of this guideline is to offer recommendations on the diagnosis, treatment and health promotion principles for the effective management of anogenital and pharyngeal gonorrhoea. It is aimed primarily at people aged 16 years and older presenting to services offering level 3 care in STI management within the United Kingdom. However, the principles of the recommendations could be adopted at all levels.

Editorial independence – this guideline was commissioned and edited by the Clinical Effectiveness Group (CEG) of the British Association for Sexual Health and HIV (BASHH). No external funding was sought or obtained.

Rigour of development – The CEG's framework for guideline development is outlined at bash.org/guidelines. This guideline has been updated by reviewing the previous guideline (2005) and medical literature since its publication. A MEDLINE search was done of published articles in any language for the years 2005-2009 using the subject headings *'gonorrhea'* and *'Neisseria gonorrheae'*. All enties in the English language or with abstracts in English were viewed because of the paucity of 'clinical trials' or 'reviews'. The Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effectiveness, and Cochrane Controlled Trials Register were reviewed using the textword 'gonorrhoea' and all entries considered. Abstracts from meetings in the relevant period were handsearched and considered. The draft guideline was appraised with the AGREE instrument, posted on the BASHH website for consultation for 3 months, and piloted in a sample of clinics.

Aetiology

Gonorrhoea is the condition of being infected with the Gram-negative diplococcus *Neisseria gonorrhoeae.* The primary sites of infection are the mucous membranes of the urethra, endocervix, rectum, pharynx and conjunctiva. Transmission is by direct inoculation of infected secretions from one mucous membrane to another.

Clinical features.

Symptoms. [1 - 3]
Men :

- urethral infection commonly causes urethral discharge (>80%) and/or dysuria (>50%), starting within 2-5 days of exposure.
- urethral infection can be asymptomatic (<10%).
- rectal infection is usually asymptomatic but may cause anal discharge (12%) or perianal/anal pain or discomfort (7%).
- pharyngeal infection is usually asymptomatic (>90%).

Women:

- infection at the endocervix is frequently asymptomatic (up to 50%).
- increased or altered vaginal discharge is the commonest symptom (up to 50%).
- lower abdominal pain may be present (up to 25%).
- urethral infection may cause dysuria (12%) but not frequency.
- gonorrhoea is a rare cause of intermenstrual bleeding or menorrhagia.
- rectal infection more frequently develops by transmucosal spread of infected genital secretions than from anal intercourse and is usually asymptomatic.
- pharyngeal infection is usually asymptomatic (>90%).

Neisseria gonorrhoeae may co-exist with other genital mucosal pathogens, notably *Chlamydia trachomatis, Trichomonas vaginalis,* and *Candida albicans* **.** If symptoms are present, they may be attributable to the co-infecting pathogen.

Signs. [1,2]
Men:

- a mucopurulent or purulent urethral discharge is commonly evident.
- rarely, epididymal tenderness/swelling or balanitis may be present.

DRAFT

Women:

- mucopurulent endocervical discharge and easily induced endocervical bleeding (<50%). [Note: mucopurulent endocervical discharge is not a sensitive predictor of cervical infection (<50%).]
- pelvic/lower abdominal tenderness (<5%).
- commonly, no abnormal findings are present on examination.

Complications.

Transluminal spread of *N. gonorrhoeae* from the urethra or endocervix may occur to cause epididymo-orchitis or prostatitis in men and pelvic inflammatory disease in women. Haematogenous dissemination may also occur from infected mucous membranes to cause skin lesions, arthralgia, arthritis and tenosynovitis. Disseminated gonoccal infection. There are no recent studies quantifying the risk of developing complicated gonococcal infection but reporting from GU Medicine clinics in the UK indicate they are uncommon [4].

Diagnosis

- This guideline should be read in conjunction with Health Protection Agency 'Guidance for Gonorrhoea Testing in England and Wales' and BASHH guidelines on /testing for STIs/ gonorrhoea [5,6].
- The diagnosis of gonorrhoea is established by the identification of *N. gonorrhoeae* at an infected site.
- The approach and method used to test for gonorrhoea will be influenced by the clinical setting, storage and transport system to the laboratory, local prevalence of infection and the range of tests available in the laboratory.
- No test for gonorrhoea offers 100% sensitivity and specificity [5,7,8,9].
- Microscopy (x1000) of Gram stained genital specimens allows direct visualization of *N. gonorrhoeae* as monomorphic Gram negative diplococci within polymorphonuclear leukocytes. It offers good sensitivity (90-95%) in men with urethral discharge and is recommended to facilitate immediate diagnosis in symptomatic men (level of evidence III; grade C recommendation). Microscopy of urethral smears in asymptomatic men is less sensitive (50-75%)[1]. In women, microscopy has poor sensitivity for the identification of gonoccal infection - 37-50% for endocervical smears and 20% for urethral smears [2]. Microscopy is not recommended for urethral smears in women or for detecting asymptomatic rectal infection because of low sensitivity (level of evidence III; grade C recommendation). Microscopy is not appropriate for diagnosing gonorrhoea in pharyngeal specimens.

- Specific identification of *N. gonorrhoeae* can be achieved by nucleic acid amplification tests (NAATs) or culture. NAATs are generally more sensitive than culture and offer testing on a wider range of specimen types [5,8-12,]. NAATs show high sensitivity (>96%) in both symptomatic and asymptomatic infection [10, 12]. They show equivalent sensitivity in urine and urethral swab specimens from men [13] and in vaginal and endocervical swabs from women [14]. The test sensitivity in female urine is significantly lower and urine is not a recommended specimen in women [5,12,15,] (level of evidence II; grade B recommendation).

DRAFT

- Persons undergoing testing for genital tract gonorrhoea are usually also tested for infection with *Chlamydia trachomatis*. NAATs are the standard test methodology for *C. trachomatis* testing and commercial tests offer dual capability to also test for *N. gonorrhoeae* on the same sample. When testing for genital tract infection, a dual NAAT for both pathogens maximizes sensitivity and operational ease of specimen collection, transport and processing.

- NAATs are significantly more sensitive than culture for detecting *N. gonorrhoeae* in the rectum and pharynx although are not yet approved for use at these sites [16-20]. Commercially available NAATs differ in their cross-reactivity to commensal *Neisseria* species which may be present at significant levels at these sites, particularly in the pharynx [21]. At present it is recommended that reactive specimens from the rectum and pharynx are confirmed by supplementary testing, ie using a different target (level of evidence III; grade C recommendation) [5,7,22].

- Culture continues to offer a specific, sensitive and cheap diagnostic test at genital sites. It allows confirmatory identification and antimicrobial susceptibility testing, which is of increasing importance as antimicrobial resistance to *N. gonorrhoeae* continues to evolve. Selective culture media containing antimicrobials are recommended to reduce contamination [23] (level of evidence II; grade B recommendation).

- Whatever the adopted testing approach, positive test results should give a positive predictive value of >90%. In areas of low gonorrhoea prevalence the use of NAATs may require supplementary testing [5,7,22]. Clinicians need to be familiar with the test performance of NAATs and be able to interpret results in their clinical setting [24,25].

<u>Specimen collection</u>.

Men:
A first pass urine is the preferred sample for NAAT testing [7,10,13,15]. Microscopy and culture require a urethral/meatal swab specimen. The collection and testing of rectal and pharyngeal swab specimens should be directed by sexual history, symptoms at these sites and also considered in men who receive oral-anal or digital-anal contact [26].

Women:
Vaginal or endocervical swab specimens are equally sensitive for detecting *N. gonorrhoeae* by NAAT testing [14]. Culture requires an endocervical and urethral swab specimen. Urine is a suboptimal sample for the detection of *N. gonorrhoeae* in women [5,7,9,12,15]. The collection and testing of rectal and pharyngeal swab specimens should be directed by sexual history, symptoms at these sites and also considered in women whose are sexual contacts of gonorrhoea.

- For culture, direct plating of genital samples and use of transport media with prompt laboratory plating both give acceptable results [22] (evidence level IV).

DRAFT

- Data is lacking on the sensitivity of a single set of tests to identify infection with *N. gonorrhoeae*. The use of a single endocervical or vulvovaginal sample will identify 90-95 % of women with gonococcal infection [2,27]. Women with *N. gonorrhoeae* infection often have infection at multiple sites [28]. A minority of MSM with gonorrhoea have infection at multiple sites and all exposed sites need sampling [18].
- To confidently exclude infection in patients who attend within three days of sexual contact, a second set of tests should be considered if epidemiological treatment with effective antimicrobial therapy is not given [29] (evidence level IV, recommendation level C). Conventionally this would be 14 days after contact.

Management.

General Advice.

- Patients should be given a detailed explanation of their condition with particular emphasis on the long-term implications for the health of themselves and their partner(s). This should be reinforced with clear and accurate written information (level of evidence IV; grade C recommendation).
- Patients should be advised to abstain from sexual intercourse until they and their partner(s) have completed treatment (level of evidence IV; grade C recommendation).

Further Investigation.

- Screening for coincident sexually transmitted infections should routinely be performed in patients with or at risk of gonorrhoea (evidence level III, recommendation level C).

Treatment.

Indications for therapy (level of evidence IV; grade C recommendation)

- Identification of intracellular Gram-negative diplococci on microscopy of a smear from the genital tract.
- a positive culture for *N. gonorrhoeae* from any site.
- a positive NAAT for *N. gonorrhoeae* from any site. Supplementary testing is recommended if positive predictive value of the test is < 90% [5,7,21].
- recent sexual partner (s) of confirmed cases of gonococcal infection,
- consider offering on epidemiological grounds following sexual assault.

Recommended treatments [30-38].

Uncomplicated anogenital infection in adults:

- Ceftriaxone 250mg IM as a single dose. (level of evidence 1b; grade A recommendation)
  or
- Cefixime 400mg oral as a single dose. (level of evidence 1b; grade A recommendation)
  or

DRAFT

- Spectinomycin* 2g IM as a single dose. (level of evidence 1b; grade A recommendation)

- *N. gonorrhoeae* has progressively acquired reduced sensitivity and resistance to many classes of antimicrobials. Published trials of gonorrhoea treatment reflect clinical efficacy in past eras of antimicrobial sensitivity. Surveillance data in the UK shows significant levels of *N. gonorrhoeae* resistance to penicillin (24% in 2007), tetracyclines (60% in 2007) and ciprofloxacin (28% in 2008)[39-41]. High-level azithromycin resistance (MIC >256 mg/L) was observed in 2007 in the UK [42]. In 2008, decreased susceptibility to cefixime (MIC ≥ 0.25mg/L) was observed at 1.5% and isolates with decreased susceptibility to ceftriaxone (MIC ≥ 0.125mg/L) were also identified[40]. Most resistant infections are acquired in the UK.
- The increasing recognition of multidrug resistant *N. gonorrhoeae* has been the driving force for the recommendation of extended spectrum cephalosporins as the preferred treatment of gonorrhea[43].
- Observations in Asia have raised serious concerns over the adequacy of the 400mg cefixime for the treatment of genital tract gonorrhoea. Repeated treatment failures have been reported with cefixime and other oral extended spectrum cephalosporins[43-44].

*Spectinomycin was not being manufactured in 2010 so may not be obtainable.

Alternative regimens

Clinicians using alternative regimens for the treatment of gonorrhoea are recommended to regularly review local and national trends in gonococcal antimicrobial resistance.

- Other single dose cephalosporin regimes, notably Cefotaxime 500mg IM as a single dose. (level of evidence Ib; grade A recommendation)
  or Cefoxitin 2g IM as a single dose plus probenecid* 1g oral.
  Alternative injectable or oral cephalosporins offer no advantage in terms of efficacy and pharmokinetics over ceftriaxone or cefixime [34].

- Cefpodoxime is an alternative oral third generation cephalosporin that as a single dose of 200mg oral is licensed for the treatment of uncomplicated gonorrhoea [45]. Published trial data are limited, but in view of its less favourable pharmokinetics than cefixime and suboptimal efficacy against pharyngeal infection, it should be used with caution at a dose of 400mg. (level of evidence II; grade C recommendation).

- Quinolones cannot generally be recommended for the treatment of gonorrhoea because of the high prevalence of quinolone resistance worldwide [40,41,46]. When an infection is known before

DRAFT

treatment to be quinolone sensitive ciprofloxacin 500mg oral as single dose or ofloxacin 400mg oral as single dose have proven efficacy (level of evidence Ib; grade A recommendation) [37,47].

- High dose azithromycin (2.0g as a single dose) has shown acceptable efficacy in clinical trials, but was associated with high gastrointestinal intolerance[48]. The clinical efficacy of azithromycin does not always correlate with *in-vitro* sensitivity testing [49-50] and high-level azithromycin resistance has been observed in the UK [42]. A single dose of azithromycin 1.0g is not recommended as treatment for gonorrhea (level of evidence II; grade C recommendation).

- The alternative treatment regimens listed do not comprise all effective treatment regimens, but reflect clinical practice in the UK.

DRAFT

Treatment of complicated infections

Gonococcal pelvic inflammatory disease (PID)

IM ceftriaxone 250 mg stat
Or
IM cefoxim 2g stat with oral Probenecid 1 g
followed by oral Doxycycline 100 mg bd plus Metronidazole 400 mg bd for 14 days
(see PID guidelines www.bashh.org.uk)

Gonococcal Epididymo-orchitis

IM Ceftriaxone 250 mg plus Doxycycline 100 mg bd for 10-14 days
(see Epididymoorchitis guideline www.bashh.org.uk)

Gonococcal Conjunctivitis

- Systemic antibiotic therapy as for genital infection
- Saline/water irrigation of eye as required (grade C recommendation)

Disseminated Gonococcal Infection (DGI) (grade C recommendation)

Ceftriaxone 1g IM or IV every 24 hours
Or
Cefotaxime 1 g IV every 8 hours
Or
Ciprofloxacin 500 mg IV every 12 hours
Or
Spectinomycin 2g IM every 12 hours

Therapy should continue for 7 days but may be switched 24-48 hours after symptoms improve to one of the following oral regimes:

Ciprofloxacin 500 mg twice daily
Or
Ofloxacin 400 mg twice daily
Or
Cefixime 400 mg twice daily

Allergy.

Third-generation cephalosporins show negligible cross-allergy with penicillins [51]. Contraindications to the administration of ceftriaxone are hypersensitivity to any cephalosporin or previous immediate and/or severe hypersensitivity reaction to a penicillin or other beta-lactam drug [52]. Recommended treatments for patients giving a history of such hypersensitivity:

- Spectinomycin* 2g IM as a single dose (level of evidence Ib; grade A recommendation). May not be obtainable (see above)

or

- Azithromycin 2.0g as a single oral dose (level of evidence Ib; grade B recommendation)

or

- Ciprofloxacin 500mg orally as a single dose when the infection is known or anticipated to be quinolone sensitive.

Pregnancy and Breastfeeding.

Pregnant and breast-feeding women should not be treated with quinolone or tetracycline antimicrobials.
Azithromycin: manufacturer advises use only if adequate alternatives are not available.
Pregnancy does not diminish treatment efficacy.

Recommended Regimes [53-55]

- Ceftriaxone 250mg IM as a single dose. (level of evidence Ib; grade A recommendation)

or

- Cefixime 400mg oral as a single dose. (level of evidence Ib;grade A recommendation)

or

- Spectinomycin* 2g IM as a single dose. (level of evidence Ib; grade A recommendation).

Pharyngeal infection.

DRAFT

Single-dose antimicrobials treatments have in general demonstrated lower efficacy (≤ 90%) in eradicating *N. gonorrhoeae* from the pharynx than in eradicating genital infection[31,56].

Recommended treatments [31,56]

- Ceftriaxone 250mg IM as a single dose (level of evidence Ib; grade B recommendation)

or

- Ciprofloxacin 500mg orally as a single dose if *N. gonorrhoeae* known to be quinolone sensitive (level of evidence Ib; grade B recommendation)

or

- Ofloxacin 400mg orally as a single dose if *N. gonorrhoeae* known to be quinolone sensitive. (level of evidence Ib; grade B recommendation).

Single dose treatment with spectinomycin has poor efficacy in eradicating gonococcal infection of the pharynx [31].

HIV Infection

Treatment for gonorrhoea in HIV infected individuals is the same as in those who are HIV negative

Co-infection with *Chlamydia trachomatis*

Genital infection with *C. trachomatis* commonly accompanies genital gonococcal infection (35% of heterosexual men and 41% of women with gonorrhea, GRASP 2008) [40]. Testing for *C. trachomatis* should routinely be performed on all adults with gonorrhoea or treatment given to eradicate possible co-infection [29,38] (level of evidence IV; grade C recommendation).

Sexual partners.

Partner notification should be pursued in all patients identified with gonococcal infection, preferably by a trained health adviser in GU Medicine. Action and outcomes should be documented[57]. Partner notification should follow national recommendations[58]:

- Male patients with symptomatic urethral infection should notify all partners with whom they had sexual contact within the preceding 2 weeks or their last partner if longer ago.
- Patients with infection at other sites or asymptomatic infection should notify all partners within the preceding 3 months.

Sex partners should be offered testing and treated epidemiologically for gonorrhoea (level of evidence IV; recommendation level C).

Follow up and test of cure.

Assessment after treatment may be helpful (level of evidence IV; grade C recommendation):

- to confirm compliance with treatment,

DRAFT

- to ensure resolution of symptoms,
- to enquire about adverse reactions,
- to take a sexual history to explore the possibility of re-infection,
- to pursue partner notification and health promotion.

A test of cure is not routinely necessary for anogenital infection if a recommended treatment has been administered [59-60]. Indications for test of cure include (level of evidence IV; grade C recommendation):

- Persistence of symptoms
- Re-exposure to infection
- When there is possible antimicrobial resistance to the therapy given
- Pharyngeal infection

If symptoms or signs persist after treatment, test of cure with culture is recommended to test for antimicrobial resistance.
(evidence level IV, recommendation C).
All treatments are less effective at eradicating pharyngeal infection [56] and test of cure is recommended following treatment of infection at this site (Level of evidence III; recommendation C).
If a test of cure is performed, culture tests should be performed at least 72 hours after completion of antimicrobial therapy [23] There is currently insufficient evidence to determine the best time to conduct a test of cure with NAAT's, but 3 weeks seems reasonable[61].
Infection identified after treatment more commonly indicates reinfection rather than treatment failure [3,60].

Auditable Outcome Measures

- All patients with gonorrhoea should be screened for genital infection with *Chlamydia trachomatis* or receive presumptive treatment for this infection.

- All patients identified with gonorrhoea should have at least one documented interview with a health adviser in GU Medicine or other health professional trained in partner notification and their action documented.

- All patients identified with gonorrhoea should have a record made of the outcome of the agreed contact action.

- All patients identified with gonorrhoea should be offered written information about sexually transmitted infections and their prevention.

- For every case of gonorrhoea the number of sexual contacts whose attendance was verified by a healthcare worker, within four weeks of the date of the first partner notification interview, should be at least 0.6. In some large cities this may be unachievable and a lower rate may need to be determined locally. [62-63]

DRAFT

Organisational and Financial Considerations

Whilst the treatments recommended differ in price, the importance of achieving a cure is so great that cost should not be a factor in chosing the most effective agent.

In some clinics, staffing levels and facilities may preclude the use of injectable antibiotics.

Qualifying statement

Decisions to follow these recommendations must be based on professional clinical judgement, consideration of individual patient circumstances and available resources. All possible care has been undertaken to ensure specification of the correct dosage of medication and route of administration. However, it remains the responsibility of the prescribing clinician to ensure the accuracy and appropriateness of the medication they prescribe.

Acknowledgments.

We wish to thank the following for their valuable contributions to this Guideline: members of the CEG, Cathy Ison, members of the National Audit Group, and the members of BASHH who made comments during the web-based consultation.

Author and Centre.

Chris Bignell, Consultant in Genitourinary Medicine
Nottingham University Hospitals NHS Trust

Editor Mark FitzGerald, Taunton & Somerset NHS Foundation Trust

Membership of the CEG.

Clinical Effectiveness Group: Chairman, Keith Radcliffe; David Daniels (BASHH National Audit Group); Mark FitzGerald; Margaret Kingston; Neil Lazaro; Gill McCarthy; Ann Sullivan (all are specialist doctors in genitourinary medicine)

Conflict of Interest.

None.

References.

1. Sherrard J, Barlow D. Gonorrhoea in men: clinical and diagnostic aspects. Genitourin Med 1996; **72:** 422-426.

2. Barlow D, Phillips I. Gonorrhoea in women: diagnostic, clinical and laboratory aspects. Lancet 1978; **i:** 761-764.

3. Lewis DA, Bond M, Butt KD, Smith CP, Shafi MS, Murphy SM. A one-year survey of gonococcal infection seen in the genitourinary medicine department of a London district general hospital. Int J STD AIDS 1999; **10**: 588-594.

4. Health Protection Agency. All new STI episodes seen at GUM clinics in the UK: 1999-2008. http://www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1215589014474 (accessed 10 Feb 2010).

DRAFT

5. Department of Health, Health Protection Agency and BASHH Feb 2010Guidance for gonorrhea testing in England and Wales. http://www.bashh.org/news/478_2010-hpa-guidance-on-gonorrhoea-testing.To be published at www.hpa.org.uk

6. Sexually Transmitted Infections: UK National Screening and Testing Guidelines. http://www.bashh.org/documents/59/59.pdf (under revision February 2010).

7. Whiley DM, Garland SM, Harnett G, Lum G, Smith DW, Tabrizi SN, et al. Exploring 'best practice' for nucleic acid detection of *Neisseria gonorrhoeae*. Sexual Health 2008; 5: 17-23.

8. Van Dyck E, Ieven M, Pattyn S, Van Damme L, Laga M. Detection of *Chlamydia trachomatis* and *Neisseria gonorrhoeae* by enzyme immunoassay, culture and three nucleic acid amplification tests. J Clin Microbiol 2001; **39**: 1751-1756.

9. Cook RL, Hutchison SL, Østergaard L, Braithwaite RS, Ness RB. Systematic Review: Non-invasive testing for *Chlamydia trachomatis* and *Neisseria goorrhoeaea.* Ann Intern Med 2005; **142**: 914-925.

10. Martin DH, Cammarata C, Van der Pol B, Jones RB, Quinn TC, Gaydos CA, et al. Multicenter evaluation of AMPLICOR and Automated COBAS AMPLICOR CT/NG tests for *Neiserria gonorrhoeae*. J Clin Microbiol 2000; 38: 3544-3549.

11. Moncada J, Schachter J, Hook EW, Ferrero D, Gaydos C, Quinn T, et al. The effect of urine testing in evaluations of the sensitivity of the Gen-Probe APTIMA Combo 2 Assay on endocervical swabs for *Chlamydia trachomatis* and *Neisseria gonorrhoeae*. Sex Trans Dis 2004; 31: 273-277.

12. Van der Pol B, Ferrero DV, Buck-Barrington L. Hook EIII, Lenderman C, Quinn TC, et al. Multicenter evaluation of the BDProbeTec ET system for detection of *Chlamydia trachomatis* and *Neisseria gonorrhoeae* in urine specimens, female endocervical and male urethral swabs. J Clin Microbiol 2001; 39: 1008-1016.

13. Chernesky MA, Martin DH, Hook EW, Willis D, Jordan J, Wang S, et al. Ability of new APTIMA CT and APTIMA GC Assays to detect *Chlamydia trachomatis* and *Neisseria gonorrhoeae* in male urine and urethral swabs. J Clin Microbiol 2005; 43: 127-131.

14. Schachter J, Chernesky MA, Willis DE, Fine PM, Martin DH, Fuller D,et al. Vaginal swabs are the specimens of choice when screening for *Chlamydia trachomatis* and *Neisseria gonorrhoeae*: results from a multicenter evaluation of the APTIMA assays for both infections. Sex Trans Dis 2005; 32: 725-728.

DRAFT

15. Association of Public Health Laboratories. Laboratory diagnostic testing for *Chlamydia trachomatis* and *Neisseria gonorrhoeae*. Expert Consultation Meeting Summary Report; January 13-15, 2009; Atlanta, GA. Silver Spring, MD: Association of Public Health Laboratories; 2009. Available at http://www.aphl.org/aphlprograms/infectious/std/documents/ctgclabguidelinesmeetingreport.pdf.

16. Schachter J, Moncada J, Liska S, Shayevich C, Klausner JD. Nucleic Acid Amplification Tests in the Diagnosis of Chlamydial and Gonococcal Infections in the Oropharynx and Rectum in Men Who Have Sex With Men. Sex Trans Dis 2008; 35: 637-642.

17. Ota KV, Tamari IE, Smieja M, Jamieson F, Jones KE, Towns L, et al. Detection of *Neisseria gonorrhoeae* and *Chlamydia trachomatis* in pharyngeal and rectal specimens using the BD Probetec ET system, the Gen-Probe Aptima Combo 2 assay and culture. Sex Trans Infect 2009; 85: 182-186.

18. Benn PD, Rooney G, Carder C, Brown M, Stevenson SR, Copas A, et al. *Chlamydia trachomatis* and *Neisseria gonorrhoeae* infection and the sexual behaviour of men who have sex with men. Sex Trans Infect 2007; 83: 106-112.

19. Page-Shafer K, Graves A, Kent C, Bals JE, Zapitz VM, Klausner JD. Increased sensitivity of DNA amplification testing for the detection of pharyngeal gonrrhoea in men who have sex with men. Clinical Infectious Diseases 2002; **34**: 173-176.

20. Alexander S. The challenges of detecting gonorrhoea and chlamydia in rectal and pharyngeal sites: could we, should we, be doing more? Sex Trans Infect 2009; 85: 159-160.

21. Palmer H, Mallinson H, Wood RL, Herring AJ. Evaluation of the specificities of five DNA amplification methods for the detection of *Neisseria gonorrhoeae*. J Clin Microbiol 2003; **41**: 835-837.

22. Health Protection Agency (2010). Detection of *Neisseria gonorrhoeae* using molecular methods. National Standard Method QSOP 62 Issue1. (http://www.hpa-standardmethods.org.uk/documents/qsop/pdf/qsop62.pdf)

23. Jephcott AE. Microbiological diagnosis of gonorrhoea. Genitourin Med 1997; **73:** 245-252.

24. Katz AR, Effler PV, Ohye RG, et al. False-positive gonorrhoea test results with a nucleic amplification test: the impact of low prevalence on positive predictive value. Clin Infect Dis 2004; 38: 814-819.

25. McNally LP, Templeton DJ, Jin F, Grulich AE, Donovan B, Whiley DM, et al. Low positive predictive value of a nucleic acid amplification test for nongenital *Neisseria gonorrhoeae* infection in homosexual men. Clin Infect Dis 2008 Jul 15;47(2):e25-e27.

DRAFT

26. Jin F, Prestage GP, Mao L, Kippax SC, Pell CM, Donovan B, et al. Incidence and risk factors for urethral and anal gonorrhoea and Chlamydia in a cohort of HIV-negative homosexual men: the Health in Men study. Sex Trans Infect 2007; 83: 113-119.

27. Ghanem M, Radcliffe K, Allan P. The role of urethral samples in the diagnosis of gonorrhoea in women. Int J STD AIDS 2004; **15**: 45-47.

28. Lavelle SJ, Jones KE, Mallinson H, Webb AMC. Finding, confirming, and managing gonorrhea in a population screened for Chlamydia using the Gen-Probe Aptima Combo2 assay. Sex Trans Infect 2006; 82: 221-224.

29. FitzGerald M, Bedford C. National standards for the management of gonorrhoea. Int J STD AIDS 1996; **7**: 298-300.

30. Newman LM, Moran JS, Workowski KA. Update on the Management of Gonorrhoea in Adults in the United States. Clin Infect Dis 2007; **44**: S84-101.

31. Moran JS, Levine WC. Drugs of choice for the treatment of uncomplicated gonococcal infections. Clin Infect Dis 1995; **20** (suppl 1): S47-65.

32. Moran JS, Zenilman JM. Therapy for gonoccocal infections: options in 1989. Rev Infect Dis 1990; **12** (suppl 6): S633-644.

33. Tapsall J. Current concepts in the management of gonorrhea. Expert Opin Pharmacother. 2002; 3: 147-157.

34. Ison CA, Mouton JW, Jones K, Fenton KA, Livermore DA. Which cephalosporin for gonorrhoea? Sex Transm Infect 2004; **80**: 386-388.

35. Korting HC, Kollman M. Effective single dose treatment of uncomplicated gonorrhoea. Int J of STD AIDS 1994; **5:** 239-243.

36. Bignell CJ. Antibiotic treatment of gonorrhoea - clinical evidence for choice. Genitourin Med 1996; **72:** 315-320.

37. Echols RM, Heyd A, O' Keeffe BJ, Schacht P. Single-dose ciprofloxacin for the treatment of uncomplicated gonorrhoea: a worldwide summary. Sex Trans Dis 1994; **21:** 345-352.

38. Centers for Disease Control and Prevention. Sexually Transmitted Diseases Treatment Guidelines 2006. MMWR 2006; **55** (No. RR-11): 42-49. (www.cdc.gov/std/treatment).

39. Health Protection Agency. Gonococcal Resistance to Antimicrobial Surveillance Programme(GRASP) Year 2007 Report . http://www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1221117895841 (accessed 10/02/2010).

DRAFT

40. Health Protection Agency. Gonococcal Resistance to Antimicrobial Surveillance Programme(GRASP) 2008 Report: Trends in Antimicrobial Resistant Gonorrhoea. June 2009. http://www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1245914960426 (accessed 10/02/2010).

41. Martin IMC, Hoffman S, Ison CA. European Surveillance of Sexually Transmitted Infections (ESSTI): the first combined antimicrobial susceptibility data for *Neisseria gonorrhoeae* in Western Europe. 2006; J Antimicrob Chemother; 58: 587-593.

42. Chisholm SA, Neal TJ, Alawattagama AB, Birley HDL, Howe RA, Ison CA. Emergence of high-level azithromycin resistance in Neisseria gonorrhoeae in England and Wales. J Antimicrob Chemother 2009; 64: 353-8.

43. Tapsall JW, Ndowa F, Lewis DA, Unemo M. Meeting the public health challenge of multidrug- and extensively drug-resistant Neisseria gonorrhoeae. Expert Rev Anti Infect Ther 2009; 7: 821-834.

44. Lo JYC, Ho KM, Leung AOC, Tiu FST, Tsang GKL, Lo ACT, Tapsall JW. Ceftibuten resistance and treatment failure of Neisseria gonorrhoeae infection. Antimicro Agents Chemother 2008; 52: 3564-3567.

45. Novak E, Paxton LM, Tubbs HJ, Turner LF, Keck CW, Yatsu J. Orally administered cefpodoxime proxetil for the treatment of uncomplicated gonococcal urethritis in males: a dose –response study. Antimicrob Agents Chemther 1992; **36**: 1764-1765.

46. Tapsall JW. Antibiotic resistance in *Neisseria gonorrhoeae*. Clin Infect Dis 2005; 41: S263-8.

47. Moran JS. Ciprofloxacin for gonorrhea - 250mg or 500mg? Sex Trans Dis 1996; **23:** 165-167.

48. Handsfield HH, Dalu ZA, Martin DH, et al. Multicenter trial of single-dose azithromycin vs ceftriaxone in the treatment of uncomplicated gonorrhoea. Sex Trans Dis 1994; **21**: 107-111.

49. Young H, Moyes A, McMillan A. Azithromycin and erythromycin resistant *Neisseria gonorrhoeae* following treatment with azithromycin. Int J STD AIDS 1997; **8**: 299-302.

50. Tapsall JW, Schultz TR, Limnios EA, Donovan B, Lum G, Mulhall BP. Failure of azithromycin therapy in gonorrhoea and discorrelation with laboratory parameters. Sex Trans Dis 1998; **25**:505-508.

51. Pichichero ME, Casey JR. Safe use of selected cephalosporins in penicillin-allergic patients: A meta-analysis. Otolaryngology-Head and Neck Surgery (2007); 136: 340-347.

DRAFT

52. Roche Products Limited. SPC Rocephin. October 2009. http://emc.medicines.org.uk/medicine/1729/SPC/Rocephin+250mg,+1g+and+2g+vials/ (accessed 05/03/2010).

53. Brocklehurst P. Antibiotics for gonorrhea in pregnancy. Cochrane Database of Systematic Reviews 2002, Issue 2. Art. No. CD000098. DOI: 10.1002/14651858. CD000098..

54. Cavenee MR, Farris JR, Spalding TR, Barnes DL, Castaneda YS, Wendel GD. Treatment of gonorrhea in pregnancy. Obstet Gynecol 1993; **81:** 33-38.

55. Ramus RM, Sheffield JS, Mayfield JA, Wendel GD. A randomised trial that compared oral cefixime and intramuscular ceftriaxone for the treatment of gonorrhoea in pregnancy. Am J Obstet Gynecol 2001;**185**:629-32.

56. Moran JS. Treating uncomplicated Neisseria gonorrhoeae infections: is the anatomic site of infection important? Sex Trans Dis 1995; **22:** 39-47.

57. Fitzgerald M, Thirlby D, Bell G, Bedford C. National standards for contact tracing in gonorrhoea. Int J STD AIDS 1996; **7**: 301.

58. Society for Sexual Health Advisers. The SSHA manual for sexual health advisers. 2004. Available at http://www.ssha.info/resources/manual-for-sexual-health-advisers/ (accessed 27 Feb 2010).

59. Holland TM, Hussey J, Pattman RS, Sankar KN, Faldon CM. Audit of gonorrhoea test of cure at the genitourinary medicine department in Newcastle upon Tyne, UK. Int J STD AIDS 2003; **14**: 630-631.

60. Komolafe AJ, Sugunendran H, Corkill JE. Gonorrhoea: test of cure for sensitive bacteria? Use of genotyping to disprove treatment failure. Int J STD AIDS 2004; **15**: 212.

61. Bachmann LH, Desmond RA, Stephens J, Hughes A, Hook EW 3rd. Duration of persistence of gonococcal DNA detected by ligase chain reaction in men and women following recommended therapy for uncomplicated gonorrhoea. J Clin Microbiol 2002; **40**: 3596-601.

62. Low N, Welch J, Radcliffe K. Developing national outcome standards for the management of gonorrhoea and genital chlamydia in genitourinary medicine clinics. Sex Transm Infect 2004; **80**: 223-229.

63. Standards for the management of sexually transmitted infections (STIs). Published by Medical Foundation for AIDS & Sexual Health (MedFASH) 2010. http://www.medfash.org.uk/Projects/BASHH%20standards/Final%20pdfs/Standards_for_the_management_of_STIs.pdf (accessed 05/03/2010).

DRAFT

Gonorrhoea patient information leaflet

British Association for Sexual Health and HIV 2010

Gonorrhoea - the basics

- It is a curable sexually transmitted infection (STI) caused by the bacterium *Neisseria gonorrhoeae.*
- Gonorrhoea can infect the cervix (neck of womb), urethra (water passage) the uterus (womb), fallopian tubes, ovaries, testicles, rectum (anus), throat and sometimes the eyes.
- Men commonly notice a discharge from the tip of the penis but most women will not notice anything wrong.
- Prompt treatment is recommended to prevent more serious problems:
    - In women the spread of infection to the reproductive organs may lead to infertility
    - In men the spread of infection to the testicles leading to pain and swelling.
- Testing is available at any specialised sexual health or Genitourinary Medicine (GUM) clinic, and in some GP surgeries and contraceptive services.
- Gonorrhoea is resistant to many commonly used antibiotics. You need to be tested in a specialised sexual health service to ensure you receive the correct treatment.
- If you have gonorrhoea we recommend that you should have routine tests for other sexually transmitted infections including chlamydia, trichomonas, syphilis and HIV.

How common is gonorrhoea?

- It is the second most common bacterial STI in the UK.
- It is found most frequently in young people under the age of 25 years, in men who have sex with men and in people living in large cities.

How do you catch gonorrhoea?

- Gonorrhoea is passed on through:
    - unprotected vaginal, anal or oral sex (or sharing sex toys) with someone that has gonorrhoea
    - from an infected mother to her baby at birth
    - sometimes from genitals to fingers to eyes where it may cause an eye infection (conjunctivitis)
- Gonorrhoea cannot be caught by kissing, or from swimming pools, saunas or toilet seats.

What would I notice if I had gonorrhoea?

- **Women** may not notice anything wrong but they can still pass the infection onto their partner.
    - Infection usually starts in the cervix (neck of the womb) and can then spread internally to the uterus (womb), fallopian tubes and ovaries. Some women may notice one or more of the following:
        - bleeding between periods or after sex
        - lower abdominal pain particularly during sex
        - 'cystitis' or burning pain when passing urine
        - increased vaginal discharge
- **Men** will usually notice:
    - a discharge from the tip of the penis
    - a burning pain when passing urine
- Symptoms in men usually appear within 2-5 days of catching the infection.
- Infections in the throat or rectum usually go unnoticed**.**

How do I get tested for gonorrhoea?

- In **women**
    - If you have symptoms it is best if a swab is taken from the cervix (neck of the womb) by a doctor or nurse during an internal examination
    - If you do not have symptoms a self-taken swab can be taken from the entrance to the vagina

DRAFT

- In **men**
    - If you have a discharge a doctor or nurse will take a swab from the tip of the penis
    - If you do not have any symptoms a urine sample will be collected – but you should not have passed urine for at least a 1 hour
- Occasionally swabs may also be taken from the throat, rectum and eye.
- Some results for gonorrhoea may be available during your first visit (by looking at the samples under a microscope).
- You will be informed about how you will receive your final results before leaving the clinic.

How is gonorrhoea treated?

- Gonorrhoea can be easily treated with a single dose of an antibiotic – either by mouth or by injection.
- Occasionally a second course of antibiotics are needed if your symptoms don't go away or you are found to have a resistant strain of gonorrhoea.
- Treatment for chlamydia is commonly prescribed at the same time as up to 40% of people will also be infected with chlamydia.
- All treatments from sexual health clinics are free and are given to you in the clinic.

Important information about your treatment

- The antibiotics are highly effective - but you need to wait 7 days before having sex again to give the antibiotics time to work.
- The antibiotics may interfere with your contraceptive pill, ring or patch and make it less effective – the doctor or nurse will advise you what to do. (The implant, coil and Depo Provera injection are not effected)

What about my partner?

- Gonorrhoea is a sexually transmitted infection so it is likely that your current partner has it too.
- It is important that all current sexual partners attend a sexual health clinic to be tested and treated before resuming sex again.
- The clinic can contact your partners anonymously for you if you wish.
- Some of your previous partners may also need treatment – you will be advised about this.

When can I have sex again?

- You must not have sex again both you and your partner have taken your treatment and waited 7 days (this includes oral sex and sex with condoms).
- Sometimes you may be advised to have another test to check the gonorrhoea has gone completely – in this case it is important not to have sex until you receive your final result.

What happens if my gonorrhoea is left untreated?

- In **women:**
    - Gonorrhoea may spread internally from the cervix (neck of the womb) to the uterus (womb), and then up into the fallopian tubes and ovaries leading to pelvic infection and pain – a condition called Pelvic Inflammatory Disease (PID) (LINK to PID)
    - PID can lead to scarring of the fallopian tubes and ectopic pregnancy and/or infertility.
- In **men:**
    - Gonorrhoea can spread from the urethra (water passage) to the testicles and cause pain. Very rarely this may affect fertility.
- In both men and women gonorrhoea can spread to the blood (septicaemia) or joints and lead to serious infection.
- All these problems can be prevented by early treatment.

Can you catch gonorrhoea again?

DRAFT

- Yes you can.
- To prevent this ensure your partners have been treated before having sex with them again.
- Protect your self with new partners by ensuring a condom is used for all vaginal/ anal/ oral contact.

Or

- Ensure that both you and a new partner have a sexual health screen **before** any unprotected sex.

Gonorrhoea in pregnancy

- Gonorrhoea can occur in pregnant women and it is important that it is treated properly to prevent infection in the baby.
- The tests and treatment are similar to that outlined above – your doctor will discuss things in more detail with you.

For more information

www.bashh.org
http://www.nhs.uk/Livewell/STIs/Pages/STIs-hub.aspx

DRAFT

MMWR™

Morbidity and Mortality Weekly Report

Recommendations and Reports | September 30, 2005 / Vol. 54 / No. RR-9

Updated U.S. Public Health Service Guidelines for the Management of Occupational Exposures to HIV and Recommendations for Postexposure Prophylaxis

INSIDE: Continuing Education Examination

DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTERS FOR DISEASE CONTROL AND PREVENTION

The *MMWR* series of publications is published by the Coordinating Center for Health Information and Service, Centers for Disease Control and Prevention (CDC), U.S. Department of Health and Human Services, Atlanta, GA 30333.

SUGGESTED CITATION

Centers for Disease Control and Prevention. Updated U.S. Public Health Service guidelines for the management of occupational exposures to HIV and recommendations for Postexposure Prophylaxis. MMWR 2005;54(No. RR-9): [inclusive page numbers].

Centers for Disease Control and Prevention

Julie L. Gerberding, MD, MPH
Director

Dixie E. Snider, MD, MPH
Chief Science Officer

Tanja Popovic, MD, PhD
Associate Director for Science

Coordinating Center for Health Information and Service

Steven L. Solomon, MD
Director

National Center for Health Marketing*

Jay M. Bernhardt, PhD, MPH
Director

Division of Scientific Communications*

Maria S. Parker
(*Acting*) *Director*

Mary Lou Lindegren, MD
Editor, MMWR *Series*

Suzanne M. Hewitt, MPA
Managing Editor, MMWR *Series*

Teresa F. Rutledge
(*Acting*) *Lead Technical Writer-Editor*

Jeffrey D. Sokolow, MA
Project Editor

Beverly J. Holland
Lead Visual Information Specialist

Lynda G. Cupell
Visual Information Specialist

Quang M. Doan, MBA
Erica R. Shaver
Information Technology Specialists

* Proposed.

CONTENTS

Introduction 1
Definition of Health-Care Personnel and Exposure 1
Risk for Occupational Transmission of HIV 2
Antiretroviral Agents for PEP 2
Antiretroviral Drugs During Pregnancy 7
Management of Occupational Exposure by Emergency Physicians 7
Occupational HIV Exposure Management and PEP Use in U.S. Hospitals 7
Recommendations for the Management of HCP Potentially Exposed to HIV 8
HIV PEP 8
Recommendations for the Selection of Drugs for HIV PEP . 8
Follow-Up of Exposed HCP 9
Reevaluation and Updating of HIV PEP Guidelines 11
Acknowledgments 11
References 11
Continuing Education Activity CE-1

Disclosure of Relationship

CDC, our planners, and our content experts wish to disclose they have no financial interests or other relationships with the manufacturers of commercial products, suppliers of commercial services, or commercial supporters.

The antiretroviral agents mentioned in the article do not have an approved indication by the FDA for postexposure prophylaxis. The material presented is based on expert review and does not reflect the views of the FDA.

Updated U.S. Public Health Service Guidelines for the Management of Occupational Exposures to HIV and Recommendations for Postexposure Prophylaxis

Prepared by
Adelisa L. Panlilio, MD[1]
Denise M. Cardo, MD[1]
Lisa A. Grohskopf, MD[2]
Walid Heneine, PhD[2]
Clara Sue Ross, MD[3]
[1]*Division of Healthcare Quality Promotion, National Center for Infectious Diseases*
[2]*Division of HIV/AIDS Prevention, National Center for HIV, STD, and TB Prevention*
[3]*Division of Surveillance, Hazard Evaluations, and Field Studies, National Institute for Occupational Safety and Health*

Summary

This report updates U.S. Public Health Service recommendations for the management of health-care personnel (HCP) who have occupational exposure to blood and other body fluids that might contain human immunodeficiency virus (HIV). Although the principles of exposure management remain unchanged, recommended HIV postexposure prophylaxis (PEP) regimens have been changed. This report emphasizes adherence to HIV PEP when it is indicated for an exposure, expert consultation in management of exposures, follow-up of exposed workers to improve adherence to PEP, and monitoring for adverse events, including seroconversion. To ensure timely postexposure management and administration of HIV PEP, clinicians should consider occupational exposures as urgent medical concerns.

Introduction

Although preventing exposures to blood and body fluids is the primary means of preventing occupationally acquired human immunodeficiency virus (HIV) infection, appropriate postexposure management is an important element of workplace safety. In 1996, the first U.S. Public Health Service (PHS) recommendations for the use of postexposure prophylaxis (PEP) after occupational exposure to HIV were published; these recommendations have been updated twice (*1*–*3*). Since publication of the most recent guidelines in 2001, new antiretroviral agents have been approved by the Food and Drug Administration (FDA), and additional information has become available regarding the use and safety of HIV PEP. In August 2003, CDC convened a meeting of a PHS interagency working group* and consultants to assess use of HIV PEP. On the basis of this discussion, the PHS working group decided that updated recommendations for the management of occupational exposure to HIV were warranted.

This report modifies and expands the list of antiretroviral medications that can be considered for use as PEP. This report also emphasizes prompt management of occupational exposures, selection of tolerable regimens, attention to potential drug interactions involving drugs that could be included in HIV PEP regimens and other medications, consultation with experts for postexposure management strategies (especially determining whether an exposure has actually occurred) and selection of HIV PEP regimens, use of HIV rapid testing, and counseling and follow-up of exposed personnel.

Recommendations on the management of occupational exposures to hepatitis B virus or hepatitis C virus have been published previously (*3*) and are not included in this report. Recommendations for nonoccupational (e.g., sexual, pediatric, and perinatal) HIV exposures also have been published previously (*4*–*6*).

* This interagency working group included representatives from CDC, FDA, the Health Resources and Services Administration, and the National Institutes of Health. Information included in these recommendations might not represent FDA approval or approved labeling for the particular product or indications in question. Specifically, the terms "safe" and "effective" might not be synonymous with the FDA-defined legal standard for product approval.

The material in this report originated in the National Center for Infectious Diseases, Anne Schuchat, MD, Acting Director; Division of Healthcare Quality Promotion, Denise M. Cardo, MD, Director.
Corresponding preparer: Adelisa L. Panlilio, MD, MPH, Division of Healthcare Quality Promotion, National Center for Infectious Diseases, CDC, 1600 Clifton Rd., NE, MS E-68, Atlanta, GA 30333. Telephone: 404-498-1265; Fax: 404-498-1244; E-mail: alp4@cdc.gov.

Definition of Health-Care Personnel and Exposure

The definitions of health-care personnel (HCP) and occupational exposures are unchanged from those used in 2001 (*3*). The term HCP refers to all paid and unpaid persons working in health-care settings who have the potential for exposure to infectious materials (e.g., blood, tissue, and specific body fluids and medical supplies, equipment, or environmental

surfaces contaminated with these substances). HCP might include, but are not limited to, emergency medical service personnel, dental personnel, laboratory personnel, autopsy personnel, nurses, nursing assistants, physicians, technicians, therapists, pharmacists, students and trainees, contractual staff not employed by the health-care facility, and persons not directly involved in patient care but potentially exposed to blood and body fluids (e.g., clerical, dietary, housekeeping, maintenance, and volunteer personnel). The same principles of exposure management could be applied to other workers who have potential for occupational exposure to blood and body fluids in other settings.

An exposure that might place HCP at risk for HIV infection is defined as a percutaneous injury (e.g., a needlestick or cut with a sharp object) or contact of mucous membrane or nonintact skin (e.g., exposed skin that is chapped, abraded, or afflicted with dermatitis) with blood, tissue, or other body fluids that are potentially infectious. In addition to blood and visibly bloody body fluids, semen and vaginal secretions also are considered potentially infectious. Although semen and vaginal secretions have been implicated in the sexual transmission of HIV, they have not been implicated in occupational transmission from patients to HCP. The following fluids also are considered potentially infectious: cerebrospinal fluid, synovial fluid, pleural fluid, peritoneal fluid, pericardial fluid, and amniotic fluid. The risk for transmission of HIV infection from these fluids is unknown; the potential risk to HCP from occupational exposures has not been assessed by epidemiologic studies in health-care settings. Feces, nasal secretions, saliva, sputum, sweat, tears, urine, and vomitus are not considered potentially infectious unless they are visibly bloody; the risk for transmission of HIV infection from these fluids and materials is low (*7*).

Any direct contact (i.e., contact without barrier protection) to concentrated virus in a research laboratory or production facility requires clinical evaluation. For human bites, clinical evaluation must include the possibility that both the person bitten and the person who inflicted the bite were exposed to bloodborne pathogens. Transmission of HIV infection by this route has been reported rarely, but not after an occupational exposure (*8–12*).

Risk for Occupational Transmission of HIV

The risks for occupational transmission of HIV have been described; risks vary with the type and severity of exposure (*2,3,7*). In prospective studies of HCP, the average risk for HIV transmission after a percutaneous exposure to HIV-infected blood has been estimated to be approximately 0.3% (95% confidence interval [CI] = 0.2%–0.5%) (*7*) and after a mucous membrane exposure, approximately 0.09% (CI = 0.006%–0.5%) (*3*). Although episodes of HIV transmission after nonintact skin exposure have been documented, the average risk for transmission by this route has not been precisely quantified but is estimated to be less than the risk for mucous membrane exposures. The risk for transmission after exposure to fluids or tissues other than HIV-infected blood also has not been quantified but is probably considerably lower than for blood exposures.

Epidemiologic and laboratory studies suggest that multiple factors might affect the risk for HIV transmission after an occupational exposure (*3*). In a retrospective case-control study of HCP who had percutaneous exposure to HIV, increased risk for HIV infection was associated with exposure to a larger quantity of blood from the source person as indicated by 1) a device (e.g., a needle) visibly contaminated with the patient's blood, 2) a procedure that involved a needle being placed directly in a vein or artery, or 3) a deep injury. The risk also was increased for exposure to blood from source persons with terminal illness, possibly reflecting either the higher titer of HIV in blood late in the course of acquired immunodeficiency syndrome (AIDS) or other factors (e.g., the presence of syncytia-inducing strains of HIV). A laboratory study that demonstrated that more blood is transferred by deeper injuries and hollow-bore needles lends further support for the observed variation in risk related to blood quantity (*3*).

The use of source-person viral load as a surrogate measure of viral titer for assessing transmission risk has not yet been established. Plasma viral load (e.g., HIV RNA) reflects only the level of cell-free virus in the peripheral blood; latently infected cells might transmit infection in the absence of viremia. Although a lower viral load (e.g., <1,500 RNA copies/mL) or one that is below the limits of detection probably indicates a lower titer exposure, it does not rule out the possibility of transmission.

Antiretroviral Agents for PEP

Antiretroviral agents from five classes of drugs are currently available to treat HIV infection (*13,14*). These include the nucleoside reverse transcriptase inhibitors (NRTIs), nucleotide reverse transcriptase inhibitors (NtRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), and a single fusion inhibitor. Only antiretroviral agents approved by FDA for treatment of HIV infection are included in these guidelines. The recommendations in this report provide guidance for two- or-more drug PEP regimens on the basis of the level of risk for HIV transmission represented by the exposure (Tables 1 and 2; Appendix).

TABLE 1. Recommended HIV postexposure prophylaxis (PEP) for percutaneous injuries

Exposure type	Infection status of source				
	HIV-positive, class 1*	HIV-positive, class 2*	Source of unknown HIV status†	Unknown source§	HIV-negative
Less severe¶	Recommend basic 2-drug PEP	Recommend expanded ≥3-drug PEP	Generally, no PEP warranted; however, consider basic 2-drug PEP** for source with HIV risk factors††	Generally, no PEP warranted; however, consider basic 2-drug PEP** in settings in which exposure to HIV-infected persons is likely	No PEP warranted
More severe§§	Recommend expanded 3-drug PEP	Recommend expanded ≥3-drug PEP	Generally, no PEP warranted; however, consider basic 2-drug PEP** for source with HIV risk factors††	Generally, no PEP warranted; however, consider basic 2-drug PEP** in settings in which exposure to HIV-infected persons is likely	No PEP warranted

* HIV-positive, class 1 — asymptomatic HIV infection or known low viral load (e.g., <1,500 ribonucleic acid copies/mL). HIV-positive, class 2 — symptomatic HIV infection, acquired immunodeficiency syndrome, acute seroconversion, or known high viral load. If drug resistance is a concern, obtain expert consultation. Initiation of PEP should not be delayed pending expert consultation, and, because expert consultation alone cannot substitute for face-to-face counseling, resources should be available to provide immediate evaluation and follow-up care for all exposures.

† For example, deceased source person with no samples available for HIV testing.

§ For example, a needle from a sharps disposal container.

¶ For example, solid needle or superficial injury.

** The recommendation "consider PEP" indicates that PEP is optional; a decision to initiate PEP should be based on a discussion between the exposed person and the treating clinician regarding the risks versus benefits of PEP.

†† If PEP is offered and administered and the source is later determined to be HIV-negative, PEP should be discontinued.

§§ For example, large-bore hollow needle, deep puncture, visible blood on device, or needle used in patient's artery or vein.

TABLE 2. Recommended HIV postexposure prophylaxis (PEP) for mucous membrane exposures and nonintact skin* exposures

Exposure type	Infection status of source				
	HIV-positive, class 1†	HIV-positive, class 2†	Source of unknown HIV status§	Unknown source¶	HIV-negative
Small volume**	Consider basic 2-drug PEP††	Recommend basic 2-drug PEP	Generally, no PEP warranted§§	Generally, no PEP warranted	No PEP warranted
Large volume¶¶	Recommend basic 2-drug PEP	Recommend expanded ≥3-drug PEP	Generally, no PEP warranted; however, consider basic 2-drug PEP†† for source with HIV risk factors§§	Generally, no PEP warranted; however, consider basic 2-drug PEP†† in settings in which exposure to HIV-infected persons is likely	No PEP warranted

* For skin exposures, follow-up is indicated only if evidence exists of compromised skin integrity (e.g., dermatitis, abrasion, or open wound).

† HIV-positive, class 1 — asymptomatic HIV infection or known low viral load (e.g., <1,500 ribonucleic acid copies/mL). HIV-positive, class 2 — symptomatic HIV infection, AIDS, acute seroconversion, or known high viral load. If drug resistance is a concern, obtain expert consultation. Initiation of PEP should not be delayed pending expert consultation, and, because expert consultation alone cannot substitute for face-to-face counseling, resources should be available to provide immediate evaluation and follow-up care for all exposures.

§ For example, deceased source person with no samples available for HIV testing.

¶ For example, splash from inappropriately disposed blood.

** For example, a few drops.

†† The recommendation "consider PEP" indicates that PEP is optional; a decision to initiate PEP should be based on a discussion between the exposed person and the treating clinician regarding the risks versus benefits of PEP.

§§ If PEP is offered and administered and the source is later determined to be HIV-negative, PEP should be discontinued.

¶¶ For example, a major blood splash.

Toxicity and Drug Interactions of Antiretroviral Agents

Persons receiving PEP should complete a full 4-week regimen (*3*). However, as a result of toxicity and side effects among HCP, a substantial proportion of HCP have been unable to complete a full 4-week course of HIV PEP (*15–20*). Because all antiretroviral agents have been associated with side effects (Table 3), the toxicity profile of these agents, including the frequency, severity, duration, and reversibility of side effects, is an important consideration in selection of an HIV PEP regimen. The majority of data concerning adverse events have been reported primarily for persons with established HIV infection receiving prolonged antiretroviral therapy and therefore might not reflect the experience of uninfected persons who take PEP. Anecdotal evidence from clinicians knowledgeable about HIV treatment indicates that antiretroviral agents are tolerated more poorly among HCP taking HIV PEP than among HIV-infected patients on antiretroviral medications.

TABLE 3. Primary side effects and toxicities associated with antiretroviral agents used for HIV postexposure prophylaxis, by class and agent

Class and agent	Side effect and toxicity
Nucleoside reverse transcriptase inhibitors (NRTI)	**Class warning: all NRTIs have the potential to cause lactic acidosis with hepatic steatosis**
Zidovudine (Retrovir®; ZDV, AZT)	Anemia, neutropenia, nausea, headache, insomnia, muscle pain, and weakness
Lamivudine (Epivir®, 3TC)	Abdominal pain, nausea, diarrhea, rash, and pancreatitis
Stavudine (Zerit™; d4T)	Peripheral neuropathy, headache, diarrhea, nausea, insomnia, anorexia, pancreatitis, elevated liver function tests (LFTs), anemia, and neutropenia
Didanosine (Videx®; ddI)	Pancreatitis, lactic acidosis, neuropathy, diarrhea, abdominal pain, and nausea
Emtricitabine (Emtriva, FTC)	Headache, nausea, vomiting, diarrhea, and rash. Skin discoloration (mild hyperpigmentation on palms and soles), primarily among nonwhites
Nucleotide analogue reverse transcriptase inhibitor (NtRTI)	**Class warning: All NtRTIs have the potential to cause lactic acidosis with hepatic steatosis**
Tenofovir (Viread®; TDF)	Nausea, diarrhea, vomiting, flatulence, and headache
Nonnucleoside reverse transcriptase inhibitors (NNRTIs)	
Efavirenz (Sustiva®; EFV)	Rash (including cases of Stevens-Johnson syndrome), insomnia, somnolence, dizziness, trouble concentrating, abnormal dreaming, and teratogenicity
Protease inhibitor	
Indinavir (Crixivan®; IDV)	Nausea, abdominal pain, nephrolithiasis, and indirect hyperbilirubinemia
Nelfinavir (Viracept®; NFV)	Diarrhea, nausea, abdominal pain, weakness, and rash
Ritonavir (Norvir®; RTV)	Weakness, diarrhea, nausea, circumoral paresthesia, taste alteration, and elevated cholesterol and triglycerides
Saquinavir (Invirase®; SQV)	Diarrhea, abdominal pain, nausea, hyperglycemia, and elevated LFTs
Fosamprenavir (Lexiva®, FOSAPV)	Nausea, diarrhea, rash, circumoral paresthesia, taste alteration, and depression
Atazanavir (Reyataz®; ATV)	Nausea, headache, rash, abdominal pain, diarrhea, vomiting, and indirect hyperbilirubinemia
Lopinavir/ritonavir (Kaletra®; LPV/RTV)	Diarrhea, fatigue, headache, nausea, and increased cholesterol and triglycerides
Fusion inhibitor	
Enfuvirtide (Fuzeon®; T-20)	Local injection site reactions, bacterial pneumonia, insomnia, depression, peripheral neuropathy, and cough

Sources: Package inserts; Panel on Clinical Practices for Treatment of HIV Infection. Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents—April 7, 2005. Washington, DC: National Institutes of Health; 2005. Available at http://aidsinfo.nih.gov/guidelines/default_db2.asp?id=50.

Side effects have been reported frequently by persons taking antiretroviral agents as PEP (*15–23*). In multiple instances, a substantial (range: 17%–47%) proportion of HCP taking PEP after occupational exposures to HIV-positive sources did not complete a full 4-week course of therapy because of inability to tolerate the drugs (*15–17,19,20*). Data from the National Surveillance System for Health Care Workers (NaSH), CDC's occupational surveillance system for occupational exposures and infections in hospitals, for June 1995–December 2004 indicate that 401 (46.9%) of 921 HCP with at least one follow-up visit after starting PEP experienced one or more symptoms. The symptom reported most frequently was nausea (26.5%), followed by malaise and fatigue (22.8%) (CDC, unpublished data, 2005). Of 503 HCP who stopped HIV PEP prematurely (<28 days), 361 (24.0%) did so because of adverse effects of the drugs. Similar data have been reported from the Italian Registry of Antiretroviral Postexposure Prophylaxis, which includes data primarily on HCP taking PEP but also collects data on those taking PEP after nonoccupational exposures (*18*). In multivariate analysis, those taking regimens that include PI were more likely to experience PEP-associated side effects and to discontinue PEP prematurely (<28 days). Because side effects are frequent and

particularly because they are cited as a major reason for not completing PEP regimens as prescribed, the selection of regimens should be heavily influenced toward those that are tolerable for short-term use.

In addition, all approved antiretroviral agents might have potentially serious drug interactions when used with certain other drugs, requiring careful evaluation of concomitant medications, including over-the-counter medications and supplements (e.g., herbals), used by an exposed person before prescribing PEP and close monitoring for toxicity of anyone receiving these drugs (*24–33*) (Tables 3–5). PIs and NNRTIs have the greatest potential for interactions with other drugs. Information regarding potential drug interactions has been published (*13,24–33*). Additional information is included in the manufacturers' package inserts. Because of interactions, certain drugs should not be administered concomitantly with PIs or with efavirenz (EFV) (Tables 4 and 5). Consultation with a pharmacist might be considered.

Selection of HIV PEP Regimens

Determining which agents and how many to use or when to alter a PEP regimen is primarily empiric (*34*). Guidelines for treating HIV infection, a condition typically involving a high total body burden of HIV, recommend use of three or more drugs (*13,14*); however, the applicability of these recommendations to PEP is unknown. Among HIV-infected patients, combination regimens with three or more antiretroviral agents have proved superior to monotherapy and dual-therapy regimens in reducing HIV viral load, reducing incidence of opportunistic infections and death, and delaying onset of drug resistance (*13,14*). In theory, a combination of drugs with activity at different stages in the viral replication cycle (e.g., nucleoside analogues with a PI) might offer an additive preventive effect in PEP, particularly for occupational exposures that pose an increased risk for transmission or for transmission of a resistant virus. Although use of a three- (or more) drug regimen might be justified for exposures that pose an increased risk for transmission, whether the potential added toxicity of a third or fourth drug is justified for lower-risk exposures is uncertain, especially in the absence of data supporting increased efficacy of more drugs in the context of occupational PEP. Offering a two-drug regimen is a viable option, primarily because the benefit of completing a full course of this regimen exceeds the benefit of adding the third agent and risking noncompletion (*35*). In addition, the total body burden of HIV is substantially lower among exposed HCP than among persons with established HIV infection. For these reasons, the recommendations in this report provide guidance for two- and three- (or more) drug PEP regimens on the basis of the level of risk for HIV transmission represented by the exposure (Tables 1 and 2; Appendix).

Resistance to Antiretroviral Agents

Known or suspected resistance of the source virus to antiretroviral agents, particularly those that might be included in a PEP regimen, is a concern for persons making decisions about PEP (*36*). Drug resistance to all available antiretroviral agents has been reported, and cross-resistance within drug classes is frequent (*37*). Although occupational transmission of drug-resistant HIV strains has been reported despite PEP

TABLE 4. Prescription and over-the-counter drugs that should not be administered with protease inhibitors (PIs) because of drug interactions*

Drug	Comment
Antimycobacterials: rifampin	Decreases plasma concentrations and area under plasma concentration curve of the majority of PIs by approximately 90%, which might result in loss of therapeutic effect and development of resistance
Benzodiazepines: midazolam, triazolam	Contraindicated because of potential for serious or life-threatening events (e.g., prolonged or increased sedation or respiratory depression)
Ergot derivatives: dihydroergotamine, ergotamine, ergonovine, methylergonovine	Contraindicated because of potential for serious or life-threatening events (e.g., acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues)
Gastrointestinal motility agent: cisapride	Contraindicated because of potential for serious or life-threatening events (e.g., cardiac arrhythmias)
HMG-CoA reductase inhibitors ("statins"): lovastatin, simvastatin	Potential for serious reactions (e.g., myopathy, including rhabdomyolysis); atorvastatin may be used cautiously, beginning with lowest possible starting dose, and monitoring for adverse events
Neuroleptic: pimozide	Contraindicated because of potential for serious or life-threatening events (e.g., cardiac arrhythmias)
Inhaled steroids: fluticasone	Coadministration of fluticasone and ritonavir-boosted protease inhibitors are not recommended unless the potential benefit to the patient outweighs the risk for systemic corticosteroid side effect
Herbal products:	Coadministration might reduce plasma concentrations of protease inhibitors, which might result in loss of therapeutic effect and development of resistance
St. John's wort (hypericum perforatum), garlic	Garlic might lower saquinavir level

* This table does not list all products that should not be administered with PIs (atazanavir, lopinavir/ritonavir, fosamprenavir, indinavir, nelfinavir, saquinavir). Product labels should be consulted for additional information regarding drug interactions.

Sources: US Department of Health and Human Services. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Washington, DC: US Department of Health and Human Services; 2005. Available at http://www.aidsinfo.nih.gov/guidelines/adult/AA_040705.pdf; University of California at San Francisco Center for HIV Information. Database of antiretroviral drug interactions. Available at http://hivinsite.ucsf.edu/InSite?page=ar-00-02.

TABLE 5. Prescription and over-the-counter drugs that should not be administered with efavirenz because of drug interactions*

Drug	Comment
Antifungal: voriconazole	Contraindicated because efavirenz substantially decreases voriconazole plasma concentrations
Benzodiazepines: midazolam, triazolam	Contraindicated because of potential for serious or life-threatening events (e.g., prolonged or increased sedation or respiratory depression)
Ergot derivatives: dihydroergotamine, ergotamine, ergonovine, methylergonovine	Contraindicated because of potential for serious or life-threatening events (e.g., acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues)
Gastrointestinal motility agent: cisapride	Contraindicated because of potential for serious or life-threatening events (e.g., cardiac arrhythmias)
Herbal products:	Coadministration might reduce plasma concentrations of protease inhibitors, which might result in loss of therapeutic effect and development of resistance
St. John's wort (hypericum perforatum), garlic	Garlic might lower saquinavir levels

* This table does not list all products that should not be coadministered with efavirenz. Efavirenz product labeling should be consulted for additional information regarding drug interactions.

Sources: US Department of Health and Human Services. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Washington, DC: US Department of Health and Human Services; 2005. Available at http://www.aidsinfo.nih.gov/guidelines/adult/AA_040705.pdf; University of California at San Francisco Center for HIV Information. Database of antiretroviral drug interactions. Available at http://hivinsite.ucsf.edu/InSite?page=ar-00-02.

with combination drug regimens (*36,38–40*), the effect of exposure to a resistant virus on transmission and transmissibility is not well understood.

Since publication of the previous guidelines, an additional report of an occupational HIV seroconversion despite combination HIV PEP has been published (Table 6) (*38*), bringing the total number of reports worldwide to six. The exposure was a percutaneous injury sustained by a nurse performing a phlebotomy on a heavily treatment-experienced patient. At the time of the exposure, the source patient was failing treatment with stavudine (d4T), lamivudine (3TC), ritonavir (RTV), and saquinavir (SQV) and had a history of previous treatment with zidovudine (ZDV) and zalcitabine (ddC). Genotypic resistance testing performed within 1 month of the exposure suggested resistance to ZDV and 3TC. Phenotypic testing confirmed resistance to 3TC but demonstrated relative susceptibility to ZDV and d4T. The source virus demonstrated no evidence of resistance to nevirapine (NVP) or other NNRTIs. The initial HIV PEP regimen started within 95 minutes of the exposure was ZDV, 3TC, and indinavir.

TABLE 6. Reported instances of failure of combination drug postexposure prophylaxis (PEP) to prevent HIV-infection among health-care personnel exposed to HIV-infected blood through percutaneous injury

Year of incident	Device	PEP regimen*	Time to first dose (hrs)	No. of days to onset of retroviral illness	No. of days to document seroconversion†	Source-patient		
						HIV-infection status	On anti retrovirals	Virus resistant to antiretrovirals§
1992¶	Biopsy needle	ZDV, ddI	0.5	23	23	AIDS, terminally ill	Yes	Unknown
1996**	Hollow-bore needle	ZDV, ddI††	1.5	45	97	Asymptomatic HIV infection	No	Not tested
1997**	Large or hollow-bore needle	ZDV, 3TC, IDV§§	1.5	40	55	AIDS	Yes	No
1998¶¶	Hollow-bore needle	ZDV, 3TC, ddI, IDV	0.7	70	83	AIDS	Yes	Yes
1999***	Unknown sharp	ddI, d4T, NVP†††	2.0	42	100	AIDS	Yes	Yes
2001§§§	Phlebotomy needle	ZDV, 3TC, IDV¶¶¶	1.6	24	~90	AIDS	Yes	Yes

* ZDV = zidovudine; ddI = didanosine; 3TC = lamivudine; IDV = indinavir; d4T = stavudine; and NVP = nevirapine.

† By enzyme immunoassay for HIV-1 antibody and Western blot.

§ By genotypic or phenotypic resistance testing.

¶ **Source:** Jochimsen EM. Failures of zidovudine postexposure prophylaxis. Am J Med 1997;102(Suppl 5B):52–5.

** **Source:** Lot F, Abiteboul D. Occupational infections with HIV in France among health-care personnel [French]. Bull Epi Hebdom 1999;18:69–70.

†† ZDV and ddI taken for 48 hours and then changed to ZDV alone.

§§ ZDV, 3TC, and IDV taken for 48 hours and then changed to d4T, 3TC, and IDV.

¶¶ **Source:** Perdue B, Wolde Rufael D, Mellors J, Quinn T, Margolick J. HIV-1 transmission by a needlestick injury despite rapid initiation of four-drug postexposure prophylaxis [Abstract no 210]. In: Program and abstracts of the 6th Conference on Retroviruses and Opportunistic Infections. Chicago, IL: Foundation for Retrovirology and Human Health; 1999.

*** **Source:** Beltrami EM, Luo C-C, de la Torre N, Cardo DM. Transmission of drug-resistant HIV after an occupational exposure despite postexposure prophylaxis with a combination drug regimen. Infect Control Hosp Epidemiol 2002;23:345–8; CDC, unpublished data, 1999.

††† ZDV and 3TC taken for 1 dose and then changed to ddI, d4T, and NVP; ddI was discontinued after 3 days as a result of severe vomiting.

§§§ **Source:** Hawkins DA, Asboe D, Barlow K, Evans B. Seroconversion to HIV-1 following a needlestick injury despite combination post-exposure prophylaxis. J Infect 2001;43:12–5.

¶¶¶ ZDV, 3TC, and IDV initially and then changed after first dose to d4T, ddI, and NVP; then ddI discontinued after 8 days; and d4T and NVP taken for 4 weeks.

The worker was referred to a hospital where the regimen was changed within 6 hours of the exposure to didanosine (ddI), d4T, and NVP because of concerns regarding possible drug resistance to certain or all of the components of the initial PEP regimen. The exposed worker stopped ddI after 8 days because of symptoms but continued to take d4T and NVP, stopping at day 24 because of a generalized macular pruritic rash and mild thrombocytopenia. Seroconversion was documented at 3 months. Sequencing of viruses from the source and exposed worker demonstrated their close relatedness. Virus from the worker demonstrated the same resistance patterns as those in the source patient. In addition, the worker's virus had a mutation suggesting resistance to the NNRTI class (*38*).

Empiric decisions regarding the presence of antiretroviral drug resistance are often difficult because patients frequently take more than one antiretroviral agent. Resistance should be suspected in a source patient when clinical progression of disease or a persistently increasing viral load or decline in CD4+ T-cell count occurs despite therapy, or when no virologic response to therapy occurs. However, resistance testing of the source virus at the time of an exposure is impractical because the results will not be available in time to influence the choice of the initial PEP regimen. No data suggest that modification of a PEP regimen after resistance testing results become available (usually 1–2 weeks) improves efficacy of PEP (*41*).

Antiretroviral Drugs During Pregnancy

Data regarding the potential effects of antiretroviral drugs on the developing fetus or neonate are limited (*3*). Carcinogenicity and mutagenicity are evident in certain in vitro screening tests for ZDV and all other FDA-licensed NRTIs. The relevance of animal data to humans is unknown; however, because teratogenic effects were reported among primates at drug exposures similar to those representing human therapeutic exposure, pregnant women should not use efavirenz (EFV). Indinavir (IDV) is associated with infrequent side effects in adults (i.e., hyperbilirubinemia and renal stones) that could be problematic for a newborn. Because the half-life of IDV in adults is short, these concerns might be relevant only if the drug is administered shortly before delivery. Other concerns regarding use of PEP during pregnancy have been raised by reports of mitochondrial dysfunction leading to neurologic disease and death among uninfected children whose mothers had taken antiretroviral drugs to prevent perinatal HIV transmission and of fatal and nonfatal lactic acidosis in pregnant women treated throughout gestation with a combination of d4T and ddI (*3*).

Management of Occupational Exposure by Emergency Physicians

Although PHS guidelines for the management of occupational exposures to HIV were first published in 1985 (*42*), HCP often are not familiar with these guidelines. Focus groups conducted among emergency department (ED) physicians in 2002 indicated that of 71 participants, >95% had not read the 2001 guidelines before being invited to participate (*43*). All physicians participating in these focus groups had managed occupational exposures to blood or body fluids. They cited three challenges in exposure management most frequently: evaluation of an unknown source patient or a source patient who refused testing, inexperience in managing occupational HIV exposures, and counseling of exposed workers in busy EDs.

Occupational HIV Exposure Management and PEP Use in U.S. Hospitals

Analysis of NaSH data for June 1995–December 2004 provides information regarding the management of occupational exposure to HIV in a convenience sample of 95 U.S. hospitals. These data indicate improved adherence to PHS recommendations concerning use of HIV PEP after occupational exposures. A total of 28,010 exposures to blood and body fluids were reported by these hospitals (CDC, unpublished data, 2005). For all 25,510 exposures with known sources, 1,350 (5.3%) were to HIV-positive sources, 15,301 (60.0%) to HIV-negative sources, and 8,859 (34.7%) to sources of unknown HIV status. Of 1,350 HCP exposed to a known HIV-positive source, 788 (58.4%) started PEP, and 317 (49%) of 647 for whom follow-up information was available took PEP for ≥21 days. The overall median duration of HIV PEP after exposure to an HIV-positive source was 27 days, increasing from 10 days in 1995 to 26.5 days in 2004; the overall median duration of HIV PEP after exposure to an HIV-negative source was 2 days, decreasing from 7.5 days in 1995 to 1 day in 2004. The use of rapid HIV tests for evaluation of source patients has increased; during 1995–1997, none of 25 NaSH facilities used rapid HIV tests, whereas in 2004, a total of 21 (84%) did (CDC, unpublished data, 2005). Rapid HIV tests could result in decreased use of PEP and spare personnel both undue anxiety and adverse effects of antiretroviral PEP (*44–47*). The annual median time to initiation of PEP was consistent (2 hours). Of 1,350 HCP with exposures to HIV-positive sources, 909 (67.1%) had at least one follow-up serologic test recorded, but only 289 (31.8%) had tests recorded at 4–6 months (CDC, unpublished data, 2005).

In 1996, of 24 HCP taking PEP after exposure to HIV-positive sources, 10 (42%) took a three-drug PEP regimen compared with 30 (76.9%) of 39 in 2004 (CDC, unpublished data, 2005). After 227 HIV exposures for which only a two-drug PEP regimen was recommended (i.e., the exposure was to mucous membranes or skin or was a superficial percutaneous injury and the source person did not have end-stage AIDS or acute HIV illness), 104 (45.8%) HCP initiated a three-drug HIV PEP regimen. The National Clinicians' Post-Exposure Prophylaxis Hotline (PEPline)† reports similar findings. PEPline staff recommended changing or discontinuing PEP regimens for 45 (38%) of 118 exposures involving source patients with known viral load or CD4 cell count concerning which they were consulted during April 2002–March 2003 (*48*; R. Goldschmidt, PEPline, personal communication, 2004). For 14 (11.9%) HCP, the recommendation was to decrease the number of drugs in the PEP regimens; for 22 (18.7%) HCP, the recommendation was to increase the number of drugs; and for nine (7.6%), the recommendation was to change the PEP regimen, keeping the same number of drugs.

Recommendations for the Management of HCP Potentially Exposed to HIV

Exposure prevention remains the primary strategy for reducing occupational bloodborne pathogen infections. However, occupational exposures will continue to occur, and PEP will remain an important element of exposure management.

HIV PEP

The recommendations provided in this report (Tables 1 and 2; Appendix) apply to situations in which HCP have been exposed to a source person who either has or is considered likely to have HIV infection. These recommendations are based on the risk for HIV infection after different types of exposure and on limited data regarding efficacy and toxicity of PEP. If PEP is offered and taken and the source is later determined to be HIV-negative, PEP should be discontinued. Although concerns have been expressed regarding HIV-negative sources being in the window period for seroconversion, no case of transmission involving an exposure source during the window period has been reported in the United States (*39*). Rapid HIV testing of source patients can facilitate making timely decisions regarding use of HIV PEP after occupational exposures to sources of unknown HIV status. Because the majority of occupational HIV exposures do not result in transmission of HIV, potential toxicity must be considered when prescribing PEP. Because of the complexity of selecting HIV PEP regimens, when possible, these recommendations should be implemented in consultation with persons having expertise in antiretroviral therapy and HIV transmission. Reevaluation of exposed HCP should be strongly encouraged within 72 hours postexposure, especially as additional information about the exposure or source person becomes available.

Timing and Duration of PEP

PEP should be initiated as soon as possible, preferably within hours rather than days of exposure. If a question exists concerning which antiretroviral drugs to use, or whether to use a basic or expanded regimen, the basic regimen should be started immediately rather than delay PEP administration. The optimal duration of PEP is unknown. Because 4 weeks of ZDV appeared protective in occupational and animal studies, PEP should be administered for 4 weeks, if tolerated (*49–52*).

Recommendations for the Selection of Drugs for HIV PEP

The selection of a drug regimen for HIV PEP must balance the risk for infection against the potential toxicities of the agent(s) used. Because PEP is potentially toxic, its use is not justified for exposures that pose a negligible risk for transmission (Tables 1 and 2). The initial HIV PEP regimens recommended in these guidelines should be viewed as suggestions that can be changed if additional information is obtained concerning the source of the occupational exposure (e.g., possible treatment history or antiretroviral drug resistance) or if expert consultation is provided. Given the complexity of choosing and administering HIV PEP, whenever possible, consultation with an infectious diseases consultant or another physician who has experience with antiretroviral agents is recommended, but it should not delay timely initiation of PEP.

Consideration should be given to the comparative risk represented by the exposure and information regarding the exposure source, including history of and response to antiretroviral therapy based on clinical response, CD4+ T-cell counts, viral load measurements, and current disease stage. When the source person's virus is known or suspected to be resistant to one or more of the drugs considered for the PEP regimen, the selection of drugs to which the source person's virus is unlikely to be resistant is recommended; expert consultation is advised. If this information is not immediately available, initiation of PEP, if indicated, should not be delayed; changes

† Administered by staff members from the University of California at San Francisco and San Francisco General Hospital; supported by the Health Resources and Services Administration Ryan White CARE Act and AIDS Education and Training Centers, and by CDC.

in the regimen can be made after PEP has started, as appropriate. For HCP who initiate PEP, re-evaluation of the exposed person should occur within 72 hours postexposure, especially if additional information about the exposure or source person becomes available.

PHS continues to recommend stratification of HIV PEP regimens based on the severity of exposure and other considerations (e.g., concern for antiretroviral drug resistance in the exposure source). The majority of HIV exposures will warrant a two-drug regimen, using two NRTIs or one NRTI and one NtRTI (Tables 1 and 2; Appendix). Combinations that can be considered for PEP include ZDV and 3TC or emtricitabine (FTC); d4T and 3TC or FTC; and tenofovir (TDF) and 3TC or FTC. In the previous PHS guidelines, a combination of d4T and ddI was considered one of the first-choice PEP regimens; however, this regimen is no longer recommended because of concerns about toxicity (especially neuropathy and pancreatitis) and the availability of more tolerable alternative regimens (*3*).

The addition of a third (or even a fourth) drug should be considered for exposures that pose an increased risk for transmission or that involve a source in whom antiretroviral drug resistance is likely. The addition of a third drug for PEP after a high-risk exposure is based on demonstrated effectiveness in reducing viral burden in HIV-infected persons. However, no definitive data exist that demonstrate increased efficacy of three- compared with two-drug HIV PEP regimens. Previously, IDV, nelfinavir (NFV), EFV, or abacavir (ABC) were recommended as first-choice agents for inclusion in an expanded PEP regimen (*3*).

PHS now recommends that expanded PEP regimens be PI-based. The PI preferred for use in expanded PEP regimens is lopinavir/ritonavir (LPV/RTV). Other PIs acceptable for use in expanded PEP regimens include atazanavir, fosamprenavir, RTV-boosted IDV, RTV-boosted SQV, or NFV (Appendix). Although side effects are common with NNRTIs, EFV may be considered for expanded PEP regimens, especially when resistance to PIs in the source person's virus is known or suspected. Caution is advised when EFV is used in women of childbearing age because of the risk of teratogenicity.

Drugs that may be considered as alternatives to the expanded regimens, with warnings about side effects and other adverse events, are EFV or PIs as noted in the Appendix in combination with ddI and either 3TC or FTC. The fusion inhibitor enfuvirtide (T20) has theoretic benefits for use in PEP because its activity occurs before viral-host cell integration; however, it is not recommended for routine HIV PEP because of the mode of administration (subcutaneous injection twice daily). Furthermore, use of T20 has the potential for production of anti-T20 antibodies that cross react with HIV gp41. This could result in a false-positive, enzyme immunoassay (EIA) HIV antibody test among HIV-uninfected patients. A confirmatory Western blot test would be expected to be negative in such cases. T20 should only be used with expert consultation.

Antiviral drugs not recommended for use as PEP, primarily because of the higher risk for potentially serious or life-threatening adverse events, include ABC, delavirdine, ddC, and, as noted previously, the combination of ddI and d4T. NVP should not be included in PEP regimens except with expert consultation because of serious reported side effects, including hepatotoxicty (with one instance of fulminant liver failure requiring liver transplantation), rhabdomyolysis, and hypersensitivity syndrome (*53–55*).

Because of the complexity of selection of HIV PEP regimens, consultation with persons having expertise in antiretroviral therapy and HIV transmission is strongly recommended. Certain institutions have required consultation with a hospital epidemiologist or infectious diseases consultant when HIV PEP use is under consideration. This can be especially important in management of a pregnant or breastfeeding worker or a worker who has been exposed to a heavily treatment-experienced source (Box 1).

Resources for consultation are available from the following sources:

- PEPline at http://www.ucsf.edu/hivcntr/Hotlines/PEPline; telephone 888-448-4911;
- HIV Antiretroviral Pregnancy Registry at http://www.apregistry.com/index.htm; Address: Research Park, 1011 Ashes Drive, Wilmington, NC 28405. Telephone: 800-258-4263; Fax: 800-800-1052; E-mail: registry@nc.crl.com;
- FDA (for reporting unusual or severe toxicity to antiretroviral agents) at http://www.fda.gov/medwatch; telephone: 800-332-1088; address: MedWatch, HF-2, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857;
- CDC (for reporting HIV infections in HCP and failures of PEP) at telephone 800-893-0485; and
- HIV/AIDS Treatment Information Service at http://aidsinfo.nih.gov.

Follow-Up of Exposed HCP

Postexposure Testing

HCP with occupational exposure to HIV should receive follow-up counseling, postexposure testing, and medical evaluation regardless of whether they receive PEP. HIV-antibody

BOX 1. Situations for which expert consultation* for HIV postexposure prophylaxis (PEP) is advised

- Delayed (i.e., later than 24–36 hours) exposure report
  - — Interval after which lack of benefit from PEP undefined
- Unknown source (e.g., needle in sharps disposal container or laundry)
  - — Use of PEP to be decided on a case-by-case basis
  - — Consider severity of exposure and epidemiologic likelihood of HIV exposure
  - — Do not test needles or other sharp instruments for HIV
- Known or suspected pregnancy in the exposed person
  - — Use of optimal PEP regimens not precluded
  - — PEP not denied solely on basis of pregnancy
- Breastfeeding in the exposed person
  - — Use of optimal PEP regimens not precluded
  - — PEP not denied solely on basis of breastfeeding
- Resistance of the source virus to antiretroviral agents
  - — Influence of drug resistance on transmission risk unknown
  - — If source person's virus is known or suspected to be resistant to one or more of the drugs considered for PEP, selection of drugs to which the source person's virus is unlikely to be resistant recommended
  - — Resistance testing of the source person's virus at the time of the exposure not recommended
  - — Initiation of PEP not to be delayed while awaiting any results of resistance testing
- Toxicity of the initial PEP regimen
  - — Adverse symptoms (e.g., nausea and diarrhea) common with PEP
  - — Symptoms often manageable without changing PEP regimen by prescribing antimotility or antiemetic agents
  - — In other situations, modifying the dose interval (i.e., taking drugs after meals or administering a lower dose of drug more frequently throughout the day, as recommended by the manufacturer) might help alleviate symptoms when they occur

* Either with local experts or by contacting the National Clinicians' Post-Exposure Prophylaxis Hotline (PEPline), telephone 888-448-4911.

testing by enzyme immunoassay should be used to monitor HCP for seroconversion for >6 months after occupational HIV exposure. After baseline testing at the time of exposure, follow-up testing could be performed at 6 weeks, 12 weeks, and 6 months after exposure. Extended HIV follow-up (e.g., for 12 months) is recommended for HCP who become infected with HCV after exposure to a source coinfected with HIV and HCV. Whether extended follow-up is indicated in other circumstances (e.g., exposure to a source co-infected with HIV and HCV in the absence of HCV seroconversion or for exposed persons with a medical history suggesting an impaired ability to mount an antibody response to acute infection) is unclear. Although rare instances of delayed HIV seroconversion have been reported (*56,57*), the infrequency of this occurrence does not warrant adding to exposed persons' anxiety by routinely extending the duration of postexposure follow-up. However, this should not preclude a decision to extend follow-up in a particular situation based on the clinical judgment of the exposed person's health-care provider. The routine use of direct virus assays (e.g., HIV p24 antigen EIA or tests for HIV ribonucleic acid) to detect infection among exposed HCP usually is not recommended (*58*). Despite the ability of direct virus assays to detect HIV infection a few days earlier than EIA, the infrequency of occupational seroconversion and increased costs of these tests do not warrant their routine use in this setting. In addition, the relatively high rate of false-positive results of these tests in this setting could lead to unnecessary anxiety or treatment (*59,60*). Nevertheless, HIV testing should be performed on any exposed person who has an illness compatible with an acute retroviral syndrome, regardless of the interval since exposure. A person in whom HIV infection is identified should be referred for medical management to a specialist with expertise in HIV treatment and counseling. Health-care providers caring for persons with occupationally acquired HIV infection can report these cases to CDC at telephone 800-893-0485 or to their state health departments.

Monitoring and Management of PEP Toxicity

If PEP is used, HCP should be monitored for drug toxicity by testing at baseline and again 2 weeks after starting PEP. The scope of testing should be based on medical conditions in the exposed person and the toxicity of drugs included in the PEP regimen. Minimally, laboratory monitoring for toxicity should include a complete blood count and renal and hepatic function tests. Monitoring for evidence of hyperglycemia should be included for HCP whose regimens include any PI; if the exposed person is receiving IDV, monitoring for crystalluria, hematuria, hemolytic anemia, and hepatitis also should be included. If toxicity is noted, modification of the regimen should be considered after expert consultation; further diagnostic studies might be indicated.

Exposed HCP who choose to take PEP should be advised of the importance of completing the prescribed regimen. Information should be provided about potential drug interactions and drugs that should not be taken with PEP, side effects of prescribed drugs, measures to minimize side effects, and methods of clinical monitoring for toxicity

during the follow-up period. HCP should be advised that evaluation of certain symptoms (e.g., rash, fever, back or abdominal pain, pain on urination or blood in the urine, or symptoms of hyperglycemia (e.g., increased thirst or frequent urination) should not be delayed.

HCP often fail to complete the recommended regimen often because they experience side effects (e.g., nausea or diarrhea). These symptoms often can be managed with antimotility and antiemetic agents or other medications that target specific symptoms without changing the regimen. In other situations, modifying the dose interval (i.e., administering a lower dose of drug more frequently throughout the day, as recommended by the manufacturer) might facilitate adherence to the regimen. Serious adverse events[§] should be reported to FDA's MedWatch program.

Although recommendations for follow-up testing, monitoring, and counseling of exposed HCP are unchanged from those published previously (*3*), greater emphasis is needed on improving follow-up care provided to exposed HCP (Box 2). This might result in increased adherence to HIV PEP regimens, better management of associated symptoms with ancillary medications or regimen changes, improved detection of serious adverse effects, and serologic testing among a larger proportion of exposed personnel to determine if infection is transmitted after occupational exposures. Closer follow-up should in turn reassure HCP who become anxious after these events (*61,62*). The psychologic impact on HCP of needlesticks or exposure to blood or body fluid should not be underestimated. Providing HCP with psychologic counseling should be an essential component of the management and care of exposed HCP.

Reevaluation and Updating of HIV PEP Guidelines

As new antiretroviral agents for treatment of HIV infection and additional information concerning early HIV infection and prevention of HIV transmission become available, the PHS Interagency Working Group will assess the need to update these guidelines. Updates will be published periodically as appropriate.

[§] Defined by FDA as follows: "Any adverse drug experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition" (*63*).

BOX 2. Follow-up of health-care personnel (HCP) exposed to known or suspected HIV-positive sources

- Exposed HCP should be advised to use precautions (e.g., avoid blood or tissue donations, breastfeeding, or pregnancy) to prevent secondary transmission, especially during the first 6–12 weeks postexposure.
- For exposures for which PEP is prescribed, HCP should be informed regarding
  - — possible drug toxicities and the need for monitoring,
  - — possible drug interactions, and
  - — the need for adherence to PEP regimens.
- Consider reevalution of exposed HCP 72 hours postexposure, especially after additional information about the exposure or source person becomes available.

Acknowledgments

David K. Henderson, MD, National Institutes of Health, Bethesda, Maryland; Kimberly A. Struble, PharmD, Food and Drug Administration, Rockville, Maryland; and Abe Macher, MD, Health Resources and Services Administration, Rockville, Maryland, assisted in the preparation of this report.

References

1. CDC. Update: provisional Public Health Service recommendations for chemoprophylaxis after occupational exposure to HIV. MMWR 1996;45:468–72.
2. CDC. Public Health Service guidelines for the management of health-care worker exposures to HIV and recommendations for postexposure prophylaxis. MMWR 1998;47(No. RR-7):1–33.
3. CDC. Updated U.S. Public Health Service guidelines for the management of occupational exposures to HBV, HCV, and HIV and recommendations for postexposure prophylaxis. MMWR 2001;50 (No. RR-11):1–52.
4. CDC. Antiretroviral postexposure prophylaxis after sexual, injection-drug use, or other nonoccupational exposure to HIV in the United States: recommendations from the U.S. Department of Health and Human Services. MMWR 2005;54(No. RR-2):1–20.
5. US Department of Health and Human Services Public Health Service Task Force. Recommendations for use of antiretroviral drugs in pregnant HIV-1 infected women for maternal health and Interventions to reduce perinatal HIV-1 transmission in the United States. Available at http://www.aidsinfo.nih.gov/guidelines/default_db2.asp?id=66.
6. Havens PL; Committee on Pediatric AIDS. Postexposure prophylaxis in children and adolescents for nonoccupational exposure to human immunodeficiency virus. Pediatrics 2003;111:1475–89.
7. Bell DM. Occupational risk of human immunodeficiency virus infection in health-care workers: an overview. Am J Med 1997;102(5B):9–15.
8. Wahn V, Kramer HH, Voit T, Bruster HT, Scrampical B, Scheid A. Horizontal transmission of HIV infection between two siblings. Lancet 1986;ii:694.
9. Anonymous. Transmission of HIV by human bite. Lancet 1987;ii:522.
10. Richman KM, Rickman LS. The potential for transmission of human immunodeficiency virus through human bites. J Acquir Immune Defic Syndr 1993;6:402–6.

11. Vidmar L, Poljak M, Tomazic J, Seme K, Klavs I. Transmission of HIV-1 by human bite. Lancet 1996;347:1762.
12. Pretty IA, Anderson GS, Sweet DJ. Human bites and the risk of human immunodeficiency virus transmission. Am J Forensic Med Pathol 1999;20:232–9.
13. Panel on Clinical Practices for Treatment of HIV Infection. Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents—April 7, 2005. Bethesda, MD: National Institutes of Health; 2005. Available at http://aidsinfo.nih.gov/guidelines/default_db2.asp?id=50.
14. Yeni PG, Hammer SM, Hirsch MS, et al. Treatment for adult HIV infection: 2004 recommendations of the International AIDS Society-USA Panel. JAMA 2004;292:251–65.
15. Wang SA, Panlilio AL, Doi PA, et al. Experience of health-care workers taking postexposure prophylaxis after occupational human immunodeficiency virus exposures: findings of the HIV Postexposure Prophylaxis Registry. Infect Control Hosp Epidemiol 2000;21:780–5.
16. Swotinsky RB, Steger KA, Sulis C, Snyder S, Craven DE. Occupational exposure to HIV: experience at a tertiary care center. J Occup Environ Med 1998;40:1102–9.
17. Parkin JM, Murphy M, Anderson J, El-Gadi S, Forster G, Pinching AJ. Tolerability and side-effects of post-exposure prophylaxis for HIV infection. Lancet 2000;355:722–3.
18. Puro V. Post-exposure prophylaxis for HIV infection [Letter]. Lancet 2000;355:1556–7.
19. Lee LM, Henderson DK. Tolerability of postexposure antiretroviral prophylaxis for occupational exposures to HIV. Drug Saf 2001;24:587–97.
20. Russi M, Buitrago M, Goulet J, et al. Antiretroviral prophylaxis of health care workers at two urban medical centers. J Occup Environ Med 2000;42:1092–100.
21. Garb JR. One-year study of occupational human immunodeficiency virus postexposure prophylaxis. J Occup Environ Med 2002;44:265–70.
22. Grime PR, Risi L, Binns C, Carruthers JR, Williams S. Pan-Thames survey of occupational exposure to HIV and the use of post-exposure prophylaxis in 71 NHS trusts. J Infect 2001;42:27–32.
23. Puro V, DeCarli G, Soldani F, et al. Adverse drug reactions associated with PEP [Poster]. In: Program and Abstracts of the 10th Conference on Retroviruses and Opportunistic Infections, Boston, Massachusetts, February 2003. Poster no. 711.
24. Moyle G, Boffito M. Unexpected drug interactions and adverse events with antiretroviral drugs. Lancet 2004;364:8–10.
25. Andrade A, Flexner C. Progress in pharmacology and drug interactions from the 10th CROI. Hopkins HIV Rep 2003;15:7,11.
26. Andrade A, Flexner C. Genes, ethnicity, and efavirenz response: clinical pharmacology update from the 11th CROI. Hopkins HIV Rep 2004;16:1–7.
27. University of California at San Francisco Center for HIV Information. Database of antiretroviral drug interactions. Available at http://hivinsite.ucsf.edu/InSite?page=ar-00-02.
28. de Maat MM, Ekhart GC, Huitema AD, Koks CH, Mulder JW, Beijnen JH. Drug interactions between antiretroviral drugs and comedicated agents. Clin Pharmacokinet 2003;42:223–82.
29. Fichtenbaum CJ, Gerber JG. Interactions between antiretroviral drugs and drugs used for the therapy of the metabolic complications encountered during HIV infection. Clin Pharmacokinet 2002;41:1195–211.
30. Edmunds-Obguokiri T. Understanding drug-drug interactions in the management of HIV disease. HIV Clin 2002;14:1–4.
31. Rainey PM. HIV drug interactions: the good, the bad, and the other. Ther Drug Monit 2002;24:26–31.
32. Dasgupta A, Okhuysen PC. Pharmacokinetic and other drug interactions in patients with AIDS. Ther Drug Monit 2001;23:591–605.
33. Piscitelli SC, Gallicano KD. Interactions among drugs for HIV and opportunistic infections. N Engl J Med 2001;334:984–96.
34. Gerberding JL. Occupational exposure to HIV in health care settings. N Engl J Med 2003;348:826–33.
35. Bassett IV, Freedberg KA,Walensky RP. Two drugs or three? Balancing efficacy, toxicity, and resistance in postexposure prophylaxis for occupational exposure to HIV. Clin Infect Dis 2004;39:395–401.
36. Beltrami EM, Cheingsong R, Heneine WM, et al. Antiretroviral drug resistance in human immunodeficiency virus–infected source patients for occupational exposures to healthcare workers. Infect Control Hosp Epidemiol 2003;24:724–30.
37. Hirsch MS, Brun-Vezinet F, Clotet B, et al. Antiretroviral drug resistance testing in adults infected with human immunodeficiency virus type 1: 2003 recommendations of an International AIDS Society-USA Panel. Clin Infect Dis 2003;37:113–28.
38. Hawkins DA, Asboe D, Barlow K, Evans B. Seroconversion to HIV-1 following a needlestick injury despite combination post-exposure prophylaxis. J Infect 2001;43:12–8.
39. Do AN, Ciesielski CA, Metler RP, Hammett TA, Li J, Fleming PL. Occupationally acquired human immunodeficiency virus (HIV) infection: national case surveillance data during 20 years of the HIV epidemic in the United States. Infect Control Hosp Epidemiol 2003;24:86–96.
40. Health Protection Agency Centre for Infections and Collaborators. Occupational transmission of HIV: summary of published reports. March 2005 edition. Data to the end of December 2002. London, UK: Health Protection Agency Centre for Infections and Collaborators. Available at http://www.hpa.org.uk/infections/topics_az/hiv_and_sti/hiv/occupational.htm.
41. Puro V. Genotypic resistance tests for the management of postexposure prophylaxis. Scand J Infect Dis Suppl 2003;(35 Suppl):106:93–8.
42. CDC. Recommendations for preventing transmission of infection with human T-lymphotropic virus type III/lymphadenopathy-associated virus in the workplace. MMWR 1985;34:681–6, 691–5.
43. Panlilio AL, Sinkowitz-Cochran R, Grady MA, Cardo DM. Barriers to and facilitators of implementing U.S. Public Health Service (PHS) guidelines on occupational exposure management by emergency physicians [Abstract]. In: Program and Abstracts of the 13th annual meeting of the Society for Health-care Epidemiology of America, Arlington, Virginia, April 5–8, 2003. Abstract no. 240.
44. Kallenborn JC, Price TG, Carrico R, Davidson AB. Emergency department management of occupational exposures: cost analysis of rapid HIV test. Infect Control Hosp Epidemiol 2001;22:289–93.
45. King AM, Osterwalder JJ, Vernazza PL. A randomised prospective study to evaluate a rapid HIV-antibody assay in the management of cases of percutaneous exposure amongst health care workers. Swiss Med Wkly 2001;131:10–3.
46. Salgado CD, Flanagan HL, Haverstick DM, Farr BM. Low rate of false-positive results with use of a rapid HIV test. Infect Control Hosp Epidemiol 2002;23:335–7.
47. Puro V, Francisci D, Sighinolfi L, et al. Benefits of a rapid HIV test for evaluation of the source patient after occupational exposure of healthcare workers. J Hosp Infect 2004;57:179–82.

48. Dong BJ, Harvey A, Aranow RA, et al. Post-exposure prophylaxis (PEP) in health care workers (HCWs) after exposure to an HIV-infected source patient (SP) [Poster]. In: Program and Abstract of the 11th Conference on Retroviruses and Opportunistic Infections, San Francisco, California, February 8–11, 2004. Poster no. 887.
49. Shih C-C, Kaneshima H, Rabin L, et al. Postexposure prophylaxis with zidovudine suppresses human immunodeficiency virus type 1 infection in SCID-hu mice in a time-dependent manner. J Infect Dis 1991;163:625–7.
50. Tsai C-C, Follis KE, Sabo A, et al. Prevention of SIV infection in macaques by (R)-9-(2-phosphonylmethoxypropyl) adenine. Science 1995;270:1197–9.
51. Tsai C-C, Emau P, Follis KE, et al. Effectiveness of postinoculation (R)-9-(2-phosphonylmethoxypropyl) adenine treatment for prevention of persistent simian immunodeficiency virus SIV_{mne} infection depends critically on timing of initiation and duration of treatment. J Virol 1998;72:4265–73.
52. Otten RA, Smith DK, Adams DR, et al. Efficacy of postexposure prophylaxis after intravaginal exposure of pig-tailed macaques to a human-derived retrovirus (human immunodeficiency virus type 2). J Virol 2000;74:9771–5.
53. Cattelan AM, Erne E, Slatino A, et al. Severe hepatic failure related to nevirapine treatment. Clin Infect Dis 1999;29:455–6.
54. Johnson S, Baraboutis JG, Sha BE, Proia LA, Kessler HA. Adverse effects associated with use of nevirapine in HIV postexposure for 2 health care workers [Letter]. JAMA 2000;284:2722–3.
55. CDC. Serious adverse events attributed to nevirapine regimens for postexposure prophylaxis after HIV exposures—worldwide, 1997–2000. MMWR 2001;49:1153–6.
56. Ridzon R, Gallagher K, Ciesielski C, et al. Simultaneous transmission of human immunodeficiency virus and hepatitis C virus from a needlestick injury. N Engl J Med 1997;336:919–22.
57. Ciesielski CA, Metler RP. Duration of time between exposure and seroconversion in healthcare workers with occupationally acquired infection with human immunodeficiency virus. Am J Med 1997;102(Suppl 5B):115–6.
58. Busch MP, Satten GA. Time course of viremia and antibody seroconversion following human immunodeficiency virus exposure. Am J Med 1997;102(Suppl 5B):117–24.
59. Rich JD, Merriman NA, Mylonakis E, et al. Misdiagnosis of HIV infection by HIV-1 plasma viral load testing: a case series. Ann Intern Med 1999;130:37–9.
60. Roland ME, Elbeik TA, Kahn JO, et al. HIV RNA testing in the context of nonoccupational postexposure prophylaxis. J Infect Dis 2004;190:598–604.
61. Armstrong K, Gorden R, Santorella G. Occupational exposure of health care workers (HCWs) to human immunodeficiency virus (HIV): stress reactions and counseling interventions. Social Work in Health Care 1995;21:61–80.
62. Meienberg F, Bucher HC, Sponagel L, Zinkernagel C, Gyr N, Battegay M. Anxiety in health care workers after exposure to potentially HIV-contaminated blood or body fluids. Swiss Med Wkly 2002;132:321–4.
63. Food and Drug Administration. 21CFR314.80. Postmarketing reporting of adverse drug experiences. Code of Federal Regulations 2005;5:114–7.

APPENDIX

Basic and Expanded HIV Postexposure Prophylaxis Regimens

BASIC REGIMEN

- **Zidovudine (Retrovir™; ZDV; AZT) + lamivudine (Epivir®; 3TC); available as Combivir™**

Preferred dosing

- ZDV: 300 mg twice daily or 200 mg three times daily, with food; total: 600 mg daily
- 3TC: 300 mg once daily or 150 mg twice daily
- Combivir: one tablet twice daily

Dosage forms

- ZDV: 100 mg capsule, 300 mg tablet
- 3TC: 150 or 300 mg tablet
- Combivir: tablet, 300 mg ZDV + 150 mg 3TC

Advantages

- ZDV associated with decreased risk for HIV transmission
- ZDV used more often than other drugs for PEP for health-care personnel (HCP)
- Serious toxicity rare when used for PEP
- Side effects predictable and manageable with antimotility and antiemetic agents
- Can be used by pregnant HCP
- Can be given as a single tablet (COMBIVIR™) twice daily

Disadvantages

- Side effects (especially nausea and fatigue) common and might result in low adherence
- Source-patient virus resistance to this regimen possible
- Potential for delayed toxicity (oncogenic/teratogenic) unknown

- **Zidovudine (Retrovir®; ZDV; AZT) + emtrictabine (Emtriva™; FTC)**

Preferred dosing

- ZDV: 300 mg twice daily or 200 mg three times daily, with food; total: 600 mg/day, in 2–3 divided doses
- FTC: 200 mg (one capsule) once daily

Dosage forms
- ZDV: see above
- FTC: 200 mg capsule

FTC general comments
- Nucleoside analogue; same structure as 3TC, except fluoride residue at position 5 on pyrimidine ring
- Same resistance and safety profile as 3TC
- No apparent advantage over 3TC; tolerability and virologic response rates appear better than regimens containing ddI + d4T

Advantages
- ZDV: see above.
- FTC
  - Convenient (once daily)
  - Well tolerated
  - Long intracellular half-life (~40 hours)

Disadvantages
- ZDV: see above.
- FTC
  - Rash perhaps more frequent than with 3TC
  - No long-term experience with this drug
  - Cross resistance to 3TC
  - Hyperpigimentation among non-Caucasians with long-term use: 3%

- **Tenofovir DF (Viread®; TDF) + lamivudine (Epivir®; 3TC)**

Preferred dosing
- TDF: 300 mg once daily
- 3TC: 300 mg once daily or 150 mg twice daily

Dosage forms
- TDF: 300 mg tablet
- 3TC: see above

Advantages
- 3TC: see above
- TDF
  - Convenient dosing (single pill once daily)
  - Resistance profile activity against certain thymidine analogue mutations
  - Well tolerated

Disadvantages
- TDF
  - Same class warnings as nucleoside reverse transcriptase inhibitors (NRTIs)
  - Drug interactions
  - Increased TDF concentrations among persons taking atazanavir and lopinavir/ritonavir; need to monitor patients for TDF-associated toxicities
- Preferred dosage of atazanavir if used with TDF: 300 mg + ritonavir 100 mg once daily + TDF 300 mg once daily

- **Tenofovir DF (Viread®; TDF) + emtricitabine (Emtriva™; FTC); available as Truvada™**

Preferred dosing
- TDF: 300 mg once daily
- FTC: 200 mg once daily
- As Truvada™: one tablet daily

Dosage forms
- TDF: 300 mg tablet
- FTC: see FTC
- Truvada™ (TDF 300 mg plus FTC 200 mg)

Advantages
- FTC: see above
- TDF
  - Convenient dosing (single pill once daily)
  - Resistance profile activity against certain thymidine analogue mutations
  - Well tolerated

Disadvantages
- TDF
  - Same class warnings as NRTIs
  - Drug interactions
  - Increased TDF concentrations among persons taking atazanavir and lopinavir/ritonavir; need to monitor patients for TDF-associated toxicities
  - Preferred dosing of atazanavir if used with TDF: 300 mg + ritonavir 100 mg once daily + TDF 300 mg once daily

ALTERNATE BASIC REGIMENS

- **Lamivudine (Epivir®; 3TC) + stavudine (Zerit®; d4T)**

Preferred dosing
- 3TC: 300 mg once daily or 150 mg twice daily
- d4T: 40 mg twice daily (can use lower doses of 20–30 mg twice daily if toxicity occurs; equally effective but less toxic among HIV-infected patients with peripheral neuropathy); 30 mg twice daily if body weight is <60 kg

Dosage forms
- 3TC: see above
- d4T: 15, 20, 30, and 40 mg tablet

Advantages
- 3TC: see above
- d4T: gastrointestinal (GI) side effects rare

Disadvantages
- Possibility that source-patient virus is resistant to this regimen
- Potential for delayed toxicity (oncogenic/teratogenic) unknown

- **Emtricitabine (Emtriva™; FTC) + stavudine (Zerit®; d4T)**

Preferrred dosing
- FTC: 200 mg daily
- d4T: 40 mg twice daily (can use lower doses of 20–30 mg twice daily if toxicity occurs; equally effective but less toxic among HIV-infected patients who developed peripheral neuropathy); if body weight is <60 kg, 30 mg twice daily

Dosage forms
- FTC: see above
- d4T: see above

Advantages
- 3TC and FTC: see above; d4T's GI side effects rare

Disadvantages
- Potential that source-patient virus is resistant to this regimen
- Unknown potential for delayed toxicity (oncogenic/teratogenic) unknown

- **Lamivudine (Epivir®; 3TC) + didanosine (Videx®; ddI)**

Preferred dosing
- 3TC: 300 mg once daily or 150 mg twice daily
- ddI: Videx® chewable/dispersible buffered tablets can be administered on an empty stomach as either 200 mg twice daily or 400 mg once daily. Patients must take at least two of the appropriate strength tablets at each dose to provide adequate buffering and prevent gastric acid degradation of ddI. Because of the need for adequate buffering, the 200-mg strength tablet should be used only as a component of a once-daily regimen. The dose is either 200 mg twice daily or 400 mg once daily for patients weighing >60 kg and 125 mg twice daily or 250 mg once daily for patients weighing >60 kg.

Dosage forms
- 3TC: 150 or 300 mg tablets
- ddI: 25, 50, 100, 150, or 200 mg buffered white tablets

Advantages
- ddI: once daily dosing option
- 3TC: see above

Disadvantages
- Tolerability: diarrhea more common with buffered preparation than with enteric-coated preparation
- Associated with toxicity: peripheral neuropathy, pancreatitis, and lactic acidosis
- Must be taken on empty stomach except with TDF
- Drug interactions
- 3TC: see above

- **Emtricitabine (Emtriva™; FTC) + didanosine (Videx®; ddI)**

Preferred dosing
- FTC: 200 mg once daily
- ddI: see above

Dosage forms
- ddI: see above
- FTC: see above

Advantages
- ddI: see above
- FTC: see above

Disadvantages
- Tolerability: diarrhea more common with buffered than with enteric-coated preparation
- Associated with toxicity: peripheral neuropathy, pancreatitis, and lactic acidosis
- Must be taken on empty stomach except with TDF
- Drug interactions
- FTC: see above

PREFERRED EXPANDED REGIMEN

Basic regimen plus:

- **Lopinavir/ritonavir (Kaletra®; LPV/RTV)**

Preferred dosing
- LPV/RTV: 400/100 mg = 3 capsules twice daily with food

Dosage form
- LPV/RTV: 133/33 mg capsules

Advantages
- Potent HIV protease inhibitor
- Generally well-tolerated

Disadvantages
- Potential for serious or life-threatening drug interactions (see Table 4)
- Might accelerate clearance of certain drugs, including oral contraceptives (requiring alternative or additional contraceptive measures for women taking these drugs)
- Can cause severe hyperlipidemia, especially hypertriglyceridemia
- GI (e.g., diarrhea) events common

ALTERNATE EXPANDED REGIMENS

Basic regimen plus one of the following:

- **Atazanavir (Reyataz®; ATV) ± ritonavir (Norvir®; RTV)**

Preferred dosing
- ATV: 400 mg once daily, unless used in combination with TDF, in which case ATV should be boosted with RTV, preferred dosing of ATV 300 mg + RTV: 100 mg once daily

Dosage forms
- — ATV: 100, 150, and 200 mg capsules
- — RTV: 100 mg capsule

Advantages
- — Potent HIV protease inhibitor
- — Convenient dosing – once daily
- — Generally well tolerated

Disadvantages
- — Hyperbilirubinemia and jaundice common
- — Potential for serious or life-threatening drug interactions (see Table 4)
- — Avoid coadministration with proton pump inhibitors
- — Separate antacids and buffered medications by 2 hours and H2-receptor antagonists by 12 hours to avoid decreasing ATV levels
- — Caution should be used with ATV and products known to induce PR prolongation (e.g., diltiazem)

- **Fosamprenavir (Lexiva®; FOSAPV) ± ritonavir (Norvir®; RTV)**

Preferred dosing
- — FOSAPV: 1400 mg twice daily (without RTV)
- — FOSAPV: 1400 mg once daily + RTV 200 mg once daily
- — FOSAPV: 700 mg twice daily + RTV 100 mg twice daily

Dosage form
- — FOSAPV: 700 mg tablets
- — RTV: 100 mg capsule

Advantages
- — Once daily dosing when given with ritonavir

Disadvantages
- — Tolerability: GI side effects common
- — Multiple drug interactions. Oral contraceptives decrease fosamprenavir concentrations
- — Incidence of rash in healthy volunteers, especially when used with low doses of ritonavir. Differentiating between early drug-associated rash and acute seroconversion can be difficult and cause extraordinary concern for the exposed person

- **Indinavir (Crixivan®; IDV) ± ritonavir (Norvir®; RTV)**

Preferred dosing
- — IDV 800 mg + RTV 100 mg twice daily without regard to food

Alternative dosing
- — IDV: 800 mg every 8 hours, on an empty stomach

Dosage forms
- — IDV: 200 mg, 333, and 400 mg capsule
- — RTV: 100 mg capsule

Advantages
- — Potent HIV inhibitor

Disadvantages
- — Potential for serious or life-threatening drug interactions (see Table 4)
- — Serious toxicity (e.g., nephrolithiasis) possible; consumption of 8 glasses of fluid/day required
- — Hyperbilirubinemia common; must avoid this drug during late pregnancy
- — Requires acid for absorption and cannot be taken simultaneously with ddI, chewable/dispersible buffered tablet formulation (doses must be separated by ≥1 hour)

- **Saquinavir (Invirase®; SQV) + ritonavir (Norvir®; RTV)**

Preferred dosing
- — SQV: 1,000 mg (given as Invirase) + RTV 100 mg, twice daily
- — SQV : five capsules twice daily + RTV: one capsule twice daily

Dosage forms
- — SQV (Invirase): 200 mg capsule
- — RTV: 100 mg capsule

Advantages
- — Generally well-tolerated, although GI events common

Disadvantages
- — Potential for serious or life-threatening drug interactions (see Table 4)
- — Substantial pill burden

- **Nelfinavir (Viracept®; NFV)**

Preferred dosing
- — NFV: 1,250 mg (2 x 625 mg or 5 x 250 mg tablets), twice daily with a meal

Dosage forms
- — NFV: 250 or 625 mg tablet

Advantages
- — Generally well-tolerated

Disadvantages
- — Diarrhea or other GI events common
- — Potential for serious and/or life-threatening drug interactions (see Table 4)

- **Efavirenz (Sustiva®; EFV)**

Preferred dosing
- — EFV: 600 mg daily, at bedtime

Dosage forms
- — EFV: 50, 100, 200 capsules
- — EFV: 600 mg tablet

Advantages
- — Does not require phosphorylation before activation and might be active earlier than other antiretroviral agents (a theoretic advantage of no demonstrated clinical benefit)
- — Once daily dosing

Disadvantages
- — Drug associated with rash (early onset) that can be severe and might rarely progress to Stevens-Johnson syndrome
- — Differentiating between early drug-associated rash and acute seroconversion can be difficult and cause extraordinary concern for the exposed person
- — Central nervous system side effects (e.g., dizziness, somnolence, insomnia, or abnormal dreaming) common; severe psychiatric symptoms possible (dosing before bedtime might minimize these side effects)
- — Teratogen; should not be used during pregnancy
- — Potential for serious or life-threatening drug interactions (see Table 5)

ANTIRETROVIRAL AGENTS GENERALLY NOT RECOMMENDED FOR USE AS PEP

- **Nevirapine (Viramune®; NVP)**

Disadvantages
- — Associated with severe hepatotoxicity (including at least one case of liver failure requiring liver transplantation in an exposed person taking PEP)
- — Associated with rash (early onset) that can be severe and progress to Stevens-Johnson syndrome
- — Differentiating between early drug-associated rash and acute seroconversion can be difficult and cause extraordinary concern for the exposed person
- — Drug interactions: can lower effectiveness of certain antiretroviral agents and other commonly used medicines

- **Delavirdine (Rescriptor®; DLV)**

Disadvantages
- — Drug associated with rash (early onset) that can be severe and progress to Stevens-Johnson syndrome
- — Multiple drug interactions

- **Abacavir (Ziagen®; ABC)**

Disadvantages
- — Severe hypersensitivity reactions can occur, usually within the first 6 weeks
- — Differentiating between early drug-associated rash/hypersensitivity and acute seroconversion can be difficult

- **Zalcitabine (Hivid®; ddC)**

Disadvantages
- — Three times a day dosing
- — Tolerability
- — Weakest antiretroviral agent

ANTIRETROVIRAL AGENT FOR USE AS PEP ONLY WITH EXPERT CONSULTATION

- **Enfuvirtide (Fuzeon™; T20)**

Preferred dosing
- — T20: 90 mg (1 ml) twice daily by subcutaneous injection

Dosage forms
- — T20: Single-dose vial, reconstituted to 90 mg/ml

Advantages
- — New class
- — Unique viral target; to block cell entry
- — Prevalence of resistance low

Disadvantages
- — Twice-daily injection
- — Safety profile: local injection site reactions
- — Never studied among antiretroviral-naïve or HIV-negative patients
- — False-positive EIA HIV antibody tests might result from formation of anti-T20 antibodies that cross-react with anti-gp41 antibodies

PHS Working Group on Occupational Postexposure Prophylaxis: Adelisa L Panlilio, Denise M. Cardo, Division of Healthcare Quality Promotion, National Center for Infectious Diseases, CDC; Lisa A. Grohskopf; Walid Heneine, Division of HIV/AIDS Prevention, National Center for HIV, STD, and TB Prevention, CDC; Clara Sue Ross, Ahmed Gomaa; Division of Surveillance and Hazard Evaluations, and Field Studies, National Institute for Occupational Safety and Health, CDC; Kimberly A. Struble, Center for Drug Evaluation and Research, FDA; Abe Macher, HIV/AIDS Bureau, HRSA; David K Henderson, Clinical Center, National Institutes of Health.

External Consultants: Henry M. Blumberg, Grady Memorial Hospital; Betty Dong, National Clinicians' Postexposure Prophylaxis Hotline (PEPline); Ron Goldschmidt, University of California, San Francisco; Michael Saag, University of Alabama, Birmingham; Michael Tapper, Lenox Hill Hospital.

MMWR™

Morbidity and Mortality Weekly Report

Recommendations and Reports | September 30, 2005 / Vol. 54 / No. RR-9

Continuing Education Activity Sponsored by CDC

Updated U.S. Public Health Service Guidelines for the Management of Occupational Exposures to HIV and Recommendations for Postexposure Prophylaxis

EXPIRATION — September 30, 2007

You must complete and return the response form electronically or by mail by **September 30, 2007**, to receive continuing education credit. If you answer all of the questions, you will receive an award letter for 1.5 hours Continuing Medical Education (CME) credit; 0.15 Continuing Education Units (CEUs); or 1.9 contact hours Continuing Nursing Education (CNE) credit. If you return the form electronically, you will receive educational credit immediately. If you mail the form, you will receive educational credit in approximately 30 days. No fees are charged for participating in this continuing education activity.

INSTRUCTIONS

By Internet

1. Read this *MMWR* (Vol. 54, RR-9), which contains the correct answers to the questions beginning on the next page.
2. Go to the *MMWR* Continuing Education Internet site at http://www.cdc.gov/mmwr/cme/conted.html.
3. Select which exam you want to take and select whether you want to register for CME, CEU, or CNE credit.
4. Fill out and submit the registration form.
5. Select exam questions. To receive continuing education credit, you must answer all of the questions. Questions with more than one correct answer will instruct you to "Indicate all that apply."
6. Submit your answers no later than **September 30, 2007**
7. Immediately print your Certificate of Completion for your records.

By Mail or Fax

1. Read this *MMWR* (Vol. 54, RR-9), which contains the correct answers to the questions beginning on the next page.
2. Complete all registration information on the response form, including your name, mailing address, phone number, and e-mail address, if available.
3. Indicate whether you are registering for CME, CEU, or CNE credit.
4. Select your answers to the questions, and mark the corresponding letters on the response form. To receive continuing education credit, you must answer all of the questions. Questions with more than one correct answer will instruct you to "Indicate all that apply."
5. Sign and date the response form or a photocopy of the form and send no later than **September 30, 2007**, to
   Fax: 770-488-8555 Mail: MMWR CE Credit
   Division of Scientific Communications
   Coordinating Center for Health Information and Service, MS K-95
   Centers for Disease Control and Prevention
   1600 Clifton Rd, N.E.
   Atlanta, GA 30333
6. Your Certificate of Completion will be mailed to you within 30 days.

ACCREDITATION

Continuing Medical Education (CME). CDC is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians. CDC designates this educational activity for a maximum of 1.5 hours in category 1 credit toward the AMA Physician's Recognition Award. Each physician should claim only those hours of credit that he/she actually spent in the educational activity.

Continuing Education Unit (CEU). CDC has been approved as an authorized provider of continuing education and training programs by the International Association for Continuing Education and Training and awards 0.15 Continuing Education Units (CEUs).

Continuing Nursing Education (CNE). This activity for 1.9 contact hours is provided by CDC, which is accredited as a provider of continuing education in nursing by the American Nurses Credentialing Center's Commission on Accreditation.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTERS FOR DISEASE CONTROL AND PREVENTION

Goal and Objectives

This report provides recommendations regarding clinical practice for managing occupational exposures to HIV in health-care settings, including appropriate use of HIV postexposure prophylaxis (PEP). The goal of this report is to provide recommendations for guiding clinical practice in managing PEP for health-care personnel (HCP) with occupational exposure to HIV. Upon completion of this educational activity, the reader should be able to a) describe occupational exposures for which exposure management is appropriate; b) describe the appropriate selection of HIV PEP; c) describe the appropriate use of HIV PEP; d) describe the follow-up evaluation of exposed HCP; e) describe the follow-up counseling of exposed HCP; and f) list situations for which expert consultation in the management of occupational exposures is recommended.

To receive continuing education credit, please answer all of the following questions.

1. Contact with which body fluid(s) poses a risk for HIV transmission in health-care settings? (*Indicate all that apply.*)

A. Blood.
B. Urine.
C. Sweat.
D. Amniotic fluid.
E. A and D.
F. B and C.

2. What is the recommended duration of HIV PEP for occupational exposures to HIV? (*Choose the one correct answer.*)

A. 7 days.
B. 14 days.
C. 21 days.
D. 28 days.
E. 2 months.

3. What is the recommended time to initiation of HIV PEP after exposure when PEP is indicated? (*Choose the one correct answer.*)

A. 2 days.
B. 24–48 hours.
C. As soon as possible (preferably within hours).

4. Follow-up after occupational exposures to HIV should include which of the following? (*Choose the one correct answer.*)

A. Serologic follow-up for HIV infection.
B. Monitoring for adverse effects of HIV postexposure prophylaxis if taken.
C. Monitoring for acute seroconversion illness.
D. Counseling on adherence with HIV PEP and the emotional stress of dealing with exposures.
E. All of the above.

5. The potential for interactions with other medications is greatest for which of the antiretroviral drug classes recommended for HIV postexposure prophylaxis? (*Choose the one correct answer.*)

A. Reverse transcriptase inhibitors (nucleoside analogues).
B. Nonnucleoside reverse transcriptase inhibitors.
C. Protease inhibitors.
D. A and B.
E. B and C.
F. A and C.

6. Which antiretrovirals are not currently recommended for use by pregnant HCP? (*Indicate all that apply.*)

A. Efavirenz.
B. Zidovudine.
C. Nelfinavir.
D. Tenofovir.

7. Resistance testing of the source-patient after an exposure should always be performed to help in selection of HIV postexposure prophylaxis regimens.

A. True.
B. False.

8. Adverse effects of antiretroviral HIV postexposure prophylaxis are uncommonly reported by HCP.

A. True.
B. False.

9. Which types of exposure pose a risk for HIV transmission in health-care settings? (*Indicate all that apply.*)

A. Intact skin exposure to blood.
B. Mucous membrane splash of urine.
C. Needlestick injury after phlebotomy.
D. Splash of blood on abraded skin.
E. C and D.
F. A and B.

10. A 12-month serologic follow-up after an occupational exposure to HIV is recommended in which situation(s)? (*Indicate all that apply.*)

A. Any percutaneous exposure to an HIV-infected source.
B. If the exposed worker takes HIV postexposure prophylaxis.
C. If the exposure source is coinfected with HIV and HCV and becomes HCV-infected.
D. None of the above.

11. Which best describes your professional activities:

A. Physician.
B. Nurse.
C. Health educator.
D. Office staff.
E. Other.

12. I plan to use these recommendations as the basis for …(*Indicate all that apply.*)

A. health education materials.
B. insurance reimbursement policies.
C. local practice guidelines.
D. public policy.
E. other.

13. Overall, the length of the journal article was…

A. much too long.
B. a little too long.
C. just right.
D. a little too short.
E. much too short.

14. After reading this report, I am confident I can describe occupational exposures for which exposure management is appropriate.

A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

15. After reading this report, I am confident I can describe the appropriate selection of HIV PEP.

A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

16. After reading this report, I am confident I can describe the appropriate use of HIV PEP.

A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

17. After reading this report, I am confident I can describe the follow-up evaluation of exposed HCP.

A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

18. After reading this report, I am confident I can describe the follow-up counseling of exposed HCP.

A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

19. After reading this report, I am confident I can list situations for which expert consultation in the management of occupational exposures is recommended.

A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

20. The learning outcomes (objectives) were relevant to the goal of this report.

A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

21. The instructional strategies used in this report (text, tables, boxes, and appendix) helped me learn the material.

A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

22. The content was appropriate given the stated objectives of the report.

A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

(Continued on pg CE-4)

Detach or photocopy.

***MMWR* Response Form for Continuing Education Credit**
September 30, 2005/Vol. 54/No. RR-9

Updated U.S. Public Health Service Guidelines for the Management of Occupational Exposures to HIV and Recommendations for Postexposure Prophylaxis

To receive continuing education credit, you must
1. provide your contact information (**please print or type**);
2. indicate your choice of CME, CME for nonphysicians, CEU, or CNE credit;
3. answer all of the test questions;
4. sign and date this form or a photocopy;
5. submit your answer form by September 30, 2007.

Failure to complete these items can result in a delay or rejection of your application for continuing education credit.

Last Name (**print or type**) First Name

Street Address or P.O. Box

Apartment or Suite

City State ZIP Code

Phone Number Fax Number

E-Mail Address

Check One
☐ CME Credit
☐ CME for nonphysicians Credit
☐ CEU Credit
☐ CNE Credit

Fill in the appropriate blocks to indicate your answers. Remember, you must answer all of the questions to receive continuing education credit!

1. [ ] A [ ] B [ ] C [ ] D [ ] E [ ] F
2. [ ] A [ ] B [ ] C [ ] D [ ] E
3. [ ] A [ ] B [ ] C
4. [ ] A [ ] B [ ] C [ ] D [ ] E
5. [ ] A [ ] B [ ] C [ ] D [ ] E [ ] F
6. [ ] A [ ] B [ ] C [ ] D
7. [ ] A [ ] B
8. [ ] A [ ] B
9. [ ] A [ ] B [ ] C [ ] D [ ] E [ ] F
10. [ ] A [ ] B [ ] C [ ] D
11. [ ] A [ ] B [ ] C [ ] D [ ] E
12. [ ] A [ ] B [ ] C [ ] D [ ] E
13. [ ] A [ ] B [ ] C [ ] D [ ] E
14. [ ] A [ ] B [ ] C [ ] D [ ] E
15. [ ] A [ ] B [ ] C [ ] D [ ] E
16. [ ] A [ ] B [ ] C [ ] D [ ] E
17. [ ] A [ ] B [ ] C [ ] D [ ] E
18. [ ] A [ ] B [ ] C [ ] D [ ] E
19. [ ] A [ ] B [ ] C [ ] D [ ] E
20. [ ] A [ ] B [ ] C [ ] D [ ] E
21. [ ] A [ ] B [ ] C [ ] D [ ] E
22. [ ] A [ ] B [ ] C [ ] D [ ] E
23. [ ] A [ ] B [ ] C [ ] D [ ] E
24. [ ] A [ ] B [ ] C [ ] D [ ] E
25. [ ] A [ ] B [ ] C [ ] D [ ] E
26. [ ] A [ ] B [ ] C [ ] D [ ] E
27. [ ] A [ ] B [ ] C [ ] D [ ] E
28. [ ] A [ ] B
29. [ ] A [ ] B [ ] C [ ] D [ ] E [ ] F

Signature ***Date I Completed Exam***

23. The content expert(s) demonstrated expertise in the subject matter.
A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

24. Overall, the quality of the journal article was excellent.
A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

25. These recommendations will improve the quality of my practice.
A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

26. The availability of continuing education credit influenced my decision to read this report.
A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

27. The *MMWR* format was conducive to leaning this content.
A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

28. Do you feel this course was commercially biased? (*Indicate yes or no; if yes, please explain in the space provided.*)
A. Yes.
B. No.

29. How did you learn about the continuing education activity?
A. Internet.
B. Advertisement (e.g., fact sheet, *MMWR* cover, newsletter, or journal).
C. Coworker/supervisor.
D. Conference presentation.
E. *MMWR* subscription.
F. Other.

Correct answers for questions 1–10.
1. E; 2. D; 3. C; 4. E; 5. E; 6. A; 7. B; 8. B; 9. E; 10. C

The *Morbidity and Mortality Weekly Report (MMWR)* Series is prepared by the Centers for Disease Control and Prevention (CDC) and is available free of charge in electronic format and on a paid subscription basis for paper copy. To receive an electronic copy each week, send an e-mail message to *listserv@listserv.cdc.gov*. The body content should read *SUBscribe mmwr-toc*. Electronic copy also is available from CDC's World-Wide Web server at *http://www.cdc.gov/mmwr* or from CDC's file transfer protocol server at *ftp://ftp.cdc.gov/pub/publications/mmwr*. To subscribe for paper copy, contact Superintendent of Documents, U.S. Government Printing Office, Washington, DC 20402; telephone 202-512-1800.

Data in the weekly *MMWR* are provisional, based on weekly reports to CDC by state health departments. The reporting week concludes at close of business on Friday; compiled data on a national basis are officially released to the public on the following Friday. Address inquiries about the *MMWR* Series, including material to be considered for publication, to Editor, *MMWR* Series, Mailstop K-95, CDC, 1600 Clifton Rd., N.E., Atlanta, GA 30333; telephone 888-232-3228.

All material in the *MMWR* Series is in the public domain and may be used and reprinted without permission; citation as to source, however, is appreciated.

All *MMWR* references are available on the Internet at http://www.cdc.gov/mmwr. Use the search function to find specific articles.

Use of trade names and commercial sources is for identification only and does not imply endorsement by the U.S. Department of Health and Human Services.

References to non-CDC sites on the Internet are provided as a service to *MMWR* readers and do not constitute or imply endorsement of these organizations or their programs by CDC or the U.S. Department of Health and Human Services. CDC is not responsible for the content of these sites. URL addresses listed in *MMWR* were current as of the date of publication.

☆U.S. Government Printing Office: 2005-733-116/00108 Region IV ISSN: 1057-5987

MMWR™

Morbidity and Mortality Weekly Report

Recommendations and Reports July 18, 2003 / Vol. 52 / No. RR-12

Incorporating HIV Prevention into the Medical Care of Persons Living with HIV

Recommendations of CDC, the Health Resources and Services Administration, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America

INSIDE: Continuing Education Examination

DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTERS FOR DISEASE CONTROL AND PREVENTION

The *MMWR* series of publications is published by the Epidemiology Program Office, Centers for Disease Control and Prevention (CDC), U.S. Department of Health and Human Services, Atlanta, GA 30333.

SUGGESTED CITATION

Centers for Disease Control and Prevention. Incorporating HIV prevention into the medical care of persons living with HIV: recommendations of CDC, the Health Resources and Services Administration, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. MMWR 2003;52(No. RR-12):[inclusive page numbers].

Centers for Disease Control and Prevention

Julie L. Gerberding, M.D., M.P.H.
Director

Dixie E. Snider, Jr., M.D., M.P.H.
(*Acting*) *Deputy Director for Public Health Science*

Donna F. Stroup, Ph.D., M.Sc.
(*Acting*) *Associate Director for Science*

Epidemiology Program Office

Stephen B. Thacker, M.D., M.Sc.
Director

Office of Scientific and Health Communications

John W. Ward, M.D.
Director
Editor, MMWR *Series*

Suzanne M. Hewitt, M.P.A.
Managing Editor, MMWR *Series*

C. Kay Smith-Akin, M.Ed.
Lead Technical Writer/Editor

Lynne McIntyre, M.A.L.S.
Project Editor

Beverly J. Holland
Lead Visual Information Specialist

Lynda G. Cupell
Malbea A. Heilman
Visual Information Specialists

Quang M. Doan
Erica R. Shaver
Information Technology Specialists

CONTENTS

Introduction 1
Risk Screening 3
Screening for Behavioral Risk Factors 3
Screening for Clinical Risk Factors 5
Behavioral Interventions 7
Structural Approaches To Support and Enhance Prevention 7
Interventions Delivered On-Site 8
Referrals for Additional Prevention Interventions and Other Services 13
Examples of Case Situations for Prevention Counseling ... 14
Partner Counseling And Referral Services, Including Partner Notification 15
Laws and Regulations Related to Informing Partners 16
Approaches to Notifying Partners 16
Acknowledgments 17
References 17

Disclosure of Relationship

The preparers of this report have no conflict of interest with the manufacturers or products discussed herein.

Incorporating HIV Prevention into the Medical Care of Persons Living with HIV

Recommendations of CDC, the Health Resources and Services Administration, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America

Summary

Reducing transmission of human immunodeficiency virus (HIV) in the United States requires new strategies, including emphasis on prevention of transmission by HIV-infected persons. Through ongoing attention to prevention, risky sexual and needle-sharing behaviors among persons with HIV infection can be reduced and transmission of HIV infection prevented. Medical care providers can substantially affect HIV transmission by screening their HIV-infected patients for risk behaviors; communicating prevention messages; discussing sexual and drug-use behavior; positively reinforcing changes to safer behavior; referring patients for services such as substance abuse treatment; facilitating partner notification, counseling, and testing; and identifying and treating other sexually transmitted diseases (STDs).

To help incorporate HIV prevention into the medical care of HIV-infected persons, CDC, the Health Resources and Services Administration, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America developed these recommendations. The recommendations are general and apply to incorporating HIV prevention into the medical care of all HIV-infected adolescents and adults, regardless of age, sex, or race/ethnicity. They are intended for all persons who provide medical care to HIV-infected persons (e.g., physicians, nurse practitioners, nurses, physician assistants); they might also be useful to those who deliver prevention messages (e.g., case managers, social workers, health educators).

The recommendations were developed by using an evidence-based approach. For each recommendation, the strength of the recommendation, the quality of available evidence supporting the recommendation, and the outcome for which the recommendation is rated are provided. The recommendations are categorized into three major components: screening for HIV transmission risk behaviors and STDs, providing brief behavioral risk-reduction interventions in the office setting and referring selected patients for additional prevention interventions and other related services, and facilitating notification and counseling of sex and needle-sharing partners of infected persons.

Introduction

Despite substantial advances in the treatment of human immunodeficiency virus (HIV) infection, the estimated number of annual new HIV infections in the United States has remained at 40,000 for over 10 years (*1*). HIV prevention in this country has largely focused on persons who are not HIV infected, to help them avoid becoming infected. However, further reduction of HIV transmission will require new strategies, including increased emphasis on preventing transmission by HIV-infected persons (*2,3*). HIV-infected persons who are aware of their HIV infection tend to reduce behaviors that might transmit HIV to others (*4–7*). Nonetheless, recent reports suggest that such behavioral changes often are not maintained and that a substantial number of HIV-infected persons continue to engage in behaviors that place others at risk for HIV infection (*8–13*).

Reversion to risky sexual behavior might be as important in HIV transmission as failure to adopt safer sexual behavior immediately after receiving a diagnosis of HIV (*14*). Unprotected anal sex appears to be occurring more frequently in some urban centers, particularly among young men who have sex with men (MSM) (*15*). Bacterial and viral sexually transmitted diseases (STDs) in HIV-infected men and women receiving outpatient care have been increasingly noted (*16,17*), indicating ongoing risky behaviors and opportunities for HIV

The material in this report originated in the National Center for HIV, STD and TB Prevention, Harold W. Jaffe, M.D., Director; Division of HIV/AIDS Prevention — Surveillance and Epidemiology, Robert S. Janssen, Director; Division of HIV/AIDS Prevention — Intervention, Research, and Support, Robert S. Janssen, M.D., Acting Director.

transmission. Further, despite declining syphilis prevalence in the general U.S. population, sustained outbreaks of syphilis among MSM, many of whom are HIV infected, continue to occur in some areas; rates of gonorrhea and chlamydial infection have also risen for this population (*18–21*). Rising STD rates among MSM indicate increased potential for HIV transmission, both because these rates suggest ongoing risky behavior and because STDs have a synergistic effect on HIV infectivity and susceptibility (*22*). Studies suggest that optimism about the effectiveness of highly active antiretroviral therapy (HAART) for HIV may be contributing to relaxed attitudes toward safer sex practices and increased sexual risk-taking by some HIV-infected persons (*12,23–27*).

Injection drug use also continues to play a key role in the HIV epidemic; at least 28% of AIDS cases among adults and adolescents with known HIV risk category reported to CDC in 2000 were associated with injection drug use (*28*). In some large drug-using communities, HIV seroincidence and seroprevalence among injection drug users (IDUs) have declined in recent years (*29,30*). This decline has been attributed to several factors, including increased use of sterile injection equipment, declines in needle-sharing, shifts from injection to noninjection methods of using drugs, and cessation of drug use (*31–33*). However, injection-drug use among young adult heroin users has increased substantially in some areas (*34,35*), a reminder that, as with sexual behaviors, changes to less risky behaviors may be difficult to sustain.

Clinicians providing medical care to HIV-infected persons can play a key role in helping their patients reduce risk behaviors and maintain safer practices and can do so with a feasible level of effort, even in constrained practice settings. Clinicians can greatly affect patients' risks for transmission of HIV to others by performing a brief screening for HIV transmission risk behaviors; communicating prevention messages; discussing sexual and drug-use behavior; positively reinforcing changes to safer behavior; referring patients for such services as substance abuse treatment; facilitating partner notification, counseling, and testing; and identifying and treating other STDs (*36,37*). These measures may also decrease patients' risks of acquiring other STDs and bloodborne infections (e.g., viral hepatitis). Managed care plans can play an important role in HIV prevention by incorporating these recommendations into their practice guidelines, educating their providers and enrollees, and providing condoms and educational materials. In the context of care, prevention services might be delivered in clinic or office environments or through referral to community-based programs. Some clinicians have expressed concern that reimbursement is often not provided for prevention services and note that improving reimbursement for such services might enhance the adoption and implementation of these guidelines.

This report provides general recommendations for incorporating HIV prevention into the medical care of all HIV-infected adolescents and adults, regardless of age, sex, or race/ethnicity. The recommendations are intended for all persons who provide medical care to HIV-infected persons (e.g., physicians, nurse practitioners, nurses, physician assistants). They may also be useful to those who deliver prevention messages (e.g., case managers, social workers, health educators). Special considerations may be needed for some subgroups (e.g., adolescents, for whom laws and regulations might exist governing providing of services to minors, the need to obtain parental consent, or duty to inform). However, it is beyond the scope of this report to address special considerations of subgroups. Furthermore, the recommendations focus on sexual and drug-injection behaviors, since these behaviors are responsible for nearly all HIV transmission in the United States. Separate guidelines have been published for preventing perinatal transmission (*38–40*).

These recommendations were developed by using an evidence-based approach (Table 1). The strength of each recommendation is indicated on a scale of A (strongest recommendation for) to E (recommendation against); the quality of available evidence supporting the recommendation is indicated on a scale of I (strongest evidence for) to III (weakest evidence for), and the outcome for which the recommendation is rated is provided. The recommendations are categorized into three

TABLE 1. Rating systems for strength of recommendations and quality of evidence supporting the recommendations

Rating	Strength of the Recommendation
A	**Should always be offered.** Both strong evidence for efficacy and substantial benefit support recommendation for use.
B	**Should generally be offered.** Moderate evidence for efficacy — or strong evidence for efficacy but only limited benefit — supports recommendation for use.
C	**Optional.** Evidence for efficacy is insufficient to support a recommendation for use.
D	**Should generally not be offered.** Moderate evidence for lack of efficacy or for adverse outcome supports a recommendation against use.
E	**Should never be offered.** Good evidence for lack of efficacy or for adverse outcome supports a recommendation against use.
	Quality of Evidence Supporting the Recommendation
I	Evidence from at least one properly randomized, controlled trial.
II	Evidence from at least one well-designed clinical trial without randomization, from cohort or case-controlled analytic studies (preferably from more than one center), or from multiple time-series studies. Or dramatic results from uncontrolled experiments.
III	Evidence from opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees.

major components: 1) screening for HIV transmission risk behaviors and STDs, 2) providing brief behavioral risk-reduction interventions in the office setting and referring selected patients for additional prevention interventions and other related services, and 3) facilitating notification and counseling of sex and needle-sharing partners of infected persons.

This report was developed by CDC, the Health Resources and Services Administration (HRSA), the National Institutes of Health (NIH), and the HIV Medicine Association (HIVMA) of the Infectious Diseases Society of America (IDSA). The recommendations will evolve as results from ongoing behavioral intervention trials become available.

Risk Screening

Risk screening is a brief assessment of behavioral and clinical factors associated with transmission of HIV and other STDs (Table 2). Risk screening can be used to identify patients who should receive more in-depth risk assessment and HIV risk-reduction counseling, other risk-reduction interventions, or referral for other services (e.g., substance abuse treatment). Risk screening identifies patients at greatest risk for transmitting HIV so that prevention and referral recommendations can be focused on these patients. Screening methods include probing for behaviors associated with transmission of HIV and other STDs, eliciting patient reports of symptoms of other STDs, and laboratory testing for other STDs. Although each of these methods has limitations, a combination of methods should increase the sensitivity and effectiveness of screening. In conducting risk screening, clinicians should recognize that risk is not static. Patients' lives and circumstances change, and a patient's risk of transmitting HIV may change from one medical encounter to another. Also, clinicians should recognize that working with adolescents may require special approaches and should be aware of and adhere to all laws and regulations related to providing services to minors.

Screening for Behavioral Risk Factors

Clinicians frequently believe that patients are uncomfortable disclosing personal risks and hesitant to respond to questions about sensitive issues, such as sexual behaviors and illicit drug use. However, available evidence suggests that patients, when asked, will often disclose their risks (*41,42*) and that some patients have reported greater confidence in their clinician's ability to provide high-quality care if asked about sexual and STD history during the initial visits (*43*).

Screening for behavioral risk factors can be done with brief self-administered written questionnaires; computer-, audio-, and video-assisted questionnaires; structured face-to-face

TABLE 2. Recommendations for screening of human immunodeficiency virus (HIV)-infected persons for HIV transmission risk

Recommendation	Rating
HIV-infected patients should be screened for behaviors associated with HIV transmission by using a straightforward, nonjudgmental approach. This should be done at the initial visit and subsequent routine visits or periodically, as the clinician feels necessary, but at a minimum of yearly. Any indication of risky behavior should prompt a more thorough assessment of HIV transmission risks.	A-II (for identifying transmission risk)
At the initial and each subsequent routine visit, HIV-infected patients should be questioned about symptoms of STDs (e.g., urethral or vaginal discharge; dysuria; intermenstrual bleeding; genital or anal ulcers; anal pruritus, burning, or discharge; and, for women, lower abdominal pain with or without fever). Regardless of reported sexual behavior or other epidemiologic risk information, the presence of such signs or symptoms should always prompt diagnostic testing and, when appropriate, treatment.	A-I (for identifying and treating STDs)
At the initial visit • All HIV-infected women and men should be screened for laboratory evidence of syphilis. Women should also be screened for trichomoniasis. Sexually active women aged ≤25 years and other women at increased risk, even if asymptomatic, should be screened for cervical chlamydial infection.	A-II (for identifying STDs)
• Consideration should be given to screening all HIV-infected men and women for gonorrhea and chlamydial infections. However, because of the cost of screening and the variability of prevalence of these infections, decisions about routine screening for these infections should be based on epidemiologic factors (including prevalence of infection in the community or the population being served), availability of tests, and cost. (Some HIV specialists also recommend type-specific serologic testing for herpes simplex virus type 2 for both men and women.).	B-II (for identifying STDs)
Screening for STDs should be repeated periodically (i.e., at least annually) if the patient is sexually active or if earlier screening revealed STDs. Screening should be done more frequently (e.g., at 3–6-month intervals) for asymptomatic persons at higher risk (see Box 2).	B-III (for identifying STDs)
At the initial and each subsequent routine visit, HIV-infected women of childbearing age should be questioned to identify possible current pregnancy, interest in future pregnancy, or sexual activity without reliable contraception. They should be referred for appropriate counseling, reproductive health care, or prenatal care, as indicated. Women should be asked whether they suspect pregnancy or have missed their menses and, if so, should be tested for pregnancy.	A-I (for preventing perinatal HIV transmission)

interviews; and personalized discussions (*41,44–53*). Screening questions can be either open-ended or closed (directed) (Box 1). Use of open-ended questions avoids simple "yes" or "no" responses and encourages patients to discuss personal risks and the circumstances in which risks occur (*15,44,54*). Open-ended questions also help the clinician gather enough detail to understand potential transmission risks and make more meaningful recommendations. However, although well received by patients, the open-ended approach may initially be difficult for clinicians schooled in directed questioning, who tend to prefer directed screening questions. Directed questions are probably useful for identifying patients with problems that should be more thoroughly discussed. Among directed approaches, technical tools like computer-, audio-, and video-assisted interviews have been found to elicit more self-reported risk behaviors than did interviewer-administered questionnaires, particularly among younger patients (*41,51–53,55*). Studies suggest that clinicians who receive some training, particularly that including role-play and feedback concerning clinical performance, are more likely to perform effective risk screening (*46–49*).

Sex-related behaviors important to address in risk screening include whether the patient has been engaging in sex; number and sex of partners; partners' HIV serostatus (infected, not infected, or unknown); types of sexual activity (oral, vaginal, or anal sex) and whether condoms are used; and barriers to abstinence or correct condom use (e.g., difficulty talking with partners about or disclosing HIV serostatus, alcohol and other drug use before or during sex). Also, because the risk for perinatal HIV transmission is high without appropriate intervention, clinicians are advised to assess whether women of childbearing age might be pregnant, are interested in becoming pregnant, or are not specifically considering pregnancy but are sexually active and not using reliable contraception (*39,56,57*). Women who are unable to become pregnant because of elective sterilization, hysterectomy, salpingo-oophorectomy, or other medical reasons might be less likely to use condoms because of a lack of concern for contraception; these women should be counseled regarding the need for use of condoms to prevent transmission of HIV. Patients who wish to conceive and whose partner is not infected also might engage in risky behavior. Patients interested in pregnancy, for themselves or their partner, should be referred to a reproductive health specialist (*58*).

Injection-drug–related behaviors important to address in screening include whether the patient has been injecting illicit drugs; whether the patient has been sharing needles and syringes or other injection equipment; how many partners the patient has shared needles with; whether needle-sharing partners are known to be HIV infected, not infected, or of

BOX 1. Examples of screening strategies to elicit patient-reported risk for human immunodeficiency virus (HIV) transmission*

Open-ended question by clinician, similar to one of the following:

- "What are you doing now that you think may be a risk for transmitting HIV to a partner?"
- "Tell me about the people you've had sex with recently."
- "Tell me about your sex life."

Screening questions (checklist) for use with a self-administered questionnaire; computer-, audio-, or video-assisted questionnaire; or a face-to-face interview: †§

"Since your last checkup here," or, if first visit, "Since you found out you were infected with HIV,":

- "Have you been sexually active; that is, have you had vaginal, anal, or oral sex with a partner?"

If yes

— "Have you had vaginal or anal intercourse without a condom with anyone?"

If yes

— "Were any of these people HIV-negative, or are you unsure about their HIV status?"

— "Have you had oral sex with someone?"

If yes

— (For a male patient) "Did you ejaculate into your partner's mouth?"

- "Have you had a genital sore or discharge, discomfort when you urinate, or anal burning or itching?"
- "Have you been diagnosed or treated for a sexually transmitted disease (STD), or do you know if any of your sex partners have been diagnosed or treated for an STD?"
- "Have you shared drug-injection equipment (needles, syringes, cotton, cooker, water) with others?"

If yes

— "Were any of these people HIV negative, or are you unsure about their HIV status?"

* Source: Adapted from CDC. Revised guidelines for HIV counseling, testing, and referral. MMWR 2001;50(No. RR-19).

† This checklist can be administered by the patient or clinician and should take approximately 4 minutes.

§ A positive response to any of the screening questions should cue the clinician to have a more in-depth discussion to ensure that specific risks are clearly understood.

unknown HIV serostatus; whether the patient has been using new or sterilized needles and syringes; and what barriers exist to ceasing illicit drug use or, failing that, to adopting safer injection practices (e.g., lack of access to sterile needles and syringes).

Approaches to Screening for Behavioral Risk Factors

The most effective manner for screening for behavioral risk factors is not well defined; however, simple approaches are more acceptable to both patients and health-care providers (*53*). Screening tools should be designed to be as sensitive as possible for identifying behavioral risks; a more detailed, personalized assessment can then be used to improve specificity and provide additional detail. The sensitivity of screening instruments depends on obtaining accurate information. However, accuracy of information can be influenced by a variety of factors: recall, misunderstanding about risk, legal concerns, concern about confidentiality of the information and how the information will be used, concern that answers may affect ability to receive services, concern that answers may affect social desirability (i.e., the tendency to provide responses that will avoid criticism), and the desire for social approval (the tendency to seek praise) (*45,55*). Interviewer factors also influence the accuracy of information. Surveys indicate that patients are more likely to discuss risk behaviors if they perceive their clinicians are comfortable talking about stigmatized topics such as sex and drug use (*46–49*) and are nonjudgmental, empathetic, knowledgeable, and comfortable counseling patients about sexual risk factors (*41,46–50*). These factors need to be considered when interpreting responses to screening questions. To the extent possible, screening and interventions should be individualized to meet patient needs. Examples of two screening approaches are provided (Box 1).

Incorporating Screening for Behavioral Risk Factors into the Office Visit

Before the patient is seen by the clinician, screening for behavioral risks can be done with a self-administered questionnaire; a computer-, audio-, or video-assisted questionnaire; or a brief interview with ancillary staff; the clinician can then review the results on the patient's medical record. Alternatively, behavioral risk screening can be done during the medical encounter (e.g., as part of the history); either open-ended questions or a checklist approach with in-depth discussion about positive responses can be used (Box 1). Because, given patients' immediate health needs, it can be difficult in the clinical care setting to remember less urgent matters such as risk screening and harm reduction, provider reminder systems (e.g., computerized reminders) have been used by health-care systems to help ensure that recommended procedures are done regularly. Multicomponent health-care system interventions that include a provider reminder system and a provider education program are effective in increasing delivery of certain prevention services (*59*). Risk screening might be more likely to occur in managed care settings if the managed care organization specifically calls for it (*60*).

Screening for Clinical Risk Factors

Screening for STDs

Recommendations for preventive measures, including medical screening and vaccinations, that should be included in the care of HIV-infected persons (*16,21,39,44,54,61–69*) have been published previously. This report is not intended to duplicate existing recommendations; it addresses screening specifically to identify clinical factors associated with increased risk for transmission of HIV from infected to noninfected persons. In this context, STDs are the primary infections of concern for three reasons. First, the presence of STDs often suggests recent or ongoing sexual behaviors that may result in HIV transmission. Second, many STDs enhance the risk for HIV transmission or acquisition (*22,70–73*). Early detection and treatment of bacterial STDs might reduce the risk for HIV transmission. Third, identification and treatment of STDs can reduce the potential for spread of these infections among high-risk groups (i.e., sex or drug-using networks).

Screening and diagnostic testing serve distinctly different purposes. By definition, screening means testing on the basis of risk estimation, regardless of clinical indications for testing, and is a cornerstone of identifying persons at risk for transmitting HIV to others. Clinicians should routinely ask about STD symptoms, including urethral or vaginal discharge; dysuria; intermenstrual bleeding; genital or anal ulcers or other lesions; anal pain, pruritus, burning, discharge, or bleeding; and, for women, lower abdominal pain with or without fever. Regardless of reported sexual behavior or other epidemiologic risk information, the presence of such symptoms should always prompt diagnostic testing and, when appropriate, treatment. However, clinical symptoms are not sensitive for identifying many infections because most STDs are asymptomatic (*74–81*); therefore, laboratory screening of HIV-infected persons is an essential tool for identifying persons at risk for transmitting HIV and other STDs.

Laboratory Testing for STDs

Identification of syphilis requires direct bacteriologic (i.e., dark-field microscopy) or serologic testing. However, noninvasive, urine-based nucleic acid amplification tests

(NAATs) have greatly simplified testing for *Neisseria gonorrhoeae* and *Chlamydia trachomatis*. Although they are more costly than other screening tests, their ease of use and sensitivity—similar to the sensitivity of culture for detection of *N. gonorrhoeae* and substantially higher than the sensitivity of all other tests for *C. trachomatis* (including culture)—for detecting genital infection are great advantages. Detection of rectal or pharyngeal gonorrhea still requires culture. Pharyngeal infection with *C. trachomatis* is uncommon, and routine screening for it is not recommended (*63,82*). NAATs have not been approved for use with specimens collected from sites other than the urethra, cervix, or urine. Recommended screening strategies and diagnostic tests for detecting asymptomatic STDs are described (Box 2, Table3).

Local and state health departments have reporting requirements, which vary among states, for HIV and other STDs. Clinicians need to be aware of and comply with requirements for the areas in which they practice; information on reporting requirements can be obtained from health departments.

Screening for Pregnancy

Women of childbearing age should be questioned during routine visits about the possibility of pregnancy. Women who state that they suspect pregnancy or have missed their menses

BOX 2. Examples of laboratory screening strategies to detect asymptomatic sexually transmitted diseases*

First Visit

For all patients

- Test for syphilis: nontreponemal serologic test (e.g., rapid plasma reagin [RPR] or Venereal Disease Research Laboratory [VDRL] test).
- Consider testing for urogenital gonorrhea: urethral (men) or cervical (women) specimen for culture, or urethral/cervical specimen or first-catch urine† (men and women) nucleic acid amplification test (NAAT) for *Neisseria gonorrhoeae.*§
- Consider testing for urogenital chlamydial infection: urethral (men) or cervical (women) specimen or first-catch urine† (men and women) specimen for NAAT for *Chlamydia trachomatis.*§

For women

- Test for trichomoniasis: wet mount examination or culture of vaginal secretions for *Trichomonas vaginalis.*
- Test for urogenital chlamydia: cervical specimen for NAAT for *C. trachomatis*§ for all sexually active women aged ≤25 years and other women at increased risk, even if asymptomatic.

For patients reporting receptive anal sex

- Test for rectal gonorrhea: anal swab culture for *N. gonorrhoeae.*§
- Test for rectal chlamydia: anal swab culture for *C. trachomatis,*§ if available.

For patients reporting receptive oral sex

- Test for pharyngeal gonococcal infection: culture for *N. gonorrhoeae.*§

Subsequent Routine Visits

- The tests described here should be repeated periodically (i.e., at least annually) for all patients who are sexually active. More frequent periodic screening (e.g., at 3-month to 6-month intervals) may be indicated for asymptomatic persons at higher risk. Presence of any of the following factors may support more frequent than annual periodic screening: 1) multiple or anonymous sex partners; 2) past history of any STD; 3) identification of other behaviors associated with transmission of HIV and other STDs; 4) sex or needle-sharing partner(s) with any of the above-mentioned risks; 5) developmental changes in life that may lead to behavioral change with increased risky behaviors (e.g., dissolution of a relationship); or 6) high prevalence of STDs in the area or in the patient population.

* These recommendations apply to persons without symptoms or signs of STDs. Patients with symptoms (e.g., urethral or vaginal discharge; dysuria; intermenstrual bleeding; genital or anal lesions; anal pruritus, burning, or discharge; and lower abdominal pain with or without fever) or known exposure should have appropriate diagnostic testing regardless of reported sexual behavior or other risk factors.

† First-catch urine (i.e., the first 10–30 mL of urine voided after initiating the stream) should be used.

§ The yield of testing for *N. gonorrhoeae* and *C. trachomatis* is likely to vary, and screening for these pathogens should be based on consideration of patient's risk behaviors, local epidemiology of these infections, availability of tests (e.g., culture for *C. trachomatis*), and cost. Appropriate diagnostic tests for different pathogens causing STDs are described (Table 3).

Note: Testing or vaccination for hepatitis, pneumococcal disease, influenza, and other infectious diseases (e.g., screening pregnant women for syphilis, gonorrhea, chlamydia, and hepatitis B surface antigen) should be incorporated into the routine care of HIV-infected persons as recommended elsewhere (*16,21,39,44,54,61–67*).

Note: Symptomatic and asymptomatic herpes simplex virus (HSV) infection, especially with HSV type 2, is prevalent among HIV-infected persons and might increase the risk of transmitting and acquiring HIV. Therefore, some HIV specialists recommend routine, type-specific serologic testing for HSV-2. Patients with positive results should be informed of the increased risk of transmitting HIV and counseled regarding recognition of associated symptoms (*16,54,67*). Only tests for detection of HSV glycoprotein G are truly type-specific and suitable for HSV-2 serologic screening.

Note: Local and state health departments have reporting requirements for HIV and other STDs, which vary among states. Clinicians should be aware of and comply with requirements for the areas in which they practice; information on reporting requirements can be obtained from health departments.

TABLE 3. Available diagnostic testing for detection of sexually transmitted diseases (STDs)*

STD	Diagnostic test†
Syphilis	Dark-field examination or direct fluorescent antibody test of exudate of lesion
	Serum nontreponemal tests, rapid plasma reagin (RPR), or Venereal Disease Research Laboratory (VDRL) for screening followed by serum treponemal tests (e.g., fluorescent treponemal antibody absorbed [FTA-ABS] or *Treponema pallidum* particle agglutination [TP-PA])
Trichonomiasis	Microscopic examination of wet mount or culture of vaginal secretions
Herpes	Viral culture of genital or other mucocutaneous ulcers
	Herpes simplex virus type-specific serologic tests
Gonorrhea	
Female genitourinary [GU] tract	Culture of endocervical swab specimen
	Nucleic acid amplification tests (NAAT) of endocervical swab specimen
	NAAT of urine§
Male GU tract	Culture of intraurethral swab
	NAAT of intraurethral swab
	NAAT of urine§
Rectum/pharynx specimen	Culture of rectal or pharyngeal swab specimen with selective medium
Chlamydia	
Female GU tract	NAAT of endocervical swab specimen
	NAAT of urine§
	Unamplified nucleic acid hybridization test, enzyme immunoassay, or direct fluorescent antibody test of endocervical swab specimen
	Culture of endocervical swab specimen
Male GU tract	NAAT of intraurethral swab specimen
	NAAT of urine§
	Non-NAAT or culture of intraurethral swab specimen
Rectum/pharynx	Culture of rectal or pharyngeal swab specimen¶
	Direct fluorescent antibody test performed on rectal or pharyngeal swab specimen¶

* **Source:** CDC. Sexually transmitted diseases treatment guidelines, 2002. MMWR 2002;51(No. RR-6). CDC Screening tests to detect *Chlamydia trachomatis* and *Neisseria gonorrhoeae* infections—2002. MMWR 2002;51(No. RR-15).
† Diagnostic tests are listed in order of preference for recommendation, with the most highly recommended test listed first. Alternative tests should be performed if a specimen cannot be obtained or if the preferred test is not available.
§ NAAT of urine is less sensitive than that of an endocervical or intraurethral swab specimen.
¶ *Chlamydia trachomatis*-major outer membrane protein (MOMP)–specific stain should be used.

should be tested for pregnancy. Early pregnancy diagnosis would benefit even women not receiving antiretroviral treatment because they could be offered treatment to decrease the risk for perinatal HIV transmission.

Behavioral Interventions

Behavioral interventions are strategies designed to change persons' knowledge, attitudes, behaviors, or practices in order to reduce their personal health risks or their risk of transmitting HIV to others (Table 4). Behavioral change can be facilitated by environmental cues in the clinic or office setting, messages delivered to patients by clinicians or other qualified staff on-site, or referral to other persons or organizations providing prevention services. Because behavior change often occurs in incremental steps, a brief behavioral intervention conducted at each clinic visit could result in patients, over time, adopting and maintaining safer practices. Behavioral interventions should be appropriate for the patient's culture, language, sex, sexual orientation, age, and developmental level (*44*). In settings where care is delivered to HIV-infected adolescents, for example, approaches need to be specifically tailored for this age group (*83*). Also, clinicians should be aware of and adhere to all laws and regulations related to providing services to minors.

Structural Approaches To Support and Enhance Prevention

Clinic or office environments can be structured to support and enhance prevention. All patients, especially new patients, should be provided printed information about HIV transmission risks, preventing transmission of HIV to others, and

TABLE 4. Recommendations for behavioral interventions to reduce human immunodeficiency virus (HIV) transmission risk

Recommendation	Rating
Clinics or office environments where patients with HIV infection receive care should be structured to support and enhance HIV prevention.	B-III (for enhancing patient recall of prevention messages)
Within the context of HIV care, brief general HIV prevention messages should be regularly provided to HIV-infected patients at each visit or periodically, as determined by the clinician, and at a minimum of twice yearly. These messages should emphasize the need for safer behaviors to protect their own health and the health of their sex or needle-sharing partners, regardless of perceived risk. Messages should be tailored to the patient's needs and circumstances.	A-III (for efficacy in promoting safer behaviors)
Patients should have adequate, accurate information regarding factors that influence HIV transmission and methods for reducing the risk for transmission to others, emphasizing that the most effective methods for preventing transmission are those that protect noninfected persons against exposure to HIV (e.g., sexual abstinence; consistent and correct use of condoms made of latex, polyurethane or other synthetic materials; and sex with only a partner of the same HIV status). HIV-infected patients who engage in high-risk sexual practices (i.e., capable of resulting in HIV transmission) with persons of unknown or negative HIV serostatus should be counseled to use condoms consistently and correctly.	A-III (for using brief clinician-delivered messages to influence patient behavior)
Patients' misconceptions regarding HIV transmission and methods for reducing risk for transmission should be identified and corrected. For example, ensure that patients know that 1) per-act estimates of HIV transmission risk for an individual patient vary according to behavioral, biologic, and viral factors; 2) highly active antiretroviral therapy (HAART) cannot be relied upon to eliminate the risk of transmitting HIV to others; and 3) nonoccupational postexposure prophylaxis is of uncertain effectiveness for preventing infection in HIV-exposed partners.	A-III (for using brief clinician-delivered messages to influence patient behavior)
Tailored HIV prevention interventions, using a risk-reduction approach, should be delivered to patients at highest risk for transmitting HIV.	A-III (for efficacy in promoting safer behaviors)
After initial prevention messages are delivered, subsequent longer or more intensive interventions in the clinic or office should be delivered, if feasible.	A-I (for efficacy of multisession, clinic-based interventions in promoting safer behaviors)
HIV-infected patients should be referred to appropriate services for issues related to HIV transmission that cannot be adequately addressed during the clinic visit.	A-I (for efficacy of HIV prevention interventions conducted in nonclinic settings)
Persons who inject illicit drugs should be strongly encouraged to cease injecting and enter into substance abuse treatment programs (e.g., methadone maintenance) and should be provided referrals to such programs.	A-II (for reducing risky drug use and associated sexual behaviors)
Persons who continue to inject drugs should be advised to always use sterile injection equipment and to never reuse or share needles, syringes, or other injection equipment and should be provided information regarding how to obtain new, sterile syringes and needles (e.g., syringe exchange program).	A-II (for reducing risk for HIV transmission)

preventing acquisition of other STDs. Information can be disseminated at various locations in the clinic; for example, posters and other visual cues containing prevention messages can be displayed in examination rooms and waiting rooms. These materials usually can be obtained through local or state health department HIV/AIDS and STD programs or from the National Prevention Information Network (NPIN) (1-800-458-5231; http://www.cdcnpin.org). Additionally, condoms should be readily accessible at the clinic. Repeating prevention messages throughout the patient's clinic visit reinforces their importance, increasing the likelihood that they will be remembered (*68*).

Interventions Delivered On-Site

Prevention Messages for All Patients

All HIV-infected patients can benefit from brief prevention messages emphasizing the need for safer behaviors to protect both their own health and the health of their sex or needle-sharing partners. These messages can be delivered by clinicians, nurses, social workers, case managers, or health educators. They include discussion of the patient's responsibility for appropriate disclosure of HIV serostatus to sex and needle-sharing partners. Brief clinician-delivered approaches have been effective with a variety of health issues, including depression (*84*), smoking (*85–90*), alcohol abuse (*91,92*), weight and diet (*93*), and physical inactivity (*94*). This diverse experience with other health behaviors suggests that similar approaches may be effective in reducing HIV-infected patients' transmission risk behaviors. For patients already taking steps to reduce their risk of transmitting HIV, hearing the messages can reinforce continued risk-reduction behaviors. These patients should be commended and encouraged to continue these behaviors.

General HIV Prevention Messages

Patients frequently have inadequate information regarding factors that influence HIV transmission and methods for

preventing transmission. The clinician should ensure that patients understand that the most effective methods for preventing HIV transmission remain those that protect noninfected persons against exposure to HIV. For sexual transmission, the only certain means for HIV-infected persons to prevent sexual transmission to noninfected persons are sexual abstinence or sex with only a partner known to be already infected with HIV. However, restricting sex to partners of the same serostatus does not protect against transmission of other STDs or the possibility of HIV superinfection unless condoms of latex, polyurethane, or other synthetic materials are consistently and correctly used. Superinfection with HIV has been reported and appears to be rare, but its clinical consequences are not known (*95,96*). For injection-related transmission, the only certain means for HIV-infected persons to prevent transmission to noninfected persons are abstaining from injection drug use or, for IDUs who are unable or unwilling to stop injecting drugs, refraining from sharing injection equipment (e.g., syringes, needles, cookers, cottons, water) with other persons. Neither antiretroviral therapy for HIV-infected persons nor postexposure prophylaxis for partners is a reliable substitute for adopting and maintaining behaviors that guard against HIV exposure (*97*).

Identifying and Correcting Misconceptions

Patients might have misconceptions about HIV transmission (*98*), particularly with regard to the risk for HIV transmission associated with specific behaviors, the effect of antiretroviral therapy on HIV transmission, or the effectiveness of postexposure prophylaxis for nonoccupational exposure to HIV.

Risk for HIV Transmission Associated with Specific Sexual Behaviors. Patients often ask their clinicians about the degree of HIV transmission risk associated with specific sexual activities. Numerous studies have examined the risk for HIV transmission associated with various sex acts (*99–113*). These studies indicate that some sexual behaviors do have a lower average per-act risk for transmission than others and that replacing a higher-risk behavior with a relatively lower-risk behavior might reduce the likelihood that HIV transmission will occur. However, risk for HIV transmission is affected by numerous biological factors (e.g., host genetics, stage of infection, viral load, coexisting STDs) and behavioral factors (e.g., patterns of sexual and drug-injection partnering) (*105,114*), and per-act risk estimates based on models that assume a constant per-contact infectivity could be inaccurate (*110,113*). Thus, estimates of the absolute per-episode risk for transmission associated with different activities could be highly misleading when applied to a specific patient or situation. Further the relative risks of becoming infected with HIV, from the perspective of a person not infected with HIV, might vary greatly according to the various choices related to sexual behavior (Table 5) (*115,116*).

Effect of Antiretroviral Therapy on HIV Transmission. High viral load is a major risk factor for HIV transmission (*117–125*). Among untreated patients, the risk for HIV transmission through heterosexual contact has been shown to increase approximately 2.5-fold for each 10-fold increase in plasma viral load (126) (Table 6). By lowering viral load, antiretroviral therapy might reduce risk for HIV transmission, as has been demonstrated with perinatal transmission (*127,128*) and indirectly suggested for transmission via genital secretions (semen and cervicovaginal fluid) (*2,129–133*). However, because HIV can be detected in the semen, rectal secretions, female genital secretions, and pharynx of HIV-infected patients with undetectable plasma viral loads (*16,134–137*) and because consistent reduction of viral load depends on high

TABLE 5. Estimated per-act relative risk for a person without human immunodeficiency virus (HIV) infection acquiring HIV infection, based on sex act* and condom use†

Risk factor	Relative risk for a person without HIV infection of acquiring HIV infection
Sex act	
Insertive fellatio§	1
Receptive fellatio§	2
Insertive vaginal sex¶	10
Receptive vaginal sex¶	20
Insertive anal sex¶	13
Receptive anal sex¶	100
Condom use	
Yes**	1
No**	20

Note: This table quantifies the relative risk for HIV transmission in a way that can help compare the effects of a person's choices of sex act and condom use. It is presented from the point of view of a person without HIV infection and should be used to educate the HIV-infected patient regarding risks for transmission to partners who are not HIV infected or have unknown HIV serostatus. These risks are estimated from available data. Risks can vary depending on several factors, including presence of STDs in either partner and the HIV-infected partner's viral load. In addition, the relative frequency of performance of higher- and lower-risk sex acts will affect risk for transmission (see Prevention Messages for All Patients).

Note: The risks of these choices are multiplicative. Compared with the lowest relative risk (performing insertive fellatio using a condom; referent group, RR = 1), the overall relative risk increases to 2,000 when performing receptive anal sex (RR = 100) without a condom (RR = 20).

* Data regarding risk for transmission from sharing drug injection equipment are too limited to be included in this table.

† **Source:** Varghese B, Maher JE, Peterman TA, Branson BM, Steketee RW. Reducing the risk of sexual HIV transmission: quantifying the per-act risk for HIV infection based on choice of partner, sex act, and condom use. Sex Transm Dis 2002;29:38–43.

§ Best guess estimate, from Varghese et al.

¶ **Source:** European Study Group. Comparison of female-to-male and male-to-female transmision of HIV in 563 stable couples. BMJ 1992;304:809–13.

** **Source:** Macaluso JM, Kelaghan J, Artz L, et al. Mechanical failure of the latex condom in a cohort of women at high STD risk. Sex Transm Dis 1999;26:450–8.

TABLE 6. Adjusted rate ratios of the risk for transmission and acquisition of human immunodeficiency virus type 1 (HIV-1) among discordant partners*

Serum viral load of HIV-infected partners (copies/mL)†	Risk for transmission to partners not infected with HIV (adjusted rate ratio; 95% confidence interval)
<3500	Referent
3500–9999	5.80 (2.26–17.80)
10,000–49,999	6.91 (2.96–20.15)
>50,000	11.87 (5.02–34.88)
Per log increment viral load	2.45 (1.85–3.26)

* **Source:** Quinn TC, Wawer MJ Sewankambo N, et al. Viral load and heterosexual transmission of human immunodeficiency virus type 1 from mother to infant. N Engl J Med 1996;335:1621–9.

† Patients in this study did not receive antiretroviral medications, and those with low viral loads might have been long-term nonprogressors. Risks might not be equivalent for treated persons with low viral loads.Viral load in the blood may not be predictive of viral load in the genital tract; therefore, risks may vary with genital tract viral load.

adherence to antiretroviral regimens, the clinician should assume that all patients who are receiving therapy, even those with undetectable plasma HIV levels, can still transmit HIV. Patients who have treatment interruptions, whether scheduled or not, should be advised that this will likely lead to a rise in plasma viral load and increased risk for transmission. Another concern related to adherence to antiretroviral therapy is the development of drug-resistant mutations with subsequent transmission of drug-resistant viral strains. Several reports suggest that transmission of drug-resistant HIV occurs in the United States (*138–141*). Recent reports suggest that drug-resistant HIV strains might be less easily transmitted than wild-type virus (*142*), but these data are limited and their significance is unclear.

Effectiveness of Postexposure Prophylaxis for Non occupational Exposure to HIV. Although the U.S. Public Health Service recommends using antiretroviral drugs to reduce the likelihood of acquiring HIV infection from occupational exposure (e.g., accidental needle sticks received by health care workers) (*143*), limited data are available on efficacy of prophylaxis for nonoccupational exposure (*97,143–147*). Observational data suggesting effectiveness have been reported (*148*); however, postexposure prophylaxis might not protect against infection in all cases, and effectiveness of these regimens might be further hindered by lack of tolerability, potential toxicity, or viral resistance. Thus, avoiding exposure remains the best approach to preventing transmission, and the potential availability of postexposure prophylaxis should not be used as justification for engaging in risky behavior.

Tailored Interventions for Patients at High Risk for Transmitting HIV

Interventions tailored to the individual patient's risks can be delivered to patients at highest risk for transmitting HIV infection and for acquiring new STDs. This includes patients whose risk screening indicates current sex or drug-injection practices that may lead to transmission, who have a current or recent STD, or who have mentioned items of concern in discussions with the clinician (*149,150*). Any positive results of screening for behavioral risks or STDs should be addressed in more detail with the patient so a more thorough risk assessment can be done and an appropriate risk-reduction plan can be discussed and agreed upon.

Although the efficacy of brief clinician-delivered interventions with HIV-infected patients has not been studied extensively, substantial evidence exists for the efficacy of provider-delivered, tailored messages for other health concerns (*151–155*). An attempt should be made to determine which of the patient's risk behaviors and underlying concerns can be addressed during clinic visits and which might require referral (Box 3).

At a minimum, an appropriate referral should be made and the patient should be informed of the risks involved in continuing the behavior. HIV-infected persons who remain sexually active should be reminded that the only certain means for preventing transmission to noninfected persons is to restrict sex to partners known to be already infected with HIV and that they have a responsibility for disclosure of HIV serostatus to prospective sex partners. For mutually consensual sex with a person of unknown or discordant HIV serostatus, consistent and correct use of condoms made of latex, polyurethane, or other synthetic materials can substantially reduce the risk for HIV transmission. Also, some sex acts have relatively less risk for HIV transmission than others (Table 5). For HIV-infected patients who continue injection drug use, the provider should emphasize the risks associated with sharing needles and should provide information regarding substance abuse treatment and access to clean needles (Box 4) (*156–158*). Examples of targeted motivational messages on condom use and needle sharing are provided (Figures 1 and 2), and providers can individualize their own messages using these as a guide.

Clinician Training

Clinicians can prepare themselves to deliver HIV prevention messages and brief behavioral interventions to their patients by 1) developing strategies for incorporating HIV risk-reduction interventions into patients' clinic visits (*159*); 2) obtaining training on speaking with patients about sex and drug-use behaviors and on giving explanations in simple, everyday language (*68,87,160,161*); 3) becoming familiar with interventions that have demonstrated effectiveness (*162*); 4) becoming familiar with the underlying causes of and concerns related to risk behaviors among HIV-infected persons

BOX 3. Examples of which concerns to address and which to refer

Topics that can be successfully addressed by clinicians and clinic support staff:

- lack of knowledge about HIV transmission risks;
- misconceptions about risk of specific types of sexual and drug-use practices;
- misconceptions about viral load and transmission of HIV;
- how to disclose HIV-seropositive status to a sex partner, family member, or friend;
- importance of using condoms or not exchanging fluids with partners;
- ways to reduce number of sex or drug partners;
- ways to keep condoms accessible;
- ways to remember to use condoms;
- how to persuade a sex partner to use a condom;
- ways to obtain support (e.g., emotional, financial) from family, friends, and lovers;
- ways to clean/disinfect injection equipment;
- ways to obtain clean needles;
- ways to avoid sharing injection equipment; or
- ways to deal with mild psychological distress stemming from situational circumstances.

Issues that might need referral to outside agencies

- need for intensive HIV prevention intervention;
- excessive use of alcohol or recreational drug use;
- drug addiction, including injection drug use;
- depression, anger, guilt, fear, or other mental health needs;
- need for social support;
- sexual compulsivity;
- sexual or physical abuse (victim or perpetrator);
- desire to have children, contraceptive counseling;
- housing or transportation needs;
- nutritional needs;
- financial emergencies;
- child custody, parole, or other legal matters; or
- insurance coverage.

(e.g., domestic violence) (*13,163*); and 5) becoming familiar with community resources that address risk reduction. Free training on risk screening and prevention can be obtained at CDC-funded STD/HIV Prevention Training Centers (http://depts.washington.edu/nnptc) and HRSA-funded AIDS Education and Training Centers (http://www.aids-ed.org), which also offer continuing medical education credit for this training. Ongoing training will help clinicians refine their counseling skills as well as keep current with prevention concerns at the community level, thus increasing their ability to appropriately counsel and provide support to patients.

BOX 4. Examples of messages that should be communicated to drug users who continue to inject*

Persons who inject drugs should be regularly counseled to do the following:

- Stop using and injecting drugs.
- Enter and complete substance abuse treatment, including relapse prevention.
- Take the following steps to reduce personal and public health risks, if they continue to inject drugs:
  - — Never reuse or share syringes, water, or drug preparation equipment.
  - — Use only syringes obtained from a reliable source (e.g., pharmacies).
  - — Use a new, sterile syringe to prepare and inject drugs.†
  - — If possible, use sterile water to prepare drugs; otherwise, use clean water from a reliable source (such as fresh tap water).
  - — Use a new or disinfected container (cooker) and a new filter (cotton) to prepare drugs.
  - — Clean the injection site with a new alcohol swab before injection.
  - — Safely dispose of syringes after one use.

In addition, drug users should be provided information regarding how to prevent HIV transmission through sexual contact and, for women, information regarding reducing the risk of mother-to-infant HIV transmission.

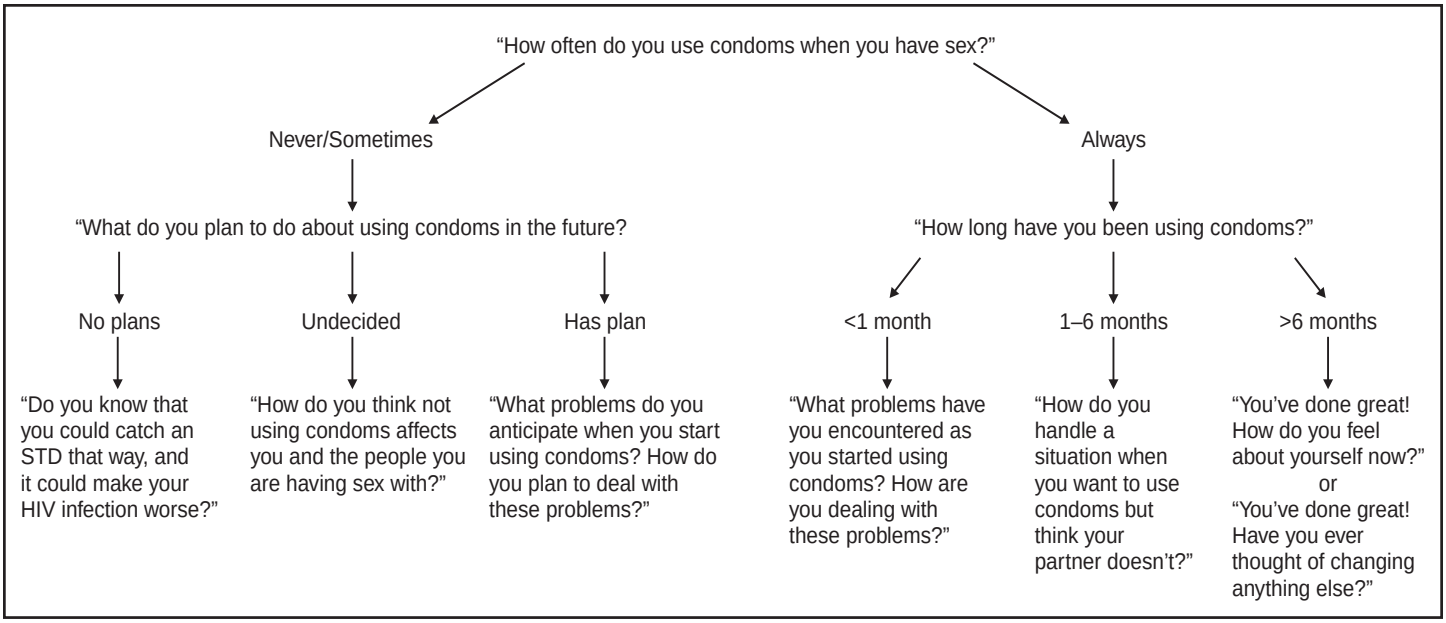
* **Source:** US Department of Health and Human Services. Medical advice for persons who inject illicit drugs. HIV Prevention Bulletin. CDC; Health Resources and Services Administration; National Institute on Drug Abuse, National Institutes of Health; Center for Substance Abuse and Mental Health Services Administration. May 1997. Available at http://www.cdc.gov/idu/pubs/hiv_prev.htm.

† If new, sterile syringes and other drug preparation and injection equipment are not available, previously used equipment should be boiled or disinfected with bleach by using the methods recommended by CDC (**Source:** CDC National Prevention Information Network. HIV connect. Vol. 11, No.8. Available at http://www.cdcnpin.org).

Ongoing Delivery of Prevention Messages

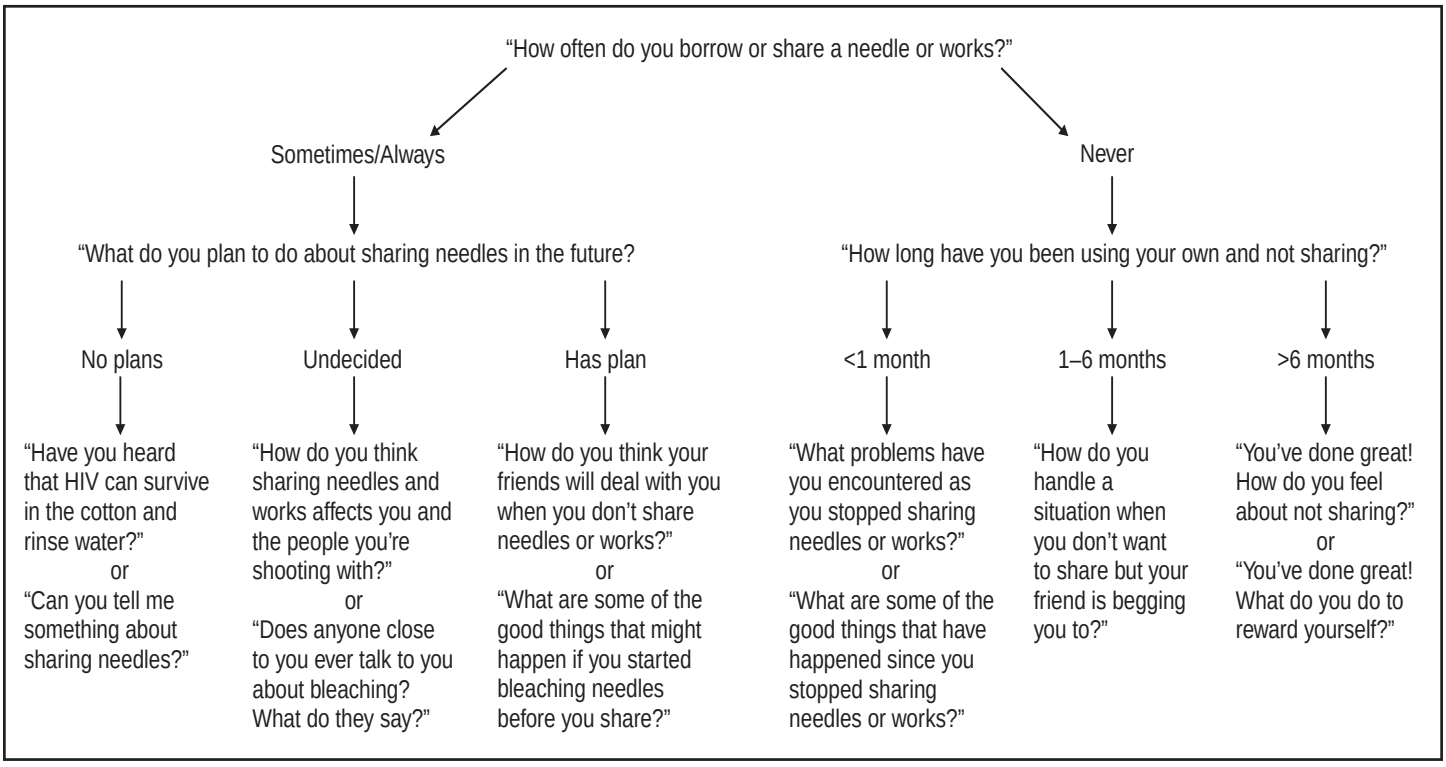
Prevention messages can be reinforced by subsequent longer or more intensive interventions in clinic or office environments by nurses, social workers, or health educators. Advantages of a multidisciplinary approach are that skill sets vary among staff members from various disciplines and that a patient may be more receptive to discussing prevention-related issues with one team member than with another. For HIV-negative persons or persons of unknown HIV serostatus, randomized controlled trials provide strong evidence for the efficacy of short, one- or two-session interventions (*164–170*) and for longer or multisession interventions in clinics for individuals and groups (*164,171–173*). For example, for persons who continue to engage in risky behaviors, CDC recommends client-centered counseling, a specific model of HIV prevention counseling

FIGURE 1. Example of tailoring messages regarding condom use for sexually active, HIV-infected persons



* This is an example, not a comprehensive list of all questions that could be asked

FIGURE 2. Example of tailoring messages regarding needle sharing for HIV-infected persons who continue to inject drugs



* This is an example, not a comprehensive list of all questions that could be asked

(*44,164*). Evidence for the efficacy of multisession interventions for HIV-infected patients, individually or in groups, in clinical settings is limited to a few randomized, controlled trials (*69,174,175*) and other studies that might not have assessed behavioral outcomes (*6,176–180*). The studies of single-session interventions for individual HIV-infected patients in clinical settings have not been randomized controlled trials (*181–187*).

Referrals for Additional Prevention Interventions and Other Services

Types of Referrals

Certain patients need more intensive or ongoing behavioral interventions than can feasibly be provided in medical care settings (*44*). Many have underlying problems that impede adoption of safer behaviors (e.g., homelessness, substance abuse, mental illness), and achieving behavioral change is often dependent on addressing these concerns. Clinicians will usually not have time or resources to fully address these issues, many of which can best be addressed through referrals for services such as intensive HIV prevention interventions (e.g., multisession risk-reduction counseling, support groups), medical services (e.g., family planning and contraceptive counseling, substance abuse treatment), mental health services (e.g., treatment of depression, counseling for sexual compulsivity), and social services (e.g., housing, child care and custody, protection from domestic violence). For example, all patients should be made aware of their responsibility for appropriate disclosure of HIV serostatus to sex and needle-sharing partners; however, full consideration of the complexities of disclosure, including benefits and potential risks, may not be possible in the time available during medical visits (*188*). Patients who are having, or are likely to have, difficulty initiating or sustaining behaviors that reduce or prevent HIV transmission might benefit from prevention case management. Prevention case management provides ongoing, intensive, one-on-one, client-centered risk assessment and prevention counseling, and assistance accessing other services to address concerns that affect patients' health and ability to change HIV-related risk-taking behavior. For HIV-seronegative persons, randomized controlled trials provide evidence for the efficacy of HIV prevention interventions delivered by health departments and community-based organizations (*164,189–198*). For HIV-infected persons, efficacy studies of such interventions are limited to a few randomized controlled trials (*199–201*), only one of which documented change in risk-related behavior (*199*), and to other studies, the majority of which did not assess behavioral outcomes (*7,202–207*).

Referrals for IDUs

For IDUs, ceasing injection-drug use is the only reliable way to eliminate the risk of injection-associated HIV transmission; however, most IDUs are unable to sustain long-term abstinence without substance abuse treatment. Several studies have examined the effect of substance abuse treatment, particularly methadone maintenance treatment, on HIV risk behaviors among IDUs (*208–210*). These include controlled (*211–217*) and noncontrolled (*218–221*) cohort studies, case-control studies (*222*), and observational studies with controls (*223,224*), and collectively they provide evidence that methadone maintenance treatment reduces risky injection and sexual behaviors and HIV seroconversion. Thus, early entry into substance abuse treatment programs, maintenance of treatment, and sustained abstinence from injecting are crucial for reducing the risk for HIV transmission from infected IDUs. For those IDUs not able or willing to stop injecting drugs, once-only use of sterile syringes can greatly reduce the risk for injection-related HIV transmission. Substantial evidence from cohort, case-control, and observational studies (*225*) indicates that access to sterile syringes through syringe exchange programs reduces HIV risk behavior and HIV seroconversion among IDUs. Physician prescribing and pharmacy programs can also increase access to sterile syringes (*226–231*). Disinfecting syringes and other injection equipment by boiling or flushing with bleach when new, sterile equipment is not available has been suggested to reduce the risk for HIV transmission (*156*); however, it is difficult to reliably disinfect syringes, and this practice is not as safe as using a new, sterile syringe (*232–234*). Information on access to sterile syringes and safe syringe disposal can be obtained through local health departments or state HIV/AIDS prevention programs.

Engaging the Patient in the Referral Process

When referrals are made, the patient's willingness and ability to accept and complete a referral should be assessed. Referrals that match the patient's self-identified priorities are more likely to be successful than those that do not; the services need to be responsive to the patient's needs and appropriate for the patient's culture, language, sex, sexual orientation, age, and developmental level. For example, adolescents should be referred to behavioral intervention programs and services that work specifically with this population. Discussion with the patient can identify barriers to the patient's completing the referral (e.g., lack of transportation or child care, work schedule, cost). Accessibility and convenience of services predict whether a referral will be completed. The patient should be given specific information regarding accessing referral services and might need assistance (e.g., scheduling appointments, obtaining transportation) in completing referrals. The likelihood that

referrals will be completed successfully could possibly be increased if clinicians or other health-care staff assist patients with making appointments to referral services. When a clinician does not have the capacity to make all appropriate referrals, or when needs are especially complex, a case manager can help make referrals and coordinate care. Outreach workers, peer counselors or educators, treatment advocates, and treatment educators can also help patients identify needs and complete referrals successfully. Health department HIV/AIDS prevention and care programs can provide information on accessing these services. Assessing the success of referrals by documenting referrals made, the status of those referrals, and patient satisfaction with referrals will further assist clinicians in meeting patient needs. Information obtained through follow-up of referrals can identify barriers to completing the referral, responsiveness of referral services to patient needs, and gaps in the referral system, and can be used to develop strategies for removing the barriers.

Referral Guides and Information

Preparation for making patient referrals includes 1) learning about local HIV prevention and supportive social services, including those supported by the Ryan White CARE Act; 2) learning about available resources and having a referral guide listing such resources; and 3) contacting staff in local programs to facilitate subsequent referrals. Referral guides and other information usually can be obtained from local and state health department HIV/AIDS prevention and care programs, which are key sources of information about services available locally. Health departments and some managed care organizations are also a source of educational materials, posters, and other prevention-related material. Health departments can provide or suggest sources of training and technical assistance on behavioral interventions. A complete listing of state AIDS directors and contact information is available from the National Alliance of State and Territorial AIDS Directors (NASTAD) at http://www.nastad.org. In addition, information can be obtained from local health planning councils, consortia, and community planning groups; local, state, and national HIV/AIDS information hotlines and Internet websites; and community-based health and human service providers (Box 5).

BOX 5. Referral resource guide, suggested contents

For each resource, the referral resource guide should specify

- name of the provider or agency;
- range of services provided;
- target population(s);
- service area(s);
- contact names and telephone and fax numbers, street addresses, e-mail addresses;
- hours of operation;
- location;
- competence in providing services appropriate to the patient's culture, language, sex, sexual orientation, age, and developmental level;
- cost for services;
- eligibility;
- application materials;
- admission policies and procedures;
- directions, transportation information, and accessibility to public transportation; and
- patient satisfaction with services.

Examples of Case Situations for Prevention Counseling

1. A patient with newly diagnosed HIV infection comes to your office for initial evaluation. Of the many things that must be addressed during this initial visit (e.g., any emergent medical or psychiatric problems, education about HIV, history, physical, initial laboratory work [if not already done]), how does one address prevention? What is the minimum that should be done, and how can it be incorporated into this visit?

Assuming no emergent issues preclude a complete history and physical examination during this visit, the following should be done:

- During the history, question how the patient might have acquired HIV, current risk behaviors, current partners and whether they have been notified and tested for HIV, and current or past STDs.
- During the physical examination, include genital and rectal examinations, evaluation and treatment of any current STD, or, if asymptomatic, appropriate screening for STDs.
- Discuss current risk behavior, at least briefly. Emphasize the importance of using condoms; address active injection-drug use.
- Discuss the need for disclosure of HIV serostatus to sex and needle-sharing partners, and discuss potential barriers to disclosure.
- Note issues that will require follow-up; e.g., risk behavior that will require continuing counseling and referral and partners who will need to be notified by either the patient or a health department.

2. A patient with chronic, stable HIV comes to you with a new STD. What prevention considerations should be covered in this visit?

For the patient who has had a stable course of disease, a new STD can be a sign of emerging social, emotional, or substance

abuse problems. These potential problems should be addressed in addition to the STD.

- During the history, cover topics related to acquisition of the new STD—number of new partners, number of episodes of unsafe sex, and types of unsafe sex.
- Address the personal risks associated with high-risk behavior, e.g., viral superinfection and HIV/STD interactions.
- Address personal or social problems (including substance abuse and domestic violence) that might have led to a change in behavior resulting in the acquisition of the new STD; refer to social services, if necessary.
- Address other issues (e.g., adherence to HAART) that may be affected by personal or social problems. Check viral load if nonadherence is evident or is suspected.
- During the physical examination, include a careful genital and rectal examination and screen for additional STDs, such as syphilis, trichomoniasis, (for women), chlamydial infection (for sexually active women aged ≤25 years and selected populations of men and women), and gonorrhea (for selected populations of men and women).
- Discuss the need for partner notification and referral for counseling and testing.
- Note in the chart that risk behavior should be addressed in future visits and that tailored counseling may be needed for the patient.

3. A patient with chronic, stable HIV has been seen regularly in a health care setting. What should be included in this patient's routine clinical care?

Discussion of sexual and needle-sharing practices should be integrated into a routine part of clinical care.

- Periodically (e.g., annually) screen for STDs. STDs to be included in screening should be determined by patient's sex, history of high-risk behavior, and local epidemiology of selected STDs.
- Reiterate general prevention messages and patient education regarding partner notification, high-risk behaviors associated with transmission, prevention of transmission, or condom use, as deemed appropriate by the clinician.

4. A patient who has been treated with HAART for 2 years comes to you. At the time of treatment initiation, CD4$^+$count was 200 cells/µL and the viral load was 50,000 copies/ml. The response to therapy was prompt; CD4$^+$ count increased to 500 cells/µL, and the viral load has been undetectable since soon after treatment began. The patient now has mildly elevated cholesterol, some mild lipodystrophy, and facial wasting. He states that he would like to stop HAART because of the side effects. What should you tell this patient?

- Inform the patient that upon stopping HAART, CD4$^+$ count and viral load will likely return to pretreatment levels with risk for opportunistic infections and progression of immune deficiency.
- Inform the patient that increase in viral load to pretreatment levels will likely result in increased infectiousness and risk for transmission of HIV to sex or needle-sharing partners.
- Counsel the patient regarding the option of changing the HAART regimen to limit progression of metabolic side effects.

Partner Counseling and Referral Services, Including Partner Notification

HIV-infected persons are often not yet aware of their infection; thus, they cannot benefit from early medical evaluation and treatment and do not know that they may be transmitting HIV to others. Reaching such persons as early after infection as possible is important for their own health and is a critical strategy for reducing HIV transmission in the community. Furthermore, interviews of HIV-infected persons in various settings suggest that >70% are sexually active after receiving their diagnosis, and many have not told their partners about their infection (*188*). Partner counseling and referral services (PCRS), including partner notification, are intended to address these problems by 1) providing services to HIV-infected persons and their sex and needle-sharing partners so the partners can take steps to avoid becoming infected or, if already infected, to avoid infecting others and 2) helping infected partners gain earlier access to medical evaluation, treatment, and other services (Table 7). A key element of PCRS involves informing current partners (and past partners who may have been exposed) that a person who is HIV infected has identified them as a sex or needle-sharing partner and advising them to have HIV counseling and testing (*235–238*).

Informing partners of their exposure to HIV is confidential; i.e., partners are not told who reported their name or when the reported exposure occurred. It is voluntary in that the infected person decides which names to reveal to the interviewer. Studies have indicated that infected persons are more likely to name their close partners than their more casual partners (*204,239,240*). Limited reports of partner violence after notification suggest a need for caution, but such violence seems to be rare (*241–2*). When asked, 92% of notified partners reported that they believe the health department should continue partner notification services (*243*). No studies have directly shown that PCRS prevents disease in a community.

TABLE 7. Recommendations for partner counseling and referral, including partner notification

Recommendation	Rating
In HIV health-care settings, all applicable requirements for reporting sex and needle-sharing partners of HIV-infected patients to the appropriate health department should be followed.	A-III (for identifying patients who should be referred for partner counseling and referral services [PCRS])
At the initial visit, patients should be asked if all of their sex and needle-sharing partners have been informed of their exposure to HIV.	A-III (for identifying patients who should be referred for PCRS)
At routine follow-up visits, patients should be asked if they have had any new sex or needle-sharing partners who have not been informed of their exposure to HIV.	A-III (for identifying patients who should be referred for PCRS)
All patients should be referred to the appropriate health department to discuss sex and needle-sharing partners who have not been informed of their exposure and to arrange for their notification and referral for HIV testing.	A-I (for increasing partner counseling and referral and voluntary testing of partners)
In HIV health-care settings, access to available community partner counseling and referral resources should be established.	A-III (for establishing a working relationship and increasing understanding about partner counseling and referral procedures)

However, studies have demonstrated that quality HIV prevention counseling can reduce the risk of acquiring a new STD (*164*) and that persons who become aware of their HIV infection can take steps to protect their health and prevent further transmission *(244)*; in addition, before–after studies have suggested that partners change their behavior after they are notified (*245*). Finally, compelling arguments have been offered regarding partners' rights to know this information that is important to their health.

Laws and Regulations Related to Informing Partners

The majority of states and some cities or localities have laws and regulations related to informing partners that they have been exposed to HIV. Certain health departments require that, even if a patient refuses to report a partner, the clinician report to the health department any partner of whom he or she is aware. Many states also have laws regarding disclosure by clinicians to third parties known to be at high risk for future HIV transmission from patients known to be infected (i.e., duty to warn) (*246*). Clinicians should know and comply with any such requirements in the areas in which they practice. With regard to PCRS, clinicians should also be aware of and adhere to all laws and regulations related to providing services to minors.

Approaches to Notifying Partners

Partners can be reached and informed of their exposure by health department staff, clinicians in the private sector, or the infected person. In the only randomized controlled trial that has been conducted to date (*175*), 35 HIV-infected persons were asked to notify their partners themselves, and 10 partners were notified. Another 39 HIV-infected persons were assigned to health department referral; and for these, 78 partners were notified. Thus, notification by the health department appears to be substantially more effective than notification by the infected person. Other studies, with less rigorous designs, have demonstrated similar results (*247,248*). Some persons, when asked, prefer to inform their partners themselves. This could have a benefit if partners provide support to the infected person. However, patients frequently find that informing their partners is more difficult than they anticipated. Certain health departments offer contract referral, in which the infected person has a few days to notify his or her partners. If by the contract date the partners have not had a visit for counseling and testing, they are then contacted by the health department. In practice, patients' difficulties in informing their partners usually means notification is done by the health department.

Although clinicians might wish to take on the responsibility for informing partners, one observational study has indicated that health department specialists were more successful than physicians in interviewing patients and locating partners (*249*). Health departments have staff who are trained to do partner notification and skilled at providing this free, confidential service. These disease intervention specialists can work closely with public and private sector clinicians who treat persons with other STDs. With regard to partner notification, the clinician should be sensitive to concerns of domestic violence or abuse by the informed partner.

All partners should be notified at least once. Persons who continue to have sex with an HIV-infected person despite an earlier notification may have erroneously concluded that someone else was the infected partner. Thus, renotification might be important, although no research is available on renotification.

Additional information, recommendations, and requirements related to PCRS are available through health department HIV/AIDS programs. A complete listing of state AIDS directors and contact information is available from the National Alliance of State and Territorial AIDS Directors (NASTAD) at http://www.nastad.org.

Acknowledgments

The preparers are grateful to P. Lynne Stockton, V.M.D, and P. Susanne Justice, CDC, for their editorial assistance and to Mark R. Vogel, M.A., HIVMA of IDSA, who assisted in coordinating responses from members of that organization.

References

1. CDC. Guidelines for national human immunodeficiency virus case surveillance, including monitoring for human immunodeficiency virus infection and acquired immunodeficiency syndrome. MMWR 1999;48(No. RR-13):1–28.
2. Janssen RS, Holtgrave DR, Valdiserri RO, Shepherd M, Gayle HD. The serostatus approach to fighting the HIV epidemic: prevention strategies for infected individuals. Am J Public Health 2001;91:1019–24.
3. Institute of Medicine, Committee on HIV Prevention Strategies in the United States. No time to lose: getting more from HIV prevention. Ruiz MS, Gable AR, Kaplan EH, Stoto MA, Fineberg HV, Trussell J, eds. Washington, DC: National Academy Press; 2001.
4. Chamot E, Coughlin SS, Farley TA, Rice JC. Gonorrhea incidence and HIV testing and counseling among adolescents and young adults seen at a clinic for sexually transmitted diseases. AIDS 1999;13:971–9.
5. Valleroy LA, MacKellar DA, Karon JM, et al. HIV prevalence and associated risk in young men who have sex with men. JAMA 2000;284:198–204.
6. Allen S, Serufilira A, Bogaerts J, et al. Confidential HIV testing and condom promotion in Africa. Impact on HIV and gonorrhea rates. JAMA 1992;268:3338–43.
7. Cleary PD, Van Devanter N, Rogers TF, et al. Behavior changes after notification of HIV infection. Am J Public Health 1991;81:1586–90.
8. CDC. Gonorrhea among men who have sex with men—selected sexually transmitted diseases clinics, 1993–1996. MMWR 1997:46: 889–92.
9. CDC. Resurgent bacterial sexually transmitted disease among men who have sex with men—King County, Washington, 1997–1999. MMWR 1999;48:773–7.
10. CDC. Increases in unsafe sex and rectal gonorrhea among men who have sex with men—San Francisco, California, 1994–1997. MMWR 1999;48:45–8.
11. CDC. Primary and secondary syphilis—United States, 1999. MMWR 2001;50:113–7.
12. Stall RD, Hays RB, Waldo CR, Ekstrand M, McFarland W. The gay '90s: a review of research in the 1990s on sexual behavior and HIV risk among men who have sex with men. AIDS 2000;14(suppl. 3):S101–14.
13. Crepaz N, Marks G. Towards an understanding of sexual risk behavior in people living with HIV: a review of social, psychological, and medical findings. AIDS 2002;16:135–49.
14. Handsfield H. Resurgent STD in gay and bisexual men: a public health crisis. Presented at the 28th Annual Meeting of the Infectious Diseases Society of America, New Orleans, Louisiana: September 7–10, 2000.
15. Risk reduction: sex without condoms. HIV counselor perspectives [newsletter] Vol. 10, No. 2, March 2001.
16. Collis TK, Celum CL. The clinical manifestations and treatment of sexually transmitted diseases in human immunodeficiency virus–positive men. Clin Infect Dis 2001;32:611–22.
17. Sheer S, Chu PL, Klausner KD, Katz MH, Schwarcz SK. Effect of highly active antiretroviral therapy on diagnoses of sexually transmitted diseases in people with AIDS. Lancet 2001;357:432–5.
18. CDC. Primary and secondary syphilis — United States, 1997. MMWR 1998:47:493–7.
19. CDC. Outbreak of syphilis among men who have sex with men—Southern California, 2000. MMWR 2001;50:117–20.
20. Williams LA, Klausner JD, Whittington WK. et al. Elimination and reintroduction of primary and secondary syphilis. Am J Public Health 1999;89:1093–7.
21. Mayer KH, Klausner JD, Handsfield HH. Intersecting epidemics and educable moments: sexually transmitted disease risk assessment and screening in men who have sex with men. Sex Transm Dis 2001;28:464–7.
22. Fleming DT, Wasserheit JN. From epidemiological synergy to public health policy and practice: the contribution of other sexually transmitted diseases to sexual transmission of HIV infection. Sex Transm Infect 1999;75:3–17.
23. Kelly JA, Otto-Salaj LL, Sikkema KJ, Pinkerton SD, Bloom FR. Implications of HIV treatment advances for behavioral research on AIDS: protease inhibitors and new challenges in HIV secondary prevention. Health Psychol 1998;17:310–9.
24. Kelly JA, Hoffman RG, Rompa D, Gray M. Protease inhibitor combination therapies and perception of gay men regarding AIDS severity and the need to maintain safer sex. AIDS 1998;12:F91–5.
25. Kravcik S, Victor G, Houston S, et al. Effect of antiretroviral therapy and viral load on the perceived risk of HIV transmission and the need for safer sexual practices. J Acquir Immune Defic Syndr Hum Retrovirol 1998;19:124–9.
26. Dilley JW, Woods WJ, MacFarland W. Are advances in treatment changing views about high-risk sex? [letter] N Engl J Med 1997;337:501–2.
27. Van de Ven P, Kippax S, Knox S, Prestage G, Crawford J. HIV treatment optimism and sexual behaviour among gay men in Sydney and Melbourne. AIDS 1999;13:2289–94.
28. CDC. US HIV and AIDS cases reported through December 2000. Vol.12 (No. 2). Atlanta, GA: US Department of Health and Human Services, CDC, 2000. Available at http://www.cdc.gov/hiv/stats/hasr1202.htm.
29. Des Jarlais DC, Perlis T, Friedman SR, et al. Declining seroprevalence in a very large HIV epidemic: injecting drug users in New York City, 1991 to 1996. Am J Public Health 1998;88:1801–6.
30. Des Jarlais DC, Marmor M, Friedman P, et al. HIV incidence among injection drug users in New York City, 1992-1997: evidence for a declining epidemic. Am J Public Health 2000;90:352–9.
31. Academy for Educational Development. A comprehensive approach: preventing blood-borne infections among injection drug users. Prepared for CDC. Washington, DC: Academy for Educational Development, December 2000. Available at http://www.cdc.gov/idu/idu.htm.
32. National Institute on Drug Abuse, Community Epidemiology Working Group (CEWG). Drug abuse highlights for the United States. 45th meeting of the Community Epidemiology Working Group, Miami, Florida: December 15–18, 1998.
33. Deren S, Robles R, Andia J, Colon HM, Kang S-Y, Perlis T. Trends in HIV seroprevalence and needle sharing among Puerto Rican drug injectors in Puerto Rico and New York: 1992–1999. J Acquir Immune Defic Syndr 2001;26:164–9.

34. Irwin KL, Edlin BR, Faruque S, et al. Crack cocaine smokers who turn to drug injection: characteristics, factors associated with injection, and implications for HIV transmission. The Multicenter Crack Cocaine and HIV Infection Study Team. Drug Alcohol Depend 1996;42:85–92.
35. CDC. Trends in injection drug use among persons entering addiction treatment — New Jersey, 1992–1999. MMWR 2001;50:378–81.
36. Epstein RM, Levenkron JC, Frarey L, Thompson J, Anderson K, Franks P. Improving physicians' HIV risk-assessment skills using announced and unannounced standardized patients. J Gen Intern Med 2001;16:176–80.
37. Veterans Health Administration. The VA HIV prevention handbook: a guide for clinicians. Washington DC: US Department of Veterans Affairs, Veterans Health Administration, January 2002; P95644.
38. National Institutes of Health. Public Health Service Task Force recommendations for the use of antiretroviral drugs in pregnant women infected with HIV-1 for maternal health and interventions for reducing perinatal HIV-1 transmission in the United States. HIV/AIDS Treatment Information Service (ATIS). Bethesda, MD: US Department of Health and Human Services, National Institutes of Health, 2003. Available at http://www. http://www.aidsinfo.nih.gov/guidelines/default_db2.asp?id=66.
39. CDC. Revised recommendations for HIV screening of pregnant women. MMWR 2001;50(No. RR-19):63–85.
40. CDC. U.S. Public Health Service Task Force recommendations for use of antiretroviral drugs in pregnant HIV-1–infected women for maternal health and interventions to reduce perinatal HIV-1 transmission in the United States. MMWR 2002;51(No. RR-18).
41. Gerbert B, Bronstone A, Pantilat S, et al. When asked, patients tell: disclosure of sensitive health-risk behaviors. Med Care 1999;37:104–11.
42. Gerbert B, Macguire BT, Coates TJ. Are patients talking to their physicians about AIDS? Am J Public Health 1990;80:467–8.
43. Lewis CE, Freeman HE, Corey CR. The sexual history-taking and counseling practices of primary care physicians. West J Med 1987;147:165–7.
44. CDC. Revised guidelines for HIV counseling, testing, and referral. MMWR 2001;50(No. RR-19):1–58.
45. Wight RG, Rotheram-Borus MJ, Klosinski L, Ramos B, Calabro M, Smith R. Screening for transmission behaviors among HIV-infected adults. AIDS Educ Prev 2000;12:431–41.
46. Rabin DL, Boekeloo BO, Marx ES, Bowman MA, Russell NK, Willis AG. Improving office-based physicians' prevention practices for sexually transmitted diseases. Ann Intern Med 1994;121:513–9.
47. DeGuzman MA, Ross MW. Assessing the application of HIV and AIDS related education and counselling on the Internet. Patient Education and Counseling 1999;36:209–28.
48. Fredman L, Rabin DL, Bowman M, et al. Primary care physicians' assessment and prevention of HIV infection. Am J Prev Med 1989;5:188–95.
49. Orlander JD, Samet JH, Kazis L, Freeberg KA Libman H. Improving medical residents' attitudes toward HIV-infected persons through training in an HIV staging and triage clinic. Acad Med 1994;69:1001–3.
50. Sullivan L, Stein MD, Savetsky, JB, Samet JH. The doctor–patient relationship and HIV-infected patients' satisfaction with primary care physicians. J Gen Intern Med 2000;15:462–9.
51. Boekeloo BO, Schiavo L, Rabin DL, Conlon RT, Jordan CS, Mundt DJ. Self-reports of HIV risk factors by patients at a sexually transmitted disease clinic: audio vs. written questionnaires. Am J Public Health 1994; 84:754–60.
52. Webb PM, Zimet GD, Fortenberry JD, Blythe MJ. Comparability of a computer-assisted versus written method for collecting health behavior information from adolescent patients. J Adolesc Health 1999;24:383–8.
53. Kissinger P, Rice J, Farley T, et al. Application of computer-assisted interviews to sexual behavior research. Am J Epidemiol 1999;149:950–4.
54. California STD Controllers Association, California Coalition of Local AIDS Directors. Guidance for STD clinical preventive services for persons infected with HIV. Sex Transm Dis 2001;28:460–3.
55. Metzger DS, Koblin B, Turner C, et al. Randomized controlled trial of audio computer-assisted self-interviewing: utility and acceptability in longitudinal studies. HIVNET Vaccine Preparedness Study Protocol Team. Am J Epidemiol 2000;152:99–106.
56. Mofenson LM, McIntyre JA. Advances and research directions in the prevention of mother-to-child HIV-1 transmission. Lancet 2000;355:2237–44.
57. Duggan J, Walerius H, Purohit A, et al. Reproductive issues in HIV-seropositive women: a survey regarding counseling, contraception, safer sex, and pregnancy choices. J Assoc Nurses AIDS Care 1999;10:84–92.
58. Ethics Committee of the American Society of Reproductive Medicine. Human immunodeficiency virus and infertility treatment. Fertil Steril 2002;77:218–22.
59. Hopkins DP, Briss PA, Ricard CJ, et al. Reviews of evidence regarding interventions to reduce tobacco use and exposure to environmental tobacco smoke. Am J Prev Med 2001;20(2 suppl):16–66.
60. Scholes D, Anderson LA, Operskalski B, BlueSpruce J, Irwin K, Magid DJ. The role of managed care in STD prevention and control. Washington, DC: American Association of Health Plans, 1999.
61. Kaplan JE, Masur H, Holmes KK, et al. An overview of the 1999 US Public Health Service/Infectious Diseases Society of America guidelines for preventing opportunistic infections in human immunodeficiency virus–infected persons. Clin Infect Dis 2000;30(suppl 1):S15–28.
62. CDC. HIV prevention through early detection and treatment of other sexually transmitted diseases—United States. Recommendations of the Advisory Committee for HIV and STD prevention. MMWR 1998;47(No. RR-12):1–24.
63. CDC. Sexually transmitted diseases treatment guidelines—2002. MMWR 2002;51(No. RR-6).
64. CDC. Hepatitis B virus: a comprehensive strategy for eliminating transmission in the United States through universal childhood vaccination: recommendations of the Immunization Practices Advisory Committee (ACIP). MMWR 1991;40:(No. RR-13).
65. CDC. Recommendations for prevention and control of hepatitis C virus (HCV) infection and HCV-related chronic disease. MMWR 1998;47(No. RR-19):1–39.
66. CDC. Prevention of hepatitis A through active or passive immunization. Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 1999;48(No. RR-12).
67. STD Control Program and the HIV/AIDS Control Program, Public Health – Seattle & King County. Sexually transmitted disease and HIV screening guidelines for men who have sex with men. Sex Transm Dis 2001;28:457–9.
68. Dodge WT, BlueSpruce J, Grothaus L, et al. Enhancing primary care HIV prevention: a comprehensive clinical intervention. Am J Prev Med 2001;20:177–83.
69. Kalichman SC, Rompa D, Cage M, et al. Effectiveness of an intervention to reduce HIV transmission risks in HIV-positive people. Am J Prev Med 2001;21:84–92.

70. Grosskurth H, Mosha F, Todd J, et al. Impact of improved treatment of sexually transmitted diseases on HIV infection in rural Tanzania: randomised controlled trial. Lancet 1995;346:530–6.
71. Wasserheit JN. Epidemiological synergy: interrelationships between human immunodeficiency virus infection and other sexually transmitted diseases. Sex Transm Dis 1992;19:61–77.
72. Cohen MS. Sexually transmitted diseases enhance HIV transmission: no longer a hypothesis. Lancet 1998;351(suppl 3):5–7.
73. Quinn TC. Association of sexually transmitted diseases and infection with the human immunodeficiency virus: biological cofactors and markers of behavioural interventions. Int J STD AIDS 1996;7(suppl 2):17–24.
74. Kamb ML, Newman D, Peterman TA, et al. Most bacterial STD are asymptomatic. [Abstract 266] In: Abstracts of STIs at the Millennium, Past, Present, and Future – A Joint Meeting of the ASTDA and the MSSVD, Baltimore, Maryland, May 2000.
75. Phillips RS, Hanff PA, Wertheimer A, Aronson MD. Gonorrhea in women seen for routine gynecologic care: criteria for testing. Am J Med 1988;85:177–82.
76. Schachter J, Stoner E, Moncada J. Screening for chlamydial infections in women attending family planning clinics. West J Med 1983;138:375–9.
77. Handsfield HH, Lipman TO, Harnisch JP, Tronca E, Holmes KK. Asymptomatic gonorrhea in men. Diagnosis, natural course, prevalence, and significance. N Engl J Med 1974;290:117–23.
78. Alexander-Rodriguez T, Vermund SH. Gonorrhea and syphilis in incarcerated urban adolescents: prevalence and physical signs. Pediatrics 1987;80:561–4.
79. Ellerbeck EF, Vlahov D, Libonati JP, Salive ME, Brewer TF. Gonorrhea prevalence in the Maryland state prisons. Sex Transm Dis 1989;16:165–7.
80. Grosskurth H, Mayaud P, Mosha F, et al. Asymptomatic gonorrhea and chlamydial infection in rural Tanzanian men. BMJ 1996;312:277–80.
81. Mehta SD, Rothman RE, Kelen GD, Quinn TC, Zenilman JM. Unsuspected gonorrhea and chlamydia in patients of an urban adult emergency department: a critical population for STD control intervention. Sex Transm Dis 2001;28:33–9.
82. CDC. Screening tests to detect *Chlamydia trachomatis* and *Neisseria gonorrhoeae* infections 2002. MMWR 2002;51(No. RR-15).
83. American Academy of Pediatrics, Committee on Pediatric AIDS and Committee on Adolescence. Adolescents and human immunodeficiency virus infection: the role of the pediatrician in prevention and intervention. Pediatrics 2001;107:188–90.
84. Rost K, Nutting PA, Smith J, Werner JJ. Designing and implementing a primary care intervention trial to improve the quality and outcome of care for major depression. Gen Hosp Psychiatry 2000;22:66–77.
85. Hollis JF, Lichtenstein, E, Vogt TM, Stevens VJ, Biglan A. Nurse-assisted counseling for smokers in primary care. Ann Intern Med 1993;118:521–5.
86. Stevens VJ, Severson H, Lichtenstein E, Little SJ, Leben J. Making the most of a teachable moment: a smokeless-tobacco cessation intervention in the dental office. Am J Public Health 1995; 85:231–5.
87. Cornuz J, Zellweger JP, Mounoud C, Decrey H, Pecoud A, Burnand B. Smoking cessation counseling by residents in an outpatient clinic. Prev Med 1997;26:292–6.
88. Hartmann KE, Thorp JM, Pahel-Short L, Koch MA. A randomized controlled trial of smoking cessation intervention in pregnancy in an academic clinic. Obstet Gynecol 1996;87:621–6.
89. Ockene, JK, Kristeller J, Goldberg R, et al.. Increasing the efficacy of physician-delivered smoking interventions: a randomized clinical trial. J Gen Intern Med 1991;6:1–8.
90. Ockene JK, Kristeller J, Pbert L, et al. The physician-delivered smoking intervention project: can short-term interventions produce long-term effects for a general outpatient population? Health Psychol 1994;13:278–81.
91. Ockene JK, Adams A, Hurley TG, Wheeler EV, Hebert JR. Brief physician- and nurse practitioner-delivered counseling for high-risk drinkers: does it work? Arch Intern Med 1999;159:2198-205.
92. Senft RA, Polen MR, Freeborn DK, Hollis JF. Brief intervention in a primary care setting for hazardous drinkers. Am J Prev Med 1997;13:464–70.
93. Ockene IS, Hebert JR, Ockene JK, et al. Effect of physician-delivered nutrition counseling training and an office-support program on saturated fat intake, weight, and serum lipid measurements in a hyperlipidemic population: Worcester Area Trial for Counseling in Hyperlipidemia (WATCH). Arch Intern Med 1999;159:725–31.
94. Calfas KJ, Long BJ, Sallis JF, Wooten WJ, Prall M, Patrick K. A controlled trial of physician counseling to promote the adoption of physical activity. Prev Med 1996;25:225–33.
95. Jost S, Bernard M-C, Kaiser L, et al. A patient with HIV-1 superinfection. N Engl J Med 2002;347:731–6.
96. Ramos A, Hu DJ, Nguyen L, et al. Intersubtype human immunodeficiency virus type 1 superinfection following seroconversion to primary infection in two injection drug users. J Virol 2002;76:7444–52.
97. CDC. Management of possible sexual, injecting-drug use, or other nonoccupational exposure to HIV, including considerations related to antiretroviral therapy. Public Health Service Statement. MMWR 1998;47(No. RR-17):1–14.
98. Essien EJ, Meshack AF, Ross MW. Misperceptions about HIV transmission among heterosexual African-American and Latino men and women. J Natl Med Assoc 2002;94:304–12.
99. Peterman TA, Stoneburner RL, Allen JR, Jaffe HW, Curran JW. Risk of human immunodeficiendy virus transmission from heterosexual adults with transfusion-associated infections. JAMA 1988;259:55–8.
100. DeGruttola V, Seage GR III, Mayer KH, Horsburgh CR Jr. Infectiousness of HIV between male homosexual partners. J Clin Epidemiol 1989;42:849–56.
101. Johnson AM, Petherick A, Davidson SJ, et al. Transmission of HIV to heterosexual partners of infected men and women. AIDS 1989;3:367–72.
102. Laga M, Taelman H, Van der Stuyft P, Bonneux L, Vercauteren G, Piot P. Advanced immunodeficiency as a risk factor for heterosexual transmission of HIV. AIDS 1989;3:361–6.
103. Wiley JA, Herschkorn SJ, Padian NS. Heterogeneity in the probability of HIV transmission per sexual contact: the case of male-to-female transmission in penile-vaginal intercourse. Stat Med 1989;8:93–102.
104. Padian NS, Shiboski SC, Jewell NP. Female-to-male transmission of human immunodeficiency virus. JAMA 1991;266:1664–7.
105. European Study Group on Heterosexual Transmission of HIV. Comparison of female to male and male to female transmission of HIV in 563 stable couples. BMJ 1992;304:809–13.
106. Saracco A, Musicco M, Nicolosi A, et al. Man-to-woman sexual transmission of HIV: longitudinal study of 343 steady partners of infected men. J Acquir Immune Defic Syndr 1993;6:497–502.
107. De Vincenzi I. A longitudinal study of human immunodeficiency virus transmission by heterosexual partners. N Engl J Med 1994;331:341–6.

108. Nicolosi A, Correa Leite ML, Musicco M, Arici C, Gavazzeni G, Lazzarin A. The efficiency of male-to-female and female-to-male sexual transmission of the human immunodeficiency virus: a study of 730 stable couples. Italian Study Group on HIV Heterosexual Transmission. Epidemiology 1994;5:570–5.
109. Nicolosi A, Musicco M, Saracco A, Lazzarin A. Risk factors for woman-to-man sexual transmission of the human immunodeficiency virus. Italian Study Group on Heterosexual Transmission. J Acquir Immune Defic Syndr 1994;7:296–300.
110. Downs AM, De Vincenzi I. Probability of heterosexual transmission of HIV: relationship to the number of unprotected sexual contacts. J Acquir Immune Defic Syndr Hum Retrovirol 1996;11:388–95.
111. Padian NS, Shiboski SC, Glass SO, Vittinghoff E. Heterosexual transmission of human immunodeficiency virus in Northern California: results from a ten-year study. Am J Epidemiol 1997;146:350–7.
112. Leynaert B, Downs AM, De Vincenzi I. Heterosexual transmission of human immunodeficiency virus: variability of infectivity throughout the course of infection. European Study Group on Heterosexual Transmission of HIV. Am J Epidemiol 1998;148:88–96.
113. Vittinghoff E, Douglas J, Judson F, McKirnan D, MacQueen K, Buchbinder SP . Per-contact risk of human immunodeficiency transmission between male sexual partners. Am J Epidemiol 1999;150: 308–11.
114. Royce RA, Sena A, Cates W Jr, Cohen MS. Sexual transmission of HIV. N Engl J Med 1997;336:1072–8.
115. Varghese B, Maher JE, Peterman TA, Branson BM, Steketee RW. Reducing the risk of sexual HIV transmission: quantifying the per-act risk for HIV on the basis of choice of partner, sex act, and condom use. Sex Transm Dis 2002;29:38–43.
116. Macaluso JM, Kelaghan J, Artz L, et al. Mechanical failure of the latex condom in a cohort of women at high STD risk. Sex Transm Dis 1999;26:450–8.
117. Schaffer N, Roongpisuthipong A, Siriwasin W, et al. Maternal virus load and perinatal human immunodeficiency virus type 1, subtype E transmission, Thailand. Bangkok Collaborative Perinatal HIV Transmission Study Group. J Infect Dis 1999;179:590–9.
118. Mofenson LM, Lambert JS, Stiehm ER, et al. Risk factors for perinatal transmission of human immunodeficiency virus type 1 in women treated with zidovudine. Pediatric AIDS Clinical Trials Group Study 185 Team. N Engl J Med 1999;341:385–93.
119. Garcia PM, Kalish LA, Pitt J, et al. Maternal levels of plasma human immunodeficiency virus type 1 RNA and the risk of perinatal transmission. Women and Infants Transmission Study Group. N Engl J Med 1999;341:394–402.
120. Busch MP, Operskalski EA, Mosley JW, et al. Factors influencing human immunodeficiency virus type 1 transmission by blood transfusion. Transfusion Safety Study Group. J Infect Dis 1996;174:26–33.
121. Operskalski EA, Stram DO, Busch MP, et al. Role of viral load in heterosexual transmission of human immunodeficiency virus type 1 by blood transfusion recipients. Am J Epidemiol 1997;146:655–61.
122. Lee T-H, Sakahara N, Fiebig E, Busch MP, O'Brien TR, Herman SA. Correlation of HIV-1 RNA levels in plasma and heterosexual transmission of HIV-1 from infected transfusion recipients. J Acquir Immune Defic Syndr Hum Retrovirol 1996;12:427–8.
123. Ragni MV, Faruki H, Kingsley LA. Heterosexual HIV-1 transmission and viral load in hemophilic patients. J Acquir Immune Defic Syndr Hum Retrovirol 1998;17:42–5.
124. Gray RH, Wawer MJ, Brookmeyer R, et al. Probability of HIV-1 transmission per coital act in monogamous, heterosexual, HIV-1-discordant couples in Rakai, Uganda. Lancet 2001;357:1149–53.
125. Chakraborty H, Sen PK, Helms RW, et al. Viral burden in genital secretions determines male-to-female sexual transmission of HIV-1: a probabilistic empiric model. AIDS 2001;15:621–7.
126. Quinn TC, Wawer MJ, Sewankambo N, et al. Viral load and heterosexual transmission of human immunodeficiency virus type 1. Rakai Project Study Group. N Engl J Med 2000;342:921–9.
127. Sperling RS, Shapiro DE, Coombs RW, et al. Maternal viral load, zidovudine treatment and the risk of transmission of human immunodeficiency virus type 1 from mother to infant. Pediatric AIDS Clinical Trials Group Protocol 076 Study Group. N Engl J Med 1996;335:1621–9.
128. Schaffer N, Chuachoowong R, Mock PA, et al. Short-course zidovudine for perinatal HIV-1 transmission in Bangkok, Thailand: a randomised controlled trial. Bangkok Collaborative Perinatal HIV Transmission Study Group. Lancet 1999;353:773–80.
129. Ghys PD, Fransen K, Diallo MO, et al. The associations between cervicovaginal HIV shedding, sexually transmitted diseases and immunosuppression in female sex workers in Abidjan, Côte d'Ivoire. AIDS 1997;11:F85–93.
130. Gupta P, Mellors J, Kingsley L, et al. High viral load in semen of human immunodeficiency virus type 1–infected men at all stages of disease and its reduction by therapy with protease and nonnucleoside reverse transcriptase inhibitors. J Virol 1997;71:6271–5.
131. Vernazza PL, Gilliam BL, Dyer J, et al. Quantification of HIV in semen: correlation with antiviral treatment and immune status. AIDS 1997;11:987–93.
132. Vernazza PL, Gilliam BL, Flepp M, et al. Effect of antiviral treatment on the shedding of HIV-1 in semen. AIDS 1997;11:1249–54.
133. Chuachoowong R, Shaffer N, Siriwasin W, et al. Short-course antenatal zidovudine reduces both cervical human immunodeficiency virus type 1 levels and risk of perinatal transmission. Bangkok Collaborative Perinatal HIV Transmission Study Group. J Infect Dis 2000;181:99–106.
134. Zhang H, Dornadula G, Beumont M, et al. Human immunodeficiency virus type 1 in the semen of men receiving highly active antiretroviral therapy. N Engl J Med 1998;339:1803–9.
135. Kiviat NB, Critchlow CW, Hawes SE, et al. Determinants of human immunodeficiency virus DNA and RNA shedding in the anal-rectal canal of homosexual men. J Infect Dis 1998;177:571–8.
136. Lampinen TM, Critchlow CW, Kuypers JM, et al. Association of antiretroviral therapy with detection of HIV-1 RNA and DNA in the anorectal mucosa of homosexual men. AIDS 2000;14:F69–75.
137. Kovacs A, Wasserman SS, Burns D, et al. Determinants of HIV-1 shedding in the genital tract of women. WIHS Study Group. Lancet 2001;358:1593–601.
138. Little SJ, Daar ES, D'Aquila RT, et al. Reduced antiretroviral drug susceptibility among patients with primary HIV infection. JAMA 1999;282:1142–9.
139. Boden D, Hurley A, Zhang L, et al. HIV-1 drug resistance in newly infected individuals. JAMA 1999;282:1135–41.
140. Little SJ. Transmission and prevalence of HIV resistance among treatment-naive subjects. Antivir Ther 2000;5:33–40.
141. Little SJ, Holte S, Routy JP, et al. Antiretroviral-drug resistance among patients recently infected with HIV. N Engl J Med 2002;347:385–94.

142. Blower SM, Aschenbach AN, Gershengorn HB, Kahn JO. Predicting the unpredictable: transmission of drug-resistant HIV. Nat Med 2001;7:1016–20.
143. CDC. Public Health Service guidelines for management of health-care worker exposures to HIV and recommendations for postexposure prophylaxis. MMWR 1998;47(No. RR-7).
144. Katz MH, Gerberding JL. Postexposure treatment of people exposed to human immunodeficiency virus through sexual contact or injection-drug use. N Engl J Med 1997;336:1097–100.
145. Katz MH, Gerberding JL. The care of persons with recent sexual exposure to HIV. Ann Intern Med 1998:128:306–12.
146. Bamberger JD, Waldo CR, Gerberding JL, Katz MH. Postexposure prophylaxis for human immunodeficiency virus (HIV) infection following sexual assault. Am J Med 1999;106:323–6.
147. Wiebe ER, Comay SE, McGregor M, Ducceschi S. Offering HIV prophylaxis to people who have been sexually assaulted: 16 months' experience in a sexual assault service. CMAJ: Canadian Medical Association Journal 2000;162:641–5.
148. Schecter M, Lago RF, Ismerio R, Mendelsohn AB, Harrison LH. Acceptability, behavioral impact, and possible efficacy of post-sexual-exposure chemoprophylaxis (PEP) for HIV. [Abstract 15]. Presented at the 9th Conference on Retroviruses and Opportunistic Infections. Seattle, Washington, February 2002.
149. Coury-Doniger P, Levenkron JC, Knox KL, Cowell S, Urban MA. Use of stage of change (SOC) to develop an STD/HIV behavioral intervention: phase 1. A system to classify SOC for STD/HIV sexual risk behaviors—development and reliability in an STD clinic. AIDS Patient Care & STDs 1999;13:493–502.
150. Temmerman M, Moses S, Kiragu D, et al. Impact of single session post-partum counselling of HIV infected women on their subsequent reproductive behaviour. AIDS Care 1990;2:247–52.
151. Bien TH, Miller WR, Tonigan JS. Brief interventions for alcohol problems: a review. Addiction 1993; 88:315–35.
152. Campbell MK, DeVellis BM, Strecher VJ, Ammerman AS, DeVellis RF, Sandler RS. Improving dietary behavior: the effectiveness of tailored messages in primary care settings. Am J Public Health 1994;84:783–7.
153. Goldberg DN, Hoffman AM, Farinha MF, et al. Physician delivery of smoking-cessation advice based on the stages-of-change model. Am J Prev Med 1994;10:267–74.
154. Rakowski W, Ehrich B, Goldstein MG, et al. Increasing mammography among women aged 40–74 by use of stage-matched, tailored intervention. Prev Med 1998;27:748–56.
155. Saunders B, Wilkinson C, Phillips M. The impact of a brief motivational intervention with opiate users attending a methadone programme. Addiction 1995;90:415–24.
156. US Department of Health and Human Services. Medical advice for persons who inject illicit drugs. HIV Prevention Bulletin. CDC; Health Resources and Services Administration; National Institute on Drug Abuse, National Institutes of Health; Substance Abuse and Mental Health Services Administration; May 1997. Available at http://www.cdc.gov/idu/pubs/hiv_prev.htm.
157. Academy for Educational Development. A comprehensive approach: preventing blood-borne infections among injection drug users. Washington, DC: Academy for Educational Development; 2001. Prepared for the CDC. Available at http://www.cdc.gov/idu/pubs/ca/comprehensive-approach.htm.
158. CDC National Prevention Information Network. HIV Connect, Vol. 11, No. 8. Available at http://www.cdcnpin.org.
159. Fisher WA, Fisher JD, Friedland G, Cornman D, Amico R. The Options Project: a physician-delivered intervention for HIV+ individuals in clinical care settings. [Abstract 249]. Presented at the 2001 National HIV Prevention Conference. Atlanta, Georgia, August, 2001.
160. DePoy E, Burke JP, Sherwen L. Training trainers: evaluating services provided to children with HIV and their families. Research on Social Work Practice 1992;2:39–55.
161. Levinson W, Cohen MS, Brady D, Duffy FD. To change or not to change: "sounds like you have a dilemma." Ann Intern Med 2001;135:386–91.
162. CDC. Compendium of HIV prevention interventions with evidence of effectiveness. Atlanta, Georgia: US Department of Health and Human Services, CDC; 1999 (Revised 2001). Available at http://www.cdc.gov/hiv/pubs/HIVcompendium/hivcompendium/pdf.
163. Collins C, Morin SD, Shriver MD, Coates TJ. Designing primary prevention for people living with HIV. [Policy monograph]. San Francisco: AIDS Research Institute, University of California, San Francisco, 2000. Available at http://ari.ucsf.edu/pdf/PrimaryPrevention.pdf.
164. Kamb ML, Fishbein M, Douglas JM Jr., et al., Project RESPECT Study Group. Efficacy of risk-reduction counseling to prevent human immunodeficiency virus and sexually transmitted diseases: a randomized controlled trial. JAMA 1998;280:1161–7.
165. Mansfield CJ, Conroy ME, Emans SJ, Woods ER. Pilot study of AIDS education and counseling of high-risk adolescents in an office setting. J Adolesc Health 1993; 14:115–9.
166. O'Donnell CR, O'Donnell L, San Doval A, Duran R, Labes K. Reductions in STD infections subsequent to an STD clinic visit. Using video-based patient education to supplement provider interactions. Sex Transm Dis 1998;25:161–8.
167. O'Donnell L, San Doval A, Duran R, O'Donnell CR. The effectiveness of video-based interventions in promoting condom acquisition among STD clinic patients. Sex Transm Dis 1995;22:97–103.
168. Cohen D, Dent C, MacKinnon D. Condom skills education and sexually transmitted disease reinfection. J Sex Res 1991;28:139–44.
169. Cohen DA, MacKinnon DP, Dent C, Mason HR, Sullivan E. Group counseling at STD clinics to promote use of condoms. Public Health Rep 1992;107:727–31.
170. Wenger NS, Greenberg JM, Hilborne LH, Kusseling F, Mangotich M, Shapiro MF. Effect of HIV antibody testing and AIDS education on communication about HIV risk and sexual behavior. A randomized, controlled trial in college students. Ann Intern Med 1992;117:905–11.
171. Hobfoll SE, Jackson AP, Lavin J, Britton P, Shepherd JB. Reducing inner-city women's AIDS risk activities: a study of single, pregnant women. Health Psychol 1994;13:397–403.
172. Kelly JA, St. Lawrence JS, Hood HV, Brasfield TL. Behavioral intervention to reduce AIDS risk activities. J Consult Clin Psychol 1989;57:60–7.
173. Kelly JA, Murphy DA, Washington CD, et al. The effects of HIV/AIDS intervention groups for high-risk women in urban clinics. Am J Public Health 1994;84:1918–22.
174. Grella CD, Annon JJ, Anglin MD. Ethnic differences in HIV risk behaviors, self-perceptions, and treatment outcomes among women in methadone maintenance treatment. J Psychoactive Drugs 1995;27:421–33.
175. Landis SE, Schoenbach VJ, Weber DJ, et al. Results of a randomized trial of partner notification in cases of HIV infection in North Carolina. N Engl J Med 1992;326:101–6.

176. Lie GT, Biswalo PM. HIV-positive patient's choice of a significant other to be informed about the HIV-test result: findings from an HIV/AIDS counselling programme in the regional hospitals of Arusha and Kilimanjaro, Tanzania. AIDS Care 1996;8:285–96.
177. Müller O, Sarangbin S, Ruxrungtham K, Sittitrai W, Phanuphak P. Sexual risk behaviour reduction associated with voluntary HIV counselling and testing in HIV infected patients in Thailand. AIDS Care 1995;7:567–72.
178. Allen S, Serufilira A, Gruber V, et al. Pregnancy and contraception use among Rwandan women after HIV testing and counseling. Am J Public Health 1993;83:705–10.
179. Fawzy FI, Namir S, Wolcott DL. Structured group intervention model for AIDS patients. Psychiatr Med 1989;7:35–45.
180. Hedge B, Glover LF. Group intervention with HIV seropositive patients and their partners. AIDS Care 1990;2:147–54.
181. Hjorther A, Nielsen FM, Segest E. Prevention of AIDS: free condoms to drug abusers in the municipality of Copenhagen. Int J Addictions 1990;25:745–53.
182. Guydish J, Temoshok L, Dilley J, Rinaldi J. Evaluation of a hospital based substance abuse intervention and referral service for HIV affected patients. Gen Hosp Psychiatry 1990;12:1–7.
183. Rao AV, Swaminathan R, Baskaran S, Belinda C, Andal G, Saleem K. Behaviour change in HIV infected subjects following health education. Indian J Med Res 1991;93:345–9.
184. Ryder RW, Batter VL, Nsuami M, et al. Fertility rates in 238 HIV-1 seropositive women in Zaire followed for 3 years post-partum. AIDS 1991;5:1521–7.
185. CDC. HIV prevention through case management for HIV-infected persons —selected sites, United States, 1989–1992. MMWR 1993;42:448–9, 455–6.
186. Ladner J, Leroy V, Msellati P, et al. Cohort study of factors associated with failure to return for HIV post-test counselling in pregnant women: Kigali, Rwanda, 1992–1993. AIDS 1996;10:69–75.
187. Pickering J, Quigley M, Pepin J, Todd J, Wilkins A. Effects of post-test counselling on condom use among prostitutes in The Gambia. AIDS 1993;7:271–3.
188. Marks G, Burris S, Peterman TA. Reducing sexual transmission of HIV from those who know they are infected: the need for personal and collective responsibility. AIDS 1999;13:297–306.
189. Des Jarlais DC, Casriel C, Friedman SR, Rosenblum A. AIDS and the transition to illicit drug injection—results of a randomized trial prevention program. British Journal of Addiction 1992;87:493–8.
190. DiClemente RJ, Wingood GM. A Randomized controlled trial of an HIV sexual risk-reduction intervention for young African-American women. JAMA 1995;274:1271–6.
191. El-Bassel N, Schilling RF. 15-month followup of women methadone patients taught skills to reduce heterosexual HIV transmission. Public Health Rep 1992;107:500–4.
192. Jemmott JB, III, Jemmott LS, Fong GT. Reductions in HIV risk-associated sexual behaviors among black male adolescents: effects of an AIDS prevention intervention. Am J Public Health 1992;82:372–7.
193. McCusker J, Stoddard AM, Zapka JG, Morrison CS, Zorn M, Lewis BF. AIDS education for drug abusers: evaluation of short-term effectiveness. Am J Public Health 1992;82:533–40.
194. Rotheram-Borus M, Van Rossem R, Lee M, et al. Reductions in HIV risk among runaway youths. Prevention Science. In press, 2003.
195. Shain RN, Piper JM, Newton ER, et al. A randomized, controlled trial of a behavioral intervention to prevent sexually transmitted disease among minority women. N Engl J Med 1999;340:93–100.
196. Stanton BF, Li X, Ricardo I, Galbraith J, Feigelman S, Kaljee L. A randomized, controlled effectiveness trail of an AIDS prevention program for low-income African-American youths. Arch Pediatr Adolesc Med 1996;150:363–72.
197. St. Lawrence JS, Brasfield TL, Jefferson KW, Alleyne E, O'Bannon RE, III, Shirley A. Cognitive-behavioral intervention to reduce African-American adolescents' risk for HIV infection. J Consult Clin Psychol 1995;63:221–37.
198. Wenger NS, Linn LS, Epstein M, Shapiro MF. Reduction of high-risk sexual behavior among heterosexuals undergoing HIV antibody testing: a randomized clinical trial. Am J Public Health 1991;81:1580–5.
199. Valdiserri RO, Lyter DW, Leviton LC, Callahan CM, Kingsley LA, Rinaldo CR. AIDS prevention in homosexual and bisexual men: results of a randomized trial evaluating two risk reduction interventions. AIDS 1989;3:21–6.
200. Coates TJ, McKusick L, Kuno R, Stites DP. Stress reduction training changed number of sexual partners but not immune function in men with HIV. Am J Public Health 1989;79:885–7.
201. Kelly JA, Murphy DA, Bahr GR, et al. Outcome of cognitive-behavioral and support group brief therapies for depressed, HIV-infected persons. Am J Psychiatry 1993;150:1679–86.
202. Darrow WW, Webster RD, Kurtz SP, Buckley AK, Patel KI, Stempel RR. Impact of HIV counseling and testing on HIV-infected men who have sex with men: the South Beach Health Survey. AIDS and Behavior 1998;2:115–26.
203. Parsons JT, Huszti HC, Crudder SO, Rich L, Mendoza J. Maintenance of safer sexual behaviors: evaluation of a theory based intervention for HIV seropositive men with haemophilia and their female partners. Haemophilia 2000;6:181–90.
204. Perry SW, Card CA, Moffatt M, Ashman T, Fishman B, Jacobsberg LB. Self-disclosure of HIV infection to sexual partners after repeated counseling. AIDS Educ Prev 1994;6:403–11.
205. Pomeroy EC, Rubin A, Van Lamingham L, Walker RJ. "Straight Talk": the effectiveness of a psychoeducational group intervention for heterosexuals with HIV/AIDS. Research on Social Work Practice 1997;7: 149–64.
206. Turnbull PJ, Dolan KA, Stimson GV. HIV testing, and the care and treatment of HIV positive people in English prisons. AIDS Care 1993;5:199–206.
207. Wong-Rieger D, David L. Causal evaluation of impact of support workshop for HIV+ men. Can J Public Health 1993;84(suppl 1):S66–70.
208. Gibson DR, Flynn NM, McCarthy JJ. Effectiveness of methadone treatment in reducing HIV risk behavior and HIV seroconversion among injecting drug users. AIDS 1999;13:1807–18.
209. National Institutes of Health (NIH) Consensus Development Program. Effective medical treatment of opiate addiction. NIH Consensus Statement Online. 1997 Nov 17–19;15(6):1–38. Available at http://odp.od.nih.gov/consensus/cons/108/108_statement.htm.
210. National Institute on Drug Abuse. Principles of drug addiction treatment: a research-based guide. Rockville, MD: US Department of Health and Human Services, National Institutes of Health, National Institute on Drug Abuse,1999; NIH Publication No. 99-4180.
211. Ball JC, Lange WR, Meyers CP, Friedman SR. Reducing the risk of AIDS through methadone maintenance treatment. J Health Soc Behav 1988;29:214–26.
212. Metzger DS, Woody GE, McLellan AT, et al. Human immunodeficiency virus seroconversion among intravenous drug users in- and out-of treatment: an 18-month prospective follow-up. J Acquir Immune Defic Syndr 1993;6:1049–56.

213. Moss AR, Vranizian K, Gorter R, Bacchetti P, Watters J, Osmond D. HIV seroconversion in intravenous drug users in San Francisco, 1985–1990. AIDS 1994;8:223–31.
214. Neaigus A, Sufian M, Friedman SR, et al. Effects of an outreach intervention on risk reduction among intravenous drug users. AIDS Educ Prev 1990;2:253–71.
215. Shore RE, Marmor M, Titus S, Des Jarlais DC. Methadone maintenance and other factors associated with intraindividual temporal trends in injection-drug use. J Subst Abuse Treat 1996;3:241–8.
216. Wells EA, Calsyn DA, Clark LL, Saxon AJ, Jackson TR. Retention in methadone maintenance is associated with reductions in different HIV risk behaviors for women and men. Am J Drug Alcohol Abuse 1996;22:509–21.
217. Zangerle R, Fuchs D, Rossler H, et al. Trends in HIV infection among intravenous drug users in Innsbruck, Austria. J Acquir Immune Defic Syndr 1992;5:865–71.
218. Condelli WS, Dunteman GH. Exposure to methadone programs and heroin use. Am J Drug Alcohol Abuse 1993;19:65–78.
219. Greenfield L, Biglow GE, Brooner RK. Validity of intravenous drug abusers' self-reported changes in HIV high-risk drug use behaviors. Drug Alcohol Depend 1995;39:91–8.
220. Martin GS, Serpelloni G, Galvan V, et al. Behavioural change in injecting drug users: evaluation of an HIV/AIDS education programme. AIDS Care 1990;2:275–9.
221. Watkins KE, Metzger D, Woody G, McLellan AT. High-risk sexual behaviors of intravenous drug users in- and out-of-treatment: implications for the spread of HIV infection. Am J Drug Alcohol Abuse 1992;18:389–98.
222. Serpelloni G, Carrieri MP, Rezza G, Morganti S, Gomma M, Binkin N. Methadone treatment as a determinant of HIV risk reduction among injecting drug users: a nested case controlled study. AIDS Care 1994;6:215–20.
223. Baker A, Kochan N, Dixon J, Wodak A, Heather N. HIV risk-taking behaviour among injecting drug users currently, previously and never enrolled in methadone treatment. Addiction 1995;90:545–54.
224. Capelhorn JR, Ross MW. Methadone maintenance and the likelihood of risky needle sharing. Int J Addictions 1995;30:685–98.
225. Gibson DR, Flynn NM, Perales D. Effectiveness of syringe exchange programs in reducing HIV risk behavior and HIV seroconversion among injecting drug users. AIDS 2001;15:1329–41.
226. Academy for Educational Development. Access to sterile syringes. Washington, DC; June 2000. Prepared for CDC. Available at http://www.cdc.gov/idu.
227. Cotten-Oldenburg NU, Carr P, DeBoer JM, Collison EK, Novotny G. Impact of pharmacy-based syringe access on injection practices among injecting drug users in Minnesota. J Acquir Immune Defic Syndr 2001;27:183–92.
228. Gleghorn AA, Wright-De Aguero L, Flynn C. Feasibility of one-time use of sterile syringes: a study of active injection drug users in seven United States metropolitan areas. J Acquir Immune Defic Syndr Hum Retrovirol 1998;18(suppl 1):S30–6.
229. Burris S, Lurie P, Abrahamson D, Rich JD. Physician prescribing of sterile injection equipment to prevent HIV infection: time for action. Ann Intern Med 2000;133:218–26.
230. Rich JD, Macalino GE, McKenzie M, Taylor LE, Burris S. Syringe prescription to prevent infection in Rhode Island: a case study. Am J Public Health 2001;91:699–700.
231. Groseclose SL, Weinstein B, Jones TS, Valleroy L, Fehrs L, Kassler WJ. Impact of increased legal access to needles and syringes on practices of injecting drug users and police officers—Connecticut, 1992–1993. J Acquir Immune Defic Syndr 1995;10:82–9.
232. Gershon RR. Infection control basis for recommending one-time use of sterile syringes and aseptic procedures for injection drug users. J Acquir Immune Defic Syndr Hum Retrovirol 1998;18(suppl 1):S20–4.
233. Gleghorn AA, Doherty MC, Vlahov D, Celentano DD, Jones TS. Inadequate bleach contact times during syringe cleaning among injection drug users. J Acquir Immune Defic Syndr 1994;7:767–72.
234. McCoy CB, Rivers JE, McCoy HV, et al. Compliance to bleach disinfection protocols among injecting drug users in Miami. J Acquir Immune Defic Syndr 1994;7:773–6.
235. Fenton K, Peterman TA. HIV partner notification: taking a new look. AIDS 1997;11:1535–46.
236. CDC. HIV partner counseling and referral services. Guidance. Atlanta, GA: US Department of Health and Human Services, CDC; 1998. Available at www.cdc.gov/hiv/pubs/pcrs/pcrs-cov.htm.
237. CDC. Program Operations. Guidelines for STD Prevention. Partner Services. Atlanta, GA: US Department of Health and Human Services, CDC. Updated June 28, 2001. Available at www.cdc.gov/std/program/partners.pdf.
238. Cowan FM, French R, Johnson AM. The role and effectiveness of partner notification in STD control: a review. Genitourin Med 1996;72:247–52.
239. Kissinger PJ, Niccolai LM, Mangus M, et al. Partner notification for HIV and syphilis: effects on sexual behaviors and relationship stability. Sex Transm Dis 2003; 30:75–82.
240. Hoxworth T, Spencer NE, Peterman TA, Craig T, Johnson S, Maher JE. Changes in partnerships and HIV risk behaviors after partner notification. Sex Transm Dis 2003;30:83–8.
241. Rothenberg KH, Paskey SJ. The risk of domestic violence and women with HIV infection: implications for partner notification, public policy, and the law. Am J Public Health 1995; 85:1569–76.
242. Maher JE, Peterson J, Hastings K, et al. Partner violence, partner notification, and women's decisions to have an HIV test. J Acquir Immune Defic Syndr 2000;25:276–82.
243. Jones JL, Wykoff RF, Hollis SL, Longshore ST, Gamble WB, Jr. Gunn RA. Partner acceptance of health department notification of HIV exposure, South Carolina. JAMA 1990;264:1284–6.
244. CDC. Notification of syringe-sharing and sex partners of HIV-infected persons—Pennsylvania, 1993–1994. MMWR 1995;44:202–4.
245. Wykoff RF, Heath CW Jr., Hollis SL, et al. Contact tracing to identify human immunodeficiency virus infection in a rural community. JAMA 1988;259:3563–6.
246. Gostin LO, Webber DW. HIV infection and AIDS in the public health and health care systems: the role of law and litigation. JAMA 1998;279:1108–13.
247. Oxman AD, Scott EA, Sellors JW, et al. Partner notification for sexually transmitted diseases: an overview of the evidence. Can J Public Health 1994;85(suppl 1):S41–7.
248. Macke BA, Maher JE. Partner notification in the United States: an evidence-based review. Am J Prev Med 1999;17:230–42.
249. Giesecke J, Ramstedt K, Granath F, Ripa T, Rado G, Westrell M. Efficacy of partner notification for HIV infection. Lancet 1991;338:1096–100.

Summary of recommendations for human immunodeficiency virus (HIV) prevention among HIV-infected persons in clinical care settings

Recommendation	Rating*
HIV-infected patients should be screened for behaviors associated with HIV transmission by using a straightforward, nonjudgmental approach. This should be done at the initial visit and subsequent routine visits or periodically, as the clinician feels necessary, but at a minimum of yearly. Any indication of risky behavior should prompt a more thorough assessment of HIV transmission risks.	A-II
At the initial and each subsequent routine visit, HIV-infected patients should be questioned about symptoms of sexually transmitted diseases (STDs) (e.g., urethral or vaginal discharge; dysuria; intermenstrual bleeding; genital or anal ulcers; anal pruritus, burning, or discharge; and, for women, lower abdominal pain with or without fever). Regardless of reported sexual behavior or other epidemiologic risk information, the presence of such signs or symptoms should always prompt diagnostic testing and, when appropriate, treatment.	A-I
At the initial visit • All HIV-infected women and men should be screened for laboratory evidence of syphilis. Women should also be screened for trichomoniasis. Sexually active women aged ≤25 years and other women at increased risk, even if asymptomatic, should be screened for cervical chlamydial infection.	A-II
• Consideration should be given to screening all HIV-infected men and women for gonorrhea and chlamydial infections. However, because of the cost of screening and the variability of prevalence of these infections, decisions about routine screening for these infections should be based on epidemiologic factors (including prevalence of infection in the community or the population being served), availability of tests, and cost. (Some HIV specialists also recommend type-specific serologic testing for herpes simplex virus type 2 for both men and women.)	B-II
Screening for STDs should be repeated periodically (i.e., at least annually) if the patient is sexually active or if earlier screening revealed STDs. Screening should be done more frequently (e.g., at 3–6-month intervals) for asymptomatic persons at higher risk.	B-III
At the initial and each subsequent routine visit, HIV-infected women of childbearing age should be questioned to identify possible current pregnancy, interest in future pregnancy, or sexual activity without reliable contraception. They should be referred for appropriate counseling, reproductive health care, or prenatal care, as indicated. Women should be asked whether they suspect pregnancy or have missed their menses and, if so, should be tested for pregnancy.	A-I
Clinics or office environments where patients with HIV infection receive care should be structured to support and enhance HIV prevention.	B-III
Within the context of HIV care, brief general HIV prevention messages should be regularly provided to HIV-infected patients at each visit, or periodically, as determined by the clinician, and at a minimum of twice yearly. These messages should emphasize the need for safer behaviors to protect their own health and the health of their sex or needle-sharing partners, regardless of perceived risk. Messages should be tailored to the patient's needs and circumstances.	A-III
Patients should have adequate, accurate information regarding factors that influence HIV transmission and methods for reducing the risk for transmission to others, emphasizing that the most effective methods for preventing transmission are those that protect noninfected persons against exposure to HIV (e.g., sexual abstinence; consistent and correct use of condoms made of latex, polyurethane or other synthetic materials; and sex with only a partner of the same HIV serostatus). HIV-infected patients who engage in high-risk sexual practices (i.e., capable of resulting in HIV transmission) with persons of unknown or negative HIV serostatus should be counseled to use condoms consistently and correctly.	A-III
Patients' misconceptions regarding HIV transmission and methods for reducing risk for transmission should be identified and corrected. For example, ensure that patients know that 1) per-act estimates of HIV transmission risk for an individual patient vary according to behavioral, biologic, and viral factors; 2) highly active antiretroviral therapy (HAART) cannot be relied upon to eliminate the risk of transmitting HIV to others; and 3) nonoccupational postexposure prophylaxis is of uncertain effectiveness for preventing infection in HIV-exposed partners.	A-III
Tailored HIV prevention interventions, using a risk-reduction approach, should be delivered to patients at highest risk for transmitting HIV.	A-III
After initial prevention messages are delivered, subsequent longer or more intensive interventions in the clinic or office should be delivered, if feasible.	A-I
HIV-infected patients should be referred to appropriate services for issues related to HIV transmission that cannot be adequately addressed during the clinic visit.	A-I
Persons who inject illicit drugs should be strongly encouraged to cease injecting and enter into substance abuse treatment programs (e.g., methadone maintenance) and should be provided referrals to such programs.	A-II
Persons who continue to inject drugs should be advised to always use sterile injection equipment and to never reuse or share needles, syringes, or other injection equipment and should be provided information regarding how to obtain new, sterile syringes and needles (e.g., syringe exchange programs).	A-II
In HIV health-care settings, all applicable requirements for reporting sex and needle-sharing partners of HIV-infected patients to the appropriate health department should be followed.	A-III
At the initial visit, patients should be asked if all of their sex and needle-sharing partners have been informed of their exposure to HIV.	A-III
At routine follow-up visits, patients should be asked if they have had any new sex or needle-sharing partners who have not been informed of their exposure to HIV.	A-III
All patients should be referred to the appropriate health department to discuss sex and needle-sharing partners who have not been informed of their exposure and to arrange for their notification and referral for HIV testing.	A-I
In HIV health-care settings, access to available community partner counseling and referral resources should be established.	A-III

* Letters indicate the strength of the recommendation, and roman numerals indicate the quality of evidence supporting it, respectively (see Table 1).

MMWR™

Morbidity and Mortality Weekly Report

Recommendations and Reports July 18, 2003 / Vol. 52 / No. RR-12

Continuing Education Activity Sponsored by CDC
Incorporating HIV Prevention into the Medical Care of Persons Living with HIV
Recommendations of CDC, the Health Resources and Services Administration, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America

EXPIRATION — July 18, 2006

You must complete and return the response form electronically or by mail by **July 18, 2006**, to receive continuing education credit. If you answer all of the questions, you will receive an award letter for 1.5 hours Continuing Medical Education (CME) credit; 0.15 Continuing Education Units (CEUs); or 1.9 contact hours Continuing Nursing Education (CNE) credit. If you return the form electronically, you will receive educational credit immediately. If you mail the form, you will receive educational credit in approximately 30 days. No fees are charged for participating in this continuing education activity.

INSTRUCTIONS

By Internet

1. Read this *MMWR* (Vol. 52, RR-12), which contains the correct answers to the questions beginning on the next page.
2. Go to the *MMWR* Continuing Education Internet site at <http://www.cdc.gov/mmwr/cme/conted.html>.
3. Select which exam you want to take and select whether you want to register for CME, CEU, or CNE credit.
4. Fill out and submit the registration form.
5. Select exam questions. To receive continuing education credit, you must answer all of the questions. Questions with more than one correct answer will instruct you to "Indicate all that apply."
6. Submit your answers no later than **July 18, 2006**.
7. Immediately print your Certificate of Completion for your records.

By Mail or Fax

1. Read this *MMWR* (Vol. 52, RR-12), which contains the correct answers to the questions beginning on the next page.
2. Complete all registration information on the response form, including your name, mailing address, phone number, and e-mail address, if available.
3. Indicate whether you are registering for CME, CEU, or CNE credit.
4. Select your answers to the questions, and mark the corresponding letters on the response form. To receive continuing education credit, you must answer all of the questions. Questions with more than one correct answer will instruct you to "Indicate all that apply."
5. Sign and date the response form or a photocopy of the form and send no later than **July 18, 2006**, to
   Fax: 404-639-4198 Mail: MMWR CE Credit
   Office of Scientific and Health Communications
   Epidemiology Program Office, MS C-08
   Centers for Disease Control and Prevention
   1600 Clifton Rd, N.E.
   Atlanta, GA 30333
6. Your Certificate of Completion will be mailed to you within 30 days.

ACCREDITATION

Continuing Medical Education (CME). CDC is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians. CDC designates this educational activity for a maximum of 1.5 hours in category 1 credit toward the AMA Physician's Recognition Award. Each physician should claim only those hours of credit that he/she actually spent in the educational activity.

Continuing Education Unit (CEU). CDC has been approved as an authorized provider of continuing education and training programs by the International Association for Continuing Education and Training and awards 0.15 Continuing Education Units (CEUs).

Continuing Nursing Education (CNE). This activity for 1.9 contact hours is provided by CDC, which is accredited as a provider of continuing education in nursing by the American Nurses Credentialing Center's Commission on Accreditation.

Goal and Objectives

This *MMWR* provides recommendations for preventing transmission of human immunodeficiency virus (HIV) by infected persons. These recommendations were developed by CDC, the Health Resources and Services Administration (HRSA), the National Institutes of Health (NIH), the HIV Medical Association (HIVMA) of the Infectious Diseases Society of America (IDSA), and others knowledgeable in HIV prevention. The goal of this report is to provide strategies for persons providing medical care to HIV-infected persons for incorporating HIV prevention into that care. Upon completion of this educational activity, the reader should be able to 1) describe why HIV-prevention efforts in the United States should focus on HIV-infected persons; 2) describe different means of screening HIV-infected patients for HIV-transmission risk behaviors during routine office visits; 3) describe behavioral interventions for HIV-infected persons to prevent HIV transmission; 4) identify reasons for referring HIV-infected persons for additional services; and 5) understand the importance of partner counseling and referral services (PCRS).

To receive continuing education credit, please answer all of the following questions.

1. Whereas HIV-prevention efforts in the United States had focused on persons who were not HIV-infected, emphasis is now placed on prevention services for HIV-infected persons because . . .

A. HIV-infected persons who are aware of their HIV infection tend to reduce behaviors that might transmit HIV to others.
B. bacterial and viral sexually transmitted diseases (STDs) among HIV-infected men and women receiving outpatient care have been increasingly noted, indicating ongoing risky behaviors.
C. optimism regarding the effectiveness of highly active antiretroviral therapy (HAART) for HIV might be contributing to relaxed attitudes toward safer sex practices and increased sexual risk-taking by HIV-infected persons.
D. all of the above.

2. All of the following sex-related behaviors are important to address in risk screening except . . .

A. age at first sexual intercourse.
B. types of sexual activity (oral, vaginal, or anal sex).
C. whether condoms are used.
D. barriers to abstinence or correct condom use.
E. number, sex, and HIV serostatus of partners.

3. Key injection-drug–related behaviors to address in screening include whether the patient has been . . .

A. injecting illicit drugs.
B. sharing needles and syringes or other injection equipment.
C. using new or sterilized needles and syringes.
D. all of the above.

4. Surveys indicate that patients are more likely to discuss risk behaviors if they perceive their clinicians as being . . .

A. comfortable talking about certain topics (e.g., sex and drug use).
B. nonjudgmental, empathetic, and knowledgeable.
C. comfortable counseling patients regarding sexual risk factors.
D. board-certified in infectious diseases.
E. A, B, C.
F. all of the above.

5. Screening HIV-infected patients for STDs has critical public health implications because . . .

A. the presence of STDs often indicates recent or ongoing sexual behaviors that can result in HIV transmission.
B. substantial evidence indicates that certain STDs enhance the risk for HIV transmission or acquisition.
C. identification and treatment of STDs can reduce spread of these infections among groups at high risk (i.e., sex or drug-using networks).
D. all of the above.

6. Which of the following statements regarding screening of HIV-infected patients is not true?

A. At the initial and each subsequent routine visit, all patients should be questioned regarding symptoms of STDs.
B. All men should be screened for gonorrhea.
C. All women and men should be screened for laboratory evidence of syphilis.
D. All women should be screened for trichomoniasis.

7. Clinical and epidemiologic studies have demonstrated the effectiveness of all of the following methods for preventing HIV transmission except . . .

A. sexual abstinence.
B. postexposure prophylaxis for partners.
C. consistent and correct use of condoms.
D. not sharing needles when injecting drugs.

8. Which statement concerning partner counseling and referral services (PCRS) is not true?

A. Certain HIV-infected persons are sexually active after receiving their diagnoses but do not tell their partners about their infection.
B. PCRS helps infected partners gain earlier access to medical evaluation, treatment, and other services.
C. Partners should be told when their HIV exposure occurred.
D. The majority of states have laws and regulations related to informing partners who have been exposed to HIV.

9. Which of the following is not a recommendation related to PCRS?

A. At the initial visit, patients should be asked if all of their sex and needle-sharing partners have been informed of their exposure to HIV.
B. At routine follow-up visits, patients should be asked if they have had any new sex or needle-sharing partners who have not been informed of their exposure to HIV.
C. Patients should be encouraged to talk to the health department disease-intervention specialist regarding sex and needle-sharing partners who have not been informed of their exposure and to arrange for their referral for testing.
D. All partners with whom an HIV-infected person has had sex in the past 15 years should be referred for testing.

10. Which statement is true regarding referring patients for additional services?

A. Achieving behavioral change is often dependent on addressing patient concerns (e.g., homelessness, substance abuse, or mental illness).
B. The majority of injection-drug users are unable to sustain long-term abstinence from drug use without substance abuse treatment.
C. Accessibility and convenience of services predict whether a referral will be completed.
D. All of the above.

11. Indicate your work setting.

A. State/local health department.
B. Other public health setting.
C. Hospital clinic/private practice.
D. Managed care organization.
E. Academic institution.
F. Other.

12. Which best describes your professional activities?

A. Physician.
B. Nurse.
C. Health educator.
D. HIV-prevention counselor.
E. Other.

13. I plan to use these recommendations as the basis for . . . (*Indicate all that apply.*)

A. health education materials.
B. insurance reimbursement policies.
C. local practice guidelines.
D. public policy.
E. other.

14. Each month, approximately how many patients with HIV do you treat?

A. None.
B. 1–5.
C. 6–20.
D. 21–50.
E. 51–100.
F. >100.

15. How much time did you spend reading this report and completing the exam?

A. <1.5 hours.
B. ≥1.5 hours but <2.0 hours.
C. ≥2.0 hours but <3.0.
D. ≥3.0 hours.

16. After reading this report, I am confident I can describe why HIV-prevention efforts in the United States should focus on HIV-infected persons.

A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

17. After reading this report, I am confident I can describe different means of screening HIV-infected patients for HIV transmission risk during routine office visits.

A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

18. After reading this report, I am confident I can describe behavioral interventions for HIV-infected persons to help prevent HIV transmission.

A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

19. After reading this report, I am confident I can identify reasons for referring HIV-infected persons for additional services.

A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

20. After reading this report, I am confident I can understand the importance of PCRS.

A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

(Continued on pg CE-4)

Detach or photocopy.

MMWR Response Form for Continuing Education Credit
July 18, 2003/Vol. 52/No. RR-12
Incorporating HIV Prevention into the Medical Care Persons Living with HIV

To receive continuing education credit, you must
1. provide your contact information;
2. indicate your choice of CME, CEU, or CNE credit;
3. answer all of the test questions;
4. sign and date this form or a photocopy;
5. submit your answer form by July 18, 2006.
Failure to complete these items can result in a delay or rejection of your application for continuing education credit.

Last Name *First Name*

Street Address or P.O. Box

Apartment *or* *Suite*

City *State* *ZIP Code*

Phone Number *Fax Number*

E-Mail Address

Check One
☐ *CME Credit*
☐ *CEU Credit*
☐ *CNE Credit*

Fill in the appropriate blocks to indicate your answers. Remember, you must answer all of the questions to receive continuing education credit!

1. [ ]A [ ]B [ ]C [ ]D	15. [ ]A [ ]B [ ]C [ ]D	
2. [ ]A [ ]B [ ]C [ ]D [ ]E	16. [ ]A [ ]B [ ]C [ ]D [ ]E	
3. [ ]A [ ]B [ ]C [ ]D	17. [ ]A [ ]B [ ]C [ ]D [ ]E	
4. [ ]A [ ]B [ ]C [ ]D	18. [ ]A [ ]B [ ]C [ ]D [ ]E	
5. [ ]A [ ]B [ ]C [ ]D	19. [ ]A [ ]B [ ]C [ ]D [ ]E	
6. [ ]A [ ]B [ ]C [ ]D	20. [ ]A [ ]B [ ]C [ ]D [ ]E	
7. [ ]A [ ]B [ ]C [ ]D	21. [ ]A [ ]B [ ]C [ ]D [ ]E	
8. [ ]A [ ]B [ ]C [ ]D	22. [ ]A [ ]B [ ]C [ ]D [ ]E	
9. [ ]A [ ]B [ ]C [ ]D	23. [ ]A [ ]B [ ]C [ ]D [ ]E	
10. [ ]A [ ]B [ ]C [ ]D	24. [ ]A [ ]B [ ]C [ ]D [ ]E	
11. [ ]A [ ]B [ ]C [ ]D [ ]E [ ]F	25. [ ]A [ ]B [ ]C [ ]D [ ]E	
12. [ ]A [ ]B [ ]C [ ]D [ ]E	26. [ ]A [ ]B [ ]C [ ]D [ ]E	
13. [ ]A [ ]B [ ]C [ ]D [ ]E	27. [ ]A [ ]B [ ]C [ ]D [ ]E	
14. [ ]A [ ]B [ ]C [ ]D [ ]E [ ]F		

Signature *Date I Completed Exam*

21. The objectives are relevant to the goal of this report.
A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

22. The teaching strategies used in this report (text, figures, boxes, and tables) were useful.
A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

23. Overall, the presentation of the report enhanced my ability to understand the material.
A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

24. These recommendations will affect my practice.
A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

25. The content of this activity was appropriate for my educational needs.
A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

26. The availability of continuing education credit influenced my decision to read this report.
A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

27. How did you learn about this continuing education activity?
A. Internet.
B. Advertisement (e.g., fact sheet, *MMWR* cover, newsletter, or journal).
C. Coworker/supervisor.
D. Conference presentation.
E. *MMWR* subscription.
F. Other.

Correct answers for questions 1–10.
1. D; 2. A; 3. D; 4. E; 5. D; 6. B; 7. B; 8. C; 9. D; 10. D.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTERS FOR DISEASE CONTROL AND PREVENTION (CDC)
ATLANTA, GEORGIA 30333

OFFICIAL BUSINESS
PENALTY FOR PRIVATE USE $300

NO POSTAGE NECESSARY IF MAILED IN THE UNITED STATES

BUSINESS REPLY MAIL
FIRST CLASS MAIL PERMIT NO. 99110 ATLANTA, GA 30333

Postage Will Be Paid by Department of Health and Human Services

MMWR CE CREDIT
OFFICE OF SCIENTIFIC AND HEALTH COMMUNICATIONS
EPIDEMIOLOGY PROGRAM OFFICE — MAILSTOP C-08
CENTERS FOR DISEASE CONTROL AND PREVENTION
1600 CLIFTON RD., N.E.
ATLANTA, GEORGIA 30333

Members of the HIV Prevention in Clinical Care Working Group

CDC: Sevgi Aral, Ph.D., Samuel W. Dooley, M.D., Mary L. Kamb, M.D., Jonathan Kaplan, M.D., Mary Spink Neumann, Ph.D., Ida M. Onorato, M.D., Thomas A. Peterman, M.D., Kathryn J. Rauch, Renee Ridzon, M.D., J. Walton Senterfitt, Ph.D., Atlanta, Georgia.

Health Resources and Services Administration: Barbara Aranda-Naranjo, Ph.D.; Michael Johnson, M.D., Rockville, Maryland.

National Institutes of Health: Christopher M. Gordon, Ph.D., Rockville, Maryland.

Infectious Diseases Society of America: John Bartlett, M.D., The Johns Hopkins University School of Medicine, Baltimore, Maryland.

Consultants to the Working Group

Bruce D. Agins, M.D., New York State Department of Health AIDS Institute, New York, New York; Kim W. Hamlett-Berry, Ph.D., Department of Veterans Affairs, Washington, D.C.; H. Hunter Handsfield, M.D., University of Washington, Public Health-Seattle and King County, Seattle, Washington; Fredrick Hecht, M.D., University of California, San Francisco AIDS Program, San Francisco, California (HIVMA of IDSA); King K. Holmes, M.D., University of Washington, Seattle, Washington; Kenneth Mayer, M.D., Brown University School of Medicine, Providence, Rhode Island (HIVMA of IDSA); Thomas C. Quinn, M.D., The Johns Hopkins University School of Medicine, Baltimore, Maryland; Julie M. Scofield, National Alliance of State and Territorial AIDS Directors, Washington, D.C.; Dan Wohlfeiler, M.P.H., California Department of Public Health, Berkeley, California.

CDC Consultants: Joanna Buffington, Ph.D., James Buehler, M.D., Alan E. Greenberg, M.D., Kathleen Irwin, M.D., Harold W. Jaffe, M.D., Robert S. Janssen, M.D., Gary Marks, Ph.D., Allyn Nakashima, M.D., Esther Sumartojo, Ph.D., Ronald O. Valdiserri, M.D., Jason Urbanowicz, J.D., Richard Wolitski, Ph.D., Kimberly Workowski, M.D., Centers for Disease Control and Prevention, Atlanta, Georgia.

---

e xperience.

For over 50 years, MMWR has been the key provider of up-to-date public health reports and news. All of our publications–the Weekly, Recommendations and Reports, and Surveillance Summaries–are available online, free of charge.

Visit **cdc.gov/mmwr** and experience timely public health information from a trusted source.

know what matters.

MMWR™ Online

The *Morbidity and Mortality Weekly Report (MMWR)* Series is prepared by the Centers for Disease Control and Prevention (CDC) and is available free of charge in electronic format and on a paid subscription basis for paper copy. To receive an electronic copy each week, send an e-mail message to *listserv@listserv.cdc.gov*. The body content should read *SUBscribe mmwr-toc*. Electronic copy also is available from CDC's World-Wide Web server at *http://www.cdc.gov/mmwr* or from CDC's file transfer protocol server at *ftp://ftp.cdc.gov/pub/publications/mmwr*. To subscribe for paper copy, contact Superintendent of Documents, U.S. Government Printing Office, Washington, DC 20402; telephone 202-512-1800.

Data in the weekly *MMWR* are provisional, based on weekly reports to CDC by state health departments. The reporting week concludes at close of business on Friday; compiled data on a national basis are officially released to the public on the following Friday. Address inquiries about the *MMWR* Series, including material to be considered for publication, to Editor, *MMWR* Series, Mailstop C-08, CDC, 1600 Clifton Rd., N.E., Atlanta, GA 30333; telephone 888-232-3228.

All material in the *MMWR* Series is in the public domain and may be used and reprinted without permission; citation as to source, however, is appreciated.

All *MMWR* references are available on the Internet at http://www.cdc.gov/mmwr. Use the search function to find specific articles.

Use of trade names and commercial sources is for identification only and does not imply endorsement by the U.S. Department of Health and Human Services.

References to non-CDC sites on the Internet are provided as a service to *MMWR* readers and do not constitute or imply endorsement of these organizations or their programs by CDC or the U.S. Department of Health and Human Services. CDC is not responsible for the content of these sites. URL addresses listed in *MMWR* were current as of the date of publication.

☆U.S. Government Printing Office: 2003-533-155/69128 Region IV

Valganciclovir Dosing in Children

The U.S. Food and Drug Administration (FDA) is notifying healthcare professionals of new pediatric dosing recommendations for Valcyte (valganciclovir hydrochloride) oral tablets and oral solution. This change is being made to prevent potential valganciclovir overdosing in children with low body weight, low body surface area, and below normal serum creatinine. The revised dosing recommendations are being updated to include an upper limit on the calculated creatinine clearance using the modified Schwartz formula, which is used to calculate the pediatric dose of Valcyte. The FDA has determined that adding an upper limit of 150 mL/min/1.73 m^2 to the creatinine clearance calculated using the Schwartz formula for the determination of pediatric doses can help prevent the potential for Valcyte overdosing. If the calculated pediatric dose of Valcyte exceeds 900 mg, a dose of 900 mg should be given to the child.

The FDA notice is available on http://www.fda.gov/Drugs/DrugSafety/ucm225727.htm#ds and is provided below:

FDA Drug Safety Communication: New dosing recommendations to prevent potential Valcyte (valganciclovir) overdose in pediatric transplant patients

Safety Announcement

[09-15-2010] The U.S. Food and Drug Administration (FDA) is notifying healthcare professionals of new pediatric dosing recommendations for Valcyte (valganciclovir hydrochloride) oral tablets and oral solution. This change is being made to prevent potential valganciclovir overdosing in children with low body weight, low body surface area, and below normal serum creatinine.

The revised dosing recommendations are being updated to include an upper limit on the calculated creatinine clearance using the modified Schwartz formula, which is used to calculate the pediatric dose of Valcyte.

Valganciclovir is an antiviral medication that can be effective for the prevention of cytomegalovirus (CMV) disease in children 4 months to 16 years of age who have undergone a kidney or heart transplant. Cytomegalovirus is a member of a group of herpes-type viruses that can cause disease in different parts of the body.[1] Patients with weakened immune systems, such as organ transplant patients, are particularly susceptible to CMV infection and must take medications such as Valcyte to prevent the disease.

See the Data Summary for the new dosing recommendations for Valcyte.

Additional Information for Patients

- Talk to your healthcare professional about any concerns with your Valcyte dose.
- The side effects from Valcyte overdosing include abdominal pain, vomiting, diarrhea, tremor or seizure.
- Report any side effects you experience to the FDA MedWatch program, using the information in the "Contact Us" box at the bottom of the page.

Additional Information for Healthcare Professionals

- The dosing recommendations for Valcyte in children have changed. The dosing calculation can be found in the Data Summary and in the drug label.
- Be aware of possible valganciclovir overdose in pediatric patients with low body weight, low body surface area, or below normal serum creatinine.
- When calculating the pediatric dose of Valcyte with the modified Schwartz formula, a maximum value of 150 mL/min/1.73 m^2 should be used in the formula.
- When the calculated pediatric dose of Valcyte exceeds 900 mg, a dose of 900 mg should be administered to the child.
- Advise patients to contact a healthcare professional immediately if they experience signs and symptoms of valganciclovir overdose while taking Valcyte.
- Report adverse events involving Valcyte to the FDA MedWatch program, using the information in the "Contact Us" box at the bottom of the page

Data Summary

Healthcare professionals should follow the updated pediatric dosing algorithm in the Valcyte label.[2] The pediatric dose of Valcyte is based on body surface area (BSA) and creatinine clearance (CrCl) derived from a modified Schwartz formula. Under the previous dosing recommendations, pediatric patients with low body weight, low body surface area, and below normal serum creatinine could have a high calculated Schwartz creatinine clearance, resulting in a pediatric dose that approached the adult dose of 900 mg. This type of patient was not routinely observed in the clinical trials used to derive and confirm the pediatric dose, and may have been overdosed according to the previous dosing algorithm. As a result, FDA has updated the dosing algorithm so that when calculating the pediatric dose, a maximum value of 150 mL/min/1.73 m^2 should be used in the formula, even if the calculated Schwartz creatinine clearance exceeds 150 mL/min/1.73 m^2. Furthermore, if the calculated Valcyte dose exceeds 900 mg, a dose of 900 mg should be given to the child.

The revised language in Section 2.3 of the label, *Pediatric Patients*, is as follows (new language underlined)[2]:

Prevention of CMV Disease: For pediatric patients 4 months to 16 years of age who have received a kidney or heart transplant, the recommended once daily dose of Valcyte starting within 10 days of transplantation until 100 days post-transplantation is based on body surface area (BSA) and creatinine clearance (CrCl) derived from a modified Schwartz formula, and is calculated using the equation below:

Pediatric Dose (mg) = 7 x BSA x CrCl (calculated using a modified Schwartz formula). If the calculated Schwartz creatinine clearance exceeds 150 mL/min/1.73 m^2, then a maximum value of 150 mL/min/1.73m^2 should be used in the equation.

$$\text{Mosteller BSA } (m^2) = \sqrt{\frac{\text{Height (cm)} \times \text{Weight (kg)}}{3600}}$$

$$\text{Schwartz Creatinine Clearance } (\text{mL/min/1.73 } m^2) = \frac{k \times \text{Height (cm)}}{\text{Serum Creatinine (mg/dL)}}$$

Where k =

0.45 for patients aged 4 months to < 1 year,

0.45 for patients aged 1 to < 2 years (note k value is 0.45 instead of the typical value of 0.55),

0.55 for boys aged 2 to < 13 years and girls aged 2 to 16 years, and

0.7 for boys aged 13 to 16 years.

In summary, the FDA has determined that adding an upper limit of 150 mL/min/1.73 m^2 to the creatinine clearance calculated using the Schwartz formula for the determination of pediatric doses can help prevent the potential for Valcyte overdosing. If the calculated pediatric dose of Valcyte exceeds 900 mg, a dose of 900 mg should be given to the child.

References

1. MedLinePlus health topics page. U.S. National Library of Medicine Web site. http://www.nlm.nih.gov/medlineplus/ency/article/000663.htm. Accessed August 25, 2010.
2. Updated Valcyte label

Related Information

- Valcyte Label - 8/05/2010
- FDA issues new dosing guide for children using Valcyte
  9/15/2010 - FDA Note To Correspondents
- Valganciclovir (marketed as Valcyte) Information

Contact Us

- Report a Serious Problem
- 1-800-332-1088
- 1-800-FDA-0178 Fax

MedWatch Online
Regular Mail: Use postage-paid FDA Form 3500
Mail to: MedWatch 5600 Fishers Lane, Rockville, MD 20857

MMWR™

Morbidity and Mortality Weekly Report

Recommendations and Reports | January 21, 2005 / Vol. 54 / No. RR-2

Antiretroviral Postexposure Prophylaxis After Sexual, Injection-Drug Use, or Other Nonoccupational Exposure to HIV in the United States

Recommendations from the U.S. Department of Health and Human Services

INSIDE: Continuing Education Examination

DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTERS FOR DISEASE CONTROL AND PREVENTION

The *MMWR* series of publications is published by the Coordinating Center for Health Information and Service,* Centers for Disease Control and Prevention (CDC), U.S. Department of Health and Human Services, Atlanta, GA 30333.

SUGGESTED CITATION

Centers for Disease Control and Prevention. Antiretroviral postexposure prophylaxis after sexual, injection-drug use, or other nonoccupational exposure to HIV in the United States: recommendations from the U.S. Department of Health and Human Services. MMWR 2005;54(No. RR-2):[inclusive page numbers].

Centers for Disease Control and Prevention

Julie L. Gerberding, MD, MPH
Director

Dixie E. Snider, MD, MPH
Chief of Science

Tanja Popovic, MD, PhD
(*Acting*) *Associate Director for Science*

Coordinating Center for Health Information and Service*

Blake Caldwell, MD, MPH, and Edward J. Sondik, PhD
(*Acting*) *Directors*

National Center for Health Marketing*

Steven L. Solomon, MD
(*Acting*) *Director*

Division of Scientific Communications*

John W. Ward, MD
(*Acting*) *Director*
Editor, MMWR *Series*

Suzanne M. Hewitt, MPA
Managing Editor, MMWR *Series*

C. Kay Smith-Akin, MEd
Lead Technical Writer-Editor

David C. Johnson
Project Editor

Beverly J. Holland
Lead Visual Information Specialist

Lynda G. Cupell
Malbea A. LaPete
Visual Information Specialists

Kim L. Bright, MBA
Quang M. Doan, MBA
Erica R. Shaver
Information Technology Specialists

* Proposed.

CONTENTS

Introduction 1
Evidence of Possible Benefits from nPEP 2
  Animal Studies 2
  Postnatal Prophylaxis 2
  Observational Studies of nPEP 3
  Case Reports 4
Evidence of Possible Risks from nPEP 4
  Effects on Risk-Reduction Behaviors 4
  Antiretroviral Side Effects and Toxicity 4
  Selection of Resistant Virus 5
Cost-Effectiveness of nPEP 5
Evidence of Current Practice 5
Evaluation of Persons Seeking Care After Potential Nonoccupational Exposure to HIV 6
  HIV Status of the Potentially Exposed Person 6
  Timing and Frequency of Exposure 6
  HIV Status of Source 7
  Transmission Risk from the Exposure 7
Evaluation for Sexually Transmitted Infections, Hepatitis, and Emergency Contraception 7
Recommendations for Use of Antiretroviral nPEP 8
Considerations for All Patients Treated with Antiretroviral nPEP 12
  Use of Starter Packs 12
  Scientific Consultation 12
  Facilitating Adherence 12
  Follow-up Testing and Care 12
  HIV Prevention Counseling 12
  Management of Source Persons 13
  Reporting and Confidentiality 14
Considerations for Vulnerable Populations 14
  Pregnant Women and Women of Childbearing Potential . 14
  Children 14
  Sexual Assault Survivors 14
  Inmates 15
  Injection-Drug Users 15
Conclusion 15
References 16
Continuing Education Activity CE-1

Disclosure of Relationship

CDC, our planners, and our content specialists wish to disclose they have no financial interests or other relationships with the manufactures of commercial products, suppliers of commercial services, or commercial supporters. This report does not include any discussion of a product under investigational use. However, this report does contain discussion of certain drugs indicated for use in a nonlabeled manner and that are not Food and Drug Administration (FDA) approved for such use. Information included in these guidelines might not represent FDA approval or approved labeling for the particular products or indications being discussed. Specifically, the terms *safe* and *effective* might not be synonymous with the FDA-defined legal standards for product approval.

Antiretroviral Postexposure Prophylaxis After Sexual, Injection-Drug Use, or Other Nonoccupational Exposure to HIV in the United States

Recommendations from the U.S. Department of Health and Human Services

Prepared by
Dawn K. Smith, MD[1]
Lisa A. Grohskopf, MD[1]
Roberta J. Black, PhD[2]
Judith D. Auerbach, PhD[2]
Fulvia Veronese, PhD[2]
Kimberly A. Struble, PharmD[3]
Laura Cheever, MD[4]
Michael Johnson, MD[4]
Lynn A. Paxton, MD[1]
Ida M. Onorato, MD[1]
Alan E. Greenberg, MD[1]
[1]Division of HIV/AIDS Prevention, National Center for HIV, STD, and TB Prevention, CDC, Atlanta, Georgia
[2]National Institutes of Health
[3]Food and Drug Administration, Washington, D.C.
[4]Health Resources and Services Administration

Summary

The most effective means of preventing human immunodeficiency virus (HIV) infection is preventing exposure. The provision of antiretroviral drugs to prevent HIV infection after unanticipated sexual or injection-drug–use exposure might be beneficial. The U.S. Department of Health and Human Services (DHHS) Working Group on Nonoccupational Postexposure Prophylaxis (nPEP) made the following recommendations for the United States. For persons seeking care ≤72 hours after nonoccupational exposure to blood, genital secretions, or other potentially infectious body fluids of a person known to be HIV infected, when that exposure represents a substantial risk for transmission, a 28-day course of highly active antiretroviral therapy (HAART) is recommended. Antiretroviral medications should be initiated as soon as possible after exposure. For persons seeking care ≤72 hours after nonoccupational exposure to blood, genital secretions, or other potentially infectious body fluids of a person of unknown HIV status, when such exposure would represent a substantial risk for transmission if the source were HIV infected, no recommendations are made for the use of nPEP. Clinicians should evaluate risks and benefits of nPEP on a case-by-case basis. For persons with exposure histories that represent no substantial risk for HIV transmission or who seek care >72 hours after exposure, DHHS does not recommend the use of nPEP. Clinicians might consider prescribing nPEP for exposures conferring a serious risk for transmission, even if the person seeks care >72 hours after exposure if, in their judgment, the diminished potential benefit of nPEP outweighs the risks for transmission and adverse events. For all exposures, other health risks resulting from the exposure should be considered and prophylaxis administered when indicated. Risk-reduction counseling and indicated intervention services should be provided to reduce the risk for recurrent exposures.

Introduction

The most effective methods for preventing human immunodeficiency virus (HIV) infection are those that protect against exposure to HIV. Antiretroviral therapy cannot replace behaviors that help avoid HIV exposure (e.g., sexual abstinence, sex only in a mutually monogamous relationship with a noninfected partner, consistent and correct condom use, abstinence from injection-drug use, and consistent use of sterile equipment by those unable to cease injection-drug use). Medi-

The material presented in this report originated in the Division of HIV/AIDS Prevention, National Center for HIV, STD, and TB Prevention, Janet L. Collins, MD, Acting Director.

Corresponding Author: Lisa A. Grohskopf, MD, Epidemiology Branch, Division of HIV/AIDS Prevention, National Center for HIV, STD and TB Prevention, CDC, 1600 Clifton Road NE, MS-E45, Atlanta, GA 30333. Telephone: 404-639-6116; Fax: 404-639-6127; e-mail: lkg6@cdc.gov.

cal treatment after sexual, injection-drug–use, or other nonoccupational HIV exposure* is less effective than preventing HIV infection by avoiding exposure.

In July 1997, CDC sponsored the External Consultants Meeting on Antiretroviral Therapy for Potential Nonoccupational Exposures to HIV. This panel of scientists, public health specialists, clinicians, ethicists, members of affected communities, and representatives from professional associations and industry evaluated the available evidence related to use of antiretroviral medications after nonoccupational HIV exposure. In 1998, DHHS issued a statement that outlined the available information and concluded that evidence was insufficient about the efficacy of nonoccupational postexposure prophylaxis (nPEP) to recommend either for or against its use (*1*).

Since 1998, additional data about the potential efficacy of nPEP have accumulated from human, animal, and laboratory studies. Clinicians and organizations have begun providing nPEP to patients they believe might benefit. In certain instances, health departments have issued advisories or recommendations or otherwise supported the establishment of nPEP treatment programs in their jurisdictions (*2*–*6*). In May 2001, CDC convened the second external consultants meeting on nonoccupational post-exposure prophylaxis to review and discuss the available data. This report summarizes knowledge about the use and potential efficacy of nPEP and details guidelines for its use in the United States.† The recommendations are intended for nonoccupational exposures and are not applicable for occupational exposures.

Evidence of Possible Benefits from nPEP

For ethical and logistical reasons, a randomized, placebo-controlled clinical trial of nPEP probably will not be performed. However, data are available from animal transmission models, perinatal clinical trials, studies of health-care workers receiving prophylaxis after occupational exposures, and from observational studies. These data indicate that nPEP might sometimes reduce the risk for HIV infection after nonoccupational exposures.

* In this report, a nonoccupational exposure is any direct mucosal, percutaneous, or intravenous contact with potentially infectious body fluids that occurs outside perinatal or occupational situations (e.g., health-care, sanitation, public safety, or laboratory employment). Potentially infectious body fluids are blood, semen, vaginal secretions, rectal secretions, breast milk or other body fluid that is contaminated with visible blood.

† Information included in these recommendations might not represent Food and Drug Administration (FDA) approval or approved labeling for the particular products or indications in question. Specifically, the terms safe and effective might not be synonymous with the FDA-defined legal standards for product approval.

Animal Studies

Animal studies have demonstrated mixed results (*1,7*). In macaques, PMPA (tenofovir) blocked simian immunodeficiency virus (SIV) infection after intravenous challenge if administered within 24 hours of exposure and continued for 28 days. PMPA was not as effective if initiated 48 or 72 hours postexposure or if continued for only 3 or 10 days (*8*). Two macaque studies of combination antiretroviral therapy (zidovudine, lamivudine, and indinavir) initiated 4 hours after simian/human immunodeficiency virus (SHIV) challenge and continued for 28 days did not protect against infection but did result in reduced viral load among the animals infected (*9*). In a macaque study designed to model nPEP for mucosal HIV exposure, all animals administered PMPA for 28 days, beginning 12 hours (four animals) or 36 hours (four animals) after vaginal HIV-2 exposure, were protected. Three of four animals treated 72 hours after exposure were also protected; the fourth animal had delayed seroconversion and maintained a low viral load after treatment (*10*).

These findings are consistent with those of macaque studies of the biology of vaginal SIV transmission. After atraumatic vaginal inoculation, lamina propria cells of the cervicovaginal subepithelium were infected first, virus was present in draining lymph nodes within 2 days, and virus was disseminated to the blood stream by 5 days (*11*). Similarly, in another study, SIV-RNA was detected in dendritic cells from the vaginal epithelium within 1 hour of intravaginal viral exposure, and SIV-infected cells were detected in the lymph nodes within 18 hours (*12*). These data indicate a small window of opportunity during which it might be possible to interrupt either the initial infection of cells in the cervicovaginal mucosa or the dissemination of local infection by the prompt administration of antiretroviral medications.

Postnatal Prophylaxis

Abbreviated regimens for reducing mother-to-child HIV transmission have been studied extensively. Certain regimens have included a postexposure component (antiretroviral medications given to the neonate). Although reduction in maternal viral load during late pregnancy, labor, and delivery seems to be a major factor in the effectiveness of these regimens, an additional effect is believed to occur because the neonate receives prophylaxis, which protects against infection from exposure to maternal HIV during labor and delivery (*13,14*). In a Ugandan perinatal trial, the rate of transmission at 14–16 weeks postpartum was substantially lower for women who received a single dose of nevirapine at the beginning of labor followed by a single dose of nevirapine to the neonate within

72 hours of birth (transmission rate: 13.1%) than for the women who received intrapartum zidovudine followed by 1 week of zidovudine to the neonate (transmission rate: 25.1%) (*15*). Similarly low transmission rates were noted in a study in South Africa in which intrapartum and postpartum antiretroviral medications were used. At 8 weeks postpartum, the transmission rate was 9.3% after intrapartum zidovudine and lamivudine followed by 1 week of zidovudine and lamivudine to mother and neonate, and the transmission rate was 12.3% after a single dose of nevirapine administered to the mother during labor and then to the neonate within 72 hours of birth (*16*). Although these studies lacked control groups, these dosing schedules could not have substantially reduced HIV exposure of the neonate through reducing maternal viral load, demonstrating that a combination of preexposure and postexposure prophylaxis for the neonate reduces HIV transmission. A study in Malawi among women who did not receive intrapartum antiretrovirals compared postnatal prophylaxis with single-dose nevirapine with and without zidovudine for 1 week. The transmission rate at 6–8 weeks was 7.7% among infants who received zidovudine plus nevirapine compared with 12.1% among those who received nevirapine alone (*17*). Although this study did not have a placebo or no-prophylaxis arm, the transmission rate for the zidovudine-nevirapine arm compares favorably with the rate of 21% at 4 weeks, noted in the placebo arm of a study of zidovudine prophylaxis conducted in Cote d'Ivoire (*18*).

Two observational studies with relatively limited numbers documented a potential effect of postnatal zidovudine prophylaxis alone (without intrapartum medication). A review of medical records in New York indicated that zidovudine monotherapy administered to the mother intrapartum or to the infant within 72 hours of birth reduced perinatal transmission >50%; initiating monotherapy for the infant >72 hours after birth was less effective (*19*). Similarly, an analysis of births in the PACTS study demonstrated that zidovudine administered to infants within 24 hours of birth, when mothers had not been treated either antepartum or intrapartum, compared with no treatment for mothers or infants, reduced perinatal transmission by 48% (*20*).

Observational Studies of nPEP

The most direct evidence supporting the efficacy of postexposure prophylaxis is a case-control study of needlestick injuries to health-care workers. In this study, the prompt initiation of zidovudine was associated with an 81% decrease in the risk for acquiring HIV (*21*). Although analogous clinical studies of nPEP have not been conducted, data are available from observational studies and registries.

In a high-risk HIV incidence cohort in Brazil, nPEP instruction and 4-day starter packs of zidovudine and lamivudine were administered to 200 homosexual and bisexual men. Men who began taking nPEP after a self-identified high-risk exposure were evaluated within 96 hours; 92% met the event eligibility criteria (clinician-defined high-risk exposure). Seroincidence was 0.7 per 100 person-years (one seroconversion) among men who took nPEP and 4.1 per 100 person-years among men who did not take nPEP (11 seroconversions) (*22,23*). Subsequent analysis of data from patients who took nPEP and had been followed for a median of 24.2 months indicated 11 seroconversions and a seroincidence of 2.9 per 100 person-years, compared with an expected seroincidence of 3.1 per 100 person years, p>0.97) (*24*). In a study of sexual assault survivors in Sao Paolo, Brazil, women who sought care within 72 hours after exposure were treated for 28 days with either zidovudine and lamivudine (for those without mucosal trauma) or zidovudine, lamivudine, and indinavir (for those with mucosal trauma or those subjected to unprotected anal sex) for 28 days. Women were not treated if they sought care >72 hours after assault, if the assailant was HIV-negative, or if a condom was used and no mucosal trauma was seen. Of 180 women treated, none seroconverted. Of 145 women not treated, four (2.7%) seroconverted (*25*). Although these studies demonstrate that nPEP might reduce the risk for infection after sexual HIV exposures, participants were not randomly assigned, and sample sizes were too small for statistically significant conclusions.

In a study of rape survivors in South Africa, of 480 initially seronegative survivors begun on zidovudine and lamivudine and followed up for at least 6 weeks, one woman seroconverted. She had started taking medications 96 hours after the assault. An additional woman, who sought treatment 12 days after assault, was seronegative at that time but not offered nPEP. At retesting 6 weeks after the assault, she had seroconverted and had a positive polymerase chain reaction result (Personal communication, A. Wulfsohn, MD, Sunninghill Hospital, Gauteng, South Africa).

In a feasibility trial of nPEP conducted in San Francisco, 401 persons with eligible sexual and injection-drug–use exposures were enrolled. No seroconversions were observed among those who completed treatment, those who interrupted treatment, or those who did not receive nPEP (*26*). In a study in British Columbia of 590 persons who completed a course of nPEP, no seroconversions were observed (*27*). In registries from four countries (Australia, France, Switzerland, and the United States), including approximately 2,000 nonoccupational exposure case reports, no confirmed seroconversions

have been attributed to a failure of nPEP in approximately 350 nPEP-treated persons reported to have been exposed to HIV-infected sources. However, the absence of seroconversions might not be attributed to receipt of nPEP but rather to the low per-act risk for infection and incomplete follow-up in the registries.

Case Reports

In addition to these studies, two case reports are of note. In one, a patient who received a transfusion of red blood cells from a person subsequently determined to have early HIV infection began taking combination PEP 1 week after transfusion and continued for 9 months. The patient did not become infected despite the high risk associated with the transfusion of HIV-infected blood (*28*). In the other case, nPEP was initiated 10 days after self-insemination with semen from a homosexual man later determined to have early HIV infection. The woman did not become infected but did become pregnant and gave birth to a healthy infant (*29*).

Although data from the studies and case reports do not provide definitive evidence of the efficacy of nPEP after sexual, injection-drug–use, and other nonoccupational exposures to HIV, the cumulative data demonstrate that antiretroviral therapy initiated soon after exposure and continued for 28 days might reduce the risk for acquiring HIV.

Evidence of Possible Risks from nPEP

Concerns about the potential risks from nPEP as a public health intervention include possible decrease in risk-reduction behaviors resulting from a perception that postexposure treatment is available, the occurrence of serious adverse effects from antiretroviral treatment in otherwise healthy persons, and potential selection for resistant virus (particularly if adherence is poor during the nPEP course). Evidence indicates that these theoretical risks might not be major problems.

Effects on Risk-Reduction Behaviors

The availability or use of nPEP might not lead to increases in risk behavior. Of participants in the nPEP feasibility study in San Francisco, 72% reported a decrease in risk behavior over the next 12 months relative to baseline reported risk behavior, 14% reported no change, and 14% reported an increase (*30*). However, 17% of participants requested a second course of nPEP during the year after the first course, indicating that although participants did not increase risk behaviors, a substantial proportion of the participants did not eliminate risk behaviors. A similar proportion of participants (14%) requested a second course of nPEP at the Fenway Clinic in Boston (*31*). In the Brazil nPEP study of homosexual and bisexual men followed up for a median of 24 months, all groups, including those who elected to take nPEP, reported decreases in risk behavior (*24,32*). Among highly educated (75% with ≥4 years of college), predominantly white (74%) homosexual men who completed a street-outreach interviewer-administered survey in San Francisco, those who reported that they were aware of the availability of nPEP did not report more risk behavior than those who were not aware (*33*). In a study of discordant heterosexual couples, none reported decreased condom use because of the availability of nPEP (*34*).

Antiretroviral Side Effects and Toxicity

Initial concerns about severe side effects and toxicities have been ameliorated by experience with health-care workers who have taken PEP after occupational exposures. Of 492 health-care workers reported to the occupational PEP registry, 63% took at least three medications. Overall, 76% of workers who received PEP and had 6 weeks of follow-up reported certain symptoms (i.e., nausea [57%] and fatigue or malaise [38%]). Only 8% of these workers had laboratory abnormalities, few of which were serious and all of which resolved promptly at the end of antiretroviral treatment (*35*). Six (1.3%) reported severe adverse events, and four stopped taking PEP because of them. Of 68 workers who stopped taking PEP despite exposure to a source person known to be HIV-positive, 29 (43%) stopped because of side effects. According to the U.S. nPEP surveillance registry, among 107 exposures for which nPEP was taken, the regimen initially prescribed was stopped or modified in 22%; modifications or stops were reported because of side effects in half of these instances (*36*). In addition to reports in these registries, serious side effects have been reported (e.g., nephrolithiasis and hepatitis) in the literature.

During 1997–2000, a total of 22 severe adverse events in persons who had taken nevirapine-containing regimens for occupational or nonoccupational postexposure prophylaxis were reported to FDA (*37–38*). Severe hepatotoxicity occurred in 12 (one requiring liver transplantation), severe skin reactions in 14, and both hepatic and cutaneous manifestations occurred in four. Because the majority of occupational exposures do not lead to HIV infection, the risk for using a nevirapine-containing regimen for occupational PEP outweighs the potential benefits. The same rationale indicates that nevirapine should not be used for nPEP.

Selection of Resistant Virus

Antiretroviral PEP does not prevent all infections in occupational and perinatal settings. Similarly, PEP is not expected to have complete efficacy after nonoccupational exposures. In instances where nPEP fails to prevent infection, selection of resistant virus by the antiretroviral drugs is theoretically possible. However, because of the relative paucity of documented nPEP failures for which resistance testing was performed, the likelihood of this occurring is unknown.

PEP failures have been documented after at least one sexual (*39*) and 21 occupational (*38,40*) exposures. Three fourths of these patients were treated with zidovudine monotherapy. Only three received three or more antiretroviral medications for PEP. Among the patients tested, several were infected with strains that were resistant to antiretroviral medications. In a study in Brazil (*24*), virus obtained on day 28 of therapy from the only treated person who seroconverted (whose regimen included 3TC) had a 3TC-resistance mutation. However, the source-person could not be tested. Therefore, whether the mutation was present when the virus was transmitted or whether it developed during nPEP could not be determined.

Selection of resistant virus might occasionally result from the use of nPEP. However, because the majority of nonoccupational exposures do not lead to HIV infection and because the use of combination antiretroviral therapy might reduce further the transmission rate, such occurrences are probably rare. For patients who seroconvert despite nPEP, resistance testing should be considered to guide early and subsequent treatment decisions.

Cost-Effectiveness of nPEP

Although the potential benefits of nPEP to persons are measured by balancing its anticipated efficacy after a given exposure against individual health risks, the value of nPEP as a public health intervention is best addressed at the population level by using techniques such as cost-benefit analysis. Such analyses have been published. One cost-effectiveness evaluation of nPEP in different potential exposure scenarios in the United States reported it to be cost-effective only in situations in which the sex partner source was known to be HIV-infected or after unprotected receptive anal intercourse with a homosexual or bisexual man of unknown serostatus (*41,42*). A similar analysis in France reported that nPEP was cost-saving for unprotected receptive anal intercourse with a partner known to be HIV-infected and cost-effective for receptive anal intercourse with a homosexual or bisexual partner of unknown serostatus. It was not cost-effective for penile-vaginal sex, insertive anal intercourse, or other exposures considered (*43*).

Another study and anecdotal reports indicate difficulty limiting nPEP to the exposures most likely to benefit from it. In British Columbia, where guidelines for nPEP use have been implemented (*5*), an analysis indicated that >50% of those receiving nPEP should not, according to the guidelines, have been treated (e.g., for exposure to intact skin). The use of nPEP in these circumstances doubled the estimated cost per HIV infection prevented ($530,000 versus $230,000) (*44*).

Even if nPEP is cost-effective for the highest risk exposures, behavioral interventions are more cost-effective (*41,45*). This emphasizes the importance, when considering nPEP, of providing risk-avoidance and risk-reduction counseling to reduce the occurrence of future HIV exposures.

Evidence of Current Practice

Although 40,000 new HIV infections occur in the United States each year, relatively few exposed persons seek care after nonoccupational exposure. Certain exposures are unrecognized. Certain patients have frequently recurring exposures and would not benefit from nPEP because 4 weeks of potential protection cannot substantially reduce their overall risk for acquiring HIV infection. In addition, certain clinicians and exposed patients are unaware of the availability of nPEP or unconvinced of its efficacy and safety. Finally, access to knowledgeable clinicians or a means of paying for nPEP might constrain its use.

Certain populations in the United States remain at high risk for exposure. In a cohort study of homosexual and bisexual men, 17% reported at least one condom failure during the 6 months preceding study enrollment (*46*). Other studies indicate that increasing use of highly active antiretroviral therapy (HAART) by HIV-infected persons might be leading some persons to have unprotected sex more frequently, in part because of the belief that lowered viral load substantially reduces infectivity (*47–50*). This finding is supported by increased rates of sexually transmitted infections among HIV-infected patients (*51*). In a California study, 69% of discordant heterosexual couples reported having had unprotected sex during the preceding 6 months (*34*).

Since 1998, certain clinicians have recommended wider availability and use of nPEP (*52–58*), and others have been more cautious about implementing it in the absence of definitive evidence of efficacy (*59,60*). Multiple public health jurisdictions, including the New York State AIDS Institute, the San Francisco County Health Department, the Massachusetts Department of Public Health, the Rhode Island

Department of Health, and the California State Office of AIDS, have issued policies or advisories for nPEP use. Some of these recommendations have focused on sexual assault survivors, who constitute few of the estimated 40,000 new HIV infections annually in the United States.

Surveys of clinicians and facilities indicate a need for more widespread implementation of guidelines and protocols for nPEP use (*61*). In a survey of Massachusetts emergency department directors, 52% of facilities had received nPEP requests during the preceding year, but only 15% had written nPEP protocols (*62*). Similarly, in a survey of Massachusetts clinicians, approximately 20% had a written nPEP protocol (*63*). Among pediatric emergency medicine specialists surveyed throughout the United States and Canada, approximately 20% had a written policy about nPEP use, but 33% had prescribed it for children and adolescents; different prescribing practices were reported (*64*). In a survey of 27 European Union countries, 23 had guidelines for occupational PEP use, but only six had guidelines for nPEP use (*65*).

Evidence indicates considerable awareness of nPEP and interest in its use among potential patients. In a cohort study of homosexual and bisexual men, 60% were willing to participate in a study of nPEP if it involved a single daily dose of medication; 30% were willing to take 3 doses daily (*66*). Among men surveyed at a "gay pride" festival in Atlanta, although only 3% had used nPEP, 26% planned to if exposed in the future (*67*). When nPEP studies were established in San Francisco, approximately 400 persons sought treatment in 2½ years (*24*). At a clinic primarily serving homosexual and bisexual men in Boston, 71 requests for nPEP were evaluated in 1½ years (*30*). In a California study of heterosexual discordant couples, 28% had heard of nPEP, 55% of seronegative partners believed that it was effective, and 78% reported they would take it if exposed (*34*).

No nationally representative data exists on nPEP use in the United States. In 1998, CDC established a national nPEP surveillance registry that accepts voluntary reports by clinicians. Although approximately 800 reports have been received, the majority of clinicians prescribing nPEP do not report to the registry. Similarly, low reporting rates were obtained in attempts to establish voluntary registries to monitor occupational PEP and antiretroviral use during pregnancy. No national surveys of clinicians have been reported. However, one multisite HIV vaccine trial largely conducted in the United States has assessed nPEP use by 5,418 participants, who included men who have sex with men (94%) and heterosexual women at high risk (6%). Two percent of trial participants from 27 study sites reported having taken nPEP during the trial. Supplementary data from six U.S. sites indicated that 46% of participants had heard of nPEP. Enrollment at one of seven California sites (odds ratio [OR] = 3.2), having a known positive partner (OR = 2.0), higher educational level (OR = 1.4), and greater recreational drug use (OR = 1.2) were significant predictors of having used nPEP ($p<0.05$) (*68*).

Evaluation of Persons Seeking Care After Potential Nonoccupational Exposure to HIV

The effective delivery of nPEP after exposures that have a substantial risk for HIV infection requires prompt evaluation of patients and consideration of biomedical and behavioral interventions to address current and ongoing health risks. This evaluation should include determination of the HIV status of the potentially exposed person, the timing and characteristics of the most recent exposure, the frequency of exposures to HIV, the HIV status of the source, and the likelihood of concomitant infection with other pathogens or negative health consequences of the exposure event.

HIV Status of the Potentially Exposed Person

Because persons who are infected with HIV might not be aware they are infected, baseline HIV testing should be performed on all persons seeking evaluation for potential nonoccupational HIV exposure. If possible, this should be done with an FDA-approved rapid test kit (with results available within an hour). If rapid tests are not available, an initial treatment decision should be made based on the assumption that the potentially exposed patient is not infected, pending HIV test results.

Timing and Frequency of Exposure

Available data indicate that nPEP is less likely to be effective if initiated >72 hours after HIV exposure. If initiation of nPEP is delayed, the likelihood of benefit might not outweigh the risks inherent in taking antiretroviral medications.

Because nPEP is not 100% effective in preventing transmission and because antiretroviral medications carry a certain risk for adverse effects and serious toxicities, nPEP should be used only for infrequent exposures. Persons who engage in behaviors that result in frequent, recurrent exposures that would require sequential or near-continuous courses of antiretroviral medications (e.g., discordant sex partners who rarely use condoms or injection-drug users who often share injection equipment) should not take nPEP. In these instances, exposed persons should instead be provided with intensive risk-reduction interventions.

HIV Status of Source

Patients who have had sexual, injection-drug–use, or other nonoccupational exposures to potentially infectious fluids of persons known to be HIV infected are at risk for acquiring HIV infection and should be considered for nPEP if they seek treatment within 72 hours of exposure. If possible, source persons should be interviewed to determine his or her history of antiretroviral use and most recent viral load because this information might provide information for the choice of nPEP medications.

Persons with exposures to potentially infectious fluids of persons of unknown HIV status might or might not be at risk for acquiring HIV infection. When the source is known to be from a group with a high prevalence of HIV infection (e.g., a homosexual or bisexual man, an injection–drug user, or a commercial sex worker), the risk for transmission might be increased. The risk for transmission might be especially great if the source person has been infected recently, when viral burden in blood and semen might be particularly high (*69,70*). However, ascertaining this in the short time available for nPEP evaluation is rarely possible. When the HIV status of the source is unknown, it should be determined whether the source is available for HIV testing. If the risk associated with the exposure is considered substantial, nPEP can be started pending determination of the HIV status of the source and then stopped if the source is determined to be noninfected.

Transmission Risk from the Exposure

Although the estimated per-act transmission risk from unprotected exposure to a partner known to be HIV infected is relatively low for different types of exposure (Table 1), different nonoccupational exposures are associated with different levels of risk (*71–79*). The highest levels of estimated per-act risk for HIV transmission are associated with blood transfusion, needle sharing by injection-drug users, receptive anal intercourse, and percutaneous needlestick injuries. Insertive anal intercourse, penile-vaginal exposures, and oral sex represent substantially less per-act risk.

TABLE 1. Estimated per-act risk for acquisition of HIV, by exposure route*

Exposure route	Risk per 10,000 exposures to an infected source	Reference
Blood transfusion	9,000	74
Needle-sharing injection-drug use	67	75
Receptive anal intercourse	50	76, 77
Percutaneous needle stick	30	78
Receptive penile-vaginal intercourse	10	76, 77, 79
Insertive anal intercourse	6.5	76, 77
Insertive penile-vaginal intercourse	5	76, 77
Receptive oral intercourse	1	77†
Insertive oral intercourse	0.5	77†

* Estimates of risk for transmission from sexual exposures assume no condom use.
† Source refers to oral intercourse performed on a man.

A history should be taken of the specific sexual, injection-drug–use, or other behaviors that might have led to, or modified, a risk for acquiring HIV infection. Eliciting a complete description of the exposure and information about the HIV status of the partner(s) can substantially lower (e.g., if the patient was the insertive partner or a condom was used) or increase (e.g., if the partner is known to be HIV-positive) the estimate of risk for HIV transmission resulting from a specific exposure.

In addition to sexual and injection-drug–use exposures, percutaneous injuries from needles discarded in public settings (e.g., parks and buses) result in requests for nPEP with a certain frequency. Although no HIV infections from such injuries have been documented, concern exists that syringes discarded by injection-drug users (e.g., for whom the HIV infection rate is higher than that for diabetics) might pose a substantial risk. However, these injuries typically involve small-bore needles that contain only limited amounts of blood, and the viability of any virus present is limited. In a study of syringes used to administer medications to HIV-infected persons, only 3.8% had detectable HIV RNA (*72*). In a study of the viability of virus in needles, viable virus was recovered from 8% at 21 days when the needles had been stored at room temperature; <1% had viable virus after 1 week of storage at higher temperatures (*73*).

Bite injuries represent another potential means of transmitting HIV. However, HIV transmission by this route has been reported rarely (*80-82*). Transmission might theoretically occur either though biting or receiving a bite from an HIV-infected person. Biting an HIV-infected person, resulting in a break in the skin, exposes the oral mucous membranes to infected blood; being bitten by an HIV-infected person exposes nonintact skin to saliva. Saliva that is contaminated with infected blood poses a substantial exposure risk. Saliva that is not contaminated with blood contains HIV in much lower titers and constitutes a negligible exposure risk (*83*).

Evaluation for Sexually Transmitted Infections, Hepatitis, and Emergency Contraception

Evaluation for sexually transmitted infections is important because these infections might increase the risk for acquiring HIV infection from a sexual exposure. In 1996, an estimated 5,042 new HIV infections were attributable to sexually transmitted infection at the time of HIV exposure (*84*). In addi-

tion, any sexual exposure that presents a risk for HIV infection might also place a patient at risk for acquiring other sexually transmitted infections, including hepatitis B. Prophylaxis for sexually transmitted disease, testing for hepatitis, and vaccination for hepatitis B (for those not immune) should be considered (*85*).

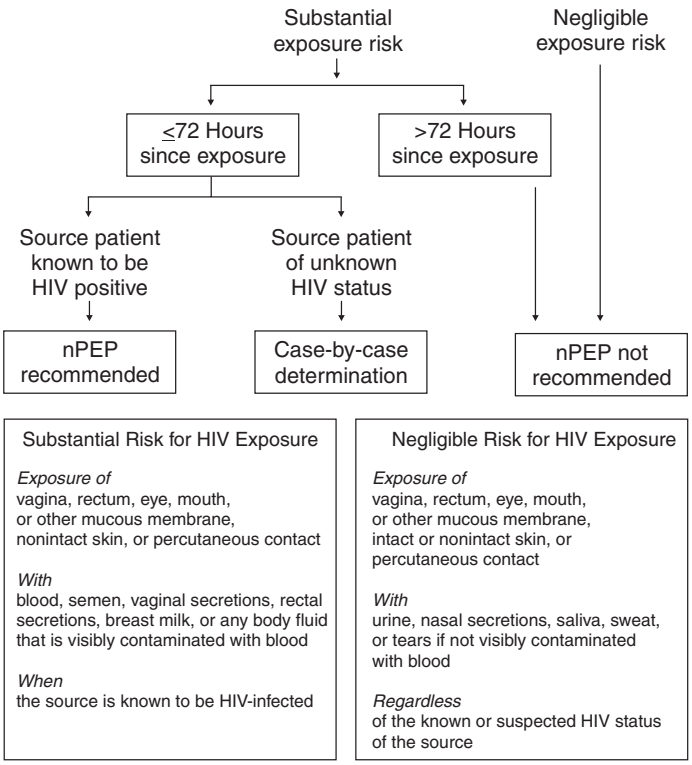
For women of reproductive capacity who have had genital exposure to semen, the risk for pregnancy also exists. In these instances, emergency contraception should be discussed with the potentially exposed patient.

Recommendations for Use of Antiretroviral nPEP

A 28-day course of HAART is recommended for persons who have had nonoccupational exposure to blood, genital secretions, or other potentially infected body fluids of a persons known to be HIV infected when that exposure represents a substantial risk for HIV transmission (Figure 1) and when the person seeks care within 72 hours of exposure. When indicated, antiretroviral nPEP should be initiated promptly for the best chance of success.

Evidence from animal studies and human observational studies demonstrate that nPEP administered within 48–72 hours and continued for 28 days might reduce the risk for acquiring HIV infection after mucosal and other nonoccupational exposures. The sooner nPEP is administered after exposure, the more likely it is to interrupt transmission. Because HIV is an incurable transmissible infection that affects the quality and duration of life, HAART should be used to maximally suppress local viral replication that otherwise might occur in the days after exposure and potentially lead to a disseminated, established infection (*11,86*). One of the HAART combinations recommended for the treatment of persons with established HIV infection should be selected on the basis of adherence, toxicity, and cost considerations (Tables 2 and 3) (*87,88*).

FIGURE 1. Algorithm for evaluation and treatment of possible nonoccupational HIV exposures



No evidence indicates that any specific antiretroviral medication or combination of medications is optimal for use as nPEP. However, on the basis of the degree of experience with individual agents in the treatment of HIV-infected persons, certain agents and combinations are preferred. Preferred regimens include efavirenz and lamivudine or emtricitabine with zidovudine or tenofovir (as a nonnucleoside-based regimen) and lopinavir/ritonavir (coformulated in one tablet as Kaletra®) and zidovudine with either lamivudine or emtricitabine. Different alternative regimens are possible (Table 2).

No evidence indicates that a three-drug HAART regimen is more likely to be effective than a two-drug regimen. The recommendation for a three-drug HAART regimen is based on the assumption that the maximal suppression of viral replication afforded by HAART (the goal in treating HIV-infected persons) will provide the best chance of preventing infection in a person who has been exposed. Clinicians and patients who are concerned about potential adherence and toxicity issues associated with a three-drug HAART regimen might consider the use of a two-drug regimen (i.e., a combination of two reverse transcriptase inhibitors). Regardless of the regimen chosen, the exposed person should be counseled about the potential associated side effects and adverse events that require immediate medical attention. The use of medications to treat symptoms (e.g., antiemetics or antimotility agents) might improve adherence in certain instances.

Although certain preliminary studies have evaluated the penetration of antiretroviral medications into genital tract secretions and tissues (*89,90*), evidence is insufficient to recommend a specific antiretroviral medication as most effective for nPEP. In addition, new antiretroviral medications might become available. As new medications and new information become available, these recommendations will be amended and updated.

When the source-person is available for interview, his or her history of antiretroviral medication use and most recent

TABLE 2. Antiretroviral regimens for nonoccupational postexposure prophylaxis of HIV infection

Preferred regimens	
NNRTI*-based	Efavirenz† plus (lamivudine or emtricitabine) plus (zidovudine or tenofovir)
Protease inhibitor (PI)-based	Lopinavir/ritonavir (co-formulated as Kaletra) plus (lamivudine or emtricitabine) plus zidovudine
Alternative regimens	
NNRTI-based	Efavirenz plus (lamivudine or emtricitabine) plus abacavrir or didanosine or stavudine§
PI-based	Atazanavir plus (lamivudine or emtricitabine) plus (zidovudine or stavudine or abacavir or didanosine) or (tenofovir plus ritonavir [100 mg/day])
	Fosamprenavir plus (lamivudine or emtricitabine) plus (zidovudine or stavudine) or (abacavir or tenofovir or didanosine)
	Fosamprenavir/ritonavir¶ plus (lamivudine or emtricitabine) plus (zidovudine or stavudine or abacavir or tenofovir or didanosine)
	Indinavir/ritonavir¶** plus (lamivudine or emtricitabine) plus (zidovudine or stavudine or abacavir or tenofovir or didanosine)
	Lopinavir/ritonavir (co-formulated as Kaletra) plus (lamivudine or emtricitabine) plus (stavudine or abacavir or tenofovir or idanosine)
	Nelfinavir plus (lamivudine or emtricitabine) plus (zidovudine or stavudine or abacavir or tenofovir or didanosine)
	Saquinavir (hgc* or sgc*)/ritonavir† plus (lamivudine or emtricitabine) plus (zidovudine or stavudine or abacavir or tenofovir or didanosine)
Triple NRTI*	Abacavir plus lamivudine plus zidovudine (only when an NONRTI- or PI-based regimen cannot or should not be used)

* NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; sgc = soft-gel saquinavir capsule (Fortovase); hgc = hard-gel saquinavir capsule (Invirase).
† Efavirenz should be avoided in pregnant women and women of childbearing potential.
§ Higher incidence of lipoatrophy, hyoerlipidemia, and mitochondrial toxicities associated with stavudine than with other NRTIs.
¶ Low-dose (100–400 mg) ritonavir. See Table 4 for doses used with specific PIs.
** Use of ritonavir with indinavir might increase risk for renal adverse events.
Source: U.S. Department of Health and Human Services. Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents, October 29,2004 revision. Available at http://www.aidsinfo.nih.gov/guidelines/default_db2.asp?id=50. This document is updated periodically; refer to website for updated versions.

viral load measurement should be considered when selecting antiretroviral medications for nPEP. This information might help avoid prescribing antiretroviral medications to which the source-virus is likely to be resistant. If the source-person is willing, the clinician might consider drawing blood for viral load and resistance testing, the results of which might be useful in modifying the initial nPEP medications if the results can be obtained promptly (*91*).

For persons who have had nonoccupational exposure to potentially infected body fluids of a person of unknown HIV infection status, when that exposure represents a substantial risk for HIV transmission (Figure 1) and when care is sought within 72 hours of exposure, no recommendations are made either for or against the use of antiretroviral nPEP. Clinicians should evaluate the risk for and benefits of this intervention on a case-by-case basis.

When a source-person is not known to be infected with HIV, the risk for exposure (and therefore the potential benefit of nPEP) is unknown. Prescribing antiretroviral medication in these cases might subject patients to risks that are not balanced with the potential benefit of preventing the acquisition of HIV infection. Judging whether the balance is appropriate depends entirely on the circumstances of the possible exposure (i.e., the risk that the source is HIV infected and the risk for transmission if the source is HIV infected) and is best determined through discussion between the clinician and the patient.

If the source-person is available for interview, additional information about risk history can be obtained and permission for an HIV test requested to assist in determining the likelihood of HIV exposure. When available, FDA-approved rapid HIV tests are preferable for obtaining this information as quickly as possible. These additional factors might assist in the decision whether to start or complete a course of nPEP. If data to clearly determine risk are not immediately available, clinicians might consider initiating nPEP while further assessments are being made and then stopping it when other information is available (e.g., the source-person is determined to be noninfected).

For persons whose exposure histories represent no substantial risk for HIV transmission (Figure 1) or who seek care >72 hours after potential nonoccupational HIV exposure, the use of antiretroviral nPEP is not recommended. When the risk for HIV transmission is negligible, limited benefit is anticipated from the use of nPEP. In addition, animal and human study data demonstrate that nPEP is less likely to prevent HIV transmission when initiated >72 hours after exposure. Because the risks associated with antiretroviral medications are likely to outweigh the potential benefit of nPEP in these circumstances, nPEP is not recommended for such exposures, regardless of the HIV status of the source. However, it cannot be concluded on the basis of the available data that nPEP will be completely ineffective when initiated >72 hours after exposure. Moreover, data do not indicate an absolute time after exposure beyond which nPEP will not be effective. When

TABLE 3. Highly active antiretroviral therapy medications, adult dosage, cost, and side effects

Medication	Adult dosage*	Cost (in dollars) for 4 weeks†	Side effects and toxicities
Combination tablets			
Lopinavir/ritonavir (Kaletra®) §	3 tablets twice daily 400 mg lopinavir/100 mg ritonavir	650	Diarrhea, nausea, vomiting; asthenia; elevated transaminases; hyperglycemia; fat redistribution; lipid abnormalities; possible increased bleeding in persons with hemophilia; and pancreatitis
Zidovudine/lamivudine (Combivir®)	1 tablet twice daily 300 mg zidovudine/150 mg lamivudine	640	See following individual medications
Zidovudine/lamivudine/abacavir (Trizivir®)	1 tablet twice daily 300 mg zidovudine/150 mg lamivudine/ 300 mg abacavir	1,020	See following individual medications
Lamivudine/abacavir (Epzicom®)	1 tablet once daily 300 mg lamivudine/600 mg abacavir	760	See following individual medications
Emtricitabine/tenofovir (Truvada®)	1 tablet once daily 200 mg emtricitabine/300 mg tenofovir	800	See following individual medications
Single agents			
Nucleoside and nucleotide reverse transcriptase inhibitors (Side effects as a class: lactic acidosis, severe hepatomegaly with steatosis, including some fatal cases)			
Abacavir (Ziagen®, ABC)§	300 mg twice daily or 600 mg once daily	400	Severe hypersensitivity reaction (can be fatal); nausea; and vomiting
Didanosine (Videx®, ddI)§	>60 kg (132 lb) body weight: 200 mg twice daily or 400 mg daily; if with tenofovir, 250 mg/daily	260	Pancreatitis; nausea, diarrhea; and peripheral neuropathy
	<60 kg (132 lb): 125 mg twice daily or 250 mg daily; if with tenofovir, dose not established		
	Do not use with stavudine (d4T, Zerit) during pregnancy; avoid ddI/d4T combination in general because of increased risk for adverse events (e.g., neuropathy, pancreatitis, and hyperlactatemia)		
Emtricitabine (Emtriva®, FTC)	200 mg once daily	280	Minimal toxicity; lactic acidosis and hepatic steatosis a rare but possibly life-threatening event
Lamivudine (Epivir®, 3TC)§	150 mg twice daily or 300 mg once daily	300	Minimal toxicity; lactic acidosis and hepatic steatosis a rare but possibly life-threatening event
Stavudine (Zerit®, d4T)§	>60 kg (132 lb) body weight: 40 mg twice daily	320	Pancreatitis; peripheral neuropathy; rapidly progressive ascending neuromuscular weakness (rare)
	<60 kg (132 lb) body weight: 30 mg twice daily		
	Do not use with didanosine (ddI, Videx) during pregnancy; avoid ddI/d4T combination in general because of increased risk for adverse events (e.g., neuropathy, pancreatitis, and hyperlactatemia)		
Tenofovir (Viread®)	300 mg daily	400	Nausea, vomiting, diarrhea; headache; asthenia; flatulence; and renal impairment
Zidovudine (Retrovir®, AZT)§	200 mg three times daily or 300 mg twice daily	350	Bone marrow suppression (anemia, neutropenia); gastrointestinal intolerance; headache; insomnia; asthenia; and myopathy

TABLE 3. (*Continued*) Highly active antiretroviral therapy medications, adult dosage, cost, and side effects

Medication	Adult dosage*	Cost (in dollars) for 4 weeks†	Side effects and toxicities
Single agents			
Non-nucleoside reverse transcriptase inhibitors (Side effects as a class: Stevens-Johnson syndrome)			
Efavirenz (Sustiva®)	600 mg daily at bedtime Do not use during known or possible pregnancy	420	Rash; central nervous system symptoms (e.g., dizziness, impaired concentration, insomnia, and abnormal dreams); transaminase elevation; and false-positive cannabinoid test
Protease inhibitors (Side effects as a class: gastrointestinal intolerance, hyperlipidemia, hyperglycemia, diabetes, fat redistribution, and possible increased bleeding in hemophiliacs)			
Atazanavir (Reyataz®)	400 mg once daily; if administered with tenofovir plus ritonavir, 300 mg once daily	760	Indirect hyperbilirubinemia; prolonged PR interval (use caution in patients with underlying cardiac conduction defects or on concomitant medications that can cause PR prolongation)
Fosamprenavir (Lexiva®)§	1,400 mg twice daily	1,260	Gastrointestinal intolerance, nausea, vomiting, diarrhea; rash; elevated transaminases; and headache
Indinavir (Crixivan®)	800 mg every 8 hours With ritonavir (might increase risk for renal adverse events): 800 mg indinavir and 100 mg ritonavir every 12 hours or 800 mg indinavir and 200 mg ritonavir every 12 hours	500	Gastrointestinal intolerance, nausea; nephrolithiasis; headache; asthenia; blurred vision; metallic taste; thrombocytopenia; hemolytic anemia; and indirect hyperbilirubinemia (inconsequential)
Nelfinavir (Viracept®)§	750 mg three times daily or 1,250 mg twice daily	600	Diarrhea; and elevated transaminases
Ritonavir (Norvir®)§	See doses used in combination with other specific protease inhibitors	700–2,800	Gastrointestinal intolerance; nausea, vomiting, diarrhea; paresthesias; hepatitis; panreatitis; asthenia; and taste perversion; many drug interactions
Saquinavir (hard-gel capsule) (Invirase®)	With ritonavir: 400 mg saquinavir and 400 mg ritonavir twice daily or 1,000 mg saquinavir and 100 mg ritonavir twice daily	270	Gastrointestinal intolerance; nausea, diarrhea; headache; and elevated transaminases
Saquinavir (soft-gel capsule) (Fortavase®)	With Ritonavir: 400 mg saquinavir and 400 mg ritonavir twice daily or 1,000 mg saquinavir and 100 mg ritonavir twice daily	460	Gastrointestinal intolerance; nausea, diarrhea; abdominal pain; dyspepsia; headache; and elevated transaminases

* For pediatric dosing information, see *Guidelines for Use of Antiretroviral Agents in Pediatric HIV Infection* (available at http://www.aidsinfo.nih.gov/guidelines/default_db2.asp?id=51)

† Available at http://www.cvs.com/CVSApp/cvs/gateway/rxpriceqrequest

§ Pediatric formulation available.

Sources: U.S. Department of Health and Human Services and the Henry J.Kaiser Family Foundation. Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents. Available at http://www.aidsinfo.nih.gov/guidelines/default_db2.asp?id=50 (refer to website for updated versions). Bartlett JG, Finkbeiner AK. HIV drugs: the guide to living with HIV infection. 2001. 11-13-2001. Available at http://www.thebody.com/jh/bartlett/drugs.html.

safer and more tolerable drugs are used, the risk-benefit ratio of providing nPEP >72 hours postexposure is more favorable. Therefore, clinicians might consider prescribing nPEP after exposures that confer a serious risk for transmission, even if the exposed person seeks care >72 hours postexposure if, in the clinician's judgment, the diminished potential benefit of nPEP outweighs the potential risk for adverse events from antiretroviral drugs.

Considerations for All Patients Treated with Antiretroviral nPEP

Use of Starter Packs

Patients might be under considerable emotional stress when seeking care after a potential HIV exposure and might not attend to, or retain, all the information relevant to making a decision about nPEP. Clinicians should give an initial prescription for 3–5 days of medication and schedule a follow-up visit to review the results of baseline HIV testing (if rapid tests are not used), provide additional counseling and support, assess medication side effects and adherence, and provide additional medication if appropriate (with an altered regimen if indicated by side effects or laboratory test results).

Scientific Consultation

When clinicians are not experienced with using HAART or when information from source-persons indicates the possibility of antiretroviral resistance, consultation with infectious disease or other HIV-care specialists, if it is available immediately, might be warranted before prescribing nPEP. Similarly, when considering prescribing nPEP to pregnant women or children, consultation with obstetricians or pediatricians might be advisable. However, if such consultation is not immediately available, initiation of nPEP should not be delayed. An initial nPEP regimen should be started and, if necessary, revised after consultation is obtained. Patients who seek nPEP might benefit from referral for psychological counseling that helps ease the anxiety about possible HIV exposure, strengthens risk-reduction behaviors, and promotes adherence to nPEP regimens if prescribed.

Facilitating Adherence

Adherence to antiretroviral medications can be challenging, even for 28 days. In addition to common side effects such as nausea and fatigue, each dose reminds the patient of his or her risk for acquiring HIV infection. Adherence has been reported to be especially poor among sexual assault survivors (*92–96*). Steps to maximize medication adherence include prescribing medications with fewer doses and fewer pills per dose, educating patients about the importance of adherence and about potential side effects, offering ancillary medications for side effects (e.g., anti-emetics) if they occur, and providing access to ongoing encouragement and consultation by phone or office visit.

Follow-up Testing and Care

All patients seeking care after HIV exposure should be tested for the presence of HIV antibodies at baseline and at 4–6 weeks, 3 months, and 6 months after exposure to determine whether HIV infection has occurred. In addition, testing for sexually transmitted diseases, hepatitis B and C, and pregnancy should be offered (Table 4).

Patients should be instructed about the signs and symptoms associated with acute retroviral infection (Table 5), especially fever and rash (*97*), and asked to return for evaluation if these occur during or after nPEP. Acute HIV infection is associated with high viral loads. However, clinicians should be aware that available assays might yield low viral-load results (e.g., <3,000) in noninfected persons. Such false-positive results can lead to misdiagnosis of HIV infection (*98*).

Transient, low-grade viremia has been observed both in macaques exposed to SIV (*99*) and humans exposed to HIV who were administered antiretroviral PEP (*100*) and did not become infected. In certain cases, this outcome might represent aborted infection rather than false-positive test results, but this can be determined only through further study. For patients with clinical or laboratory evidence of acute HIV infection, continuing antiretroviral therapy for >28 days might be prudent because such early treatment (no longer prophylaxis) might slow the progression of HIV disease (*101*). Patients with acute HIV infection should be transferred to the care of HIV treatment specialists.

In addition, clinicians who provide nPEP should monitor liver function, renal function, and hematologic parameters as indicated by the prescribing information found in antiretroviral treatment guidelines (*87,102,103*), package inserts, and the *Physician's Desk Reference* (Table 3). Unusual or severe toxicities from antiretroviral drugs should be reported to the manufacturer or FDA.

HIV Prevention Counseling

The majority of persons who seek care after a possible HIV exposure do so because of failure to initiate or maintain effective risk-reduction behaviors. Notable exceptions are sexual assault survivors and children with community-acquired needlestick injuries.

TABLE 4. Recommended laboratory evaluation for nonoccupational postexposure prophylaxis (nPEP) of HIV infection

Test	Baseline	During nPEP*	4–6 Weeks after exposure	3 Months after exposure	6 Months after exposure
HIV antibody testing	E†, S§		E	E	E
Complete blood count with differential	E	E			
Serum liver enzymes	E	E			
Blood urea nitrogen/creatinine	E	E			
Sexually transmitted diseases screen (gonorrhea, chlamydia, syphilis)	E, S	E¶	E¶		
Hepatitis B serology	E, S		E¶	E¶	
Hepatitis C serology	E, S			E	E
Pregnancy test (for women of reproductive age)	E	E¶	E¶		
HIV viral load	S		E**	E**	E**
HIV resistance testing	S		E**	E**	E**
$CD4^+$T lymphocyte count	S		E**	E**	E**

* Other specific tests might be indicated dependent on the antiretrovirals prescribed. Literature pertaining to individual agents should be consulted.
† E = exposed patient, S = source.
§ HIV antibody testing of the source patient is indicated for sources of unknown serostatus.
¶ Additional testing for pregnancy, sexually transmitted diseases, and hepatitis B should be performed as clinically indicated.
** If determined to be HIV infected on follow-up testing; perform as clinically indicated once diagnosed.

TABLE 5. Expected frequency of associated signs and symptoms among persons with signs and symptoms of acute retroviral syndrome

Symptom/sign	%
Fever	96
Lymphadenopathy	74
Pharyngitis	70
Rash Erythematous maculopapular with lesions on face, trunk and sometimes extremities, including palms and soles; mucocutaneous ulceration involving mouth, esophagus or genitals	70
Myalgia or arthralgia	54
Diarrhea	32
Headache	32
Nausea and vomiting	27
Hepatosplenomegaly	14
Weight loss	13
Thrush	12
Neurologic symptoms Meningoencephalitis or aseptic meningitis; peripheral neuropathy or radiculopathy; facial palsy; Guillain-Barré syndrome; brachial neuritis; or cognitive impairment or psychosis	12

Although nPEP might reduce the risk for HIV infection, it is not believed to be 100% effective. Therefore, patients should practice protective behaviors with sex partners (e.g., abstinence or consistent use of male condoms) or drug-use partners (e.g., avoidance of shared injection equipment) throughout the course of nPEP to avoid transmission to others if they become infected, and after nPEP to avoid future HIV exposures.

At follow-up visits, clinicians should assess their patients' needs for behavioral intervention, education, and services. This assessment should include frank, nonjudgmental questions about sexual behaviors, alcohol use, and illicit drug use. Clinicians should help patients identify ongoing risk issues and develop plans for improving their use of protective behaviors (*104*).

To help patients obtain indicated interventions and services, clinicians should be aware of local resources for high-quality HIV education and ongoing behavioral risk reduction, counseling and support, inpatient and outpatient alcohol and drug-treatment services, substance/drug abuse treatment programs, family and mental health counseling services, and support programs for HIV-infected persons. Information about publicly funded HIV prevention programs can be obtained from state or local health departments.

Management of Source Persons

When source-persons are seen during the course of evaluating a patient for potential HIV exposure, clinicians should also assess the source-person's access to relevant medical care, behavioral intervention, and social support services. If needed care cannot be provided directly, clinicians should help source-persons obtain care in the community.

If a new diagnosis of HIV infection is made or evidence of other sexually transmitted infection is identified, the patient

should be assisted in notifying their sexual and drug-use contacts. Assistance with confidential partner notification (without revealing the patient's identity) is available through local health departments.

Reporting and Confidentiality

Because of the emotional, social, and potential financial consequences of possible HIV infection, clinicians should handle nPEP evaluations with the highest level of confidentiality. Confidential reporting of sexually transmitted infections and newly diagnosed HIV infections to health departments should take place as dictated by local law and regulations.

For cases of sexual assault, clinicians should document their findings and assist patients with notifying local authorities. HIV test results should be recorded separately from the findings of the sexual assault examination to protect patients' confidentiality in the event that medical records are later released for legal proceedings. Certain states and localities have special programs to provide reimbursement for medical therapy, including antiretroviral medication after sexual assault, and these areas might have specific reporting requirements. When the sexual abuse of a child is suspected or documented, the clinician should report it in compliance with state and local law and regulations.

Considerations for Vulnerable Populations

Pregnant Women and Women of Childbearing Potential

Considerable experience has been gained in recent years in the safe and appropriate use of antiretroviral medications during pregnancy, either for the benefit of the HIV-infected woman's health or to prevent transmission to newborns. To facilitate the selection of antiretroviral medications likely to be both effective and safe for the developing fetus, clinicians should consult DHHS guidelines (*102*) before prescribing nPEP for a woman who is or might be pregnant.

Because of potential teratogenicity, efavirenz should not be used in any nPEP regimen during pregnancy or among women of childbearing age at risk for becoming pregnant during the course of antiretroviral prophylaxis (Table 3). A protease inhibitor- or nucleoside reverse transcriptase inhibitor-based regimen should be considered in these circumstances. When efavirenz is prescribed to women of childbearing potential, they should be instructed about the need to avoid pregnancy. Because the effect of efavirenz on hormonal contraception is unknown, women using such contraception should be informed of the need to use an additional method (e.g., barrier contraception). In addition, because of reports of maternal and fetal mortality attributed to lactic acidosis associated with prolonged use of d4T in combination with ddI in HIV-infected pregnant women, this combination is not recommended for use in an nPEP regimen (*105*).

Children

Potential HIV exposures in children occur most often by accident (e.g., needlesticks in the community, fights, or playground incidents resulting in bleeding by an HIV-infected child) or by sexual abuse or assaults (*106*). In a review of charts from 1 year in the pediatric emergency department of one hospital, 10 children considered for nPEP were identified (six because of sexual assault and four because of needlestick injury). Eight began taking nPEP, but only two completed the 4-week course (*63,107*). An analysis of 9,136 reported acquired immunodeficiency syndrome cases in children identified 26 who were sexually abused with confirmed or suspected exposure to HIV infection (*108*).

The American Academy of Pediatrics has issued nPEP guidelines for pediatric patients (*109*). In addition, DHHS pediatric antiretroviral treatment guidelines (*103*) provide information about the use of antiretroviral agents in children. For young children who cannot swallow capsules or tablets and to ensure appropriate dosing for drugs that do not have capsule/tablet formulations that allow pediatric dosing, drugs for which pediatric formulations are available might need to be prescribed (Table 3). Adherence to the prescribed medications will depend on the involvement of, and support provided to, parents or guardians.

Sexual Assault Survivors

Use of nPEP for sexual assault survivors has been widely encouraged both in the United States and elsewhere (*56, 94,110,111*). Sexual assault is relatively common among women: 13% of a national sample of adult women reported having ever been raped (60% before age 18), and 5% reported having been raped more than once (*112*). Sexual assault is not uncommon among men. In one series from an emergency department, 5% of reported rapes involved men sexually assaulted by men (*113*). Males accounted for 11.6 % of rapes reported among persons aged ≥12 years who responded to the National Crime Victimization Survey in 1999 (*114*). However, only three documented cases of HIV infection resulting from sexual assault have been published (*94,115,116*). In observational studies, HIV infections have been temporally associated with sexual assault (Personal communication,

A. Wulfsohn, MD, Sunninghill Hospital, Gauteng, South Africa).

Studies have examined HIV infection rates for sexual assailants (*117,118*). The largest of these, an evaluation of men incarcerated in Rhode Island, determined that 1% of those convicted of sexual assault were HIV infected when they entered prison, compared with 3% of all prisoners and 0.3% of the general male population (*119*).

Sexual assault typically has multiple characteristics that increase the risk for HIV transmission if the assailant is infected. In one prospective study of 1,076 sexual assault cases, 20% were attacked by multiple assailants, 39% were assaulted by strangers, 83% of females were vaginally penetrated, and 17% overall were sodomized. Genital trauma was documented in 53% of those assaulted, and sperm or semen was detected in 48% (*120*). In another study, in which toluidine blue dye was used as an adjunct to naked-eye examination, 40% of assaulted women (70% of nulliparas) had detectable vaginal lacerations, compared with 5% of women examined after consensual sex (*121*).

Despite these risks and the establishment of multidisciplinary support services, sexual assault survivors often decline nPEP, and many who do take it do not complete the 28-day course. This pattern has been reported in several countries and several programs in North America. In Vancouver, 71 of 258 assault survivors accepted the 5-day starter pack of nPEP, 29 returned for additional doses, and eight completed 4 weeks of therapy (*96*). Those with the highest risk for HIV exposure (i.e., source known to be HIV infected, a homosexual or bisexual man, or an injection-drug user) were more likely to begin and complete nPEP.

Patients who have been sexually assaulted will benefit from supportive services to improve adherence to nPEP if it is prescribed, and from psychological and other support provided by sexual assault crisis centers. All sexually assaulted patients should be tested and administered prophylaxis for sexually transmitted infections (*85*), and women who might become pregnant should be offered emergency contraception (*122*).

Inmates

Certain illegal behaviors that result in imprisonment (e.g., prostitution and injection-drug use) also might be associated with a higher prevalence of HIV infection among prison inmates than among the general population (*119*). However, studies indicate that the risk for becoming infected in prison is probably less than the risk outside prison (*122–125*). However, when exposure does occur, because sexual contact and injection-drug use are prohibited in jails and prisons, prisoners who have experienced such exposures might be unable or unwilling to report the behaviors to health-care providers.

Administrators and health-care providers working in correctional settings should develop and implement systems to make HIV education and risk-reduction counseling, nPEP, voluntary HIV testing, and HIV care confidentially available to inmates. Such programs will allow inmates to benefit from nPEP when indicated, facilitate treatment services for those with drug addiction, and assist in the identification and treatment of sexual assault survivors.

Injection-Drug Users

A history of injection-drug use should not deter clinicians from prescribing nPEP if the exposure provides an opportunity to reduce the risk for consequent HIV infection. A survey of clinicians serving injection-drug users determined a high degree of willingness to provide nPEP after different types of potential HIV exposure (*126*).

In judging whether exposures are isolated, episodic, or ongoing, clinicians should consider that persons who continue to engage in risk behaviors (e.g., commercial sex workers or users of illicit drugs) might be practicing risk reduction (e.g., using condoms with every client, not sharing syringes, and using a new sterile syringe for each injection). Therefore, a high-risk exposure might represent an exceptional occurrence for such persons despite their ongoing risk behavior.

Injection-drug users should be assessed for their interest in substance abuse treatment and their knowledge and use of safe injection and sex practices. Patients desiring substance abuse treatment should be referred for such treatment. Persons who continue to inject or who are at risk for relapse to injection-drug use should be instructed in the use of a new sterile syringe for each injection and the importance of avoiding the sharing of injection equipment. In areas where programs are available, health-care providers should refer such patients to appropriate sources of sterile injection equipment.

Conclusion

Accumulated data from animal and human clinical and observational studies demonstrate that antiretroviral therapy initiated as soon as possible within 48–72 hours of sexual, injection-drug–use, and other substantial nonoccupational HIV exposure and continued for 28 days might reduce the likelihood of transmission. Because of these findings, DHHS recommends the prompt initiation of nPEP with HAART when persons seek care within 72 hours after exposure, the source is known to be HIV infected, and the exposure event presents a substantial risk for transmission. When the HIV

status of the source is not known and the patient seeks care within 72 hours after exposure, DHHS does not recommend for or against nPEP but encourages clinicians and patients to weigh the risks and benefits on a case-by-case basis. When the transmission risk is negligible or when patients seek care >72 hours after a substantial exposure, nPEP is not recommended; however, clinicians might consider prescribing nPEP for patients who seek care >72 hours after a substantial exposure if, in their judgment, the diminished potential benefit of nPEP outweighs the potential risk for adverse events from antiretroviral medications. These recommendations are intended for the United States and might not apply in other countries.

References

1. CDC. Management of possible sexual, injecting-drug-use, or other nonoccupational exposure to HIV, including considerations related to antiretroviral therapy: Public Health Service statement. MMWR 1998;47(No. RR-17).
2. Stevens L; New York State Department of Health, New York AIDS Institute. Sexual assault post exposure: putting policy into action. HIV Medical Alert 2001;5:1–7.
3. Commonwealth of Massachusetts Department of Public Health. Clinical Advisory: HIV prophylaxis for non-occupational exposures. 2000. Available at http://www.mass.gov/dph/aids/guidelines/ca_exposure_nonwork.htm.
4. California Department of Health Services. Offering HIV prophylaxis following sexual assault: recommendations for the State of California. Available at http://www.dhs.ca.gov/ps/ooa/reports/PDF/HIVProphylaxisFollowingSexualAssault.pdf.
5. British Columbia Centre for Excellence in HIV/AIDS. Management of accidental exposure to HIV. Available at http://cfeweb.hivnet.ubc.ca/guide/open.html.
6. Merchant RC, Mayer KH, Browning CA. Nonoccupational HIV postexposure prophylaxis: guidelines for Rhode Island from the Brown University AIDS Program and the RI Department of Health. Med Health RI 2002;85:244–8.
7. Black RJ. Animal studies of prophylaxis. Am J Med 1997;102:39–44.
8. Tsai CC, Emau P, Follis KE, et al. Effectiveness of postinoculation (R)-9-(2-phosphonylmethoxypropyl) adenine treatment for prevention of persistent simian immunodeficiency virus SIV_{mne} infection depends critically on timing of initiation and duration of treatment. J Virol 1998;72:4265–73.
9. Le Grand R, Vaslin B, Larghero J, et al. Post-exposure prophylaxis with highly active antiretroviral therapy could not protect macaques from infection with SIV/HIV chimera. AIDS 2000;14:1864–6.
10. Otten RA, Smith DK, Adams DR, et al. Efficacy of postexposure prophylaxis after intravaginal exposure of pig-tailed macaques to a human-derived retrovirus (human immunodeficiency virus type 2). J Virol 2000;74:9771–5.
11. Spira AI, Marx PA, Patterson BK, et al. Cellular targets of infection and route of viral dissemination after an intravaginal inoculation of simian immunodeficiency virus into rhesus macaques. J Exp Med 1996;183:215–25.
12. Hu J, Gardner MB, Miller CJ. Simian immunodeficiency virus rapidly penetrates the cervicovaginal mucosa after intravaginal inoculation and infects intrepithelial dendritic cells. J Virol 2000;74:6087–95.
13. Sperling RS, Shapiro DE, Coombs RW, et al. Maternal viral load, zidovudine treatment, and the risk of transmission of human immunodeficiency virus type 1 from mother to infant. N Engl J Med 1996;335:1621–9.
14. Shaffer N, Chuachoowong R, Mock PA, et al. Short-course zidovudine for perinatal HIV-1 transmission in Bangkok, Thailand: a randomised controlled trial. Lancet 1999;353:773–80.
15. Guay LA, Musoke P, Fleming T, et al. Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: HIVNET 012 randomised trial. Lancet 1999;354:795–802.
16. Moodley D, Moodley J, Coovadia H, et al. A multicenter randomized controlled trial of nevirapine versus a combination of zidovudine and lamivudine to reduce intrapartum and early postpartum mother-to-child transmission of human immunodeficiency virus type 1. J Infect Dis 2003;187:725–35.
17. Taha TE, Kumwenda NI, Gibbons A, et al. Short postexposure prophylaxis in newborn babies to reduce mother-to-child transmission of HIV-1: NVAZ ransomised clinical trial. Lancet 2003;362 (9391):1171–7
18. Wiktor SZ, Ekpini E, Karon JM, et al. Short-course oral zidovudine for prevention of mother-child transmission of HIV-1 in Abidjan, Cote d'Ivoire: a randomized trial. Lancet 1999;353:781–5.
19. Wade NA, Birkhead GS, Warren BL, et al. Abbreviated regimens of zidovudine prophylaxis and perinatal transmission of the human immunodeficiency virus. N Engl J Med 1998;339:1409–14.
20. Bulterys M, Orloff S, Abrams E, et al. Impact of zidovudine postperinatal exposure prophylaxis on vertical HIV-1 transmission: a prospective cohort study in 4 U.S. cities [abstract]. Presented at the 2nd International Conference on Global Strategies for the Prevention of HIV Transmission from Mothers to Infants, Montreal, Canada, September 1999.
21. Cardo DM, Culver DH, Ciesielski CA, et al. A case-control study of HIV seroconversion in health care workers after percutaneous exposure. N Engl J Med 1997;337:1485–90.
22. Harrison LH, Do Lago RF, Moreira RI, Mendelsohn AB, Schechter Ml. Post-sexual-exposure chemoprophylaxis (PEP) for HIV: a prospective cohort study of behavioral impact [Abstract 225]. Presented at the 8th Conference on Retroviruses and Opportunistic Infections, Chicago, Illinois, February 4–8, 2001.
23. Harrison LH, Do Lago RF, Moreira RI, Schechter M. Demand for post-sexual-exposure chemoprophylaxis for the prevention of HIV infection in Brazil [abstract 492]. Presented at the 7th Conference on Retroviruses and Opportunistic Infections, San Francisco, California, January 30–February 2, 2000.
24. Schechter M, Do Lago RF, Mendelsohn AB, et al. Behavioral impact, acceptability, and HIV incidence among homosexual men with access to postexposure chemoprophylaxis for HIV. JAIDS 2004;35:519–25.
25. Drezett J. Post-exposure prophylaxis in raped women. In: IV International Conference on HIV infection in women and children. Rio de Janeiro: Livro de Resumos. Universidade, Federal do Rio De Janeiro e Institute of Virology of Maryland; 2002.
26. Kahn JO, Martin JN, Roland ME, et al. Feasibility of postexposure prophylaxis (PEP) against human immunodeficiency virus infection after sexual or injection drug use exposure: the San Francisco PEP Study. J Infect Dis 2001;183:707–14.

27. Braitstein P, Chan K., Beardsell A., et al. Side effects associated with post-exposure prophylaxis in a population based setting [Abstract 153]. Presented at the 1st IAS Conference on Pathogenesis and Treatment, Buenos Aires, Argentina, July 9–11, 2001. Available at http://www.ias.se/abstract/show.asp?abstract_id=153.
28. Katzenstein TL, Dickmeiss E, Aladdin H, et al. Failure to develop HIV infection after receipt of HIV-contaminated blood and postexposure prophylaxis. Ann Intern Med 2000;133:31–4.
29. Bloch M, Carr A, Vasak E, Cunningham P, Smith D, Smith D. The use of human immunodeficiency virus postexposure prophylaxis after successful artificial insemination. Am J Obstet Gynecol 1999;181:760–1.
30. Martin JN, Roland ME, Bamberger JD, et al. Post-exposure prophylaxis (PEP) for sexual exposure to HIV does not lead to increases in high risk behavior: the San Francisco PEP Project [Abstract 224]. Presented at the 8th Conference on Retroviruses and Opportunistic Infections, Chicago, Illinois, February 4–8, 2001.
31. Kwong J, Mayer K, LaSalvia T, et al. Non-occupational HIV post exposure prophylaxis at a Boston community health center [Abstract 362]. Presented at the National HIV Prevention Conference, Atlanta, Georgia, August 29–September 1,1999.
32. Schechter M, Lago R, Moreira R, Mendelsohn A, Harrison L. Behavioral impact of the availability of post-sexual-exposure chemoprophylaxis (PEP) for HIV: a prospective cohort study [abstract 154]. Presented at the 1st IAS Conference on Pathogenesis and Treatment, Buenos Aires, Argentina, July 9–11, 2001. Available at http://www.ias.se/abstract/show.asp?abstract_id=154.
33. Waldo CR, Stall RD, Coates TJ. Is offering post-exposure prevention for sexual exposures to HIV related to sexual risk behavior in gay men? AIDS 2000;14:1035–9.
34. Van der Straten A, Gomez CA, Saul J, Padian N. Awareness of PEP and viral suppressive therapy have little effect on sexual risk behavior in heterosexual HIV-discordant couples [Abstract]. Presented at the XII International Conference on AIDS, Geneva, Switzerland, June 28–July 3, 1998.
35. Wang SA, Panlilio AL, Doi PA, White AD, Stek M Jr, Saah A; HIV PEP Registry Group. Experience of healthcare workers taking postexposure prophylaxis after occupational HIV exposures: findings of the HIV Postexposure Prophylaxis Registry. Infect Control Hosp Epidemiol 2000;21:780–5.
36. Grohskopf LA, Smith DK, Kunches LK, et al. Surveillance of post-exposure prophylaxis for non-occupational HIV exposures through the U.S. national registry [Abstract MoOrD1107]. Presented at the XIV International Conference on AIDS, Barcelona, Spain, July 7–12, 2002.
37. CDC. Serious adverse events attributed to nevirapine regimens for postexposure prophylaxis after HIV exposures–worldwide, 1997–2000. MMWR 2001;49:1153–6.
38. CDC. Updated U.S. Public Health Service guidelines for the management of occupational exposures to HBV, HCV, and HIV and recommendations for postexposure prophylaxis. MMWR 2001;50 (No. RR-11).
39. Fournier S, Maillard A, Molina JM. Failure of postexposure prophylaxis after sexual exposure to HIV. AIDS 2001;15:430.
40. Beltrami EM, Luo C-C, De La Torre N, Cardo DM. Transmission of a drug-resistant HIV after an occupational exposure despite postexposure prophylaxis with a combination drug regimen. Infect Control Hosp Epidemiol 2002;23:345–8.
41. Pinkerton SD, Holtgrave DR. Prophylaxis after sexual exposure to HIV [Letter]. Ann Intern Med 1998;129:671.
42. Pinkerton SD, Holtgrave DR, Bloom FR. Postexposure treatment of HIV [Letter]. N Engl J Med 1997;337:500–1.
43. Hamers FF, Lot F, Larsen C, Laporte, A. Cost-effectiveness of prophylaxis following non-occupational exposure to HIV infection in France [Abstract 230]. Presented at the 8th Conference on Retroviruses and Opportunistic Infections, Chicago, Illinois, February 2–4, 2001.
44. Braitstein P, Chan K, Beardsell A, et al. How much is it worth? Actual versus expected costs of a population-based post-exposure prophylaxis program [Abstract 153]. Presented at the 1st IAS Conference on Pathogenesis and Treatment, Buenos Aires, Argentina, July 9–11, 2001.
45. Pinkerton SD, Holtgrave DR, Kahn JG. Is post-exposure prophylaxis affordable? [Letter] AIDS 2000;14:325.
46. Stone E, Heagerty P, Vittinghoff E, et al. Correlates of condom failure in a sexually active cohort of men who have sex with men. J Acquir Immune Defic Syndr Hum Retrovirol 1999;20:495–501.
47. Huebner DM, Gerend MA. The relationship between beliefs about drug treatments for HIV and sexual risk behavior in gay and bisexual men. Ann Behav Med 2001;23:304–12.
48. Suarez TP, Kelly JA, Pinkerton SD, et al. Influence of a partner's HIV serostatus, use of highly active antiretroviral therapy, and viral load on perceptions of sexual risk behavior in a community sample of men who have sex with men. J Acquir Immune Defic Syndr 2001;28:471–7.
49. Vlahov D, Safaien M, Lai S, et al. Sexual and drug risk-related behaviors after initiating highly active antiretroviral therapy among injection drug users. AIDS 2001;15:2311–6.
50. Stolte IG, Dukers NH, deWit JB, Fennema JS, Coutinho RAl. Increase in sexually transmitted infections among homosexual men in Amsterdam in relation to HAART. Sex Transm Infect 2001;77:184–6.
51. Scheer S, Chu PL, Klausner JD, Katz MH, Schwarcz SK. Effect of highly active antiretroviral therapy on diagnoses of sexually transmitted diseases in people with AIDS. Lancet 2001;357:432–5.
52. Katz MH, Gerberding JL. The care of persons with recent sexual exposure to HIV. Ann Intern Med 1998;128:306–12.
53. Katz MH, Gerberding JL. Postexposure treatment of people exposed to the human immunodeficiency virus through sexual contact or injection-drug use. N Engl J Med 1997;336:1097–100.
54. Gerberding JL, Katz MH. Post-exposure prophylaxis for HIV [review]. Adv Exp Med Biol 1999;458:213–22.
55. Mayer KH, Kwong J, Singal R, Boswell S. Non-occupational postexposure HIV prophylaxis: clinical issues and public health questions. Med Health R I 2000;83:210–3.
56. Lurie P, Miller S, Hecht F, Chesney M, Lo B. Postexposure prophylaxis after nonoccupational HIV exposure: clinical, ethical, and policy considerations. JAMA 1998;280:1769–73.
57. Desmond NM, Coker RJ. Should preventive antiretroviral treatment be offered following sexual exposure to HIV? The case for. Sex Transm Infect 1998;74:144–5.
58. Desmond NM, King EC, Dawson SG. Sexual exposure to HIV infection: is there a role for emergency prophylaxis? Int J STD AIDS 1998;9:51–2.
59. Mackie NE, Coker RJ. Post-exposure prophylaxis following non-occupational exposure to HIV: risks, uncertainties, and ethics. Int J STD AIDS 2000;11:424–7.
60. Evans B, Darbyshire J, Cartledge J. Should preventive antiretroviral treatment be offered following sexual exposure to HIV? Not yet! Sex Transm Infect 1998;74:146–8.

61. Merchant RC. Post-exposure prophylaxis affordability: a clearer reality. AIDS 2001;15:541–2.
62. Kunches LM, Meehan TM, Boutwell RC, McGuire JF. Survey of nonoccupational HIV postexposure prophylaxis in hospital emergency departments. J Acquir Immune Defic Syndr 2001;26:263–5.
63. Mayer KH, Kwong J, Church D, et al. HIV prophylaxis after nonoccupational exposure in Massachusetts [abstract 220]. Presented at the National HIV Prevention Conference, Atlanta, Georgia, August 29–September 1,1999.
64. Babl FE, Cooper ER, Kastner B, Kharasch S. Prophylaxis against possible human immunodeficiency virus exposure after nonoccupational needlestick injuries or sexual assaults in children and adolescents. Arch Pediatr Adolesc Med 2001;155:680–2.
65. Rey D, Bendiane M-K, Moatti J-P, Wellings K, Danziger R, MacDowall W; European Study Group on HIV Testing Policies and Practices in Europe. Post-exposure prophylaxis after occupational and non-occupational exposures to HIV: an overview of the policies implemented in European countries. AIDS Care 2000;12:695–701.
66. Gross M, Holte S, Seage GR III, Buchbinder SP, Metzger DS, Mayer KH. Feasibility of chemoprophylaxis studies in high risk HIV-seronegative populations. AIDS Educ Prev 2000;12:71–8.
67. Kalichman SC. Post-exposure prophylaxis for HIV infection in gay and bisexual men: implications for the future of HIV prevention. Am J Prev Med 1998;15:120–7.
68. Ackers ML, Buchbinder S, McKirnan D, et al. Post-exposure prophylaxis among HIV-uninfected participants in a phase III HIV vaccine efficacy trial [abstract WePpD2105]. Presented at the XIV International Conference on AIDS, Barcelona, Spain, July 7–12, 2002.
69. Pilcher CD, Eron JJ Jr, Vernazza PL, et al. Sexual transmission during the incubation period of primary HIV infection. JAMA 2001;286:1713–4.
70. Chakraborty H, Sen PK, Helms RW, et al. Viral burden in genital secretions determines male-to-female sexual transmission of HIV-1: a probabilistic empiric model. AIDS 2001;15:621–7.
71. Royce RA, Sena A, Cates W, Cohen MS. Sexual transmission of HIV. N Engl J Med 1997;336:1072–8.
72. Rich JD, Dickinson BP, Carney JM, Fisher A, Heimer R. Detection of HIV-1 nucleic acid and HIV-1 antibodies in needles and syringes used for non-intravenous injection. AIDS 1998;12:2345–50.
73. Abdala N, Reyes R, Carney JM, Heimer R. Survival of HIV-1 in syringes: effects of temperature during storage. Subst Use Misuse 2000;35:1369–83.
74. Donegan E, Stuart M, Niland JC, et al. Infection with human immunodeficiency virus type 1 (HIV-1) among recipients of antibody–positive blood donations. Ann Intern Med 1990;113:733–9.
75. Kaplan EH, Heimer R. HIV incidence among New Haven needle exchange participants: updated estimates from syringe tracking and testing data. J Acquir Immune Defic Syndr 1995;10:175–6.
76. European Study Group on Heterosexual Transmission of HIV. Comparison of female to male and male to female transmission of HIV in 563 stable couples. BMJ 1992;304:809–13.
77. Varghese B, Maher JE, Peterman TA, Branson BM, Steketee RW. Reducing the risk of sexual HIV transmission: quantifying the per-act risk for HIV on the basis of choice of partner, sex act, and condom use. Sex Transm Dis 2002;29:38–43.
78. Bell DM. Occupational risk of human immunodeficiency virus infection in healthcare workers: an overview. Am J Med 1997;102:9–15.
79. Leynaert B, Downs AM, De Vincenzi I; European Study Group on Heterosexual Transmission of HIV. Heterosexual transmission of HIV: variability of infectivity throughout the course of infection. Am J Epidemiol 1998;148:88–96.
80. Wahn V, Kramer HH, Voit T, Bruster HT, Scrampical B, Scheid A. A horizontal transmission of HIV infection between two siblings. Lancet 1986;2:694.
81. Anonymous. Transmission of HIV by a human bite. Lancet 1987; 2:522.
82. Vidmar L, Poljak M, Tomazic J, Seme K, Klavs I. Transmission of HIV-1 by a human bite. Lancet 1996;347:1762.
83. Richman KM, Rickman LS. The potential for transmission of human immunodeficiency virus through human bites. J Acquir Immune Defic Syndr 1993;6:402–6.
84. Chesson HW, Pinkerton SD. Sexually transmitted diseases and the increased risk for HIV transmission: implications for cost-effectiveness analyses of sexually transmitted disease prevention interventions. J Acquir Immune Defic Syndr 2000;24:48–56.
85. CDC. Sexually transmitted diseases guidelines, 2002. MMWR 2002;51(No. RR-6).
86. Schacker T, Collier AC, Hughes J, Shea T, Corey L. Clinical and epidemiologic features of primary HIV infection. Ann Intern Med 1996;125:257–64.
87. U.S. Department of Health and Human Services, the Henry J. Kaiser Family Foundation. Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents. Available at http://www.aidsinfo.nih.gov/guidelines/default_db2.asp?id=50.
88. HIV drugs. Excerpt from Chapter 3, HIV Infection and its Treatment. In: Bartlett JG, Finkbeiner AK. The guide to living with HIV infection (fifth edition). Baltimore, MD: The Johns Hopkins University Press; 2001. Available at http://www.thebody.com/jh/bartlett/drugs.html.
89. Chaudry NI, Eron JJ, Naderer OJ, et al. Effects of formulation and dosing strategy on amprenavir concentrations in the seminal plasma of human immunodeficiency virus type 1-infected men. Clin Infect Dis 2002;35:760–2.
90. Reddy YS, Gotzkowsky SK, Eron JJ, et al. Pharmacokinetic and pharmacodynamic investigation of efavirenz in the semen and blood of human immunodeficiency virus type 1-infected men. J Infect Dis 2002;186:1339–43.
91. Hirsch MS, Brun-Vézinet F, D'Aquila RT, et al. Antiretroviral drug resistance testing in adult HIV-1 infection: recommendations of an International AIDS Society–USA Panel. JAMA 2000;283:2417–26.
92. Opio G, Torres R, Alvalle R. Post-sexual exposure prophylaxis (PSEP) with HAART after sexual assault [abstract]. Presented at the XII International Conference on AIDS, Geneva, Switzerland, June 28–July 3, 1998;12:626–7.
93. Bamberger JD, Waldo CR, Gerberding JL, Katz MH. Postexposure prophylaxis for human immunodeficiency virus (HIV) infection following sexual assault. Am J Med 1999;106:323–6.
94. Claydon E, Murphy S, Osborne EM, Kitchen V, Smith JR, Harris JRW. Rape and HIV. Int J STD AIDS 1991;2:200–1.
95. Klemens S, Avery L, Weaver G, Wong C, Sable N Sr. HIV prophylaxis following sexual assault: experience with 30 survivors [Abstract 736]. Presented at the 39th Annual Meeting of the Infectious Diseases Society of America, San Francisco, California, October 25–28, 2001.

96. Wiebe ER, Comay SE, McGregor M, Ducceschi S. Offering HIV prophylaxis to people who have been sexually assaulted: 16 months' experience in a sexual assault service. CMAJ 2000;162:641–5.
97. Hecht FM, Busch MP, Rawal B, et al. Use of laboratory tests and clinical symptoms for identification of primary HIV infection. AIDS 2002;16:1119–29.
98. Rich JD, Merriman NA, Mylonakis E, et al. Misdiagnosis of HIV infection by HIV-1 plasma viral load testing: a case series. Ann Intern Med 1999;130:37–9.
99. Van Rompay KK, Marthas ML, Lifson JD, et al. Administration of 9-[2-(phosphonomethoxy)propyl] adenine (PMPA) for prevention of perinatal simian immunodeficiency virus infection in rhesus macaques. AIDS Res Hum Retroviruses 1998;14:761–73.
100. Puro V, Calcagno G, Anselmo M, et al. Transient detection of plasma HIV-1 RNA during postexposure prophylaxis. Infect Control Hosp Epidemiol 2000;21:529–31.
101. Berrey MM, Schacker T, Collier AC, et al. Treatment of primary human immunodeficiency virus type 1 infection with potent antiretroviral therapy reduces frequency of rapid progression to AIDS. J Infect Dis 2001;183:1466–75.
102. U.S. Department of Health and Human Services. Public Health Service Task Force recommendations for the use of antiretroviral drugs in pregnant HIV-1 infected women for maternal health and interventions to reduce perinatal HIV-1 transmission in the United States. Available at http://www.aidsinfo.nih.gov/guidelines/default_db2.asp?id=66.
103. U.S. Department of Health and Human Services. Guidelines for the use of antiretroviral agents in pediatric HIV-infection. Available at http://www.aidsinfo.nih.gov/guidelines/default_db2.asp?id=51.
104. Peterson J, Di Clemente R, eds. The handbook of HIV prevention. New York: Kluwer Academic/Plenum, 2000.
105. U.S. Food and Drug Administration. FDA/Bristol Myers Squibb issues caution for HIV combination therapy with Zerit and Videx in pregnant women. Rockville, MD: U.S. Department of Health and Human Services; 2001. Available at http://www.fda.gov/bbs/topics/ANSWERS/2001/ANS01063.html.
106. Nourse CB, Charles CA, McKay M, Keenan P, Butler KM. Childhood needlestick injuries in the Dublin metropolitan area. Ir Med J 1997;90:66–9.
107. Babl FE, Cooper ER, Damon B, Louie T, Kharasch S, Harris JA. HIV postexposure prophylaxis for children and adolescents. Am J Emerg Med 2000;18:282–7.
108. Lindegren ML, Hanson IC, Hammett TA, Beil J, Fleming PL, Ward JW. Sexual abuse of children: intersection with the HIV epidemic. Pediatrics 1998;102:46.
109. Havens PL, Committee on Pediatric AIDS. Postexposure prophylaxis in children and adolescents for nonoccupational exposure to human immunodeficiency virus. Pediatrics 2003;111:1475–89.
110. Myles JE, Hirozawa A, Katz MH, Kimmerling R, Bamberger JD. Postexposure prophylaxis for HIV after sexual assault. JAMA 2000;284:1516–8.
111. Fong C. Post-exposure prophylaxis for HIV infection after sexual assault: when is it indicated? Emerg Med J 2001;18:242–5.
112. Kilpatrick DG, Edmunds CN, Seymour AK. Rape in America: a report to the nation. Arlington, VA: National Crime Victims Research and Treatment Center and Medical University of South Carolina; 1992.
113. Lipscomb GH, Muram D, Speck PM, Mercer BM. Male victims of sexual assault. JAMA 1992;267:3064–6.
114. U.S. Department of Justice. National Crime Victimization Survey: criminal victimization in United States, 1999 statistical tables. Available at http://www.ojp.usdoj.gov/bjs/pub/pdf/cvus99.pdf.
115. Albert J, Wahlberg J, Leitner T, Escanilla D, Uhlen M. Analysis of a rape case by direct sequencing of the human immunodeficiency virus type I pol and gag genes. J Virol 1994;68:5918–24.
116. Murphy S, Kitchen V, Harris JR, Forster SM. Rape and subsequent seroconversion to HIV. BMJ 1989;299:718.
117. Larkin H, Cosby C, Petti L, Paolinetti L, Harada N. The seroprevalence of HIV and other viral STDs in sexual assault suspects and survivors [Abstract]. Presented at the XII International Conference on AIDS, Geneva, Switzerland, June 28–July 3, 1998;12:605.
118. DiGiovanni C, Berlin F, Casterella P, Redfield R, Hiken M, Falck A. Prevalence of HIV antibody among a group of paraphilic sex offenders [Abstract]. Presented at the VI International Conference on AIDS, San Francisco, California, June 20–24,1990;6:348.
119. Spaulding A, Salas C, Cleaver D, et al. HIV seroprevalence in male sexual offenders in Rhode Island: implications for post-exposure prophylaxis [Abstract]. Presented at the 8th Conference on Retroviruses and Opportunistic Infections, Chicago, Illinois, February 2–4, 2001.
120. Riggs N, Houry D, Long G, Markovchick V, Feldhaus KM. Analysis of 1,076 cases of sexual assault. Ann Emerg Med 2000;35:358–62.
121. Lauber AA, Souma ML. Use of toluidine blue for documentation of traumatic intercourse. Obstet Gynecol 1982;60:644–8.
122. Trussel K, Koenig J, Ellertson C, Stewart F. Preventing unintended pregnancy: the cost-effectiveness of three methods of emergency contraception. Am J Public Health 1997;87:932–7.
123. Wohl AR, Johnson D, Jordan W, et al. High-risk behaviors during incarceration in African-American men treated for HIV at three Los Angeles public medical centers. J Acquir Immune Defic Syndr 2000;24:386–92.
124. Mutter RC, Grimes RM, Labarthe D. Evidence of intraprison spread of HIV infection. Arch Intern Med 1994;154:793–5.
125. Brewer TF, Vlahov D, Taylor E, Hall D, Munoz A, Polk BF. Transmission of HIV-1 within a statewide prison system. AIDS 1988;2:363–7.
126. O'Connor PG. HIV post-exposure therapy for drug users in treatment. J Subst Abuse Treat 2000;18:17–21.

MMWR™

Morbidity and Mortality Weekly Report

Recommendations and Reports | January 21, 2005 / Vol. 54 / No. RR-2

Continuing Education Activity Sponsored by CDC

Antiretroviral Postexposure Prophylaxis After Sexual, Injection-Drug Use, or Other Nonoccupational Exposure to HIV in the United States

Recommendations from the U.S. Department of Health and Human Services

EXPIRATION — January 21, 2008

You must complete and return the response form electronically or by mail by **January 21, 2008**, to receive continuing education credit. If you answer all of the questions, you will receive an award letter for 2.0 hours Continuing Medical Education (CME) credit; 0.15 Continuing Education Units (CEUs); or 2.2 contact hours Continuing Nursing Education (CNE) credit. If you return the form electronically, you will receive educational credit immediately. If you mail the form, you will receive educational credit in approximately 30 days. No fees are charged for participating in this continuing education activity.

INSTRUCTIONS

By Internet

1. Read this *MMWR* (Vol. 54, RR-2), which contains the correct answers to the questions beginning on the next page.
2. Go to the *MMWR* Continuing Education Internet site at http://www.cdc.gov/mmwr/cme/conted.html.
3. Select which exam you want to take and select whether you want to register for CME, CEU, or CNE credit.
4. Fill out and submit the registration form.
5. Select exam questions. To receive continuing education credit, you must answer all of the questions. Questions with more than one correct answer will instruct you to "Indicate all that apply."
6. Submit your answers no later than **January 21, 2008**.
7. Immediately print your Certificate of Completion for your records.

By Mail or Fax

1. Read this *MMWR* (Vol. 54, RR-2), which contains the correct answers to the questions beginning on the next page.
2. Complete all registration information on the response form, including your name, mailing address, phone number, and e-mail address, if available.
3. Indicate whether you are registering for CME, CEU, or CNE credit.
4. Select your answers to the questions, and mark the corresponding letters on the response form. To receive continuing education credit, you must answer all of the questions. Questions with more than one correct answer will instruct you to "Indicate all that apply."
5. Sign and date the response form or a photocopy of the form and send no later than **January 21, 2008**, to
   Fax: 404-498-6035 Mail: MMWR CE Credit
   Division of Scientific Communications
   Coordinating Center for Health Information and Service, MS E-96
   Centers for Disease Control and Prevention
   1600 Clifton Rd, N.E.
   Atlanta, GA 30333
6. Your Certificate of Completion will be mailed to you within 30 days.

ACCREDITATION

Continuing Medical Education (CME). CDC is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians. CDC designates this educational activity for a maximum of 2.0 hours in category 1 credit toward the AMA Physician's Recognition Award. Each physician should claim only those hours of credit that he/she actually spent in the educational activity.

Continuing Education Unit (CEU). CDC has been approved as an authorized provider of continuing education and training programs by the International Association for Continuing Education and Training and awards 0.15 Continuing Education Units (CEUs).

Continuing Nursing Education (CNE). This activity for 2.2 contact hours is provided by CDC, which is accredited as a provider of continuing education in nursing by the American Nurses Credentialing Center's Commission on Accreditation.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTERS FOR DISEASE CONTROL AND PREVENTION

Goal and Objectives

This *MMWR* describes the potential risks and benefits of antiretroviral postexposure prophylaxis after nonoccupational exposures to human immunodeficiency virus (HIV). These recommendations were developed by CDC staff in collaboration with scientists, public health officials, clinicians, ethicists, members of affected communities, and representatives from professional associations and industry. The goal of this report is to provide information on which to base decisions regarding postexposure prophylaxis after a nonoccupational exposure to HIV. After completing this educational activity, the reader should be able to 1) describe the characteristics of a potential HIV exposure; 2) describe situations in which postexposure prophylaxis is most likely to be beneficial; 3) describe sources for obtaining information on antiretroviral regimens; and 4) describe appropriate follow-up schedules for persons who are prescribed antiretroviral postexposure prophylaxis.

To receive continuing education credit, please answer all of the following questions.

1. Evidence from controlled studies among humans indicates that the administration of antiretroviral postexposure prophylaxis after nonoccupational exposures to HIV is an effective means of preventing HIV infection.

A. True.
B. False.

2. On the basis of available evidence from animal studies, antiretroviral postexposure prophylaxis is most likely to be beneficial when initiated as soon as possible after exposure, and in the majority of cases, should not be initiated if >____ hours have elapsed since exposure.

A. 72.
B. 24.
C. 36.
D. None of the above.

3. Contact of which of the following body sites with HIV-infected bodily fluids constitutes a substantial HIV exposure?

A. Vagina.
B. Eye.
C. Intact skin.
D. Rectum.
E. A and D are correct.
F. A, B, and D are correct.

4. In a person with HIV infection, potentially infectious fluids include all of the following, except . . .

A. blood.
B. saliva visibly contaminated with blood.
C. urine not visibly contaminated with blood.
D. genital secretions.
E. none of the above; all are potentially infectious.

5. Which of the following lists of exposure types are correctly ordered from greatest risk of infection to least risk of infection?

A. Insertive anal is greater than insertive oral, which is greater than insertive vaginal.
B. Receptive anal is greater than receptive vaginal, which is greater than receptive oral.
C. Insertive anal is greater than receptive anal, which is greater than receptive oral.
D. None of the above.

6. The recommended duration of antiretroviral postexposure prophylaxis is . . .

A. 10 days.
B. 14 days.
C. 28 days.
D. none of the above.

7. Antiretroviral medications that should be avoided for pregnant women and women of childbearing potential include . . .

A. efavirenz.
B. nevirapine.
C. azidothymidine (AZT).
D. stavudine (D4T) in combination with didanosine (ddI).
E. A, B, and D.

8. Patients who are prescribed antiretroviral postexposure prophylaxis should be instructed about the symptoms of acute retroviral infection, which can include . . .

A. thrush.
B. fever.
C. rash.
D. all of the above.
E. B and C only.

9. Follow-up visits and testing of persons who are prescribed antiretroviral postexposure prophylaxis should be performed at approximately . . .

A. 4–6 weeks.
B. 3 months.
C. 6 months.
D. all of the above.

10. In addition to HIV antibody testing, follow-up laboratory testing of persons who are prescribed antiretroviral postexposure prophylaxis should include . . .

A. hepatitis A serology.
B. hepatitis B serology.
C. hepatitis C serology.
D. complete blood count, blood urea nitrogen/creatinine, and hepatic enzymes.
E. all of the above.
F. B, C, and D.

11. Which best describes your professional activities?

A. Physician.
B. Nurse.
C. Health educator.
D. Office staff.
E. Other.

12. I plan to use these recommendations as the basis for . . . (*Indicate all that apply.*)

A. health education materials.
B. insurance reimbursement policies.
C. local practice guidelines.
D. public policy.
E. other.

13. Each month, approximately how many patients with a potential HIV exposure do you treat?

A. None.
B. 1–5.
C. 6–20.
D. 21–50.
E. 51–100.
F. >100.

14. How much time did you spend reading this report and completing the exam?

A. <2.0 hours.
B. >2.0 hours but <3.0 hours.
C. >3.0 hours but <4.0.
D. >4.0 hours.

15. After reading this report, I am confident I can describe the characteristics of a potential HIV exposure.

A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

16. After reading this report, I am confident I can describe situations in which postexposure prophylaxis is most likely to be beneficial.

A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

17. After reading this report, I am confident I can describe sources for obtaining information on antiretroviral regimens.

A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

18. After reading this report, I am confident I can describe appropriate follow-up schedules for persons who are prescribed antiretroviral postexposure prophylaxis.

A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

(Continued on pg CE-4)

Detach or photocopy.

MMWR Response Form for Continuing Education Credit
January 21, 2005/Vol. 54/No. RR-2

Antiretroviral Postexposure Prophylaxis After Sexual, Injection-Drug Use, or Other Nonoccupational Exposure to HIV in the United States
Recommendations from the U.S. Department of Health and Human Services

To receive continuing education credit, you must
1. provide your contact information;
2. indicate your choice of CME, CME for nonphysicians, CEU, or CNE credit;
3. answer all of the test questions;
4. sign and date this form or a photocopy;
5. submit your answer form by January 21, 2008.
Failure to complete these items can result in a delay or rejection of your application for continuing education credit.

Last Name *First Name*

Street Address or P.O. Box

Apartment *or* *Suite*

City *State* *ZIP Code*

Phone Number *Fax Number*

E-Mail Address

Check One
☐ *CME Credit*
☐ *CME for nonphysicians Credit*
☐ *CEU Credit*
☐ *CNE Credit*

Fill in the appropriate blocks to indicate your answers. Remember, you must answer all of the questions to receive continuing education credit!

1. [ ]A [ ]B
2. [ ]A [ ]B [ ]C [ ]D
3. [ ]A [ ]B [ ]C [ ]D [ ]E [ ]F
4. [ ]A [ ]B [ ]C [ ]D [ ]E
5. [ ]A [ ]B [ ]C [ ]D
6. [ ]A [ ]B [ ]C [ ]D
7. [ ]A [ ]B [ ]C [ ]D [ ]E
8. [ ]A [ ]B [ ]C [ ]D [ ]E
9. [ ]A [ ]B [ ]C [ ]D
10. [ ]A [ ]B [ ]C [ ]D [ ]E [ ]F
11. [ ]A [ ]B [ ]C [ ]D [ ]E
12. [ ]A [ ]B [ ]C [ ]D [ ]E
13. [ ]A [ ]B [ ]C [ ]D [ ]E [ ]F
14. [ ]A [ ]B [ ]C [ ]D
15. [ ]A [ ]B [ ]C [ ]D [ ]E
16. [ ]A [ ]B [ ]C [ ]D [ ]E
17. [ ]A [ ]B [ ]C [ ]D [ ]E
18. [ ]A [ ]B [ ]C [ ]D [ ]E
19. [ ]A [ ]B [ ]C [ ]D [ ]E
20. [ ]A [ ]B [ ]C [ ]D [ ]E
21. [ ]A [ ]B [ ]C [ ]D [ ]E
22 [ ]A [ ]B [ ]C [ ]D [ ]E
23. [ ]A [ ]B [ ]C [ ]D [ ]E
24. [ ]A [ ]B [ ]C [ ]D [ ]E
25. [ ]A [ ]B [ ]C [ ]D [ ]E [ ]F

Signature ***Date I Completed Exam***

19. The objectives are relevant to the goal of this report.

A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

20. The teaching strategies used in this report (text, figure, and tables) were useful.

A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

21. Overall, the presentation of the report enhanced my ability to understand the material.

A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

22. These recommendations will affect my practice.

A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

23. The content of this activity was appropriate for my educational needs.

A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

24. The availability of continuing education credit influenced my decision to read this report.

A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

25. How did you learn about this continuing education activity?

A. Internet.
B. Advertisement (e.g., fact sheet, *MMWR* cover, newsletter, or journal).
C. Coworker/supervisor.
D. Conference presentation.
E. *MMWR* subscription.
F. Other.

Correct answers for questions 1–10.
1. B, 2. A, 3. F, 4. C, 5. B, 6. C, 7. E, 8. D, 9. D, 10. F.

PHS Working Group on Nonoccupational Postexposure Prophylaxis: Alan E. Greenberg, Lisa A. Grohskopf, Lynn A Paxton, Ida M. Onorato, Dawn K. Smith, Division of HIV/AIDS Prevention, National Center for HIV, STD, and TB Prevention, CDC; Harry Haverkos, Kimberly A. Struble, Center for Drug Evaluation and Research, FDA; Laura Cheever, Michael Johnson, HIV/AIDS Bureau, HRSA; Judith D. Auerbach, Office of AIDS Research; Roberta J. Black, National Institute of Allergy and Infectious Diseases; Fulvia Veronese, Office of the Director, National Institutes of Health.

Federal Consultants: Deborah von Zinkernagel, Office of the Secretary, U.S. Department of Health and Human Services; Andrea Washington, Division of Applied Public Health Training, Epidemiology Program Office, CDC; John Miles, Ron Valdiserri, Office of the Director, National Center for HIV, STD, and TB Prevention, CDC; Marc Bulterys, Ken Dominguez, Donatus Ekwueme, Kathleen Gallagher, Richard Garfein, Robert Janssen, Division of HIV/AIDS Prevention, National Center for HIV, STD, and TB Prevention, CDC; Elise Beltrami, Adelisa Panlilio, Division of Healthcare Quality Promotion, National Center for Infectious Diseases, CDC; Kim Workowski, Division of STD Prevention, National Center for HIV, STD, and TB Prevention, CDC; Sara Critchley, Bruce Evatt, Ron Otten, Division of AIDS, STD, and TB Laboratory Research, National Center for Infectious Diseases, CDC; Eben Ingram, Division of Violence Prevention, National Center for Injury Prevention and Control, CDC; Kevin Ryan, National Institute of Allergy and Infectious Diseases, NIH, Cedric Dumont, Athena Moundalexis, U. S. Department of State; Newton Kendig, Mike Nelson, Federal Bureau of Prisons.

External Consultants: *Bruce Agins, New York State AIDS Institute; James Aldridge, National Alliance of State and Territorial AIDS Directors; Beth Barnhill, National Alliance of Sexual Assault Coalitions; Carol Berkowitz, University of California, Los Angeles Medical Center; Barry Bernstein, Abbot Pharmaceuticals; Ricky Blumenthal, RAND Corporation; Stephen Boswell, Fenway Community Health Center; Helena Brett-Smith, Bristol-Myers Squibb; Jordi Casabona, Centre d'Estudis Epidemiològics de la SIDA a Catalunya; David Cochetto, GlaxoSmithKline; Myron Cohen, University of North Carolina, Chapel Hill; Roxanne Cox-Hamu, Whitman -Walker Clinic; Tim Cuniff, Agouron-Pfizer; Brian Edlin, University of California, San Francisco; Richard Ellison, University of Massachusetts Medical Center; Janet Endress Squires, Children's Medical Center of Dallas; Bruce Ewenstein, Boston Hemophilia Center, Susan Forlenza, New York City Department of Health; David Gootnick, Peace Corps; Peter L. Havens, American Academy of Pediatrics, Pediatric AIDS Committee, Barbara Herbert, Lawrence General Hospital; David Holtgrave, Rollins School of Public Health, Emory University; Michael Imperiale, Boeringer-Ingelheim; Asim Jani, Florida Department of Health; Mitchell Katz, San Francisco Department of Public Health; Laureen Kunches, John Snow, Incorporated; Jean Maguire, Massachusetts Department of Health; Laurent Mandelbrot, Groupe Hospitalier Cochin; Ken Mayer, Fenway Community Health Center; Michael Meit, National Association of County and City Health Officials; Diego Miralles, Trimeris, Inc.; Patrick O'Connor, Yale University; Amrita Paul, Canadian Non-Occupational Post-exposure Prophylaxis Working Group; Bea Pearce, National Hemophilia Foundation; Steve Pinkerton, University of Wisconsin; Josiah Rich, The Miriam Hospital; Laurie Robert, John Snow, Incorporated; Pierre Robillard, Canadian Non-Occupational Post-exposure Prophylaxis Working Group; Michelle Roland, University of California, San Francisco; Jim Rooney, Gilead Sciences; Richard Rothman, Johns Hopkins University; Elise Roy, Canadian Non-Occupational Post-exposure Prophylaxis Working Group; Miklos Salgo, Roche Laboratories; Brian Saltzman, Harvard Medical School; Susie Sargent, Roche; Timothy Schacker, University of Minnesota; Mauro Schechter, Hospital Universitario Clementino Fraga Filho; Gerry Schochetman, Abbot Diagnostics; Michael Tapper, Lenox Hill Hospital; Mark Waters, New York AIDS Institute.*

trust•wor•thy: *adj*

('trəst-"wər-thē) 1 : worthy of belief

2 : capable of being depended upon;

see also *MMWR*.

know what matters.

MMWR™

The *Morbidity and Mortality Weekly Report (MMWR)* Series is prepared by the Centers for Disease Control and Prevention (CDC) and is available free of charge in electronic format and on a paid subscription basis for paper copy. To receive an electronic copy each week, send an e-mail message to *listserv@listserv.cdc.gov*. The body content should read *SUBscribe mmwr-toc*. Electronic copy also is available from CDC's World-Wide Web server at *http://www.cdc.gov/mmwr* or from CDC's file transfer protocol server at *ftp://ftp.cdc.gov/pub/publications/mmwr*. To subscribe for paper copy, contact Superintendent of Documents, U.S. Government Printing Office, Washington, DC 20402; telephone 202-512-1800.

Data in the weekly *MMWR* are provisional, based on weekly reports to CDC by state health departments. The reporting week concludes at close of business on Friday; compiled data on a national basis are officially released to the public on the following Friday. Address inquiries about the *MMWR* Series, including material to be considered for publication, to Editor, *MMWR* Series, Mailstop E-96, CDC, 1600 Clifton Rd., N.E., Atlanta, GA 30333; telephone 888-232-3228.

All material in the *MMWR* Series is in the public domain and may be used and reprinted without permission; citation as to source, however, is appreciated.

All *MMWR* references are available on the Internet at http://www.cdc.gov/mmwr. Use the search function to find specific articles.

Use of trade names and commercial sources is for identification only and does not imply endorsement by the U.S. Department of Health and Human Services.

References to non-CDC sites on the Internet are provided as a service to *MMWR* readers and do not constitute or imply endorsement of these organizations or their programs by CDC or the U.S. Department of Health and Human Services. CDC is not responsible for the content of these sites. URL addresses listed in *MMWR* were current as of the date of publication.

☆U.S. Government Printing Office: 2005-733-116/00064 Region IV ISSN: 1057-5987

Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

August 16, 2010

Developed by the Panel on Antiretroviral Therapy
and Medical Management of HIV-Infected Children

François-Xavier Bagnoud Center, UMDNJ
The Health Resources and Services Administration
The National Institutes of Health

How to Cite the Pediatric Guidelines:
Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children. Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection. August 16, 2010; pp 1-219. Available at **http://aidsinfo.nih.gov/ContentFiles/PediatricGuidelines.pdf**. Accessed (insert date) [include page numbers, table number, etc. if applicable]

Use of antiretrovirals in pediatric patients is evolving rapidly.
These guidelines are updated regularly to provide current information.
The most recent information is available at **http://aidsinfo.nih.gov**.

What's New in the Pediatric Guidelines?

The updated *Guidelines for the Use of Antiretroviral Agents in Pediatric Infection* include the following changes made to the February 23, 2009, version of the guidelines. Key updates are also highlighted throughout the guidelines.

Ratings for Primary Recommendations

The key change prominent in the current guidelines is development of a ratings system to indicate strength and quality of evidence for each major recommendation. The strength of each recommendation is indicated by a letter (A = Strong, B = Moderate, C = Optional); the quality of the evidence supporting each recommendation is represented by a Roman numeral (I, II, III). In addition, because many pediatric recommendations will be based on data from clinical trials or observational studies in adults, with only safety and pharmacokinetic data in children, evidence ratings that are based on adult data will be indicated with an asterisk (*).

Format Changes/New Sections

Previous Appendix B: Characteristics of Available Antiretroviral Drugs and Supplement I: Pediatric Antiretroviral Drug Information

- Information in the previous Appendix B: Characteristics of Available Antiretroviral Drugs and pevious Supplement I: Pediatric Antiretroviral Drug Information of the February 23, 2009, guidelines has been combined into a new format with a table for each drug summarizing drug formulation, dosing recommendations, important adverse effects, and special instructions. Each table is followed by a short text section that includes important pediatric experience and references for that particular drug. Updated information on drugs is provided.

Previous Supplement III: Adverse Drug Effects

- This supplement to the previous version of the guidelines describes specific adverse drug effects observed in children, including lactic acidosis, hepatic toxicity, fat maldistribution and body habitus changes, hyperlipidemia, hyperglycemia, osteopenia, hematological complications, and hypersensitivity reactions and skin rashes. The supplement has been modified into a table format and included in the body of the current guidelines, with information on common causative drugs, estimated frequency of occurrence, timing of symptoms, risk factors, potential preventive measures, and suggested clinical management strategies and provides selected references regarding these toxicities in pediatric patients.

Previous Supplement II: Managing Complications of HIV Infection in HIV-Infected Children on Antiretroviral Therapy

- This supplement on pain management and nutrition included in the previous version of the guidelines has been retired. (See *Supplement II: Managing Complications of HIV Infection in HIV-Infected Children on Antiretroviral Therapy* in the archived February 23, 2009, *Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection* at **http://www.aidsinfo.nih.gov**.)

Key Updates

Updates to the various sections of the guidelines include the following new information/key changes:

Diagnosis of HIV Infection in Infants

- Viral diagnostic testing at birth is recommended for infants at high risk of HIV infection, such as infants born to HIV-infected mothers who did not receive prenatal care or prenatal antiretroviral therapy or who had HIV viral loads $\geq$1,000 copies/mL close to time of delivery (BIII). Viral diagnostic testing continues to be recommended for all HIV-exposed infants at age 14–21 days, 1–2 months, and 4–6 months (AII).

- An HIV qualitative RNA assay (APTIMA HIV-1 RNA Qualitative Assay) is an alternative diagnostic test that can be used for infant virologic diagnostic testing (AII).

When to Start

- Antiretroviral therapy continues to be recommended for all children younger than 12 months of age regardless of clinical, immunologic, or virologic symptoms (AI).
- However, whereas prior guidelines said antiretroviral therapy could be *considered* for asymptomatic or mildly symptomatic children with CD4 ≥25% (or ≥350 cells/uL if age ≥5 years) and HIV RNA ≥100,000 copies/mL, the current guidelines now *recommend* therapy in this situation (BII). Additionally, whereas prior guidelines recommended *deferral* of therapy for asymptomatic or mildly symptomatic children with CD4 ≥25% (or ≥350 cells/uL if age ≥5 years) and HIV RNA <100,000 copies/mL, the current guidelines say therapy can be *considered or deferred* (CIII). Specific recommendations are:
    - Initiation of antiretroviral therapy is *recommended* for children age ≥1 year with AIDS or significant symptoms (Clinical Category C or most Clinical Category B conditions), regardless of CD4 percentage/count or plasma HIV RNA level (AI*).
    - Initiation of antiretroviral therapy is also *recommended* for children age ≥1 year who have met the age-related CD4 threshold for initiating treatment (CD4 <25% for children 1 to <5 years of age (AII) and <350 cells/mm^3 for children ≥5 years of age (AI*), regardless of symptoms or plasma HIV RNA level).
    - Initiation of antiretroviral therapy is also *recommended* for children age ≥1 year who are asymptomatic or have mild symptoms (Clinical Categories N and A or the following Clinical Category B conditions: single episode of serious bacterial infection or lymphoid interstitial pneumonitis) *and* have CD4 ≥25% for children 1 to <5 years of age or ≥350 cells/mm^3 for children ≥5 years of age *and* have plasma HIV RNA ≥100,000 copies/mL (BII).
    - Initiation of antiretroviral therapy may be *considered or deferred* for children age ≥1 year who are asymptomatic or have mild symptoms and who have CD4 ≥25% for children 1 to <5 years of age and ≥350 cell/mm^3 for children ≥5 years of age *and* have plasma HIV RNA <100,000 copies/mL (CIII).

What Drugs to Start: Initial Combination Therapy for Antiretroviral-Naïve Children

- Recent data from clinical trials of nevirapine versus lopinavir/ritonavir-based therapy in children with single-dose nevirapine exposure for prevention of mother-to-child transmission of HIV are discussed.
- NNRTI-based therapy is not recommended for infants or children age <3 years with single-dose nevirapine exposure (AI).
- Darunavir in combination with low-dose ritonavir is now recommended as an alternative protease inhibitor for initial therapy in children age ≥6 years (AI*).
- Nelfinavir has been moved from an alternative protease inhibitor for initial therapy to a protease inhibitor for use in special circumstances in children age ≥2 years (AII).

Adherence to Antiretroviral Therapy in HIV-Infected Children and Adolescents

- Results of several new studies regarding interventions to improve adherence in children and/or adolescents are described.

Additional Updates

- References have been updated in many sections.

Table of Contents

GUIDELINES PANEL MEMBERS viii

INTRODUCTION 1
- Guidelines Development Process 2
- Concepts Considered in the Formulation of Pediatric Treatment Guidelines 5

IDENTIFICATION OF PERINATAL HIV EXPOSURE 8
- Repeat HIV Testing in the Third Trimester 9
- Rapid HIV Testing During Labor in Women with Unknown HIV Status 9
- HIV Counseling and Testing During Postnatal Period 9

DIAGNOSIS OF HIV INFECTION IN INFANTS 11
- Choice of Diagnostic Test 11
- Issues Related to Diagnosis of Non-Subtype B HIV Infection 12
- Timing of Diagnostic Testing in Infants with Known Perinatal HIV Exposure 13

LABORATORY MONITORING OF PEDIATRIC HIV INFECTION 18
- Immunologic Monitoring in Children 18
- HIV RNA Monitoring in Children 19

TREATMENT RECOMMENDATIONS 30
- General Considerations 30
- Goals of Antiretroviral Treatment 31

WHEN TO INITIATE THERAPY IN ANTIRETROVIRAL-NAÏVE CHILDREN 35
- Antiretroviral-Naïve HIV-Infected Infants Younger Than Age 12 Months 35
- Antiretroviral-Naïve HIV-Infected Children Age 1 Year or Older 37

WHAT DRUGS TO START: INITIAL COMBINATION THERAPY FOR ANTIRETROVIRAL-NAÏVE CHILDREN 43
- General Considerations 43
- Regimens Recommended for Initial Therapy of Antiretroviral-Naïve Children 44
- Preferred Regimens for Initial Therapy of Children 46

MONITORING OF CHILDREN ON ANTIRETROVIRAL THERAPY 75

SPECIFIC ISSUES IN ANTIRETROVIRAL THERAPY FOR HIV-INFECTED ADOLESCENTS 77
Background 77
Dosing of Antiretroviral Therapy for HIV-Infected Adolescents 77
Adolescent Contraception, Pregnancy, and Antiretroviral Therapy 78
Transition of Adolescents into Adult HIV Care Settings 78

ADHERENCE TO ANTIRETROVIRAL THERAPY IN HIV-INFECTED CHILDREN AND ADOLESCENTS 80
Background 80
Specific Adherence Issues in Children 80
Specific Adherence Issues for Adolescents 81
Adherence Assessment and Monitoring 81
Strategies to Improve and Support Adherence 82

MANAGEMENT OF MEDICATION TOXICITY OR INTOLERANCE 88

ANTIRETROVIRAL TREATMENT FAILURE IN INFANTS, CHILDREN, AND ADOLESCENTS 116
Overview 116
Assessment of Patients with Antiretroviral Treatment Failure 123
Approach to the Management of Antiretroviral Treatment Failure 126
Choice of Next Antiretroviral Regimen for Treatment Failure with Evidence of Drug Resistance 130
The Use of Antiretroviral Agents Not Approved for Use in Children 135
Role of Therapeutic Drug Monitoring in Management of Treatment Failure 137
Discontinuation or Interruption of Therapy 140

ANTIRETROVIRAL DRUG-RESISTANCE TESTING 143
Overview of HIV Drug-Resistance and Resistance Assays 143

CONCLUSION 148

LIST OF TABLES AND FIGURES
Table 1. Outline of the Guidelines Development Process 2
Table 2. Rating Scheme for Recommendations 5
Table 3. Likelihood of Developing AIDS or Death Within 12 Months, by Age and $CD4^+$ T-Cell Percentage or Log_{10} HIV-1 RNA Copy Number in HIV-Infected Children Receiving No Therapy or Zidovudine Monotherapy 22
Table 4. Death and AIDS/Death Rate per 100 Person-Years by Current Absolute CD4 Count and Age in HIV-Infected Children Receiving No Therapy or Zidovudine Monotherapy (HIV Paediatric Prognostic Markers Collaborative Study) and Adult Seroconverters (CASCADE Study) 23

Table 5. Association of Baseline Human Immunodeficiency Virus (HIV) RNA Copy Number and $CD4^+$ T-Cell Percentage with Long-Term Risk of Death in HIV-Infected Children 24
Figure 1. Estimated Probability of AIDS Within 12 Months by Age and CD4 Percentage in HIV-Infected Children Receiving No Therapy or Zidovudine Monotherapy 25
Figure 2. Estimated Probability of Death Within 12 Months by Age and CD4 Percentage in HIV-Infected Children Receiving No Therapy or Zidovudine Monotherapy 25
Figure 3. Death Rate per 100 Person-Years in HIV-Infected Children Age 5 Years or Older in the HIV Pediatric Prognostic Marker Collaborative Study and HIV-Infected Seroconverting Adults from the CASCADE Study 26
Figure 4. Estimated Probability of AIDS Within 12 Months by Age and HIV RNA Copy Number in HIV-Infected Children Receiving No Therapy or Zidovudine Monotherapy 27
Figure 5. Estimated Probability of Death Within 12 Months by Age and HIV RNA Copy Number in HIV-Infected Children Receiving No Therapy or Zidovudine Monotherapy 27
Table 6. 1994 Revised Human Immunodeficiency Virus Pediatric Classification System: Clinical Categories 32
Table 7. Indications for Initiation of Antiretroviral Therapy in HIV-Infected Children 40
Table 8. Antiretroviral Regimens Recommended for Initial Therapy for Human Immunodeficiency Virus (HIV) Infection in Children 57
Table 9. Antiretroviral Regimens or Components that Should Never Be Offered for Treatment of Human Immunodeficiency Virus (HIV) Infection in Children 59
Table 10. Advantages and Disadvantages of Different Nucleoside or Nucleotide Analogue Reverse Transcriptase Inhibitor (NRTI, NtRTI) Backbone Combinations for Use in Highly Active Antiretroviral Combination Regimens for Initial Therapy in Children 60
Table 11. Advantages and Disadvantages of Different Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) for Use in Highly Active Antiretroviral Combination Regimens for Initial Therapy in Children 62
Table 12. Advantages and Disadvantages of Different Protease Inhibitors (PIs) for Use in Highly Active Antiretroviral Combination Regimens for Initial Therapy in Children 64
Table 13. Advantages and Disadvantages of Entry Inhibitors for Use in Highly Active Antiretroviral Combination Regimens 67
Table 14. Advantages and Disadvantages of Integrase Inhibitors for Use in Highly Active Antiretroviral Combination Regimens 67
Table 15. Example of Minimum Schedule for Monitoring of Children on Antiretroviral Therapy 76
Table 16. Strategies to Improve Adherence with Antiretroviral Medications 84

Table 17a. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations – Hematologic Effects 90
Table 17b. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations – Hepatic Events 93
Table 17c. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations – Insulin Resistance, Asymptomatic Hyperglycemia, Diabetes Mellitus 96
Table 17d. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations – Dyslipidemia 99
Table 17e. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations – Skin Rash, SJS/EM/TEN, HSR 102
Table 17f. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations – Lipodystrophy, Lipohypertrophy, Lipoatrophy 107
Table 17g. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations – Lactic Acidosis 111
Table 17h. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations – Osteopenia, Osteoporosis, Osteonecrosis 114
Table 18. Considerations for Changing Antiretroviral Therapy for Human Immunodeficiency Virus (HIV)-Infected Children 121
Table 19. Assessment of Antiretroviral Treatment Failure 125
Table 20. Options for Regimens with at Least Two Fully Active Agents Following Failure of Antiretroviral Regimen with Evidence for Viral Resistance to Therapy with Goal of Virologic Suppression 133
Table 21. Suggested Minimum Target Trough Concentrations 139

APPENDIX A: FINANCIAL DISCLOSURE FOR PANEL MEMBERS 149

APPENDIX B: PEDIATRIC ANTIRETROVIRAL DRUG INFORMATION 151
Nucleoside and Nucleotide Analogue Reverse Transcriptase Inhibitors 151
Abacavir (ABC, Ziagen) 151
Didanosine (ddI, Videx) 154
Emtricitabine (FTC, Emtriva) 158
Lamivudine (3TC/Epivir) 160
Stavudine (d4T, Zerit) 163
Tenofovir Disoproxil Fumarate (TDF, Viread) 166
Zidovudine (ZDV, AZT, Retrovir) 170
Non-Nucleoside Analogue Reverse Transcriptase Inhibitors 173
Efavirenz (EFV, Sustiva) 173
Etravirine (ETR, Intelence, TMC 125) 177
Nevirapine (NVP, Viramune) 179

Protease Inhibitors 183
Atazanavir (ATV, Reyataz) 183
Darunavir (DRV, Prezista) 187
Fosamprenavir (FPV, Lexiva) 189
Indinavir (IDV, Crixivan) 192
Lopinavir/Ritonavir (LPV/r, Kaletra) 195
Nelfinavir (NFV, Viracept) 201
Ritonavir (RTV, Norvir) 205
Saquinavir (SQV, Invirase) 208
Tipranavir (TPV, Aptivus) 211
Entry and Fusion Inhibitors 214
Enfuvirtide (ENF, T-20, Fuzeon) 214
Maraviroc (MVC, Selzentry) 217
Integrase Inhibitors 218
Raltegravir (RAL, Isentress) 218

Members of Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children

These updated *Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection* were developed by the Department of Health and Human Services (HHS) Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children convened by the National Resource Center at the François-Xavier Bagnoud Center (FXBC), University of Medicine and Dentistry of New Jersey (UMDNJ); the Health Resources and Services Administration (HRSA); and the National Institutes of Health (NIH).

Panel Co-Chairs:

Peter Havens, MS, MD	Medical College of Wisconsin, Milwaukee, WI
Russell Van Dyke, MD	Tulane University School of Medicine, New Orleans, LA
Geoffrey A. Weinberg, MD	University of Rochester School of Medicine and Dentistry, Rochester, NY

Panel Executive Secretary:

Lynne Mofenson, MD	National Institutes of Health, Rockville, MD

Members of the Panel:

Elaine J. Abrams, MD	Columbia University, New York, NY
Edmund Capparelli, MD	University of California – San Diego, La Jolla, CA
Diana Clarke, PharmD	Boston Medical Center, Boston, MA
Patricia M. Flynn, MD	St. Jude's Medical Center, Memphis, TN
Marc D. Foca, MD, MPH	Columbia University College of Physicians and Surgeons, New York, NY
Nancy Hutton, MD	Johns Hopkins School of Medicine, Baltimore, MD
Ebony Johnson, MHS	Children's National Medical Center, Washington DC
Paul A. Krogstad, MD	University of California – Los Angeles, Los Angeles, CA
James McAuley, MD, MPH	Rush University Medical Center, Chicago, IL
Mark Mirochnick, MD	Boston Medical Center, Boston, MA
Paul Palumbo, MD	Dartmouth Medical School, Dartmouth, NH
Mary E. Paul, MD	Baylor College of Medicine, Houston, TX
Vicki B. Peters, MD	New York City Department of Health and Mental Hygiene, New York, NY
Richard M. Rutstein, MD	Children's Hospital of Philadelphia, Philadelphia, PA
Dorothy Shaw, BA	Birmingham, AL
Andrew Wiznia, MD	Jacob Medical Center, Bronx, NY

Members from the Department of Health and Human Services:

Kenneth L. Dominguez, MD, MPH	Centers for Disease Control and Prevention, Atlanta, GA
Brian Feit, MPA	Health Resources and Services Administration, Rockville, MD
Edward Handelsman, MD	National Institutes of Health, Bethesda, MD
Rohan Hazra, MD	National Institutes of Health, Bethesda, MD
Patrick Jean-Philippe, MD	National Institutes of Health, Bethesda, MD
Linda Lewis, MD	Food and Drug Administration, Rockville, MD
George Siberry, MD, MPH	National Institutes of Health, Bethesda, MD

Nonvoting Observers from the François-Xavier Bagnoud Center:

Carolyn Burr, RN, EdD	François-Xavier Bagnoud Center, UMDNJ, Newark, NJ
Supriya Modey, MPH, MBBS	François-Xavier Bagnoud Center, UMDNJ, Newark, NJ
Andrea Norberg, MS, RN	AETC National Resource Center at the François-Xavier Bagnoud Center, UMDNJ, Newark, NJ
Deborah Storm, PhD	François-Xavier Bagnoud Center School of Nursing, UMDNJ, Newark, NJ

Introduction (Updated August 16, 2010)

These guidelines address issues specific to the use of antiretroviral therapy for HIV-infected infants, children, and prepubertal adolescents. Included is information on the management of adverse events of antiretroviral drugs in children and details on pediatric data related to antiretroviral agents. The Department of Health and Human Services (HHS) Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children, a working group of the Office of AIDS Research Advisory Council (OARAC), reviews new data on an ongoing basis and provides regular updates to the guidelines. The guidelines are available on the AIDS*info* Web site at **http://aidsinfo.nih.gov**.

Separate sets of guidelines for the prevention and treatment of opportunistic infections in HIV-exposed and -infected children *[1]* and for the use of antiretroviral agents in HIV-infected postpubertal adolescents and adults *[2]* are also available on the AIDS*info* Web site. Because these guidelines were developed for the United States, they may not be applicable in other countries. The World Health Organization provides guidelines for resource-limited settings at **http://www.who.int/hiv/pub/arv/en.**

Since the development of the initial guidelines in 1993 (with the support of the François-Xavier Bagnoud Center [FXBC], University of Medicine and Dentistry of New Jersey [**http://www.fxbcenter.org**]), dramatic advances in medical management have followed the results of clinical trials of antiretroviral combination therapies in children. HIV mortality has decreased by more than 80%–90% since the introduction of protease inhibitor-containing combinations, and opportunistic and other related infections have significantly decreased in the era of highly active antiretroviral therapy (HAART) *[3-8]*. Advances including resistance testing and the ability to measure antiretroviral drug levels have enabled clinicians to more carefully choose very effective initial regimens while preserving selected drugs and drug classes for second- or third-line regimens. Therapeutic strategies continue to focus on early initiation of antiretroviral regimens capable of maximally suppressing viral replication to prevent disease progression, preserve immunologic function, and reduce the development of resistance. At the same time, availability of new drugs and drug formulations has led to regimens that improve adherence with less frequent dosing schedules. Improved monitoring and dosing schedules have also led to a decrease in drug failure due to toxicity. The use of antiretroviral therapy during pregnancy in HIV-infected women has resulted in a dramatic decrease in the transmission rate to infants, which is currently less than 2% in the United States, and the number of infants with AIDS in the United States continues to decline *[9]*. Finally, children living with HIV infection are, as a group, growing older, bringing new challenges of adherence, drug resistance, and management of multiple drugs.

Although the pathogenesis of HIV infection and the general virologic and immunologic principles underlying the use of antiretroviral therapy are similar for all HIV-infected people, there are unique considerations for HIV-infected infants, children, and adolescents, including:

- Acquisition of infection through perinatal exposure for many infected children;
- *In utero*, intrapartum, and/or postpartum neonatal exposure to zidovudine and other antiretroviral drugs in most perinatally infected children;
- Requirement for use of HIV virologic tests to diagnose perinatal HIV infection in infants younger than 18 months;
- Age-specific differences in CD4 cell counts;
- Changes in pharmacokinetic parameters with age caused by the continuing development and maturation of organ systems involved in drug metabolism and clearance;
- Differences in the clinical and virologic manifestations of perinatal HIV infection secondary to the occurrence of primary infection in growing, immunologically immature persons; and
- Special considerations associated with adherence to antiretroviral treatment for infants, children, and adolescents.

These recommendations represent the current state of knowledge regarding the use of antiretroviral drugs in children and are based on published and unpublished data regarding the treatment of HIV infection in infants,

children, adolescents, and adults and, when no definitive data were available, the clinical expertise of the Panel members. The Panel intends the guidelines to be flexible and not to replace the clinical judgment of experienced health care providers.

GUIDELINES DEVELOPMENT PROCESS

An outline of the composition of the Panel and the guidelines process can be found in Table 1.

Table 1. Outline of the Guidelines Development Process

Page 1 of 2

Topic	Comment
Goal of the Guidelines	Provide guidance to HIV care practitioners on the optimal use of antiretroviral agents in HIV-1-infected infants, children, and adolescents (through puberty) in the United States.
Panel members	The Panel is composed of approximately 25 voting members who have expertise in the management of HIV infection in infants, children, and adolescents. Members include representatives from the Committee on Pediatric AIDS of the American Academy of Pediatrics and community representatives with knowledge of pediatric HIV infection. The Panel also includes at least one representative from each of the following HHS agencies: Centers for Disease Control and Prevention (CDC), Food and Drug Administration (FDA), Health Resources and Services Administration (HRSA), and the National Institutes of Health (NIH). The U.S. government representatives are appointed by their respective agencies; nongovernmental members are selected after an open announcement to call for nominations. Each member serves on the Panel for a 3-year term with an option for reappointment. A list of current members can be found on **page viii** of this document.
Financial disclosure	All members of the Panel submit a written financial disclosure annually. A list of the latest disclosures can be found in **Appendix A** of this document.
Users of the guidelines	Providers of care to HIV-infected infants, children, and adolescents
Funding source	Office of AIDS Research, NIH
Evidence collection	The recommendations are generally based on studies published in peer-reviewed journals. On some occasions, particularly when new information may affect patient safety, unpublished data presented at major conferences or prepared by the FDA and/or manufacturers as warnings to the public may be used as evidence to revise the guidelines.
Recommendation grading	As described in **Table 2**.
Method of synthesizing data	Each section of the guidelines is assigned to a small group of Panel members with expertise in the area of interest. The members synthesize the available data and propose a recommendation to the Panel. All proposals are discussed at monthly teleconferences and then are voted on by the Panel members before being endorsed as official recommendations.

Topic	Comment
Other guidelines	These guidelines focus on HIV-infected infants, children, and adolescents through puberty. Separate guidelines outline the use of antiretroviral therapy in pregnant HIV-infected women and interventions for prevention of mother-to-child transmission, antiretroviral therapy for nonpregnant HIV-infected adults and postpubertal adolescents, and antiretroviral prophylaxis for those who experience occupational or nonoccupational exposure to HIV. These guidelines are also available at the AIDS*info* Web site (**http://www.aidsinfo.nih.gov**). These guidelines focus on HIV-infected children from infancy through puberty. For more detailed discussion on issues of treatment of postpubertal adolescents, the Panel defers to the designated expertise offered by the Panel on Antiretroviral Guidelines for Adults and Adolescents.
Update plan	The Panel meets monthly by teleconference to review data that may warrant modification of the guidelines. Updates may be prompted by new drug approvals (or new indications, formulations, or frequency of dosing), new significant safety or efficacy data, or other information that may have a significant impact on the clinical care of patients. For cases in which significant new data become available that may affect patient safety, a warning announcement with the Panel's recommendations may be made on the AIDS*info* Web site until appropriate changes can be made in the guidelines document. Updated guidelines are available at the AIDS*info* Web site (**http://www.aidsinfo.nih.gov**).
Public comments	A 2-week public comment period follows release of the updated guidelines on the AIDS*info* Web site. The Panel reviews comments received to determine whether additional revisions to the guidelines are indicated. The public may also submit comments to the Panel at any time at **contactus@aidsinfo.nih.gov**.

Basis for Recommendations

Recommendations in these guidelines are based upon scientific evidence and expert opinion. Each recommendation includes a letter (**A**, **B**, or **C**) that represents the strength of the recommendation and a Roman numeral (**I**, **II**, or **III**) that represents the quality of the evidence that supports the recommendation.

Because licensure of drugs in children often relies on efficacy data from adult trials in addition to safety and pharmacokinetic data in children, recommendations for antiretroviral drugs may need to rely on data from clinical trials or studies in adults. Pediatric drug approval may be based on evidence from adequate and well-controlled investigations in adults if:

(1) it is expected that the course of the disease and the effects of the drug are sufficiently similar in the pediatric and adult populations to permit extrapolation of adult efficacy data to pediatric patients;
(2) there are supplemental data on pharmacokinetics of the drug in children so that systemic exposure in adults and children are similar; and
(3) studies supporting the safety of the drug in pediatric patients are provided *[10]*.

In addition, if there was a concern that concentration-response relationships may be different in children, studies relating activity of the drug-to-drug levels (pharmacodynamic data) in children should be available.

In many cases, there is substantially greater evidence from adult studies (especially randomized clinical trials) than from pediatric studies related to use of antiretroviral drugs. Therefore, for pediatric recommendations, the following rationale has been used when the quality of evidence from pediatric studies is limited:

- **Quality of Evidence I—Randomized Clinical Trial Data.** In the absence of large pediatric randomized trials, adult data may be used if there are substantial pediatric data consistent with high-quality adult studies.
    - Quality of Evidence Rating I will be used if there are data from large randomized trials in children with clinical and/or validated laboratory endpoints.
    - Quality of Evidence Rating I* will be used if there are high-quality randomized clinical trial data in adults with clinical and/or validated laboratory endpoints and pediatric data from well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes that are consistent with the adult studies. For example, if a randomized Phase III clinical trial in adults demonstrates a drug is effective in antiretroviral-naïve patients and data from a nonrandomized pediatric trial demonstrate adequate and consistent safety and pharmacokinetic data in the pediatric population, a rating of I* may be used for quality of evidence.
- **Quality of Evidence Rating II—Nonrandomized Clinical Trials or Observational Cohort Data.** In the absence of large, well-designed, pediatric, nonrandomized trials or observational data, adult data may be used if there are sufficient pediatric data consistent with high-quality adult studies.
    - Quality of Evidence Rating II will be used if there are data from well-designed nonrandomized trials or observational cohorts in children.
    - Quality of Evidence Rating II* will be used if there are well-designed nonrandomized trials or observational cohort studies in adults with supporting and consistent information from smaller nonrandomized trials or cohort studies with clinical outcome data in children. For example, if a large observational study in adults demonstrates clinical benefit to initiating treatment at a certain CD4 cell count and observational data in children indicate that that a similar CD4 count is associated with clinical outcomes in children older than a specific age, a rating of II* may be used for quality of evidence.
- **Quality of Evidence Rating III—Expert opinion.** The criteria do not differ for adults and children.

Table 2. Rating Scheme for Recommendations

Strength of Recommendation	Quality of Evidence for Recommendation
A: Strong recommendation for the statement **B:** Moderate recommendation for the statement **C:** Optional recommendation for the statement	**I:** One or more randomized trials in children† with clinical outcomes and/or validated laboratory endpoints **I*:** One or more randomized trials in adults with clinical outcomes and/or validated laboratory endpoints with accompanying data in children† from one or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes **II:** One or more well-designed, nonrandomized trials or observational cohort studies in children† with long-term clinical outcomes **II*:** One or more well-designed, nonrandomized trials or observational cohort studies in adults with long-term clinical outcomes with accompanying data in children† from one or more smaller nonrandomized trials or cohort studies with clinical outcome data **III:** Expert opinion

†Studies that include children or children/adolescents but not studies limited to postpubertal adolescents

CONCEPTS CONSIDERED IN THE FORMULATION OF PEDIATRIC TREATMENT GUIDELINES

The following concepts were considered in the formulation of these guidelines.

- Prenatal HIV testing and counseling should be the standard of care for all pregnant women in the United States *[11-13]*. Identification of HIV-infected women before or during pregnancy is critical to providing optimal therapy for both infected women and their infants and for reduction of perinatal transmission. Access to prenatal care is essential for all pregnant women.
- Enrollment of pregnant HIV-infected women; their HIV-exposed newborns; and infected infants, children, and adolescents into clinical trials offers the best means of determining safe and effective therapies.*
- The pharmaceutical industry and the federal government should continue collaboration that assures that drug formulations suitable for administration to infants and children are available for all antiretroviral drugs produced.
- Although some information regarding the efficacy of antiretroviral drugs for children can be extrapolated from clinical trials involving adults, concurrent clinical trials for children are needed to determine the impact of the drug on specific manifestations of HIV infection in children, including growth, development, and neurologic disease. However, the absence of Phase III efficacy trials addressing pediatric-specific manifestations of HIV infection does not preclude the use of any approved antiretroviral drug in children.

* In areas where enrollment in clinical trials is possible, enrolling the child in available trials should be discussed with the caregivers of the child. Information about clinical trials for HIV-infected adults and children can be obtained from the AIDS*info* Web site (**http://aidsinfo.nih.gov/ClinicalTrials/**) or by telephone at 1-800-448-0440.

- Treatment of HIV infection in infants, children, and adolescents is rapidly evolving and becoming increasingly complex; therefore, wherever possible, their treatment should be managed by a specialist in pediatric and adolescent HIV infection. If this is not possible, such experts should be consulted.
- Effective management of the complex and diverse needs of HIV-infected infants, children, adolescents, and their families requires a multidisciplinary team approach that includes physicians, nurses, nutritionists, pharmacists, dentists, psychologists, social workers, and outreach workers.
- Health care providers considering antiretroviral treatment for infants, children, or adolescents should consider certain factors influencing adherence to therapy, including:
    - availability and palatability of drug formulations;
    - impact of the medication schedule on quality of life, including number of medications, frequency of administration, ability to coadminister with other prescribed medications, and need to take with or without food;
    - ability of the child's caregiver or the adolescent to administer complex drug regimens and availability of resources that might be effective in facilitating adherence; and
    - potential for drug interactions.
- The choice of initial antiretroviral regimen should include consideration of factors that may limit future treatment options, such as the presence of or potential for the development of antiretroviral resistance. HIV resistance assays have proven useful in guiding initial therapy and in changing failing regimens, but expert clinical interpretation is required.
- Monitoring growth and development, short- and long-term drug toxicities, neurodevelopment, symptom management, and nutrition are all essential in the care of HIV-infected children because they may significantly influence quality of life.

References

1. Centers for Disease Control and Prevention (CDC). Guidelines for the Prevention and Treatment of Opportunistic Infections among HIV-exposed and HIV-infected children. *MMWR.* 2009;58(RR-11):1-176.
2. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. December 1, 2009:1-161. http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf.
3. Gortmaker S, Hughes M, Cervia J, et al. Effect of combination therapy including protease inhibitors on mortality among children and adolescents infected with HIV-1. *N Engl J Med.* 2001;345(21):1522-1528.
4. Gona P, van Dyke R, Williams PL, et al. Incidence of opportunistic and other infections in HIV-infected children in the HAART era. *JAMA.* 2006;296(3):292-300.
5. Selik RM, Lindegren ML. Changes in deaths reported with human immunodeficiency virus infection among United States children less than thirteen years old, 1987 through 1999. *Pediatr Infect Dis J.* 2003;22(7):635-641.
6. Gibb DM, Duong T, Tookey PA, et al. National Study of HIV in Pregnancy and Childhood Collaborative HIV Paediatric Study. Decline in mortality, AIDS, and hospital admissions in perinatally HIV-1 infected children in the United Kingdom and Ireland. *BMJ.* 2003;327(7422):1019.
7. McConnell MS, Byers RH, Frederick T, et al. Trends in antiretroviral therapy use and survival rates for a large cohort of HIV-infected children and adolescents in the United States, 1989-2001. *J Acquir Immune Defic Syndr.* 2005;38(4):488-494.
8. Judd A, Doerholt K, Tookey PA, et al. Morbidity, mortality, and response to treatment by children in the United Kingdom and Ireland with perinatally acquired HIV infection during 1996-2006: planning for teenage and adult care. *Clin Infect Dis.* 2007;45(7):918-924.
9. Centers for Disease Control and Prevention. Reduction in perinatal transmission of HIV infection - United States, 1985-2005. *MMWR.* 2006;55(21):592-597.
10. Food and Drug Administration. Guidance for Industry: General considerations for pediatric pharmacokinetic studies for drugs and biological products. November 30, 1998. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072114.pdf
11. Centers for Disease Control and Prevention. Revised guidelines for HIV counseling, testing, and referral and revised recommendations for HIV screening of pregnant women. *MMWR.* 2001;50(RR-19):1-110.

12. Mofenson LM. Technical report: perinatal human immunodeficiency virus testing and prevention of transmission. Committee on Pediatric Aids. *Pediatrics.* 2000;106(6):E88.
13. American College of Obstetricians and Gynecologists. Human immunodeficiency virus infections in pregnancy. *Int J Gynaecol Obstet.* 1997;57(1):73-80.

Identification of Perinatal HIV Exposure

(Updated August 16, 2010)

Panel's Recommendations:

- ***Universal counseling and voluntary HIV testing early in pregnancy, including opt-out testing, are recommended as standard of care for all pregnant women in the United States (AII).***
- ***Repeat HIV testing is recommended in the third trimester for women who have negative HIV antibody tests earlier in pregnancy if they are at high risk of HIV infection because of behavior or residence in a high-prevalence area (AII).***
- ***Women seen at labor with undocumented HIV status should undergo rapid HIV antibody testing, and women with a positive antibody test should initiate intrapartum antiretroviral prophylaxis (AII).***
- ***If acute HIV infection is suspected in a pregnant woman, a virologic test (e.g., plasma HIV RNA assay) should be performed because serologic testing may be negative at this early stage of infection (AII).***
- ***Women who have not been tested for HIV prior to or during labor should be offered rapid HIV antibody testing during the immediate postpartum period or their newborns should undergo rapid HIV antibody testing; if the mother or infant is HIV antibody positive, infant antiretroviral prophylaxis should be initiated as soon as possible and the mother advised not to breastfeed pending results of confirmatory HIV antibody testing (AII).***

Appropriate treatment of HIV-infected infants requires HIV-exposed infants to be identified as soon as possible, which can be best accomplished through the identification of HIV-infected women before or during pregnancy. Universal HIV counseling and voluntary HIV testing, including consent using an opt-out approach, are recommended as the standard of care for all pregnant women in the United States by the Panel, the U.S. Public Health Service (USPHS), the American Academy of Pediatrics, the American College of Obstetricians and Gynecologists, and the U.S. Preventive Services Task Force *[1-6]*. An opt-out approach notifies a pregnant woman that HIV testing will be performed as part of routine care unless she chooses not to be tested for HIV *[7]*.

Early identification of HIV-infected women is crucial for their health and for the care of HIV-exposed and HIV-infected children. Knowledge of antenatal maternal HIV infection enables:

- HIV-infected women to receive appropriate antiretroviral therapy and prophylaxis against opportunistic infections for their own health;
- Provision of antiretroviral chemoprophylaxis during pregnancy, during labor, and to the newborn to reduce the risk of HIV transmission from mother to child *[8]*;
- Counseling of HIV-infected women about the indications for and potential benefits of scheduled cesarean section delivery to reduce perinatal HIV transmission *[8-11]*;
- Counseling of HIV-infected women about the risks of HIV transmission through breast milk and advising against breastfeeding in the United States and other countries where safe alternatives to breast milk are available *[12]*;
- Initiation of prophylaxis against *Pneumocystis jiroveci* pneumonia (PCP) in all HIV-exposed infants with indeterminate HIV infection status or who have documented HIV infection beginning at age 4 to 6 weeks *[13]*; and
- Early diagnostic evaluation of HIV-exposed infants to permit early initiation of antiretroviral therapy in infected infants *[2, 14]*.

REPEAT HIV TESTING IN THE THIRD TRIMESTER

Repeat HIV testing is recommended in the third trimester, preferably <36 weeks gestation, for women with initially negative HIV antibody tests who are at high risk of HIV infection and may be considered for all pregnant women. A second HIV test during the third trimester is recommended for women who meet 1 or more of the following criteria: women who receive health care in jurisdictions with elevated incidence of HIV or AIDS among women 15–45 years of age; women who receive health care in facilities in which prenatal screening identifies at least 1 HIV-infected pregnant woman per 1,000 women screened; women who are known to be at high risk of acquiring HIV (e.g., injection drug users or partners of injection drug users, women who exchange sex for money or drugs, women who are sex partners of HIV-infected persons, and women who have had a new or more than 1 sex partner during this pregnancy or diagnosis of a new sexually transmitted infection during pregnancy); and women who have signs or symptoms of acute HIV infection *[3-4, 15]*. Women who have declined testing earlier in pregnancy should have testing offered again during the third trimester. There is evidence that the risk of HIV acquisition may be significantly higher during pregnancy than in the postpartum period *[16]*. If acute HIV infection is suspected, a virologic test (e.g., plasma HIV RNA assay) should be performed because serologic testing may be negative at this early stage of infection.

RAPID HIV TESTING DURING LABOR IN WOMEN WITH UNKNOWN HIV STATUS

Use of rapid test kits or an expedited enzyme-linked immunosorbant assay (ELISA) to detect HIV antibody is recommended to screen women who are seen at labor and have undocumented HIV status in order to identify HIV exposure in their infants *[2-4, 14]*. Any hospital offering intrapartum care should have rapid HIV testing available and should have in place policies and procedures to assure that staff are prepared to provide patient education about rapid HIV testing, that appropriate antiretroviral medications are available whenever needed, and that follow-up procedures for women found to be HIV infected and their infants are in place. Rapid tests have been found to be feasible, accurate, timely, and useful both in providing prompt access to intrapartum and neonatal antiretroviral prophylaxis and in reducing perinatal HIV transmission *[17]*. Results of rapid tests can be obtained within minutes to a few hours and are as accurate as standard ELISA antibody testing *[18-19]*. A positive rapid HIV test result must be followed by a confirmatory test such as a Western blot (or immunofluorescent antibody [IFA]); a standard ELISA should not be used as a confirmatory test for a rapid HIV antibody test *[19]*. A negative single rapid test does not need confirmation. The immediate initiation of antiretroviral prophylaxis for prevention of mother-to-child transmission of HIV is strongly recommended while awaiting confirmatory testing results after an initial positive rapid HIV test *[2, 6, 8, 14]*.

HIV COUNSELING AND TESTING DURING POSTNATAL PERIOD

Women who have not been tested for HIV prior to or during labor should be offered rapid testing during the immediate postpartum period or their newborns should undergo rapid HIV antibody testing, with counseling and consent of the mother unless state law allows testing without consent *[3, 8, 20-21]*. Because neonatal antiretroviral chemoprophylaxis should be initiated as soon as possible after birth to be effective in preventing mother-to-child transmission, use of rapid HIV antibody assays or expedited ELISA testing to allow prompt identification of HIV-exposed infants is critical. It is strongly recommended that infant antiretroviral prophylaxis be initiated while awaiting confirmatory testing results after an initial positive rapid test in the mother or the infant, and women with positive rapid HIV test results should be advised not to initiate breastfeeding pending results of confirmatory testing. If the confirmatory test is negative, the infant antiretroviral prophylaxis can be discontinued and the mother can initiate breastfeeding. Mechanisms should be developed to facilitate rapid HIV screening for infants who have been abandoned and are in the custody of the state.

References

1. American Academy of Pediatrics Committee of Pediatric AIDS and American College of Obstetrics and Gynecology. Human immunodeficiency virus screening. Joint statement of the American Academy of Pediatrics and the American College of Obstetricians and Gynecologists. *Pediatrics.* 1999;104(1 Pt 1):128.
2. American Academy of Pediatrics Committee on Pediatric AIDS. HIV testing and prophylaxis to prevent mother-to-child transmission in the United States. *Pediatrics.* 2008;122(5):1127-1134.
3. American College of Obstetricians and Gynecologists. ACOG committee opinion number 304, November 2004. Prenatal and perinatal human immunodeficiency virus testing: expanded recommendations. *Obstet Gynecol.* 2004;104(5 Pt 1):1119-1124.
4. CDC. Revised recommendations for HIV testing of adults, adolescents, and pregnant women in health care-settings. *MMWR.* 2006;55(No. RR-14).
5. Mofenson LM. Technical report: perinatal human immunodeficiency virus testing and prevention of transmission. Committee on Pediatric Aids. *Pediatrics.* 2000;106(6):E88.
6. U.S. Preventive Task Force. Screening for HIV: recommendation statement. *Ann Intern Med.* 2005;143(1):32-37.
7. Centers for Disease Control and Prevention (CDC). HIV testing among pregnant women--United States and Canada, 1998-2001. *MMWR Morb Mortal Wkly Rep.* 2002;51(45):1013-1016.
8. Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission. Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States. May 24, 2010:1-117. http://aidsinfo.nih.gov/contentfiles/PerinatalGL.pdf.
9. American College of Obstetricians and Gynecologists. ACOG committee opinion scheduled Cesarean delivery and the prevention of vertical transmission of HIV infection. Number 234, May 2000 (replaces number 219, August 1999). *Int J Gynaecol Obstet.* 2001;73(3):279-281.
10. Jamieson DJ, Read JS, Kourtis AP, et al. Cesarean delivery for HIV-infected women: recommendations and controversies. *Am J Obstet Gynecol.* 2007;197(3 Suppl):S96-100.
11. Tubiana R, Le Chenadec J, Rouzioux C, et al. Factors associated with mother-to-child transmission of HIV-1 despite a maternal viral load <500 copies/ml at delivery: a case-control study nested in the French perinatal cohort (EPF-ANRS CO1). *Clin Infect Dis.* 2010;50(4):585-596.
12. Read JS. Human milk, breastfeeding, and transmission of human immunodeficiency virus type 1 in the United States. American Academy of Pediatrics Committee on Pediatric AIDS. *Pediatrics.* 2003;112(5):1196-1205.
13. Centers for Disease Control and Prevention (CDC). Guidelines for the prevention and treatment of opportunistic infections among HIV-exposed and HIV-infected children. *MMWR.* 2009;58(RR-11):1-176.
14. Havens PL, Mofenson LM. Evaluation and management of the infant exposed to HIV-1 in the United States. *Pediatrics.* 2009;123(1):175-187.
15. Sansom SL, Jamieson DJ, Farnham PG, et al. Human immunodeficiency virus retesting during pregnancy: costs and effectiveness in preventing perinatal transmission. *Obstet Gynecol.* 2003;102(4):782-790.
16. Gray RH, Li X, Kigozi G, et al. Increased risk of incident HIV during pregnancy in Rakai, Uganda: a prospective study. *Lancet.* 2005;366(9492):1182-1188.
17. Bulterys M, Jamieson DJ, O'Sullivan MJ, et al. Rapid HIV-1 testing during labor: a multicenter study. *JAMA.* 2004;292(2):219-223.
18. Centers for Disease Control and Prevention (CDC). Rapid HIV-1 antibody testing during labor and delivery for women of unknown HIV status: A practical guide and model protocol 2004.
19. Centers for Disease Control and Prevention (CDC). Protocols for confirmation of reactive rapid hiv tests. *MMWR.* 2004;53(10):221-222.
20. New York State Department of Public Health. HIV testing and diagnosis in infants and children. 2005; http://www.hivguidelines.org/wp-content/uploads/2009/05/p-test.pdf.
21. New York State Register. Title 10 NYCRR, Subpart 69-1.3, revision effective 08/01/99. 1998;20(51):8-11.

Diagnosis of HIV Infection in Infants

(Updated August 16, 2010)

Panel's Recommendations:

- ***Virologic assays that directly detect HIV must be used to diagnose HIV infection in infants younger than 18 months, because maternal HIV antibody may persist in this age group and give a false-positive antibody test in an uninfected child (AII).***
- ***Virologic diagnostic testing in infants with known perinatal HIV exposure is recommended at age 14–21 days; 1–2 months; and 4–6 months (AII).***
- ***Virologic diagnostic testing at birth should be considered for infants at high risk of HIV infection (BIII).***
- ***HIV DNA PCR and HIV RNA assays are recommended as preferred virologic assays (AII).***
- ***Confirmation of HIV infection should be based on two positive virologic tests from separate blood samples (AI).***
- ***Definitive exclusion of HIV infection should be based on at least two negative virologic tests (one at ≥1 month and one at ≥4 months of age) (AII).***
- ***Some experts confirm the absence of HIV infection at 12–18 months of age in infants with prior negative virologic tests by performing an antibody test to document loss of HIV antibody (BIII).***
- ***In children age ≥18 months, HIV antibody assays alone can be used for diagnosis (AII).***

CHOICE OF DIAGNOSTIC TEST

HIV infection can be definitively diagnosed through the use of virologic assays in most nonbreastfed HIV-infected infants by 1 month of age and in virtually all infected infants by 4 months of age. Tests for antibodies to HIV, including newer rapid tests, do not establish the presence of HIV infection in infants because of transplacental transfer of maternal antibodies; therefore a virologic test should be used *[1]*. A positive virologic test (i.e., detection of HIV by DNA polymerase chain reaction [PCR] or RNA assays) indicates likely HIV infection and should be confirmed by a repeat virologic test on a second specimen as soon as possible after the first test result becomes available. HIV culture is not used for routine HIV diagnostic testing. The use of the currently approved HIV p24 antigen assay is not recommended for infant diagnosis in the United States because the sensitivity and specificity of the assay in the first months of life are less than that of other HIV virologic tests *[2-3]*.

HIV DNA PCR

HIV DNA PCR is a sensitive technique used to detect specific HIV viral DNA in a patient's peripheral blood mononuclear cells (PBMCs). The sensitivity of a single HIV DNA PCR test performed at <48 hours of age is less than 40% but increases to more than 90% by 2–4 weeks of age *[4-8]*.

In a meta-analysis, 38% (90% confidence interval [CI] = 29%–46%) of infected children had positive HIV DNA PCR tests by 48 hours of age *[9]*. No substantial change in sensitivity during the first week of life was observed, but sensitivity increased rapidly during the second week, with 93% of infected children (90% CI = 76%–97%) testing positive by HIV DNA PCR by age 14 days. By age 28 days, HIV DNA PCR had 96% sensitivity and 99% specificity to identify HIV proviral DNA in PBMCs.

HIV RNA Assays

HIV quantitative RNA assays detect extracellular viral RNA in the plasma and are as sensitive as HIV DNA PCR for early diagnosis of HIV infection in HIV-exposed infants. Studies have demonstrated sensitivities of 25%–40% during the first weeks of life, increasing to 90%–100% by 2–3 months of age *[7-8, 10-16]*. Similarly, specificity is comparable between the two tests, although the detection of low levels of HIV RNA

(<5,000 copies/mL) may not be reproducible and tests with low levels of HIV RNA should be repeated before they are interpreted as documenting the presence of HIV infection in an infant. An HIV RNA assay can be used as the confirmatory test for infants who have an initial positive HIV DNA PCR test. In addition to providing virologic confirmation of infection status, the expense of repeat HIV DNA PCR testing is spared and an HIV RNA measurement is available to assess baseline viral load. HIV RNA assays may be more sensitive than HIV DNA PCR for detecting HIV non-subtype B (see HIV subtype section below). However, although HIV DNA PCR remains positive even in individuals receiving highly active antiretroviral therapy *[17]*, it is unknown whether the sensitivity of RNA assays might be affected by maternal antenatal treatment with combination antiretroviral drugs and/or infant antiretroviral prophylaxis.

HIV qualitative RNA assay (APTIMA HIV-1 RNA Qualitative Assay) is an alternative diagnostic test that can be used for infant testing *[18-21]*.

HIV Culture

HIV culture is not used for routine HIV diagnostic testing. It is generally not available outside of research laboratories. Although HIV culture has a sensitivity similar to that of HIV DNA PCR *[22]*, it is more complex and expensive to perform than DNA PCR or RNA assays and may require 2–4 weeks for definitive results.

ISSUES RELATED TO DIAGNOSIS OF NON-SUBTYPE B HIV INFECTION

Although HIV subtype B is the predominant viral subtype found in the United States, non-subtype B viruses predominate in some other parts of the world, such as subtype C in regions of Africa and India and subtype CRF01 in much of Southeast Asia *[23-25]*. Currently available HIV DNA PCR tests are less sensitive in the detection of non-subtype B HIV, and false-negative HIV DNA PCR assays have been reported in infants infected with non-subtype B HIV *[26-29]*. In an evaluation of perinatally infected infants diagnosed in New York State in 2001–2002, 16.7% of infants were infected with a non-subtype B strain of HIV, compared with 4.4% of infants diagnosed between 1998 and 1999 *[30]*.

Some of the currently available HIV RNA assays have improved sensitivity for detection of non-subtype B HIV infection *[31-34]*, although even these assays may not detect or properly quantify some non-B subtypes, particularly the more uncommon group O HIV subtypes *[33, 35-36]*. When non-subtype B perinatal exposure is suspected in infants with negative HIV DNA PCR, repeat testing using one of the newer RNA assays shown to be more sensitive in the detection of non-subtype B HIV is recommended (e.g., Amplicor HIV-1 Monitor 1.5 [Roche Molecular Systems, Pleasanton, CA], NucliSens HIV-1 QT [bioMerieux, Inc., Durham, NC], Versant Quantiplex HIV RNA 3.0 [bDNA] [Bayer Corporation, Tarrytown, NY]; AmpliPrep/TaqMan HIV-1 Test [Roche Diagnostics, Indianapolis, IN]; Real Time HIV-1 Assay [Abbott Molecular Incorporated, Des Plaines, IL] and the APTIMA HIV-1 RNA Qualitative Assay [Gen-Probe Incorporated San Diego, CA]).

When evaluating an infant whose mother and/or father comes from an area endemic for non-subtype B HIV, such as Africa and Southeast Asia, clinicians should consider conducting initial testing using one of the assays more sensitive for non-subtype B virus (for example, one of the newer RNA assays mentioned above) *[33, 37]*. In a child with negative HIV DNA PCR and RNA assays but in whom non-subtype B infection is suspected, the clinician should consult with an expert in pediatric HIV infection and the child should undergo close clinical monitoring and definitive HIV serologic testing at age 18 months.

TIMING OF DIAGNOSTIC TESTING IN INFANTS WITH KNOWN PERINATAL HIV EXPOSURE

Virologic diagnostic testing of the HIV-exposed infant should be performed at age 14–21 days, at age 1–2 months, and at age 4–6 months. Virologic diagnostic testing at birth should be considered for infants at high risk of HIV infection.

HIV infection is diagnosed by two positive HIV virologic tests performed on separate blood samples, regardless of child's age. A positive HIV antibody test with confirmatory Western blot (or IFA) at age ≥18 months confirms HIV infection with the exception of rare late seroreverters (see HIV antibody section below) *[1]*.

HIV infection can be *presumptively* excluded in nonbreastfed infants with two or more negative virologic tests, with one test obtained at ≥14 days of age and one obtained at ≥1 month of age; or one negative virologic test result obtained at ≥2 months of age; or one negative HIV antibody test result obtained at ≥6 months of age *[1, 38]*. *Pneumocystis jiroveci* pneumonia (PCP) prophylaxis is recommended for infants with indeterminate HIV infection status starting at 4–6 weeks of age until they are determined to be HIV uninfected or *presumptively* uninfected with HIV *[39]*. Thus, initiation of PCP prophylaxis can be avoided or, if prophylaxis was initiated, can be stopped, if the infant has negative virologic tests at 2 weeks of age and at 1 month of age, or if virologic testing is negative at or beyond 2 months of age. *Definitive* exclusion of HIV infection in a nonbreastfed infant is based on two or more negative virologic tests, with one obtained at ≥1 month of age and one at ≥4 months of age, or two negative HIV antibody tests from separate specimens obtained at ≥6 months of age. For both *presumptive* and *definitive* exclusion of HIV infection, the child must have no other laboratory (e.g., no positive virologic test results or low CD4 count/percent) or clinical evidence of HIV infection. Many experts confirm the absence of HIV infection in infants with negative virologic tests by performing an antibody test at 12–18 months of age to document seroreversion to HIV antibody negative status.

Virologic Testing at Birth (Optional)

Virologic testing at birth may be considered for newborns at high risk of HIV infection, such as infants born to HIV-infected mothers who did not receive prenatal care, prenatal antiretroviral therapy, or who had HIV viral loads ≥1,000 copies/mL close to time of delivery. As many as 30%–40% of HIV-infected infants can be identified by 48 hours of age *[4, 9]*. Blood samples from the umbilical cord should not be used for diagnostic evaluations due to the potential contamination with maternal blood. Working definitions have been proposed to differentiate acquisition of HIV infection during the intrauterine period from the intrapartum period. Infants who have a positive virologic test at or before age 48 hours are considered to have early (i.e., intrauterine) infection, whereas infants who have a negative virologic test during the first week of life and subsequent positive tests are considered to have late (i.e., intrapartum) infection *[40]*. Some researchers have proposed that infants with early infection may have more rapid disease progression than those with late infection and therefore should receive more aggressive therapy *[40-41]*. However, data from prospective cohort studies have demonstrated that although early differences in HIV RNA levels were present between infants with a positive HIV culture within 48 hours of birth and those with a first positive culture after 7 days of age, these differences were no longer statistically significant after 2 months of age *[42]*. HIV RNA levels after the first month of life were more predictive of rapid disease progression than the time at which HIV culture tests were positive *[42]*.

Virologic Testing at Age 14–21 Days

The diagnostic sensitivity of virologic assays increases rapidly by age 2 weeks *[9]*, and early identification of infection would permit discontinuation of neonatal antiretroviral prophylaxis and further evaluation for initiation of combination antiretroviral therapy (see **When to Initiate Therapy in Antiretroviral-Naïve HIV-Infected Infants Younger than 12 Months** and **Table 7**).

Virologic Testing at Age 1–2 Months

Infants with negative virologic tests before 1 month of age should be retested at 1–2 months of age. Most HIV-exposed neonates will receive 6 weeks of neonatal antiretroviral prophylaxis. Although antiretroviral agents could theoretically affect the predictive value of HIV virologic testing in neonates, the use of antepartum/intrapartum/neonatal zidovudine single-drug prophylaxis did not delay the detection of HIV by culture in infants in PACTG protocol 076 and has not decreased the sensitivity and predictive values of many virologic assays *[10, 12-13, 16, 38, 43-44]*. The affect of prenatal and neonatal combination antiretroviral regimens on the sensitivity of virologic tests for HIV-exposed infants needs to be examined. An infant with two negative virologic tests, one at ≥14 days and one at ≥1 month of age can be viewed as *presumptively* uninfected and would not need to initiate PCP prophylaxis, assuming the child has no laboratory (e.g., no positive virologic test results or low CD4 count) or clinical evidence of HIV infection.

Virologic Testing at Age 4–6 Months

HIV-exposed children who have had repeatedly negative virologic assays at 14–21 days of age and at 1–2 months of age should be retested at 4–6 months of age for *definitive* exclusion of HIV infection.

Antibody Testing at Age 6 Months or Older

Two or more negative HIV antibody tests performed at ≥6 months of age can also be used to *definitively* exclude HIV infection in HIV-exposed children with no clinical or virologic laboratory evidence of HIV infection.

Antibody Testing at Age 12–18 Months to Document Seroreversion

Many experts confirm the absence of HIV infection in infants with negative virologic tests by performing serology repeated between ages 12–18 months to confirm that maternal HIV antibodies transferred to the infant *in utero* have disappeared, if there has not been previous confirmation of two negative antibody tests. Although the proportion of infants who serorevert between 15 and 18 months of age is close to 100%, as many as 95% of infants may serorevert by 12 months of age; factors that might influence the time to seroreversion include the staging of maternal disease or the sensitivity of the assay *[1, 45-48]*.

Antibody Testing at Age 18 Months or Older

HIV infection can be diagnosed in children 18 months of age or older with a positive HIV antibody test and a confirmatory Western blot (or IFA). On rare occasions, nonbreastfed HIV-exposed infants with no other route of HIV transmission (e.g., sexual abuse or receipt of solid food premasticated by an HIV-1–infected caregiver) and no prior clinical or virologic laboratory evidence of HIV infection may have residual antibody at 18 months of age. These infants should have monthly repeat antibody testing because they may be late seroreverters, as late as 24 months *[48]*.

References

1. Schneider E, Whitmore S, Glynn KM, et al. Revised surveillance case definitions for HIV infection among adults, adolescents, and children aged <18 months and for HIV infection and AIDS among children aged 18 months to <13 years--United States, 2008. *MMWR Recomm Rep.* 2008;57(RR-10):1-12.
2. Guay LA, Hom DL, Kabengera SR, et al. HIV-1 ICD p24 antigen detection in ugandan infants: use in early diagnosis of infection and as a marker of disease progression. *J Med Virol.* 2000;62(4):426-434.
3. New York State Department of Public Health. HIV testing and diagnosis in infants and children. 2005; http://www.hivguidelines.org/wp-content/uploads/2009/05/p-test.pdf.
4. Bremer JW, Lew JF, Cooper E, et al. Diagnosis of infection with human immunodeficiency virus type 1 by a DNA polymerase chain reaction assay among infants enrolled in the Women and Infants' Transmission Study. *J Pediatr.* 1996;129(2):198-207.

5. Charbonneau TT, Wade NA, Weiner L, et al. Vertical transmission of HIV in New York State: a basis for statewide testing of newborns. *AIDS Patient Care STDS.* 1997;11(4):227-236.
6. Pugatch D. Testing infants for human immunodeficiency virus infection. *Pediatr Infect Dis J.* 2002;21(7):711-712.
7. Havens PL, Mofenson LM. Evaluation and management of the infant exposed to HIV-1 in the United States. *Pediatrics.* 2009;123(1):175-187.
8. American Academy of Pediatrics Committee on Pediatric AIDS. HIV testing and prophylaxis to prevent mother-to-child transmission in the United States. *Pediatrics.* 2008;122(5):1127-1134.
9. Dunn DT, Brandt CD, Krivine A, et al. The sensitivity of HIV-1 DNA polymerase chain reaction in the neonatal period and the relative contributions of intra-uterine and intra-partum transmission. *AIDS.* 1995;9(9):F7-11.
10. Cunningham CK, Charbonneau TT, Song K, et al. Comparison of human immunodeficiency virus 1 DNA polymerase chain reaction and qualitative and quantitative RNA polymerase chain reaction in human immunodeficiency virus 1-exposed infants. *Pediatr Infect Dis J.* 1999;18(1):30-35.
11. Delamare C, Burgard M, Mayaux MJ, et al. HIV-1 RNA detection in plasma for the diagnosis of infection in neonates. The French Pediatric HIV Infection Study Group. *J Acquir Immune Defic Syndr Hum Retrovirol.* 1997;15(2):121-125.
12. Lambert JS, Harris DR, Stiehm ER, et al. Performance characteristics of HIV-1 culture and HIV-1 DNA and RNA amplification assays for early diagnosis of perinatal HIV-1 infection. *J Acquir Immune Defic Syndr.* 2003;34(5):512-519.
13. Nesheim S, Palumbo P, Sullivan K, et al. Quantitative RNA testing for diagnosis of HIV-infected infants. *J Acquir Immune Defic Syndr.* 2003;32(2):192-195.
14. Simonds RJ, Brown TM, Thea DM, et al. Sensitivity and specificity of a qualitative RNA detection assay to diagnose HIV infection in young infants. Perinatal AIDS Collaborative Transmission Study. *AIDS.* 1998;12(12):1545-1549.
15. Steketee RW, Abrams EJ, Thea DM, et al. Early detection of perinatal human immunodeficiency virus (HIV) type 1 infection using HIV RNA amplification and detection. New York City Perinatal HIV Transmission Collaborative Study. *J Infect Dis.* 1997;175(3):707-711.
16. Young NL, Shaffer N, Chaowanachan T, et al. Early diagnosis of HIV-1-infected infants in Thailand using RNA and DNA PCR assays sensitive to non-B subtypes. *J Acquir Immune Defic Syndr.* 2000;24(5):401-407.
17. Saitoh A, Hsia K, Fenton T, et al. Persistence of human immunodeficiency virus (HIV) type 1 DNA in peripheral blood despite prolonged suppression of plasma HIV-1 RNA in children. *J Infect Dis.* 2002;185(10):1409-1416.
18. Kerr RJ, Player G, Fiscus SA, et al. Qualitative human immunodeficiency virus RNA analysis of dried blood spots for diagnosis of infections in infants. *J Clin Microbiol.* 2009;47(1):220-222.
19. U.S. Food and Drug Administration. APTIMA HIV-1 RNA Qualitative Assay. 2009; http://www.fda.gov/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/BloodDonorScreening/InfectiousDisease/ucm149922.htm.
20. Stevens WS, Noble L, Berrie L, et al. Ultra-high-throughput, automated nucleic acid detection of human immunodeficiency virus (HIV) for infant infection diagnosis using the Gen-Probe Aptima HIV-1 screening assay. *J Clin Microbiol.* 2009;47(8):2465-2469.
21. Walter J, Kuhn L, Semrau K, et al. Detection of low levels of human immunodeficiency virus (HIV) may be critical for early diagnosis of pediatric HIV infection by use of dried blood spots. *J Clin Microbiol.* 2009;47(9):2989-2991.
22. McIntosh K, Pitt J, Brambilla D, et al. Blood culture in the first 6 months of life for the diagnosis of vertically transmitted human immunodeficiency virus infection. The Women and Infants Transmission Study Group. *J Infect Dis.* 1994;170(4):996-1000.
23. Osmanov S, Pattou C, Walker N, et al. Estimated global distribution and regional spread of HIV-1 genetic subtypes in the year 2000. *J Acquir Immune Defic Syndr.* 2002;29(2):184-190.
24. Auwanit W, Isarangkura-Na-Ayuthaya P, Kasornpikul D, et al. Detection of drug resistance-associated and background mutations in human immunodeficiency virus type 1 CRF01_AE protease and reverse transcriptase derived from drug treatment-naive patients residing in central Thailand. *AIDS Res Hum Retroviruses.* 2009;25(6):625-631.
25. Deshpande A, Jauvin V, Pinson P, et al. Phylogenetic analysis of HIV-1 reverse transcriptase sequences from 382 patients recruited in JJ Hospital of Mumbai, India, between 2002 and 2008. *AIDS Res Hum Retroviruses.* 2009;25(6):633-635.

26. Haas J, Geiss M, Bohler T. False-negative polymerase chain reaction-based diagnosis of human immunodeficiency virus (HIV) type 1 in children infected with HIV strains of African origin. *J Infect Dis.* 1996;174(1):244-245.
27. Kline NE, Schwarzwald H, Kline MW. False negative DNA polymerase chain reaction in an infant with subtype C human immunodeficiency virus 1 infection. *Pediatr Infect Dis J.* 2002;21(9):885-886.
28. Obaro SK, Losikoff P, Harwell J, et al. Failure of serial human immunodeficiency virus type 1 DNA polymerase chain reactions to identify human immunodeficiency virus type 1 clade A/G. *Pediatr Infect Dis J.* 2005;24(2):183-184.
29. Zaman MM, Recco RA, Haag R. Infection with non-B subtype HIV type 1 complicates management of established infection in adult patients and diagnosis of infection in newborn infants. *Clin Infect Dis.* 2002;34(3):417-418.
30. Karchava M, Pulver W, Smith L, et al. Prevalence of drug-resistance mutations and non-subtype B strains among HIV-infected infants from New York State. *J Acquir Immune Defic Syndr.* 2006;42(5):614-619.
31. Antunes R, Figueiredo S, Bartolo I, et al. Evaluation of the clinical sensitivities of three viral load assays with plasma samples from a pediatric population predominantly infected with human immunodeficiency virus type 1 subtype G and BG recombinant forms. *J Clin Microbiol.* 2003;41(7):3361-3367.
32. Plantier JC, Gueudin M, Damond F, et al. Plasma RNA quantification and HIV-1 divergent strains. *J Acquir Immune Defic Syndr.* 2003;33(1):1-7.
33. Swanson P, de Mendoza C, Joshi Y, et al. Impact of human immunodeficiency virus type 1 (HIV-1) genetic diversity on performance of four commercial viral load assays: LCx HIV RNA Quantitative, AMPLICOR HIV-1 MONITOR v1.5, VERSANT HIV-1 RNA 3.0, and NucliSens HIV-1 QT. *J Clin Microbiol.* 2005;43(8):3860-3868.
34. Triques K, Coste J, Perret JL, et al. Efficiencies of four versions of the AMPLICOR HIV-1 MONITOR test for quantification of different subtypes of human immunodeficiency virus type 1. *J Clin Microbiol.* 1999;37(1):110-116.
35. Geelen S, Lange J, Borleffs J, et al. Failure to detect a non-B HIV-1 subtype by the HIV-1 Amplicor Monitor test, version 1.5: a case of unexpected vertical transmission. *AIDS.* 2003;17(5):781-782.
36. Krogstad P, Eshleman SH, Geng Y, et al. Mother-to-child transmission in the United States of subtypes D and A/G human immunodeficiency virus type 1. *AIDS Res Hum Retroviruses.* 2002;18(6):413-417.
37. Rouet F, Montcho C, Rouzioux C, et al. Early diagnosis of paediatric HIV-1 infection among African breast-fed children using a quantitative plasma HIV RNA assay. *AIDS.* 2001;15(14):1849-1856.
38. Read JS. Diagnosis of HIV-1 infection in children younger than 18 months in the United States. *Pediatrics.* 2007;120(6):e1547-1562.
39. Mofenson LM, Brady MT, Danner SP, et al. Guidelines for the Prevention and Treatment of Opportunistic Infections among HIV-exposed and HIV-infected children: recommendations from CDC, the National Institutes of Health, the HIV Medicine Association of the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the American Academy of Pediatrics. *MMWR Recomm Rep.* 2009;58(RR-11):1-166.
40. Bryson YJ, Luzuriaga K, Sullivan JL, et al. Proposed definitions for in utero versus intrapartum transmission of HIV-1. *N Engl J Med.* 1992;327(17):1246-1247.
41. Mayaux MJ, Burgard M, Teglas JP, et al. Neonatal characteristics in rapidly progressive perinatally acquired HIV-1 disease. The French Pediatric HIV Infection Study Group. *JAMA.* 1996;275(8):606-610.
42. Shearer WT, Quinn TC, LaRussa P, et al. Viral load and disease progression in infants infected with human immunodeficiency virus type 1. Women and Infants Transmission Study Group. *N Engl J Med.* 1997;336(19):1337-1342.
43. Connor EM, Sperling RS, Gelber R, et al. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. Pediatric AIDS Clinical Trials Group Protocol 076 Study Group. *N Engl J Med.* 1994;331(18):1173-1180.
44. Kovacs A, Xu J, Rasheed S, et al. Comparison of a rapid nonisotopic polymerase chain reaction assay with four commonly used methods for the early diagnosis of human immunodeficiency virus type 1 infection in neonates and children. *Pediatr Infect Dis J.* 1995;14(11):948-954.
45. Alcantara KC, Pereira GA, Albuquerque M, et al. Seroreversion in children born to HIV-positive and AIDS mothers from Central West Brazil. *Trans R Soc Trop Med Hyg.* 2009;103(6):620-626.
46. Gulia J, Kumwenda N, Li Q, et al. HIV seroreversion time in HIV-1-uninfected children born to HIV-1-infected mothers in Malawi. *J Acquir Immune Defic Syndr.* 2007;46(3):332-337.
47. Moodley D, Bobat RA, Coutsoudis A, et al. Predicting perinatal human immunodeficiency virus infection by antibody patterns. *Pediatr Infect Dis J.* 1995;14(10):850-852.

48. Sohn AH, Thanh TC, Thinh le Q, et al. Failure of human immunodeficiency virus enzyme immunoassay to rule out infection among polymerase chain reaction-negative Vietnamese infants at 12 months of age. *Pediatr Infect Dis J*. 2009;28(4):273-276.

Laboratory Monitoring of Pediatric HIV Infection (Updated August 16, 2010)

***Panel's Recommendations*:**

- ***The age of the child must be considered when interpreting the risk of disease progression based on CD4 percentage or count and plasma HIV RNA level (AII). For any given CD4 percentage or count, younger children, especially those in the first year of life, face higher risk of progression than do older children.***
- ***In children younger than 5 years of age, CD4 percentage is preferred for monitoring immune status because of age-related changes in absolute CD4 count in this age group (AII).***
- ***CD4 percentage or count should be measured at the time of diagnosis of HIV infection and at least every 3–4 months thereafter (AIII).***
- ***Plasma HIV RNA should be measured to assess viral load at the time of diagnosis of HIV infection and at least every 3–4 months thereafter (AIII).***
- ***More frequent CD4 cell and plasma HIV RNA monitoring should be considered in infants younger than 6–12 months of age; in children with suspected clinical, immunologic, or virologic deterioration; to confirm an abnormal value; or when initiating or changing therapy (AIII).***
- ***An ultrasensitive viral load assay should be used to confirm that antiretroviral therapy is producing maximal suppression of viremia (AIII).***

IMMUNOLOGIC MONITORING IN CHILDREN

Clinicians interpreting CD4 count for children must consider age as a variable. CD4 count and percentage values in healthy infants who are not infected with HIV are considerably higher than values observed in uninfected adults and slowly decline to adult values by age 5 years *[1-2]*. In children younger than 5 years of age, the absolute CD4 count tends to vary more with age within an individual child than does CD4 percentage. Therefore, in HIV-infected children younger than 5 years of age, CD4 percentage is preferred for monitoring immune status, whereas absolute CD4 count can be used in older children *[3-5]*.

In HIV-infected children, as in infected adults, the CD4 count and percentage decline as HIV infection progresses, and patients with lower CD4 values have a poorer prognosis than patients with higher values (**Tables 3–5**). Consequently, CD4 values should be obtained as soon as possible after a child has a positive test for HIV and subsequently every 3–4 months. Increased frequency of evaluations may be needed for children with suspected clinical, immunologic, or virologic deterioration; to confirm an abnormal value; or when initiating or changing therapy. Because young infants with HIV infection may have rapid disease progression *[6-7]*, some experts monitor CD4 percentage more frequently (e.g., every 1–2 months) in untreated infants younger than 6 to 12 months of age. Because of the risk of rapid progression, initiation of antiretroviral treatment is now recommended for all HIV-infected infants younger than 12 months of age (see **When to Initiate Therapy in Antiretroviral-Naïve Children**). For adolescents who are adherent to therapy with sustained viral suppression and stable clinical status for more than 2–3 years, some experts monitor CD4 counts and HIV RNA levels less frequently.

The prognostic value of CD4 percentage and HIV RNA copy number was assessed in a large individual patient meta-analysis (the HIV Pediatric Prognostic Markers Collaborative Study), which incorporated clinical and laboratory data from 17 pediatric studies and included 3,941 HIV-infected children receiving either no therapy or only zidovudine monotherapy *[4]*. The analysis looked at the short-term (12-month) risk of developing AIDS or death based on the child's age and selected values of CD4 percentage and HIV RNA copy number at baseline. **Figures 1 and 2** and **Table 3** depict age-associated 1-year risk of developing AIDS or death as a function of CD4 percentage. In a separate analysis of this data set, predictive value of absolute CD4 cell count for risk of death or AIDS/death in HIV-infected children 5 years of age or older was similar to that observed in

young adults, with an increase in the risk of mortality when CD4 cell count fell less than 350 cells/mm^3 (**Table 4** and **Figure 3**) *[3, 8]*.

The risk of disease progression associated with a specific CD4 percentage or count varies with the age of the child. Infants in the first year of life experience higher risks of progression or death than older children for any given CD4 stratum. For example, comparing a 1-year-old child with CD4 percentage of 25% to a 5-year-old child with the same CD4 percentage, there is an approximately fourfold increase in the risk of AIDS and sixfold increase in the risk of death in the 1-year-old child (**Figures 1 and 2**). Children 5 years of age or older have a lower risk of progression than younger children, with the increase in risk of AIDS or death corresponding to absolute CD4 levels more similar to those in young adults (**Figure 3**). In the HIV Pediatric Prognostic Marker Collaborative Study, there were no deaths among children 5 years of age or older with CD4 count greater than 350 cells/mm^3, although in younger children there continued to be a significant risk of death even with a CD4 cell count greater than 500 cells/mm^3 (**Table 4**).

These risk profiles form the rationale for recommendations on when to initiate therapy in a treatment-naïve HIV-infected child (see **When to Initiate Therapy in Antiretroviral-Naïve Children**). A Web site using the meta-analysis from the HIV Pediatric Prognostic Markers Collaborative Study (HPPMCS) is available to estimate the short-term risk of progression to AIDS or death in the absence of effective antiretroviral therapy according to age and the most recent CD4 percentage or HIV-1 RNA viral load measurement (**http://hppmcs.org**) *[4]*.

Measurement of CD4 values can be associated with considerable intrapatient variation *[5]*. Even mild intercurrent illness or the receipt of vaccinations can produce a transient decrease in CD4 count and percentage; thus, CD4 values are best measured when patients are clinically stable. No modification in therapy should be made in response to a change in CD4 values until the change has been substantiated by at least a second determination, with a minimum of 1 week between measurements.

HIV RNA MONITORING IN CHILDREN

Viral burden in peripheral blood can be determined by using quantitative HIV RNA assays. During the period of primary infection in adults, HIV RNA copy number initially rises to high peak levels and then declines by as much as 2–3 $\log_{10}$ copies to reach a stable lower level (the virologic set point) approximately 6–12 months following acute infection *[9-10]*. In infected adults, the viral set point correlates with the subsequent risk of disease progression or death *[11-12]*. On the basis of data from studies in infected adults, recommendations for the use of HIV RNA copy number in managing antiretroviral therapy have been developed for adults *[13]*. These recommendations also are applicable to infected adolescents.

The HIV RNA pattern in perinatally infected infants differs from that in infected adults and adolescents. High HIV RNA copy numbers persist in infected children for prolonged periods *[14-15]*. In one prospective study, HIV RNA levels generally were low at birth (i.e., <10,000 copies/mL), increased to high values by age 2 months (most infants had values >100,000 copies/mL, ranging from undetectable to nearly 10 million copies/mL), and then decreased slowly; the mean HIV RNA level during the first year of life was 185,000 copies/mL *[16]*. Additionally, in contrast to the adult pattern, after the first year of life, HIV RNA copy number slowly declines over the next few years *[16-19]*. This pattern probably reflects the lower efficiency of an immature, but developing, immune system in containing viral replication and possibly the rapid expansion of HIV-susceptible cells that occurs with somatic growth *[20]*.

High HIV RNA levels (i.e., >299,000 copies/mL) in infants age <12 months have been correlated with disease progression and death, but RNA levels overlap considerably in young infants who have rapid disease progression and those who do not *[14, 16]*. High RNA levels (i.e., levels of >100,000 copies/mL) in older children have also been associated with high risk of disease progression and mortality, particularly if CD4 percentage is <15% (**Table 5**) *[18-19]*. The most robust data set available to elucidate the predictive value of plasma RNA for disease progression in children was assembled in the HIV Pediatric Prognostic Markers Collaborative Study (see **Immunologic Monitoring in Children**) *[4]*. As for CD4 percentage, analyses were performed for age-associated risk in the context of plasma RNA levels in a cohort of children receiving either

no therapy or only zidovudine monotherapy. Similar to data from previous studies *[18-19]*, the risk of clinical progression to AIDS or death dramatically increases when HIV RNA exceeds 100,000 copies (5.0 $\log_{10}$ copies)/mL; at lower values, only older children show much variation in risk (**Figures 4 and 5** and **Table 3**). At any given level of HIV RNA, infants younger than 1 year of age were at higher risk of progression than older children, although these differences were less striking than those observed for the CD4 percentage data.

Despite data indicating that high plasma HIV RNA concentrations are associated with disease progression, the predictive value of specific HIV RNA concentrations for disease progression and death for an individual child is moderate *[18]*. HIV RNA concentration may be difficult to interpret during the first year of life because values are high and are less predictive of disease progression risk than in older children *[15]*. In both HIV-infected children and adults, CD4 percentage or count and HIV RNA copy number are independent predictors of disease progression and mortality risk, and use of the two markers together more accurately defines prognosis *[18-19, 21-23]*.

HIV RNA copy number should be assessed as soon as possible after a child has a positive virologic test for HIV and every 3–4 months thereafter; increased frequency of evaluations may be needed for children experiencing virologic, immunologic, or clinical deterioration; to confirm an abnormal value; or when initiating or changing antiretroviral therapy (see **Antiretroviral Treatment Failure in Infants, Children, and Adolescents**). Because young infants with HIV infection may have rapid disease progression, some experts monitor HIV RNA concentration more frequently (e.g., every 1–2 months) in untreated infants younger than 6–12 months of age.

Methodological Considerations in Interpretation and Comparability of HIV RNA Assays

The use of HIV RNA assays for clinical purposes requires specific considerations *[24]*, which are discussed more completely elsewhere *[13]*. Several different methods can be used for quantitating HIV RNA, each has a different level of sensitivity. Although the results of the assays are correlated, the absolute HIV RNA copy number obtained from a single specimen tested by two different assays can differ by twofold (0.3 $\log_{10}$ units) or more *[25-28]*.

There are currently five FDA-approved viral load assays using one of three different methodologies:

- HIV-1 reverse transcriptase (RT) quantitative PCR assays: the Amplicor HIV-1 Monitor Test, version 1.5 (Roche Diagnostics), for which the lower limit of detection differs between the "ultrasensitive" assay (<50 copies/mL) and the "regular sensitivity" assay (<400 copies/mL); the AmpliPrep/TaqMan HIV-1 Test (Roche Diagnostics); and the Real Time HIV-1 Assay (Abbott Molecular Incorporated);
- HIV-1 nucleic acid sequence-based amplification test (NucliSens HIV-1 QT, bioMerieux); and
- HIV-1 *in vitro* signal amplification, branched chain nucleic acid probe assay (bDNA) (VERSANT HIV-1 RNA 3.0 Assay, Bayer).

The lower limits of detection of the assays differ (<40 copies/mL for the Abbott Real Time HIV-1 test, <48 copies/mL for the AmpliPrep/TaqMan HIV-1 Test, <50 copies/mL for the Amplicor HIV-1 Monitor Test, <80 copies/mL for the NucliSens HIV-1 QT assay, and <75 copies/mL for the VERSANT assay). Use of ultrasensitive viral load assays to confirm that antiretroviral therapy is producing maximal suppression of viremia is recommended. Because of the variability of assay techniques and quantitative HIV RNA measurements between these assays, a single HIV RNA assay method should be used consistently for monitoring an individual patient, if possible.

The predominant virus subtype in the United States is B, which is the subtype for which all initial assays were targeted. Current kit configurations for all companies have been designed to detect and quantitate essentially all viral subtypes, with the exception of the uncommon O subtypes *[29-30]*. This is important for many regions of the world where non-B subtypes are predominant, as well as for the United States, where a small subset of individuals are infected with non-B viral subtypes *[31-33]*. Choice of HIV RNA assay, particularly for young children, may be influenced by the amount of blood required for the assay. The NucliSens assay requires the

least amount of blood (100 µL of plasma), followed by the RT PCR assays such as Amplicor HIV-1 Monitor (200 µL of plasma) and the VERSANT assays (1 mL of plasma).

Biologic variation in HIV RNA levels within one person is well documented. In adults, repeated measurement of HIV RNA levels using the same assay can vary by as much as threefold (0.5 $\log_{10}$) in either direction over the course of a day or on different days *[13, 21, 27]*. This biologic variation may be greater in infected infants and young children. In children with perinatally acquired HIV infection, RNA copy number slowly declines even without therapy during the first several years after birth, although it persists at higher levels than those observed in most infected adults *[16-18]*. This decline is most rapid during the first 12–24 months after birth, with an average decline of approximately 0.6 $\log_{10}$ per year; a slower decline continues until approximately 4–5 years of age (average decline of 0.3 $\log_{10}$ per year).

This inherent biologic variability must be considered when interpreting changes in RNA copy number in children. Thus, only changes after repeated testing greater than fivefold (0.7 $\log_{10}$) in infants younger than 2 years of age and greater than threefold (0.5 $\log_{10}$) in children 2 years of age and older should be considered reflective of a biologically and clinically substantial change.

No alteration in therapy should be made as a result of a change in HIV copy number unless the change is confirmed by a second measurement. Because of the complexities of HIV RNA testing and the age-related changes in HIV RNA in children, interpretation of HIV RNA levels for clinical decision making should be done by or in consultation with an expert in pediatric HIV infection.

Table 3. Likelihood of Developing AIDS or Death Within 12 Months, by Age and $CD4^+$ T-Cell Percentage or Log_{10} HIV-1 RNA Copy Number in HIV-Infected Children Receiving No Therapy or Zidovudine Monotherapy

	CD4 Percentage				Log_{10} HIV RNA Copy Number		
Age	**10%**	**20%**	**25%**	**30%**	**6.0**	**5.0**	**4.0**
Percent Mortality (95% Confidence Interval)							
6 Months	28.7	12 .4	8.5	6.4	9.7	4.1	2.7
1 Year	19.5	6.8	4.5	3.3	8.8	3.1	1.7
2 Years	11.7	3.1	2.0	1.5	8.2	2.5	1.1
5 Years	4.9	0.9	0.6	0.5	7.8	2.1	0.7
10 Years	2.1	0.3	0.2	0.2	7.7	2.0	0.6
Percent Developing AIDS (95% Confidence Interval)							
6 Months	51.4	31.2	24.9	20.5	23.7	13.6	10.9
1 Year	40.5	20.9	15.9	12.8	20.9	10.5	7.8
2 Years	28.6	12 .0	8.8	7.2	18.8	8.1	5.3
5 Years	14.7	4.7	3.7	3.1	17.0	6.0	3.2
10 Years	7.4	2.2	1.9	1.8	16.2	5.1	2.2

Table modified from: HIV Paediatric Prognostic Markers Collaborative Study Group. *Lancet* 2003; 362:1605-11.

Table 4. Death and AIDS/Death Rate per 100 Person-Years by Current Absolute CD4 Count and Age in HIV-Infected Children Receiving No Therapy or Zidovudine Monotherapy (HIV Paediatric Prognostic Markers Collaborative Study) and Adult Seroconverters (CASCADE Study)*

Age (Years)	Absolute CD4 cell count (cells/mm^3)					
	<50	**50–99**	**100–199**	**200–349**	**350–499**	**500+**
Rate of Death Per 100 Patient-Years						
0–4	59.3	39.6	25.4	11.1	10.0	3.5
5–14	28.9	11.8	4.3	0.89	0.00	0.00
15–24	34.7	6.1	1.1	0.71	0.58	0.65
25–34	47.7	10.8	3.7	1.1	0.38	0.22
35–44	58.8	15.6	4.5	0.92	0.74	0.85
45–54	66.0	18.8	7.7	1.8	1.3	0.86
55+	91.3	21.4	17.6	3.8	2.5	0.91
Rate of AIDS or Death per 100 Patient-Years						
0–4	82.4	83.2	57.3	21.4	20.7	14.5
5–14	64.3	19.6	16.0	6.1	4.4	3.5
15–24	61.7	30.2	5.9	2.6	1.8	1.2
25–34	93.2	57.6	19.3	6.1	2.3	1.1
35–44	88.1	58.7	25.5	6.6	4.0	1.9
45–54	129.1	56.2	24.7	7.7	3.1	2.7
55+	157.9	42.5	30.0	10.0	5.1	1.8

* Modifed from HIV Paediatric Prognostic Markers Collaborative Study and the CASCADE Collaboration. *J Infect Dis* 2008;197:398-404.

Table 5. Association of Baseline Human Immunodeficiency Virus (HIV) RNA Copy Number and CD4+ T-Cell Percentage with Long-Term Risk of Death in HIV-Infected Children*

Baseline HIV RNA§ (copies/mL)/Baseline CD4+ T-cell percentage	No. patients¶	Deaths†	
		No.	(%)
≤ 100,000			
≥ 15%	103	15	(15%)
< 15%	24	15	(63%)
> 100,000			
≥ 15%	89	32	(36%)
< 15%	36	29	(81%)

* Data from the National Institute of Child Health and Human Development Intravenous Immunoglobulin Clinical Trial.

† Mean follow-up: 5.1 years.

§ Tested by NASBA® assay (manufactured by Organon Teknika, Durham, North Carolina) on frozen stored serum.

¶ Mean age: 3.4 years.

Source: Mofenson LM, Korelitz J, Meyer WA, et al. The relationship between serum human immunodeficiency virus type 1 (HIV-1) RNA level, CD4 lymphocyte percent, and long-term mortality risk in HIV-1-infected children. *J Infect Dis*, 1997. 175(5):1029–38.

Figure 1. Estimated Probability of AIDS Within 12 Months by Age and CD4 Percentage in HIV-Infected Children Receiving No Therapy or Zidovudine Monotherapy *[modified from Lancet 2003;362:1605-11]*

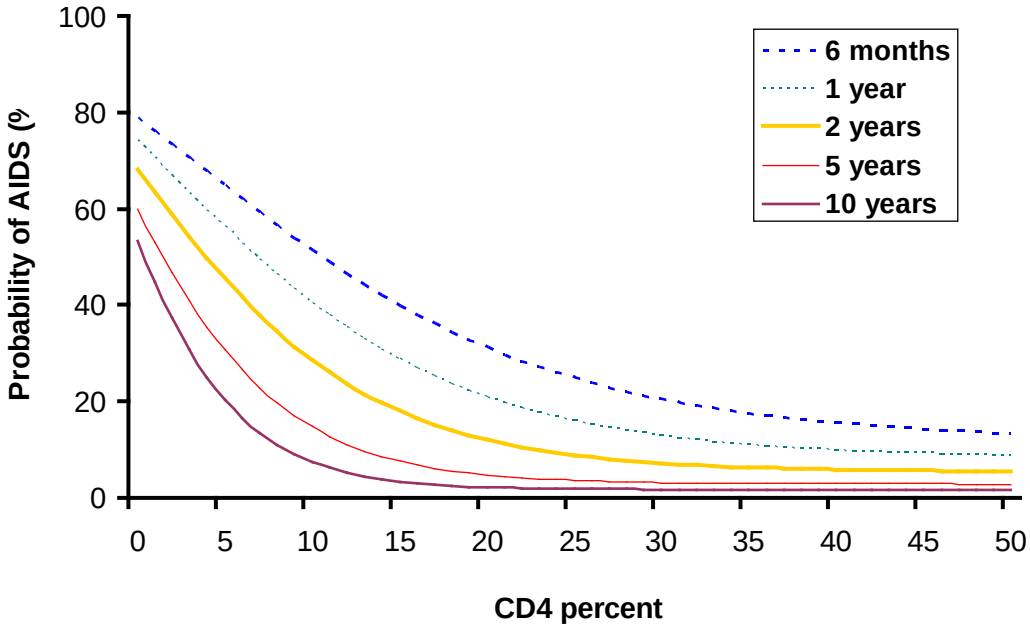


Figure 2. Estimated Probability of Death Within 12 Months by Age and CD4 Percentage in HIV-Infected Children Receiving No Therapy or Zidovudine Monotherapy *[modified from Lancet 2003;362:1605-11]*

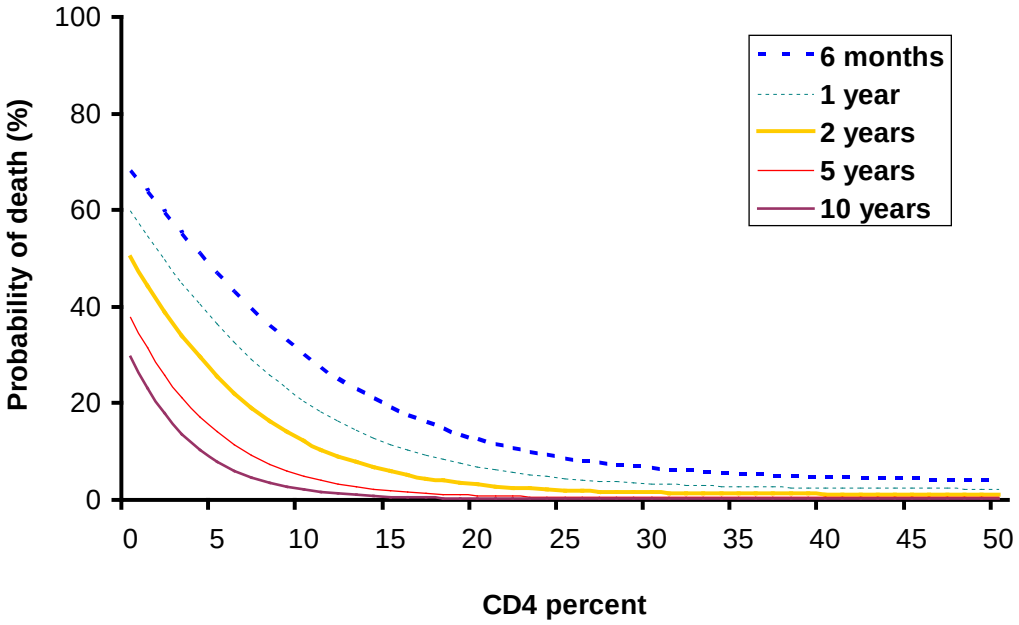
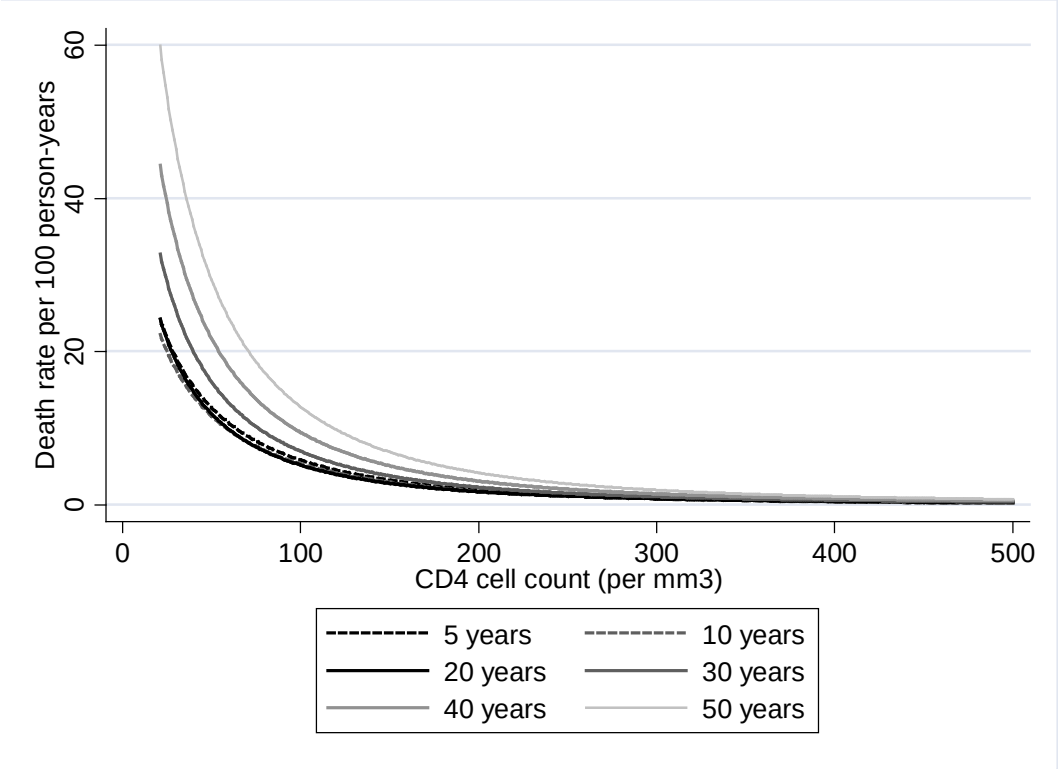


Figure 3. Death Rate per 100 Person-Years in HIV-Infected Children Age 5 years or Older in the HIV Pediatric Prognostic Marker Collaborative Study and HIV-Infected Seroconverting Adults from the CASCADE Study*



* Modifed from HIV Paediatric Prognostic Markers Collaborative Study and the CASCADE Collaboration. *J Infect Dis* 2008;197:398-404.

Figure 4. Estimated Probability of AIDS Within 12 Months by Age and HIV RNA Copy Number in HIV-Infected Children Receiving No Therapy or Zidovudine Monotherapy *[modified from Lancet 2003;362:1605-11]*

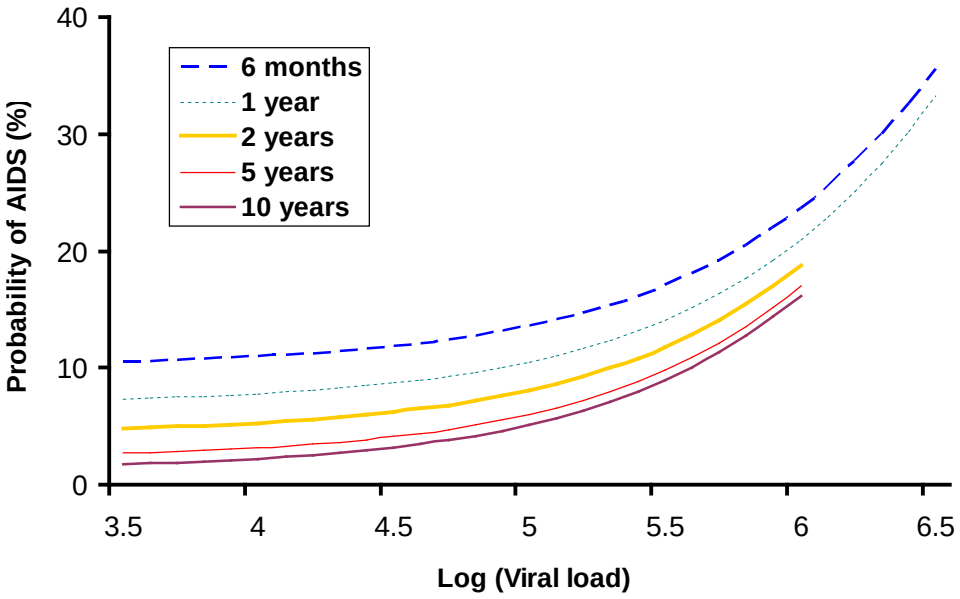
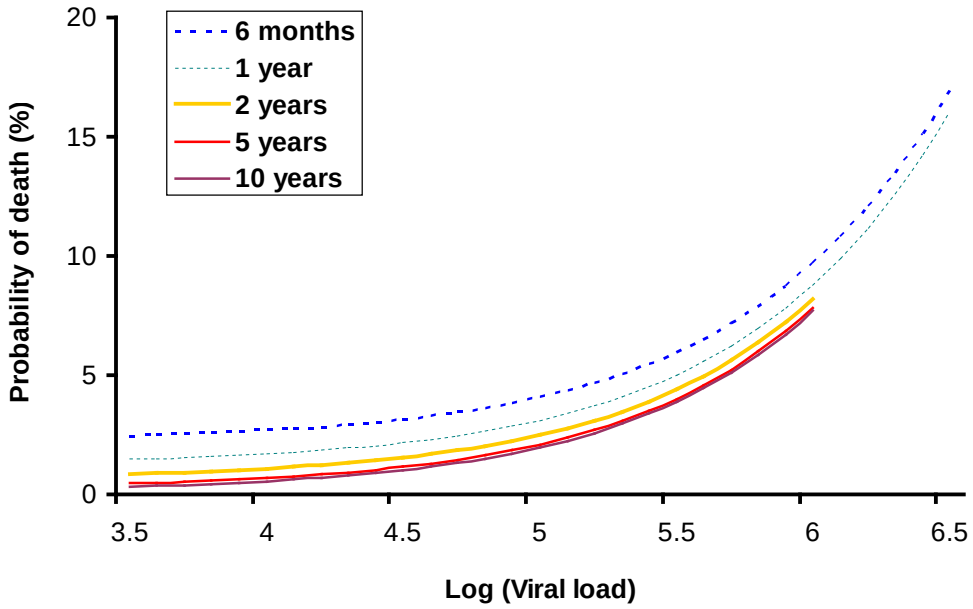


Figure 5. Estimated Probability of Death Within 12 Months by Age and HIV RNA Copy Number in HIV-Infected Children Receiving No Therapy or Zidovudine Monotherapy *[modified from Lancet 2003;362:1605-11]*



References

1. European Collaborative Study. Age-related standards for T lymphocyte subsets based on uninfected children born to human immunodeficiency virus 1-infected women. The European Collaborative Study. *Pediatr Infect Dis J.* 1992;11(12):1018-1026.
2. Shearer WT, Rosenblatt HM, Gelman RS, et al. Lymphocyte subsets in healthy children from birth through 18 years of age: the Pediatric AIDS Clinical Trials Group P1009 study. *J Allergy Clin Immunol.* 2003;112(5):973-980.
3. HIV Paediatric Prognostic Markers Collaborative Study. Predictive value of absolute CD4 cell count for disease progression in untreated HIV-1-infected children. *AIDS.* 2006;20(9):1289-1294.
4. Dunn D. Short-term risk of disease progression in HIV-1-infected children receiving no antiretroviral therapy or zidovudine monotherapy: a meta-analysis. *Lancet.* 2003;362(9396):1605-1611.
5. Raszka WV, Jr., Meyer GA, Waecker NJ, et al. Variability of serial absolute and percent CD4+ lymphocyte counts in healthy children born to human immunodeficiency virus 1-infected parents. Military Pediatric HIV Consortium. *Pediatr Infect Dis J.* 1994;13(1):70-72.
6. Simonds RJ, Lindegren ML, Thomas P, et al. Prophylaxis against Pneumocystis carinii pneumonia among children with perinatally acquired human immunodeficiency virus infection in the United States. Pneumocystis carinii Pneumonia Prophylaxis Evaluation Working Group. *N Engl J Med.* 1995;332(12):786-790.
7. Violari A, Cotton MF, Gibb DM, et al. Early antiretroviral therapy and mortality among HIV-infected infants. *N Engl J Med.* 2008;359(21):2233-2244.
8. Dunn D, Woodburn P, Duong T, et al. Current CD4 cell count and the short-term risk of AIDS and death before the availability of effective antiretroviral therapy in HIV-infected children and adults. *J Infect Dis.* 2008;197(3):398-404.
9. Henrard DR, Phillips JF, Muenz LR, et al. Natural history of HIV-1 cell-free viremia. *JAMA.* 1995;274(7):554-558.
10. Katzenstein TL, Pedersen C, Nielsen C, et al. Longitudinal serum HIV RNA quantification: correlation to viral phenotype at seroconversion and clinical outcome. *AIDS.* 1996;10(2):167-173.
11. Clementi M, Menzo S, Bagnarelli P, et al. Clinical use of quantitative molecular methods in studying human immunodeficiency virus type 1 infection. *Clin Microbiol Rev.* 1996;9(2):135-147.
12. Mellors JW, Kingsley LA, Rinaldo CR, Jr., et al. Quantitation of HIV-1 RNA in plasma predicts outcome after seroconversion. *Ann Intern Med.* 1995;122(8):573-579.
13. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. December 1, 2009:1-161. http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf.
14. Abrams EJ, Weedon J, Steketee RW, et al. Association of human immunodeficiency virus (HIV) load early in life with disease progression among HIV-infected infants. New York City Perinatal HIV Transmission Collaborative Study Group. *J Infect Dis.* 1998;178(1):101-108.
15. Palumbo PE, Kwok S, Waters S, et al. Viral measurement by polymerase chain reaction-based assays in human immunodeficiency virus-infected infants. *J Pediatr.* 1995;126(4):592-595.
16. Shearer WT, Quinn TC, LaRussa P, et al. Viral load and disease progression in infants infected with human immunodeficiency virus type 1. Women and Infants Transmission Study Group. *N Engl J Med.* 1997;336(19):1337-1342.
17. McIntosh K, Shevitz A, Zaknun D, et al. Age- and time-related changes in extracellular viral load in children vertically infected by human immunodeficiency virus. *Pediatr Infect Dis J.* 1996;15(12):1087-1091.
18. Mofenson LM, Korelitz J, Meyer WA, 3rd, et al. The relationship between serum human immunodeficiency virus type 1 (HIV-1) RNA level, CD4 lymphocyte percent, and long-term mortality risk in HIV-1-infected children. National Institute of Child Health and Human Development Intravenous Immunoglobulin Clinical Trial Study Group. *J Infect Dis.* 1997;175(5):1029-1038.
19. Palumbo PE, Raskino C, Fiscus S, et al. Predictive value of quantitative plasma HIV RNA and CD4+ lymphocyte count in HIV-infected infants and children. *JAMA.* 1998;279(10):756-761.
20. Krogstad P, Uittenbogaart CH, Dickover R, et al. Primary HIV infection of infants: the effects of somatic growth on lymphocyte and virus dynamics. *Clin Immunol.* 1999;92(1):25-33.
21. Hughes MD, Johnson VA, Hirsch MS, et al. Monitoring plasma HIV-1 RNA levels in addition to CD4+ lymphocyte count improves assessment of antiretroviral therapeutic response. ACTG 241 Protocol Virology Substudy Team. *Ann Intern Med.* 1997;126(12):929-938.

22. Mellors JW, Munoz A, Giorgi JV, et al. Plasma viral load and CD4+ lymphocytes as prognostic markers of HIV-1 infection. *Ann Intern Med.* 1997;126(12):946-954.
23. O'Brien WA, Hartigan PM, Daar ES, et al. Changes in plasma HIV RNA levels and CD4+ lymphocyte counts predict both response to antiretroviral therapy and therapeutic failure. VA Cooperative Study Group on AIDS. *Ann Intern Med.* 1997;126(12):939-945.
24. Reichelderfer PS, Coombs RW. Virologic parameters as surrogate markers for clinical outcome in HIV-1 disease: verification, variation, and validation. *J Acquir Immune Defic Syndr Hum Retrovirol.* 1995;10 Suppl 2:S19-24.
25. Brambilla D, Leung S, Lew J, et al. Absolute copy number and relative change in determinations of human immunodeficiency virus type 1 RNA in plasma: effect of an external standard on kit comparisons. *J Clin Microbiol.* 1998;36(1):311-314.
26. Goetz M, Moatamed F, Howanitz J. Measurement of plasma HIV viral load (VL) by bDNA versus RT PCR (PCR) assays. *Clin Infect Dis.* 1997;25(394):Abstract 207.
27. Raboud JM, Montaner JS, Conway B, et al. Variation in plasma RNA levels, CD4 cell counts, and p24 antigen levels in clinically stable men with human immunodeficiency virus infection. *J Infect Dis.* 1996;174(1):191-194.
28. Vandamme AM, Schmit JC, Van Dooren S, et al. Quantification of HIV-1 RNA in plasma: comparable results with the NASBA HIV-1 RNA QT and the AMPLICOR HIV monitor test. *J Acquir Immune Defic Syndr Hum Retrovirol.* 1996;13(2):127-139.
29. Antunes R, Figueiredo S, Bartolo I, et al. Evaluation of the clinical sensitivities of three viral load assays with plasma samples from a pediatric population predominantly infected with human immunodeficiency virus type 1 subtype G and BG recombinant forms. *J Clin Microbiol.* 2003;41(7):3361-3367.
30. Plantier JC, Gueudin M, Damond F, et al. Plasma RNA quantification and HIV-1 divergent strains. *J Acquir Immune Defic Syndr.* 2003;33(1):1-7.
31. Haas J, Geiss M, Bohler T. False-negative polymerase chain reaction-based diagnosis of human immunodeficiency virus (HIV) type 1 in children infected with HIV strains of African origin. *J Infect Dis.* 1996;174(1):244-245.
32. Kline NE, Schwarzwald H, Kline MW. False negative DNA polymerase chain reaction in an infant with subtype C human immunodeficiency virus 1 infection. *Pediatr Infect Dis J.* 2002;21(9):885-886.
33. Zaman MM, Recco RA, Haag R. Infection with non-B subtype HIV type 1 complicates management of established infection in adult patients and diagnosis of infection in newborn infants. *Clin Infect Dis.* 2002;34(3):417-418.

Treatment Recommendations (Updated August 16, 2010)

GENERAL CONSIDERATIONS

Treatment of pediatric HIV infection in the United States has evolved since antiretroviral therapy began in the late 1980s. Prior to the availability of antiretroviral drugs for children, care focused on prevention and management of HIV-related complications and provision of palliative care. Initial studies of monotherapy in children in the early 1990s demonstrated significant clinical and immunologic benefit with treatment *[1-4]*; further research demonstrated that combination therapy (initially dual-NRTI treatment) led to better clinical, immunologic, and virologic outcomes than monotherapy *[5]*. Currently, highly active combination regimens including at least three drugs are recommended; such regimens have been associated with enhanced survival, reduction in opportunistic infections and other complications of HIV infection, improved growth and neurocognitive function, and improved quality of life in children *[6-10]*. In the United States and the United Kingdom, significant declines (81%–93%) in mortality have been reported in HIV-infected children between 1994 and 2006, concomitant with increased use of highly active combination regimens *[11-12]*; significant declines in HIV-related morbidity and hospitalizations in children have been observed in the United States and Europe over the same time period *[10, 12]*.

The increased survival of HIV-infected children is associated with challenges in selecting successive new antiretroviral drug regimens. Additionally, therapy is associated with short- and long-term toxicities, some of which are only now beginning to be recognized in children *[13-14]*.

Antiretroviral drug-resistant virus can develop in both multidrug experienced children and children who received initial regimens containing one or two drugs that incompletely suppressed viral replication. Additionally, drug resistance may be seen in antiretroviral-naïve children who have become infected with HIV despite maternal/infant antiretroviral prophylaxis *[15-16]*. Thus, decisions about when to start therapy and what drugs to choose in antiretroviral-naïve children and on how to best treat antiretroviral-experienced children remain complex. Whenever possible, decisions regarding the management of pediatric HIV infection should be directed by or made in consultation with a specialist in pediatric and adolescent HIV infection. Treatment of antiretroviral-naïve children (when and what to start), when to change therapy, and treatment of antiretroviral-experienced children will be discussed in separate sections of the guidelines.

A number of factors need to be considered in making decisions about initiating and changing antiretroviral therapy in children, including:

- severity of HIV disease and risk of disease progression, as determined by age, presence or history of HIV-related or AIDS-defining illnesses (see pediatric clinical staging system for HIV, **Table 6**) *[17-18]*, level of CD4 cell immunosuppression, and magnitude of HIV plasma viremia;
- availability of appropriate (and palatable) drug formulations and pharmacokinetic information on appropriate dosing in the child's age group;
- potency, complexity (e.g., dosing frequency, food and fluid requirements), and potential short- and long-term adverse effects of the antiretroviral regimen;
- effect of initial regimen choice on later therapeutic options;
- presence of comorbidity, such as tuberculosis, hepatitis B or C virus infection, or chronic renal or liver disease, that could affect drug choice;
- potential antiretroviral drug interactions with other prescribed, over-the-counter, or complementary/alternative medications taken by the child; and
- the ability of the caregiver and child to adhere to the regimen.

The following recommendations provide general guidance for decisions related to treatment of HIV-infected children, and flexibility should be exercised according to a child's individual circumstances. Guidelines for treatment of HIV-infected children are evolving as new data from clinical trials become available. Although

prospective, randomized, controlled clinical trials offer the best evidence for formulation of guidelines, most antiretroviral drugs are approved for use in pediatric patients based on efficacy data from clinical trials in adults, with supporting pharmacokinetic and safety data from Phase I/II trials in children. Additionally, efficacy has been defined in most adult trials based on surrogate marker data, as opposed to clinical endpoints. For the development of these guidelines, the Panel reviewed relevant clinical trials published in peer-reviewed journals or in abstract form, with attention to data from pediatric populations when available.

GOALS OF ANTIRETROVIRAL TREATMENT

Current antiretroviral therapies do not eradicate HIV infection due to the long half-life of latently infected CD4 cells *[19-21]*; some data suggest that the half-life of intracellular HIV proviral DNA is even longer in infected children than in adults (median 14 months vs. 5–10 months, respectively) *[21]*. Thus, based on currently available data, HIV causes a chronic infection likely requiring treatment for life once a child starts therapy. The goals of antiretroviral therapy for HIV-infected children include:

- reducing HIV-related mortality and morbidity;
- restoring and/or preserving immune function;
- maximally and durably suppressing viral replication;
- minimizing drug-related toxicity;
- maintaining normal physical growth and neurocognitive development; and
- improving quality of life.

Strategies to achieve these goals require complex balancing of sometimes competing considerations.

Use and selection of combination antiretroviral therapy: At present, the treatment of choice for HIV-infected children is at least three drugs, which include at least two classes of antiretroviral drugs. The Panel has recommended several preferred and alternative regimens (see **What Drugs to Start: Initial Combination Therapy for Antiretroviral-Naïve Children**). The most appropriate regimen for an individual child depends on multiple factors, including age of the child and availability of appropriate drug formulations; the potency, complexity, and toxicity of the regimen; the child and caregiver's ability to adhere to the regimen; the child's home situation; and the child's antiretroviral treatment history.

Drug sequencing and preservation of future treatment options: The choice of antiretroviral treatment regimens should include consideration of future treatment options, such as the presence of or potential for drug resistance. Multiple changes in antiretroviral drug regimens can rapidly exhaust treatment options and should be avoided unless required (e.g., severe toxicity or intolerance or significant clinical, immunologic, or virologic progression). Appropriate sequencing of drugs for use in initial and second-line therapy can preserve future treatment options and is another strategy to maximize long-term benefit from therapy. Currently, recommendations for initial therapy are to use two classes of drugs—two NRTIs combined with either an NNRTI or a PI—thereby sparing three classes of drugs for later use.

Maximizing adherence: As discussed in **Adherence to Antiretroviral Therapy in HIV-Infected Children and Adolescents**, lack of adherence to prescribed regimens can lead to subtherapeutic levels of antiretroviral medications, which enhances the risk of the development of drug resistance and likelihood of virologic failure. Participation by the caregivers and child in the decision-making process is crucial. Issues related to adherence to therapy should be fully assessed, discussed, and addressed with the child's caregiver and the child (when age appropriate) before the decision to initiate therapy is made. Potential problems should be identified and resolved prior to starting therapy, even if this delays initiation of therapy. Additionally, frequent follow-up is important to provide assessment of virologic response to therapy, drug intolerance, viral resistance, and adherence. Finally, in patients who experience virologic failure, it is critical to fully assess adherence before making changes to the antiretroviral regimen.

Table 6. 1994 Revised Human Immunodeficiency Virus Pediatric Classification System: Clinical Categories*

Category N: Not Symptomatic

Children who have no signs or symptoms considered to be the result of HIV infection or who have only one of the conditions listed in category A.

Category A: Mildly Symptomatic

Children with **two** or more of the following conditions but none of the conditions listed in Categories B and C:

- Lymphadenopathy (≥0.5 cm at more than two sites; bilateral = one site)
- Hepatomegaly
- Splenomegaly
- Dermatitis
- Parotitis
- Recurrent or persistent upper respiratory infection, sinusitis, or otitis media

Category B: Moderately Symptomatic

Children who have symptomatic conditions, other than those listed for Category A or Category C, that are attributed to HIV infection. Examples of conditions in Clinical Category B include, but are not limited to, the following:

- Anemia (<8 gm/dL), neutropenia (<1,000 cells/mm^3), or thrombocytopenia (<100,000 cells/mm^3) persisting ≥30 days
- Bacterial meningitis, pneumonia, or sepsis (single episode)
- Candidiasis, oropharyngeal (i.e., thrush) persisting for >2 months in children age >6 months
- Cardiomyopathy
- Cytomegalovirus infection with onset before age 1 month
- Diarrhea, recurrent or chronic
- Hepatitis
- Herpes simplex virus (HSV) stomatitis, recurrent (i.e., more than two episodes within 1 year)
- HSV bronchitis, pneumonitis, or esophagitis with onset before age 1 month
- Herpes zoster (i.e., shingles) involving at least two distinct episodes or more than one dermatome
- Leiomyosarcoma
- Lymphoid interstitial pneumonia (LIP) or pulmonary lymphoid hyperplasia complex
- Nephropathy
- Nocardiosis
- Fever lasting >1 month
- Toxoplasmosis with onset before age 1 month
- Varicella, disseminated (i.e., complicated chickenpox)

Category C: Severely Symptomatic

Children who have any condition listed in the 1987 surveillance case definition for acquired immunodeficiency syndrome (below), with the exception of LIP (which is a Category B condition):

- Serious bacterial infections, multiple or recurrent (i.e., any combination of at least two culture-confirmed infections within a 2-year period), of the following types: septicemia, pneumonia, meningitis, bone or joint infection, or abscess of an internal organ or body cavity (excluding otitis media, superficial skin or mucosal abscesses, and indwelling catheter-related infections)
- Candidiasis, esophageal or pulmonary (bronchi, trachea, lungs)
- Coccidioidomycosis, disseminated (at site other than or in addition to lungs or cervical or hilar lymph nodes)
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis or isosporiasis with diarrhea persisting >1 month
- Cytomegalovirus disease with onset of symptoms at age >1 month (at a site other than liver, spleen, or lymph nodes)
- Encephalopathy (at least one of the following progressive findings present for at least 2 months in the absence of a concurrent illness other than HIV infection that could explain the findings): a) failure to attain or loss of developmental milestones or loss of intellectual ability, verified by standard developmental scale or neuropsychological tests; b) impaired brain growth or acquired microcephaly demonstrated by head circumference measurements or brain atrophy demonstrated by computerized tomography or magnetic resonance imaging (serial imaging is required for children <2 years of age); c) acquired symmetric motor deficit manifested by two or more of the following: paresis, pathologic reflexes, ataxia, or gait disturbance
- Herpes simplex virus infection causing a mucocutaneous ulcer that persists for >1 month or bronchitis, pneumonitis, or esophagitis for any duration affecting a child >1 month of age
- Histoplasmosis, disseminated (at a site other than or in addition to lungs or cervical or hilar lymph nodes)
- Kaposi's sarcoma
- Lymphoma, primary, in brain
- Lymphoma, small, noncleaved cell (Burkitt's), or immunoblastic or large cell lymphoma of B-cell or unknown immunologic phenotype
- Mycobacterium tuberculosis, disseminated or extrapulmonary
- Mycobacterium, other species or unidentified species, disseminated (at a site other than or in addition to lungs, skin, or cervical or hilar lymph nodes)
- *Mycobacterium avium* complex or *Mycobacterium kansasii*, disseminated (at site other than or in addition to lungs, skin, or cervical or hilar lymph nodes)
- *Pneumocystis jiroveci* pneumonia
- Progressive multifocal leukoencephalopathy
- Salmonella (nontyphoid) septicemia, recurrent
- Toxoplasmosis of the brain with onset at >1 month of age
- Wasting syndrome in the absence of a concurrent illness other than HIV infection that could explain the following findings: a) persistent weight loss >10% of baseline; OR b) downward crossing of at least two of the following percentile lines on the weight-for-age chart (e.g., 95th, 75th, 50th, 25th, 5th) in a child ≥1 year of age; OR c) <5th percentile on weight-for-height chart on two consecutive measurements, ≥30 days apart **PLUS** 1) chronic diarrhea (i.e., ≥ two loose stools per day for >30 days), **OR** 2) documented fever (for ≥30 days, intermittent or constant)

* Centers for Disease Control and Prevention. 1994 Revised classification system for human immunodeficiency virus infection in children less than 13 years of age. *MMWR*, 1994. 43 (No. RR-12): p. 1–10.

References

1. Butler KM, Husson RN, Balis FM, et al. Dideoxyinosine in children with symptomatic human immunodeficiency virus infection. *N Engl J Med.* 1991;324(3):137-144.
2. Lewis LL, Venzon D, Church J, et al. Lamivudine in children with human immunodeficiency virus infection: a phase I/II study. The National Cancer Institute Pediatric Branch-Human Immunodeficiency Virus Working Group. *J Infect Dis.* 1996;174(1):16-25.
3. McKinney RE, Jr., Maha MA, Connor EM, et al. A multicenter trial of oral zidovudine in children with advanced human immunodeficiency virus disease. The Protocol 043 Study Group. *N Engl J Med.* 1991;324(15):1018-1025.
4. Pizzo PA, Eddy J, Falloon J, et al. Effect of continuous intravenous infusion of zidovudine (AZT) in children with symptomatic HIV infection. *N Engl J Med.* 1988;319(14):889-896.
5. Resino S, Resino R, Micheloud D, et al. Long-term effects of highly active antiretroviral therapy in pretreated, vertically HIV type 1-infected children: 6 years of follow-up. *Clin Infect Dis.* 2006;42(6):862-869.
6. Lindsey JC, Malee KM, Brouwers P, et al. Neurodevelopmental functioning in HIV-infected infants and young children before and after the introduction of protease inhibitor-based highly active antiretroviral therapy. *Pediatrics.* 2007;119(3):e681-693.
7. Nachman SA, Lindsey JC, Moye J, et al. Growth of human immunodeficiency virus-infected children receiving highly active antiretroviral therapy. *Pediatr Infect Dis J.* 2005;24(4):352-357.
8. Paediatric European Network for Treatment of Aids (PENTA). Five year follow up of vertically HIV infected children in a randomised double blind controlled trial of immediate versus deferred zidovudine: the PENTA 1 trial. *Arch Dis Child.* 2001;84(3):230-236.
9. Storm DS, Boland MG, Gortmaker SL, et al. Protease inhibitor combination therapy, severity of illness, and quality of life among children with perinatally acquired HIV-1 infection. *Pediatrics.* 2005;115(2):e173-182.
10. Viani RM, Araneta MR, Deville JG, et al. Decrease in hospitalization and mortality rates among children with perinatally acquired HIV type 1 infection receiving highly active antiretroviral therapy. *Clin Infect Dis.* 2004;39(5):725-731.
11. Brady MT, Oleske JM, Williams PL, et al. Declines in mortality rates and changes in causes of death in HIV-1-infected children during the HAART era. *J Acquir Immune Defic Syndr.* 2010;53(1):86-94.
12. Judd A, Doerholt K, Tookey PA, et al. Morbidity, mortality, and response to treatment by children in the United Kingdom and Ireland with perinatally acquired HIV infection during 1996-2006: planning for teenage and adult care. *Clin Infect Dis.* 2007;45(7):918-924.
13. Van Dyke RB, Wang L, Williams PL. Toxicities associated with dual nucleoside reverse-transcriptase inhibitor regimens in HIV-infected children. *J Infect Dis.* 2008;198(11):1599-1608.
14. Aurpibul L, Puthanakit T, Lee B, et al. Lipodystrophy and metabolic changes in HIV-infected children on non-nucleoside reverse transcriptase inhibitor-based antiretroviral therapy. *Antivir Ther.* 2007;12(8):1247-1254.
15. Delaugerre C, Chaix ML, Blanche S, et al. Perinatal acquisition of drug-resistant HIV-1 infection: mechanisms and long-term outcome. *Retrovirology.* 2009;6:85.
16. Persaud D, Palumbo P, Ziemniak C, et al. Early archiving and predominance of nonnucleoside reverse transcriptase inhibitor-resistant HIV-1 among recently infected infants born in the United States. *J Infect Dis.* 2007;195(10):1402-1410.
17. Centers for Disease Control and Prevention (CDC). 1994 revised classification system for human immunodeficiency virus infection in children less than 13 years of age. *MMWR.* 1994;43(RR-12):1-10.
18. Schneider E, Whitmore S, Glynn KM, et al. Revised surveillance case definitions for HIV infection among adults, adolescents, and children aged <18 months and for HIV infection and AIDS among children aged 18 months to <13 years--United States, 2008. *MMWR Recomm Rep.* 2008;57(RR-10):1-12.
19. Persaud D, Siberry GK, Ahonkhai A, et al. Continued production of drug-sensitive human immunodeficiency virus type 1 in children on combination antiretroviral therapy who have undetectable viral loads. *J Virol.* 2004;78(2):968-979.
20. Pomerantz RJ. Residual HIV-1 infection during antiretroviral therapy: the challenge of viral persistence. *AIDS.* 2001;15(10):1201-1211.
21. Saitoh A, Hsia K, Fenton T, et al. Persistence of human immunodeficiency virus (HIV) type 1 DNA in peripheral blood despite prolonged suppression of plasma HIV-1 RNA in children. *J Infect Dis.* 2002;185(10):1409-1416.

When to Initiate Therapy in Antiretroviral-Naïve Children (Updated August 16, 2010)

The choice of whether to start therapy early, while an individual is still asymptomatic, versus delaying therapy until clinical or immunologic deterioration occurs continues to generate considerable controversy among HIV experts. Some experts favor starting aggressive therapy in the early stages of HIV infection in the hope that early antiretroviral intervention will control viral replication prior to the onset of rapid genetic mutation and evolution into multiple quasi-species. This could result in a lower viral set point, fewer mutant viral strains, and potentially less drug resistance. Early therapy would slow immune system destruction and preserve immune function, preventing clinical disease progression. On the other hand, delaying therapy until later in the course of HIV infection, when clinical or immunologic symptoms appear, may result in reduced evolution of drug-resistant virus due to a lack of drug selection pressure, greater adherence to the therapeutic regimen when the patient is symptomatic rather than asymptomatic, and reduced or delayed adverse effects of antiretroviral therapy.

Recommendations for when to initiate therapy have generally been more aggressive in children than adults because HIV infection is primarily transmitted from mother to child, thereby allowing identification of the timing of infection in children; HIV disease progression in children is more rapid than in adults; and laboratory parameters are less predictive of risk of disease progression in children, particularly for young infants. As discussed in **Laboratory Monitoring of Pediatric HIV Infection**, CD4 count and HIV RNA values vary considerably by age in children, and both markers are poorly predictive of disease progression and mortality in children younger than 12 months. Hence, recommendations for when to start therapy differ by age of the child. As discussed earlier, in the HIV Pediatric Prognostic Markers Collaborative Study meta-analysis, CD4 percentage and HIV RNA levels were both independently predictive of the risk of clinical progression or death in children older than 12 months, although CD4 percentage was a stronger predictor of risk than HIV RNA levels *[1]*. Based on data showing that surrogate marker-based risk of progression varies considerably by age but that CD4 count-associated risk of progression in children age 5 years or older is similar to young adults, the Panel has moved to recommendations for three age bands for initiation of treatment: infants younger than age 12 months, children age 1 to <5 years, and children and adolescents age ≥5 years.

ANTIRETROVIRAL-NAÏVE HIV-INFECTED INFANTS YOUNGER THAN AGE 12 MONTHS

Panel's Recommendations (Table 7):

- ***Initiation of antiretroviral therapy is recommended for infants age <12 months, regardless of clinical status, CD4 percentage, or viral load (AI).***
- ***Issues associated with adherence must be fully assessed and discussed with the HIV-infected infant's caregivers before therapy is initiated (AIII).***

Data from the South African CHER Trial (Children with HIV Early Antiretroviral Therapy) demonstrated that initiation of triple-drug antiretroviral therapy prior to 12 weeks of age in asymptomatic perinatally infected children with normal CD4 percentage (CD4 >25%), compared with waiting to start treatment until the child met clinical or immune criteria, resulted in a 75% reduction in early mortality*[2]*. Most of the deaths in the children in the delayed arm occurred in the first 6 months after study entry. Because the risk of rapid progression is so high in young infants and based on the data from the CHER study, the Panel recommends initiation of therapy for all infants age <12 months regardless of clinical status, CD4 percentage, or viral load (**Table 7**). It is critical that issues associated with adherence are fully assessed and discussed with the HIV-infected infant's caregivers and addressed before therapy is initiated.

The risk of disease progression is inversely correlated with the age of the child, with the youngest children at greatest risk of rapid disease progression. Progression to moderate or severe immune suppression is also frequent in infected infants; by 12 months of age, approximately 50% of children develop moderate immune suppression and 20% develop severe immune suppression *[3]*. In the HIV Pediatric Prognostic Markers Collaborative Study meta-analysis, the 1-year risk of AIDS or death was substantially higher in younger than in older children at any given level of CD4 percentage, particularly for infants age <12 months *[4]*. Unfortunately, although the risk of progression is greatest in the first year of life, the ability to differentiate children at risk of rapid versus slower disease progression by clinical and laboratory parameters is also most limited in young infants. No specific "at-risk" viral or immunologic threshold can be easily identified, and progression of HIV disease and opportunistic infections can occur in young infants with normal CD4 counts *[4]*.

Identification of HIV infection during the first few months of life permits clinicians to initiate antiretroviral therapy during the initial phases of primary infection. Data from a number of observational studies in the United States and Europe suggest that infants who receive early treatment are less likely to progress to AIDS or death than those who started therapy later. Analyses from a prospective study of 360 HIV-infected children in the United States (Perinatal AIDS Collaborative Transmission Study [PACTS]) showed that infants who received early treatment (prior to age 2 years, with nearly half starting in the first year of life) were significantly less likely to progress to AIDS or death compared with those who received no therapy, adjusting for year of birth and maternal disease factors *[5]*. In the European Infant Collaboration Group, starting antiretroviral therapy before the age of 3 months was associated with a significant reduction in progression to AIDS or death compared with deferring therapy *[6]*. In an analysis from the European Collaborative Study, HIV-infected children who initiated potent therapy before age 5 months were more likely to achieve CD4 recovery (defined as 20% increase in CD4 *z* score) than children initiating therapy at older ages *[7]*.

Several small studies have demonstrated that despite the very high levels of viral replication in perinatally infected infants, early initiation of treatment can result in durable viral suppression and normalization of immunologic responses to non-HIV antigens in some infants. In infants with sustained control of plasma viremia, there has also been lack of detection of extra-chromosomal replication intermediates, suggesting near-complete control of viral replication. Some of these infants have become HIV seronegative and have lost HIV-specific immune responses. However, therapy is not curative; proviral HIV-1 DNA continues to be detectable in peripheral blood lymphocytes and viral replication resumes if therapy is discontinued *[8-9]*.

There are, however, potential problems with treatment of asymptomatic infants. Virologic suppression may take longer in young children (given their higher viral load at the time of initiation of therapy) than in older children or adults *[10]*, and the rates of virologic failure with therapy started early in life may be higher than when started later *[11]*. Incomplete viral suppression can lead to the development of drug resistance and compromise future treatment options *[12]*. Possible reasons for the poor response in infants include very high viral loads in young infants, inadequate antiretroviral drug levels, and poor adherence due to the difficulties in administering complex regimens to infants. However, with currently available drug regimens, rates of viral suppression of 70%–80% have been reported in HIV-infected infants initiating therapy at age <12 months *[13-15]*. In a 5-year follow-up study of 40 HIV-infected children who initiated treatment at age <6 months, 98% had CD4 >25% and 78% had undetectable viral load with median follow-up of 5.96 years *[13]*.

Information on appropriate drug dosing in infants younger than age 3–6 months is limited. Hepatic and renal functions are immature in the newborn undergoing rapid maturational changes during the first few months of life which can result in substantial differences in antiretroviral dose requirements between young infants and older children. When drug concentrations are subtherapeutic, either because of inadequate dosing, poor absorption, or incomplete adherence, antiretroviral drug resistance can develop rapidly, particularly in the setting of high levels of viral replication in young infants. It is particularly critical to discuss fully the importance of treatment adherence with the caregivers and to identify and resolve potential problems prior to initiation of therapy, even if this delays starting treatment. Frequent follow-up and continued assessment and support of adherence are especially important in the treatment of young infants (see **Adherence to Antiretroviral Therapy in HIV-Infected Children and Adolescents**).

Finally, the possibility of toxicities—such as lipodystrophy, dyslipidemia, glucose intolerance, osteopenia, and mitochondrial dysfunction—with prolonged therapy is a concern *[16]*. Concerns about toxicities are particularly relevant because life-long administration of therapy may be necessary. Whether it might be possible to stop therapy begun in early infancy after a defined period of treatment (e.g., 1–2 years) that protected the child during the period of greatest risk of HIV disease progression and mortality, and then restart therapy when the child meets standard age-related criteria, is under assessment in clinical trials in South Africa and Kenya.

ANTIRETROVIRAL-NAÏVE HIV-INFECTED CHILDREN AGE 1 YEAR OR OLDER

Panel's Recommendations (Table 7):

- ***Initiation of antiretroviral therapy is recommended for children age ≥1 year with AIDS or significant symptoms (Clinical Category C or most Clinical Category B conditions), regardless of CD4 percentage/count or plasma HIV RNA level (AI*).***
- ***Initiation of antiretroviral therapy is also recommended for children age ≥1 year who have met the age-related CD4 threshold for initiating treatment (CD4 <25% for children age 1 to <5 years (AII) and <350 cells/mm^3 for children age ≥5 years (AI*), regardless of symptoms or plasma HIV RNA level).***
- ***Initiation of antiretroviral therapy is also recommended for children age ≥1 year who are asymptomatic or have mild symptoms (Clinical Categories N and A or the following Clinical Category B conditions: single episode of serious bacterial infection or lymphoid interstitial pneumonitis) and have CD4 ≥25% for children age 1 to <5 years or ≥350 cells/mm^3 for children age ≥5 years and have plasma HIV RNA ≥100,000 copies/mL (BII).***
- ***Initiation of antiretroviral therapy may be considered or deferred for children age ≥1 year who are asymptomatic or have mild symptoms and who have CD4 ≥25% for children age 1 to <5 years and ≥350 cells/mm^3 for children age ≥5 years and have plasma HIV RNA <100,000 copies/mL (CIII).***

The risk of disease progression slows in children age ≥1 year. It is clear that children with clinical AIDS or significant symptoms (Clinical Category C or B—**Table 6**) *[17]* are at high risk of disease progression and death; treatment is recommended by the Panel for all such children, regardless of immunologic or virologic status. However, children age ≥1 year with mild clinical symptoms (Clinical Category A) or who are asymptomatic (Clinical Category N) are at lower risk of disease progression than those with more severe clinical symptoms *[18]*. It should also be noted that some Clinical Category B conditions—a single episode of serious bacterial infection or lymphoid interstitial pneumonitis—are less prognostic of the risk of disease progression. Consideration of CD4 count and viral load may be useful in determining the need for therapy in children with these conditions.

In adults, considerations related to initiation of antiretroviral therapy are based primarily on risk of disease progression as determined by baseline CD4 count *[19]*. In adults, both clinical trial and observational data support initiation of treatment in individuals with CD4 count <350 cells/mm^3. In HIV-infected adults in Haiti, a randomized clinical trial found significant reductions in mortality and morbidity with initiation of treatment when CD4 count fell to <350 cells/mm^3 compared with deferring treatment until CD4 count fell to <200 cell/mm^3*[20]*. In observational data in adults, a collaborative analysis of data from 12 adult cohorts in North America and Europe on 20,379 adults starting treatment between 1995 and 2003, the risk of AIDS or death was significantly less in those who started treatment with CD4 count of 200–350 cells/mm^3 compared with those who started at <200 cells/mm^3 *[21]*.

There are no randomized trial data to address the comparative efficacy of starting versus deferring treatment at higher CD4 thresholds in HIV-infected adults or children. Two observational studies in adults, the ART Cohort Collaboration (ART-CC) and NA-Accord, suggest a higher rate of progression to AIDS or death in patients deferring treatment until CD4 count <350 cells/mm^3 compared with starting when CD4 count was 351 to 450–500 cells/mm^3 *[22-23]*. However, although the relative risk was increased, the overall number of events was small. The NA-Accord study demonstrated a benefit of starting treatment when CD4 count was >500 cell/mm^3

compared with starting when CD4 fell below this threshold *[22]*; however the ART-CC cohort found no additional benefit for patients starting antiretroviral therapy with CD4 counts greater than 450 cells/mm^3 *[23]*. The HHS Adult Antiretroviral Guidelines Panel was split on recommendations regarding starting therapy in HIV-infected adults with CD4 count 350–500 cells/mm^3 (moderate to strong recommendation) and >500 cells/mm^3 (moderate recommendation to optional) *[19]*.

In children, the prognostic significance of a specific CD4 percentage or count varies with age *[4, 24]*. Data from pediatric studies also suggest the immune response to treatment in children is better when treatment is initiated at higher CD4 percentage/count levels *[11, 25]*. In data from the HIV Pediatric Prognostic Markers Collaborative Study meta-analysis, derived from 3,941 children with 7,297 child-years of follow-up, the risk of mortality or progression to AIDS per 100 child-years is significantly higher for any given CD4 count among children age 1–4 years than among children age ≥5 years (**Tables 3–4** and **Figures 1–2**). Data from the HIV Pediatric Prognostic Markers Collaborative Study suggest that absolute CD4 cell count is a useful prognostic marker for disease progression in children age ≥5 years, in whom the estimated risk of disease progression increases when the count falls below 350 cells/mm^3, similar to data in adults (**Table 4**) *[1, 4]*. For children age 1 to <5 years, a similar increase in risk of AIDS or death is seen when CD4 percentage drops below 25% (**Table 3**).

The level of plasma HIV RNA may provide useful information in terms of risk of progression, although its prognostic significance is weaker than CD4 count *[4]*. Several studies have shown that older children with HIV RNA levels ≥100,000 copies/mL are at high risk of mortality *[26-27]*; similar data have been reported in adults *[28]*. Similarly, in the HIV Pediatric Prognostic Markers Collaborative Study meta-analysis, the 1-year risk of progression to AIDS or death rose sharply for children age >1 year when HIV RNA levels were ≥100,000 copies/mL (**Table 3** and **Figures 4–5**) *[4]*. For example, the estimated 1-year risk of death was 2–3 times higher in children with plasma HIV RNA of 100,000 copies/mL compared with 10,000 copies/mL and 8–10 times higher if plasma HIV RNA was >1,000,000 copies/mL.

Based on these data, the Panel has the following recommendations for treatment of children age 1 to <5 years. Initiation of antiretroviral therapy is recommended for children age 1 to <5 years who have AIDS or significant HIV-related symptoms (CDC Clinical Categories C and B, except for the following Category B conditions: single episode of serious bacterial infection or lymphoid interstitial pneumonitis [**Table 6**]), regardless of CD4 percentage/count or HIV RNA level. Additionally, treatment is recommended for children in this age group if they have a CD4 percentage <25%, regardless of clinical symptoms or HIV RNA level. Treatment is also recommended for children who are asymptomatic or have mild symptoms (Clinical Categories N and A, or Clinical Category B disease due to a single episode of serious bacterial infection or lymphoid interstitial pneumonitis [**Table 6**]) with CD4 percentage ≥25% if plasma HIV RNA is >100,000 copies/mL. Antiretroviral therapy may be considered or deferred in asymptomatic children age 1 to <5 years who have CD4 ≥25% and who also have plasma HIV RNA levels <100,000 copies/mL.

For children who are age 5 years or older, initiation of antiretroviral therapy is recommended if they have AIDS or significant HIV-related symptoms (CDC Clinical Categories C and B, except for the following Category B conditions: single episode of serious bacterial infection or lymphoid interstitial pneumonitis [**Table 6**]), regardless of CD4 percentage/count or HIV RNA level. Additionally, treatment is recommended for children in this age group if they have CD4 <350 cells/mm^3, regardless of clinical symptoms or HIV RNA level. Treatment is also recommended for children who are asymptomatic or have mild symptoms (Clinical Categories N and A, or Clinical Category B disease due to a single episode of serious bacterial infection or lymphoid interstitial pneumonitis [**Table 6**]) with CD4 ≥350 cells/mm^3 if HIV RNA is >100,000 copies/mL. Antiretroviral therapy may be considered or deferred for asymptomatic or mildly symptomatic children age ≥5 years who have CD4 ≥350 cells/mm^3 and who also have plasma HIV RNA levels <100,000 copies/mL.

If therapy is deferred, the health care provider should closely monitor virologic, immunologic, and clinical status (see **Laboratory Monitoring of Pediatric HIV Infection**). Factors to consider in deciding when to initiate therapy in children in whom treatment was deferred include:

- Increasing HIV RNA levels (e.g., HIV RNA levels approaching 100,000 copies/mL);
- Rapidly declining CD4 count or percentage to values approaching the age-related threshold for consideration of therapy;
- Development of clinical symptoms; and
- The ability of caregiver and child to adhere to the prescribed regimen.

Table 7. Indications for Initiation of Antiretroviral Therapy in HIV-Infected Children

This table provides general guidance rather than absolute recommendations for an individual patient. Factors to be considered in decisions about initiation of therapy include the risk of disease progression as determined by CD4 percentage or count and plasma HIV RNA copy number, the potential benefits and risks of therapy, and the ability of the caregiver to adhere to administration of the therapeutic regimen. Issues associated with adherence should be fully assessed, discussed, and addressed with the child, if age appropriate, and the caregiver before the decision to initiate therapy is made.

Age	Criteria	Recommendation
<12 months	• Regardless of clinical symptoms, immune status, or viral load	*Treat (AI)*
1–<5 years	• AIDS or significant HIV-related symptoms[1]	*Treat (AI*)*
	• CD4 <25%, regardless of symptoms or HIV RNA level	*Treat (AII)*
	• Asymptomatic or mild symptoms[2] *and* o CD4 ≥25% *and* o HIV RNA ≥100,000 copies/mL	*Treat (BII)*
	• Asymptomatic or mild symptoms[2] *and* o CD4 ≥25% *and* o HIV RNA <100,000 copies/mL	*Consider or Defer*[3] *(CIII)*
≥5 years	• AIDS or significant HIV-related symptoms[1]	*Treat (AI*)*
	• CD4 <350 cells/mm^3	*Treat (AI*)*
	• Asymptomatic or mild symptoms[2] *and* o CD4 ≥350 cells/mm^3 *and* o HIV RNA ≥100,000 copies/mL	*Treat (BII)*
	• Asymptomatic or mild symptoms[2] *and* o CD4 ≥350 cells/mm^3 *and* o HIV RNA <100,000 copies/mL	*Consider or Defer*[3] *(CIII)*

[1] CDC Clinical Categories C and B (except for the following Category B conditions: single episode of serious bacterial infection or lymphoid interstitial pneumonitis)

[2] CDC Clinical Category A or N or the following Category B conditions: single episode of serious bacterial infection or lymphoid interstitial pneumonitis

[3] Clinical and laboratory data should be re-evaluated every 3 to 4 months.

References

1. Dunn D, Woodburn P, Duong T, et al. Current CD4 cell count and the short-term risk of AIDS and death before the availability of effective antiretroviral therapy in HIV-infected children and adults. *J Infect Dis.* 2008;197(3):398-404.
2. Violari A, Cotton MF, Gibb DM, et al. Early antiretroviral therapy and mortality among HIV-infected infants. *N Engl J Med.* 2008;359(21):2233-2244.
3. Gray L, Newell ML, Thorne C, et al. Fluctuations in symptoms in human immunodeficiency virus-infected children: the first 10 years of life. *Pediatrics.* 2001;108(1):116-122.
4. HIV Paediatric Prognostic Markers Collaborative Study. Predictive value of absolute CD4 cell count for disease progression in untreated HIV-1-infected children. *AIDS.* 2006;20(9):1289-1294.
5. Abrams EJ, Wiener J, Carter R, et al. Maternal health factors and early pediatric antiretroviral therapy influence the rate of perinatal HIV-1 disease progression in children. *AIDS.* 2003;17(6):867-877.
6. Goetghebuer T, Haelterman E, Le Chenadec J, et al. Effect of early antiretroviral therapy on the risk of AIDS/death in HIV-infected infants. *AIDS.* 2009;23(5):597-604.
7. Newell ML, Patel D, Goetghebuer T, et al. CD4 cell response to antiretroviral therapy in children with vertically acquired HIV infection: is it associated with age at initiation? *J Infect Dis.* 2006;193(7):954-962.
8. Persaud D, Siberry GK, Ahonkhai A, et al. Continued production of drug-sensitive human immunodeficiency virus type 1 in children on combination antiretroviral therapy who have undetectable viral loads. *J Virol.* 2004;78(2):968-979.
9. Saitoh A, Hsia K, Fenton T, et al. Persistence of human immunodeficiency virus (HIV) type 1 DNA in peripheral blood despite prolonged suppression of plasma HIV-1 RNA in children. *J Infect Dis.* 2002;185(10):1409-1416.
10. Chadwick EG, Capparelli EV, Yogev R, et al. Pharmacokinetics, safety and efficacy of lopinavir/ritonavir in infants less than 6 months of age: 24 week results. *AIDS.* 2008;22(2):249-255.
11. Walker AS, Doerholt K, Sharland M, et al. Response to highly active antiretroviral therapy varies with age: the UK and Ireland Collaborative HIV Paediatric Study. *AIDS.* 2004;18(14):1915-1924.
12. Aboulker JP, Babiker A, Chaix ML, et al. Highly active antiretroviral therapy started in infants under 3 months of age: 72-week follow-up for CD4 cell count, viral load and drug resistance outcome. *AIDS.* 2004;18(2):237-245.
13. Chiappini E, Galli L, Tovo PA, et al. Five-year follow-up of children with perinatal HIV-1 infection receiving early highly active antiretroviral therapy. *BMC Infect Dis.* 2009;9:140.
14. Chadwick EG, Pinto J, Yogev R, et al. Early initiation of lopinavir/ritonavir in infants less than 6 weeks of age: pharmacokinetics and 24-week safety and efficacy. *Pediatr Infect Dis J.* 2009;28(3):215-219.
15. Van der Linden D, Hainaut M, Goetghebuer T, et al. Effectiveness of early initiation of protease inhibitor-sparing antiretroviral regimen in human immunodeficiency virus-1 vertically infected infants. *Pediatr Infect Dis J.* 2007;26(4):359-361.
16. Aurpibul L, Puthanakit T, Lee B, et al. Lipodystrophy and metabolic changes in HIV-infected children on non-nucleoside reverse transcriptase inhibitor-based antiretroviral therapy. *Antivir Ther.* 2007;12(8):1247-1254.
17. Centers for Disease Control and Prevention (CDC). 1994 revised classification system for human immunodeficiency virus infection in children less than 13 years of age. *MMWR.* 1994;43(RR-12):1-10.
18. Galli L, de Martino M, Tovo PA, et al. Predictive value of the HIV paediatric classification system for the long-term course of perinatally infected children. *Int J Epidemiol.* 2000;29(3):573-578.
19. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. December 1, 2009:1-161. http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf.
20. Severe P, Pape J, Fitzgerald D, et al. A randomized clinical trial of early versus standard antiretroviral therapy for HIV-infected patients with a CD4 T cell count of 200 - 350 cells/ml (CIPRAHT001). Paper presented at: Interscience Conference on Antimicrobial Agents and Chemotherapy; September 12-15, 2009; San Francisco, CA.
21. May M, Sterne JA, Sabin C, et al. Prognosis of HIV-1-infected patients up to 5 years after initiation of HAART: collaborative analysis of prospective studies. *AIDS.* 2007;21(9):1185-1197.
22. Kitahata MM, Gange SJ, Abraham AG, et al. Effect of early versus deferred antiretroviral therapy for HIV on survival. *N Engl J Med.* 2009;360(18):1815-1826.
23. Sterne JA, May M, Costagliola D, et al. Timing of initiation of antiretroviral therapy in AIDS-free HIV-1-infected patients: a collaborative analysis of 18 HIV cohort studies. *Lancet.* 2009;373(9672):1352-1363.

24. Dunn D. Short-term risk of disease progression in HIV-1-infected children receiving no antiretroviral therapy or zidovudine monotherapy: a meta-analysis. *Lancet.* 2003;362(9396):1605-1611.
25. Soh CH, Oleske JM, Brady MT, et al. Long-term effects of protease-inhibitor-based combination therapy on CD4 T-cell recovery in HIV-1-infected children and adolescents. *Lancet.* 2003;362(9401):2045-2051.
26. Mofenson LM, Korelitz J, Meyer WA, 3rd, et al. The relationship between serum human immunodeficiency virus type 1 (HIV-1) RNA level, CD4 lymphocyte percent, and long-term mortality risk in HIV-1-infected children. National Institute of Child Health and Human Development Intravenous Immunoglobulin Clinical Trial Study Group. *J Infect Dis.* 1997;175(5):1029-1038.
27. Palumbo PE, Raskino C, Fiscus S, et al. Predictive value of quantitative plasma HIV RNA and CD4+ lymphocyte count in HIV-infected infants and children. *JAMA.* 1998;279(10):756-761.
28. Egger M, May M, Chene G, et al. Prognosis of HIV-1-infected patients starting highly active antiretroviral therapy: a collaborative analysis of prospective studies. *Lancet.* 2002;360(9327):119-129.

What Drugs to Start: Initial Combination Therapy for Antiretroviral-Naïve Children

(Updated August 16, 2010)

Panel's Recommendations:

- ***Antiretroviral drugs initiated for chemoprophylaxis of maternal-child HIV transmission should be discontinued in infants who are identified as HIV infected (AI) and treatment initiated with combination therapy as described below.***
- ***Antiretroviral drug-resistance testing is recommended prior to initiation of therapy in all treatment-naïve children (AII infants; AIII children).***
- ***The goal of therapy in treatment-naïve children is to reduce plasma HIV RNA levels to below the limits of quantitation on ultrasensitive assays and to preserve or normalize immune status (AI).***
- ***Combination therapy with at least three drugs, including either a non-nucleoside reverse transcriptase inhibitor or protease inhibitor plus a dual nucleoside analogue reverse transcriptase inhibitor backbone, is recommended for initial treatment of HIV-infected children (AI).***

GENERAL CONSIDERATIONS

As of August 2010, 22 antiretroviral drugs are approved for use in HIV-infected adults and adolescents; 17 of these have an approved pediatric treatment indication and 15 are available as a pediatric formulation or capsule size. These drugs fall into several major classes: nucleoside analogue or nucleotide analogue reverse transcriptase inhibitors (NRTIs, NtRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), entry inhibitors (including fusion inhibitors and CCR5 antagonists), and integrase inhibitors. Brief information on drug formulation, pediatric dosing, and toxicity for the individual drugs and detailed information on drug interactions can be found in **Appendix B: Pediatric Antiretroviral Drug Information**. It is likely that new drugs and drug combinations that demonstrate sustainable viral load suppression and acceptable toxicity and dosing profiles will become available over time, which will increase treatment options for children.

Combination antiretroviral therapy with at least three drugs from at least two classes of drugs is recommended for initial treatment of infected infants, children, and adolescents because it provides the best opportunity to preserve immune function and delay disease progression *[1-4]*. The goal of antiretroviral therapy is to maximally suppress viral replication, preferably to undetectable levels, for as long as possible while preserving and/or restoring immune function and minimizing drug toxicity. Combination therapy slows disease progression and improves survival, results in a greater and more sustained virologic and immunologic response, and delays development of virus mutations that confer resistance to the drugs being used *[3-5]*.

Because antiretroviral therapy will need to be administered lifelong, considerations related to the choice of initial antiretroviral regimen should also include an understanding of barriers to adherence, including the complexity of schedules and food requirements for different regimens; differing formulations; palatability problems; and potential limitations in subsequent treatment options should resistance develop.

Monotherapy and two-drug therapy with the currently available antiretroviral drugs are not recommended to treat HIV infection *[1, 6]*. Use of zidovudine as a single agent is appropriate only when used in infants of indeterminate HIV status during the first 6 weeks of life to prevent perinatal HIV transmission. Infants confirmed as HIV infected while receiving chemoprophylaxis should have prophylactic antiretroviral drugs discontinued and treatment initiated with a combination regimen of at least 3 drugs (which may include zidovudine as part of the regimen if sensitive). The choice of regimen should be based on results from

antiretroviral drug resistance testing. Treatment should only be initiated following assessment and counseling of the caregivers regarding adherence to therapy *[1, 6]*.

Antiretroviral drug-resistance testing is recommended prior to the initiation of therapy in all treatment-naïve children. Treatment-naïve children with perinatal HIV infection can acquire drug-resistant virus from their mothers (because the mothers were initially infected with drug-resistant virus or acquired drug resistance during treatment or during use of antiretroviral drugs for prevention of mother-to-child transmission of HIV [PMTCT]), or the infant can develop resistance during the period of infant antiretroviral prophylaxis prior to diagnosis of HIV infection. Drug-resistant virus has been identified in 6%–16% of antiretroviral-naïve adults and 18% of behaviorally infected adolescents with recent infection in United States and Europe *[7-11]*. Data from children are limited. In a study in New York State, genotypic drug resistance was identified in 12% of 91 HIV-infected infants born from 1998 to 1999 and 19% of 42 infants born from 2000 to 2001 *[12-13];* detection of resistance in the infants was not signficantly associated with a history of maternal and infant antiretroviral prophylaxis. Similarly, following initiation of treatment, 24% of 21 infants (median age 9.7 weeks) were found to have mutations associated with drug resistance, most of which were not associated with maternal/infant prophylaxis regimens; resistant virus was found to be persistently archived in the resting CD4 cell reservoir *[14]*. Thus, the prevalence of infants infected with antiretroviral drug-resistant virus may be increasing and may not necessarily be predicted by the drug prophylaxis regimen received by the mother. In a recent trial, pretreatment detection of nevirapine resistance mutations was associated with a significantly higher rate of virologic failure of a nevirapine-based regimen among infants exposed to peripartum nevirapine used as maternal-infant prophylaxis *[15]*. For antiretroviral-naïve children beyond infancy, limited available data do not demonstrate that resistance testing prior to initiation of therapy correlates with greater success of initial antiretroviral therapy *[16]*. Nevertheless, the prevalence of resistance in HIV-infected children is sufficiently high that, based on expert opinion, the Panel recommends resistance testing prior to initiation of therapy in all treatment-naïve children and use of resistance testing results to refine selection of drugs for inititial combination therapy, similar to recommendations for HIV-infected adults *[17]*. Infants exposed to peripartum nevirapine as part of maternal-infant prophylaxis should not use nevirapine-based regimens for initial combination therapy, even if baseline resistance testing with standard commercial assays fails to demonstrate mutations associated with nevirapine resistance because the presence of minor resistance variants may be associated with virologic failure of NNRTI-based therapy *[18]*.

REGIMENS RECOMMENDED FOR INITIAL THERAPY OF ANTIRETROVIRAL-NAÏVE CHILDREN (TABLES 8 AND 9)

Criteria Used for Recommendations

There are few randomized, Phase III clinical trials of combination antiretroviral therapy among pediatric patients that provide direct comparison of different treatment regimens; most pediatric drug data come from Phase I/II safety and pharmacokinetic trials and nonrandomized, open-label studies. The Panel reviews both pediatric and adult clinical trial data published in peer-reviewed journals, data prepared by manufacturers for FDA review, and data presented in abstract format at major scientific meetings. In general, even in studies in adults, assessment of efficacy and potency is primarily based on surrogate marker endpoints, such as CD4 cell count and HIV RNA levels. Recommendations on the optimal initial therapy for children are continually being modified as new data become available, new therapies or drug formulations are developed, and late toxicities become recognized.

Criteria used by the Panel for recommending specific drugs or regimens include:

- Data demonstrating durable viral suppression, immunologic improvement, and clinical improvement (when such data are available) with the regimen, preferably in children as well as adults;
- The extent of pediatric experience with the particular drug or regimen;
- Incidence and types of short- and long-term drug toxicity with the regimen, with special attention to toxicity reported in children;

- Availability and acceptability of formulations appropriate for pediatric use, including palatability, ease of preparation (e.g., powders), volume of syrups, and pill size and number;
- Dosing frequency and food and fluid requirements; and
- Potential for drug interactions.

Drugs or drug combinations are classified in one of several categories as follows:

- ***Preferred:*** Drugs or drug combinations are designated as preferred for use in treatment-naïve children when clinical trial data in children or, more often, in adults have demonstrated optimal efficacy and durability with acceptable toxicity and ease of use, and studies have been performed to demonstrate safety and surrogate marker efficacy in children; additional considerations are listed above.
- ***Alternative:*** Drugs or drug combinations are designated as alternatives for initial therapy when clinical trial data in children or adults show efficacy but there are disadvantages compared with preferred regimens in terms of more limited experience in children; the extent of antiviral efficacy or durability is less well defined in children or less than a preferred regimen in adults; there are specific toxicity concerns; or there are dosing, formulation, administration, or interaction issues for that drug or regimen.
- ***Use in Special Circumstances:*** Some drugs or drug combinations are recommended for use as initial therapy only in special circumstances, when preferred or alternative drugs cannot be used.
- ***Not Recommended:*** A list of drugs and drug combinations that are not recommended for initial therapy in children is shown in **Table 9**. These drugs and drug combinations are not recommended either because of inferior virologic response, potential serious safety concerns (including potentially overlapping toxicities), or pharmacologic antagonism.
- ***Insufficient Data to Recommend:*** For a number of drugs and drug combinations approved for use in adults, pharmacokinetic or safety data in children are not available or are too limited to make recommendation on use of the drugs as initial therapy in children. Some of these drugs and drug combinations may be appropriate for consideration in the management of the treatment-experienced child, even though they are not recommended for initial therapy in children (see **Antiretroviral Treatment Failure in Infants, Children, and Adolescents**).

The most extensive clinical trial data on initial therapy regimens in adults and children are available for three types of regimens based on drug class: NNRTI based (two NRTIs plus an NNRTI); PI based (two NRTIs plus a PI); and NRTI only (three NRTI drugs). NNRTI- or PI-based regimens are preferred for initial therapy; decisions about which type of regimen to choose should be individualized based on patient characterisitics. Each class-based regimen has advantages and disadvantages that are delineated in more detail in the sections that follow and in **Tables 10–13**.

Choice of NNRTI- Versus PI-Based Initial Regimens for Children Younger Than 3 Years of Age

One special scenario is the choice of initial therapy for children < 3 years of age. The only preferred regimens for children < 3 years are coformulated lopinavir/ritonavir-based therapy and nevirapine-based therapy. Infants exposed to nevirapine in the peripertum period as part of PMTCT strategy should not be treated with nevirapine-based combination therapy because of the established higher risk of treatment failure due to nevirapine resistance *[15, 19]*, and lopinavir/ritonavir-based combination therapy would be the only recommended, preferred initial regimen. In addition, many experts in the United States recommend coformulated lopinavir/ritonavir-based therapy over nevirapine-based therapy even in the absence of peripartum nevirapine exposure because of concern about greater potential hepatotoxicity, lower barrier to resistance, and higher rate of virologic failure with nevirapine compared with lopinavir/ritonavir *[20-22]*. However, evidence is lacking for increased toxicity of nevirapine compared with lopinavir/ritonavir in infants *[15]* and some experts prefer nevirapine-based therapy because of the poor palatability of liquid lopinavir/ritonavir. Ongoing studies are expected to provide clearer evidence about the relative superiority of NNRTI- versus PI-based regimens in infants and children.

PREFERRED REGIMENS FOR INITIAL THERAPY OF CHILDREN (TABLE 8)

NNRTI-Based Regimens (one NNRTI + two-NRTI backbone)

Panel's Recommendations:

- ***Preferred NNRTI:***
  - ***Nevirapine in combination with two NRTIs for children age <3 years who have not been exposed to nevirapine as part of maternal-infant prophylaxis or who require a liquid formulation (BI*).***
  - ***Efavirenz in combination with two NRTIs for children age ≥3 years (AI*).***
- ***Alternative NNRTI:***
  - ***Nevirapine in combination with two NRTIs (for children age ≥3 years) (BI*).***

The Panel does not recommend the following NNRTIs as part of initial therapy in children:

- ***Etravirine is not recommended due to lack of pediatric formulation, pediatric pharmacokinetic data, efficacy or safety data in children, and lack of data in antiretroviral-naïve patients (BIII).***
- ***Nevirapine is not recommended for infants exposed to nevirapine as part of maternal-infant prophylaxis (AI).***
- ***Nevirapine is not recommended for postpubertal girls with CD4 count >250/mm^3 (AII*).***
- ***Efavirenz is not recommended for sexually active female adolescents when reliable contraception cannot be assured (BIII).***
- ***Efavirenz is not recommended for children <3 years of age (BIII).***

Summary: NNRTI-Based Regimens

Nevirapine and efavirenz both have an approved pediatric indication. Nevirapine is available in a liquid formulation, but efavirenz is not available in a liquid formulation in the United States. Advantages and disadvantages of different NNRTI drugs are delineated in **Table 11**. Use of NNRTIs as initial therapy preserves the PI class for future use, and less dyslipidemia and fat maldistribution have been reported with the NNRTI class than with the PI class. Additionally, there is generally a lower pill burden with these agents when compared with PI-based regimens for children taking solid formulations. The major disadvantages of the current NNRTI drugs approved for use in children arethat a single viral mutation can confer drug resistance, and cross resistance develops between nevirapine and efavirenz. In infants exposed to nevirapine as part of PMTCT, higher virologic failure rates have been demonstrated with nevirapine-based regimens compared with lopinavir/ritonavir-based regimens *[15]*. Rare but serious and potentially life-threatening skin and hepatic toxicity can occur with all drugs in this class, but is most frequent with nevirapine, at least in HIV-infected adults. NNRTI drugs have the potential for drug interactions due to metabolism via hepatic enzymes; however, these are less frequent than those of boosted PI regimens.

Efavirenz, in combination with two NRTIs, is the preferred NNRTI for initial therapy of children age ≥3 years based on clinical trial experience in children and because higher rates of toxicity have been observed with nevirapine in clinical trials in adults. Results of studies comparing virologic response to nevirapine- versus efavirenz-based regimens in adults are conflicting, and no randomized studies have been done in children. Because nevirapine therapy is associated with the rare occurrence of significant hypersensitivity reactions, including Stevens-Johnson syndrome and rare but potentially life-threatening hepatitis *[23-24]*, nevirapine is recommended as an alternative, rather than a preferred, NNRTI for initial treatment of antiretroviral-naïve children age ≥3 years. In infants and children <3 years who require a liquid NNRTI-based regimen, nevirapine is preferred.

Efavirenz as preferred NNRTI: In clinical trials in HIV-infected adults, a PI-sparing regimen of efavirenz in combination with zidovudine and lamivudine was associated with an excellent virologic response, with 70% of treated individuals having plasma HIV RNA <400 copies/mL at 48 weeks *[25]*. In randomized controlled trials in treatment-naïve adults, superior or similar virologic activity has been demonstrated in efavirenz-treated

patients compared with individuals receiving PI- or triple NRTI-based regimens *[26-29]*. Clinical trials in adults are conflicting in terms of comparative efficacy of efavirenz and nevirapine (see discussion below) *[30-34]*. No comparative trials have been conducted in children. However, an analysis of children and adults starting first-line antiretroviral therapy in Uganda has demonstrated the superiority of an efavirenz-based regimen compared with a nevirapine-based regimen in 222 children and adolescents (mean age, 9.2 years) *[22]*.

Efavirenz has been studied in HIV-infected children in combination with two NRTIs or with an NRTI and a PI *[35-41]*. Results are comparable to those seen in adults. At this time, no pediatric formulation of efavirenz is available in the United States. The appropriate dose of efavirenz for children age <3 years has not been determined, and it is therefore not recommended for this age group. Some clinicians would recommend opening the capsules and adding the contents to food or liquid for children age ≥3 years who cannot swallow pills; however, there are no pharmacokinetic data on use in this fashion and it is not recommended.

The major limitations of efavirenz are central nervous system side effects in both children and adults; reported side effects include fatigue, poor sleeping patterns, vivid dreams, poor concentration, agitation, depression, and suicidal ideation. Although in most patients this toxicity is transient, in some patients the symptoms may persist or occur months after first initiating efavirenz. In several studies, the incidence of such side effects was correlated with efavirenz plasma concentrations and occurred more frequently in adult patients with higher levels of drug *[42-45]*. In patients with pre-existing psychiatric conditions, efavirenz should be used cautiously for initial therapy. Rash may also occur with efavirenz treatment; it is generally mild and transient but appears to be more common in children than adults *[39, 41]*. Additionally, efavirenz is potentially teratogenic to the fetus if taken by a pregnant woman during the first trimester of pregnancy (see **Appendix B: Pediatric Antiretroviral Drug Information** for detailed information). Unless adequate contraception can be ensured, it is not recommended for initial therapy in adolescent females who are sexually active and may become pregnant.

Nevirapine as alternative NNRTI: Nevirapine has extensive clinical and safety experience in HIV-infected children and has shown antiretroviral efficacy in a number of different combination regimens (see **Appendix B: Pediatric Antiretroviral Drug Information** for detailed information) *[46]*. Nevirapine has been studied in HIV-infected children in combination with two NRTIs or with an NRTI and a PI *[47-49]*.

In a large adult trial (2NN trial), although virologic efficacy was comparable between nevirapine and efavirenz (plasma HIV RNA <50 copies/mL at 48 weeks in 56% of those receiving nevirapine vs. 62% of those receiving efavirenz), serious hepatic toxicity was more frequent in the nevirapine arm than the efavirenz arm (hepatic laboratory toxicity in 8%–14% of those on nevirapine, compared with 5% on efavirenz) *[34]*. Other studies in adults have indicated potentially increased risk of hepatic toxicity with nevirapine-based compared with efavirenz-based regimens *[50]*. Additionally, data in adults indicate that symptomatic hepatic toxicity is more frequent in individuals with higher CD4 count and in women, particularly women with CD4 >250 cells/mm^3 and men with CD4 >400 cells/mm^3. This may be less of an issue for prepubertal children. In the published literature, hepatic toxicity appears to be less frequent in children receiving chronic nevirapine therapy than in adults *[48-49, 51]*. In an FDA review of 783 HIV-infected pediatric patients, there was only 1 case of hepatitis, which was reported in a 17-year-old; there was no evidence of a serious hepatic event associated with nevirapine use in any child prior to adolescence *[51]*. In contrast, skin and hypersensitivity reactions have been reported in children *[52]*. The safety of substituting efavirenz for nevirapine in patients who have experienced nevirapine-associated hepatic toxicity is unknown; efavirenz use in this situation has been well tolerated in the very limited number of patients in whom it has been reported but should be attempted with caution *[53]*.

Because of the higher potential for toxicity and possibly an increased risk of virologic failure, nevirapine-based regimens are considered as alternative rather than preferred NNRTI in children age ≥3 years. Because appropriate dosing information for nevirapine in young children is available and there is a liquid formulation, nevirapine is the preferred NNRTI for children who are age <3 years or those who require a liquid formulation. Nevirapine should not be used in infants exposed to nevirapine as part of PMTCT *[15]*. Similar to recommendations in adults, nevirapine also should not be used in postpubertal adolescent girls with CD4

count >250/mm^3 due to the increased risk of symptomatic hepatic toxicity, unless the benefit clearly outweighs the risk *[24]*.

PI-Based Regimens (PIs [boosted or unboosted] + two- NRTI backbone)

Panel's Recommendations:

- ***Preferred PI:***
  - ***Lopinavir/ritonavir in combination with two NRTIs (AI*).***
- ***Alternative PI (listed alphabetically):***
  - ***Atazanavir in combination with low-dose ritonavir and two NRTIs for children age ≥6 years (AI*).***
  - ***Darunavir in combination with low-dose ritonavir and two NRTIs for children ≥6 years (AI*).***
  - ***Fosamprenavir in combination with low-dose ritonavir and two NRTIs for children age ≥6 years (AI*).***
- ***Use in special circumstances:***
  - ***Atazanavir unboosted (for treatment-naïve adolescents age ≥13 years and >39 kg who are unable to tolerate ritonavir) in combination with two NRTIs (unboosted atazanavir should not be used with tenofovir) (BII*).***
  - ***Fosamprenavir unboosted (for children age ≥2 years) in combination with two NRTIs (BIII).***
  - ***Nelfinavir in combination with two NRTIs (for children age >2 years) (BI*).***

The Panel does not recommend including the following PIs in initial therapy in children because of insufficient data, data related to toxicity or potency, or inconvenient dosing:

- ***Indinavir, saquinavir, or tipranavir (AIII).***
- ***Dual (full-dose) PIs (AIII).***
- ***Full-dose ritonavir or use of ritonavir as the sole PI (AIII).***
- ***Unboosted atazanavir in children age <13 years and/or <39 kg (AIII).***
- ***Nelfinavir in children age <2 years (AII).***
- ***Unboosted darunavir (AIII).***
- ***Once-daily dosing of lopinavir/ritonavir, boosted darunavir, or boosted or unboosted fosamprenavir (AII).***

Summary: PI-Based Regimens

Nine PIs are currently approved for use, 7 of which are approved for use in children and have pediatric drug formulations. Advantages and disadvantages of different PIs are delineated in **Table 12**. Advantages of PI-based regimens include excellent virologic potency, high barrier for development of drug resistance (requires multiple mutations), and sparing of the NNRTI drug class. However, the drugs have potential for multiple drug interactions due to metabolism via hepatic enzymes and may be associated with metabolic complications such as dyslipidemia, fat maldistribution, and insulin resistance. Factors to be considered in selecting a PI-based regimen for treatment-naïve children include virologic potency, dosing frequency, pill burden, food or fluid requirements, availability of palatable pediatric formulations, drug interaction profile, toxicity profile (particularly related to metabolic complications), and availability of data in children (see **Table 12** for advantages and disadvantages and **Appendix B: Pediatric Antiretroviral Drug Information** for detailed pediatric information on each drug).

Ritonavir acts as a potent inhibitor of the cytochrome P450 3A4 (CYP3A4) isoenzyme, thereby inhibiting the metabolism of other PIs, and has been used in low doses combined with another PI as a "pharmacokinetic booster," increasing drug exposure by prolonging the second drug's half-life. Boosted PI-based regimens are commonly used in treatment of adults, but adequate pediatric data are only available for coformulated lopinavir/ritonavir in children older than 6 weeks of age *[54]* and for atazanavir, fosamprenavir, darunavir, and

tipranavir with low-dose ritonavir in children age ≥6 years. Additionally, the use of low-dose ritonavir increases the potential for hyperlipidemia *[55]* and drug-drug interactions.

The Panel recommends coformulated lopinavir/ritonavir as the preferred PI for the treatment-naïve child based on virologic potency in adult and pediatric studies, high barrier to development of drug resistance, excellent toxicity profile in adults and children, availability of appropriate dosing information for children as young as age 6 weeks, and extensive experience as initial therapy in both resource-rich and resource-limited areas. However, data comparing the efficacy of lopinavir/ritonavir to other PIs are not available in children. Three PIs can be considered as alternative PIs for use in children age ≥6 years when used in combination with low-dose ritonavir: atazanavir, darunavir, and fosamprenavir. Other PIs that can be considered in special circumstances when preferred and alternative drugs are not available or are not tolerated include fosamprenavir without boosting ritonavir in children age ≥2 years, atazanavir without boosting ritonavir in adolescents age ≥13 years and >39 kg, and nelfinavir in children age ≥2 years. A saquinavir/ritonavir (1,000/100 mg twice daily)-based regimen compared with a lopinavir/ritonavir-based regimen demonstrated comparable virologic and immunologic outcomes when used as initial therapy in treatment-naïve adults *[56]* and is recommended as an alternative PI for initial therapy in the guidelines for adults and adolescents *[24]*. However, saquinavir is not recommended for initial therapy in children because there is no pediatric formulation and there are limited dosing and outcome data in children. Although good virologic and immunologic responses have been observed with indinavir-based regimens in adults, there is no liquid formulation and there has been a high rate of hematuria, sterile leukocyturia, and nephrolithiasis reported in pediatric patients with this drug *[57-60]*. The incidence of hematuria and nephrolithiasis with indinavir therapy may be higher in children than adults *[57, 60]*. Therefore, indinavir alone or with ritonavir boosting is not recommended as initial therapy. Additionally, tipranavir is not recommended for initial therapy at the present time due to limited experience in treatment-naïve children, but it may be considered for use with treatment failure.

Due to the limited data on pharmacokinetics of full-dose dual PI combination regimens in children (e.g., saquinavir plus coformulated lopinavir/ritonavir or plus nelfinavir) *[61-63]*, these combinations are not recommended as initial therapy in children, although they may have utility as components of secondary regimens for children who have failed initial therapy.

Lopinavir/ritonavir as preferred PI: In clinical trials in adults, regimens containing lopinavir/ritonavir plus 2 NRTIs have been found to have potent virologic activity in treatment-naïve patients. In a comparative trial of lopinavir/ritonavir versus nelfinavir (both combined with stavudine/lamivudine), lopinavir/ritonavir had superior virologic efficacy to nelfinavir (plasma HIV RNA <400 copies/mL in 84% vs. 66% of patients, respectively), and drug-resistant virus in patients with detectable plasma viral load at 48 weeks was detected in none of 51 lopinavir/ritonavir-treated patients, compared with 45% of 43 nelfinavir-treated patients *[64-65]*. The rate of toxicity was similar between the groups. Lopinavir/ritonavir has been studied in both antiretroviral-naïve and -experienced children and has demonstrated durable virologic activity and low toxicity *[5, 15, 54, 66-68]*. In a study of 44 treatment-naïve children, 84% had plasma HIV RNA <400 copies/mL and 71% <50 copies/mL after 48 weeks of therapy (see **Appendix B: Pediatric Antiretroviral Drug Information** for detailed information) *[68]*. In addition, dosing and efficacy data in infants as young as 6 weeks of age are available *[5, 54, 69]*. Although once-daily lopinavir/ritonavir is FDA approved for initial therapy in adults, pharmacokinetic data in children do not support a recommendation for once-daily dosing in children *[70-71]*.

Atazanavir with low-dose ritonavir as alternative PI (for children ≥6 years): Atazanavir is a once-daily PI that was approved for use in children ≥6 years of age in March 2008. It has equivalent efficacy to efavirenz-based and lopinavir/ritonavir-based combination therapy when given in combination with zidovudine and lamivudine in treatment-naïve adults *[72-73]*. Seventy-three percent of 48 treatment-naïve South African children achieved viral load <400 copies/mL by 48 weeks when given atazanavir with or without low-dose ritonavir in combination with 2 NRTIs *[74]*. Among 41 treatment-naïve children age 6–18 in IMPAACT/PACTG P1020A who received the capsule formulation of atazanavir with or without ritonavir, 68% and 59% achieved viral load <400 copies/mL and <50copies/mL, respectively, by 48 weeks *[75]*. When given with low-dose ritonavir boosting, atazanavir achieves enhanced concentrations compared with the unboosted drug in adults and children ≥6 years of age *[76-77]* and in antiretroviral-naïve adults appears to be associated with fewer PI resistance mutations at virologic failure compared with atazanavir given without

ritonavir boosting *[78]*. The main adverse effect associated with atazanavir/low-dose ritonavir is indirect hyperbilirubinemia, with or without jaundice or scleral icterus, but without concomitant hepatic transaminase elevations. Although atazanavir is associated with fewer lipid abnormalities than other PIs, lipid levels are higher when using low-dose ritonavir boosting than atazanavir alone *[55]*.

Darunavir with low-dose ritonavir as alternative PI (for children ≥6 years): Darunavir combined with low-dose ritonavir boosting is approved for antiretroviral-naïve and -experienced adults and for children age ≥6 years. Darunavir/ritonavir (800/100 mg once daily) has been found to be noninferior to lopinavir/ritonavir (once or twice daily), both in combination with tenofovir/emtricitabine, in an adult randomized, open-label trial. Plasma HIV RNA levels were <50 copies/mL in 84% of darunavir/ritonavir recipients and in 78% of lopinavir/ritonavir recipients ($p < 0.001$). Adverse events were also less common in the darunavir/ritonavir group ($p < 0.01$) *[79]*. There are no published data about use of darunavir as part of initial treatment in children or use of once-daily darunavir in children. In a study of treatment-experienced children (6–17 years of age), twice-daily darunavir/ritonavir-based therapy was well tolerated and resulted in 48% achieving HIV-1 RNA less than 50 copies/mL, by 48 weeks *[80]*. Darunavir with low-dose ritonavir is recommended as an alternative initial therapy in HIV-infected children based on data from one study in treatment-experienced children and the finding of high potency and low toxicity in adults. Some experts would only recommend boosted darunavir for treatment-experienced children and reserve its use for patients with PI resistant mutations. Once-daily dosing of darunavir is not recommended for children.

Fosamprenavir with low-dose ritonavir as alternative PI (for children ≥6 years): Fosamprenavir (the prodrug of amprenavir) is now available in a pediatric liquid formulation and a tablet formulation. Amprenavir is no longer manufactured. In June 2007, fosamprenavir suspension was approved for use in pediatric patients ≥2 years of age. The approval was based on two open-label studies in pediatric patients between 2 and 18 years of age *[81-82]*. Overall, fosamprenavir was well tolerated and effective in suppressing viral load and increasing CD4 cell count (see **Appendix B: Pediatric Antiretroviral Drug Information** for detailed information). There is less pediatric experience with fosamprenavir than with lopinavir/ritonavir. In an adult clinical trial, fosamprenavir with low-dose ritonavir was demonstrated to be noninferior to lopinavir/ritonavir r *[83]*. In children age ≥6 years, fosamprenavir should be used in combination with low-dose ritonavir boosting to ensure adequate drug levels. Data on appropriate dosing of fosamprenavir in combination with low-dose ritonavir in children age <6 years are not available; therefore, this combination cannot be recommended in that age group. Once-daily dosing of fosamprenavir is not recommended for pediatric patients.

PIs for use in special circumstances

Atazanavir without ritonavir boosting in children age ≥13 years: Although unboosted atazanavir is approved for treatment-naïve adolescents age ≥13 years and >39 kg who are unable to tolerate ritonavir, data from the ongoing IMPAACT/PACTG 1020A study indicate that higher doses (on a mg/m^2 basis) are required to achieve adequate drug concentrations (see **Appendix B: Pediatric Antiretroviral Drug Information** for detailed information on dosing used in IMPAACT/PACTG P1020A). If using unboosted atazanavir in treatment-naïve patients, clinicians should consider using a dual-NRTI combination other than didanosine/emtricitabine because of inferior virologic response demonstrated for this combination in adults in ACTG 5175 *[84]*. If these agents are to be used in combination, patients should be instructed to take them at least 2 hours apart, to take atazanavir with food, and to take didanosine on an empty stomach.

Fosamprenavir without ritonavir boosting in children age ≥2 years: Fosamprenavir without ritonavir boosting has been studied in children age ≥2 years but is only recommended in special circumstances when preferred or alternative PI-based regimens cannot be used.

Nelfinavir for children ≥2 year): Nelfinavir in combination with two NRTIs is an acceptable PI choice for initial treatment of children age ≥2 years in special circumstances. There is extensive pediatric experience with nelfinavir-based regimens in antiretroviral-naïve and -experienced children, with follow-up in children receiving the regimen for as long as 7 years *[85]*. The drug has been well tolerated, with diarrhea as the primary side effect, but virologic potency has been highly variable between studies, with reported rates of virologic suppression ranging 26%–69% (see **Appendix B: Pediatric Antiretroviral Drug Information** for

detailed information). Several studies have shown a correlation between nelfinavir trough concentrations and virologic response in treatment-naïve pediatric patients *[86]*. In one such study, virologic response at Week 48 was observed in 29% of children with subtherapeutic nelfinavir troughs (<0.8 mg/L) versus 80% in children with therapeutic nelfinavir troughs (>0.8 mg/L) *[86]*. There is large interpatient variability in plasma concentrations in children, with lower levels in younger children *[87-92]*. The optimal dose of nelfinavir in younger children, particularly those age <2 years, has not been well defined, and higher doses of nelfinavir (relative to body size) are required to achieve adequate drug levels in infants than in older children *[87]*. Pharmacokinetic parameters in adolescent patients have not been well studied, and doses higher than those recommended in adults may be required for some patients. These data, combined with data in adults showing lesser potency of nelfinavir compared with other protease inhibitors and efavirenz, balanced against the advantage of a protease inhibitor that is not coadminstered with low-dose ritonavir for boosting *[65, 93-96]*, make nelfinavir an agent for use in special circumstances in treatment-naïve children age ≥2 years and not recommended for treatment of children age <2 years.

The pediatric powder formulation of nelfinavir has a poor acceptance rate when mixed with food or formula, and the pharmacokinetics of the drug is extremely variable in children. To overcome the problems associated with this formulation, tablets are dissolved in water or other liquids to make a slurry that is then ingested by children unable to swallow whole tablets. Dissolving nelfinavir tablets in water and swallowing whole tablets resulted in comparable pharmacokinetic parameters in a study in adults *[97]*.

Triple-NRTI Regimens

Panel's Recommendations:

- ***Preferred: None***
- ***Alternative: None***
- ***Use in special circumstances:***
  - ***A three-NRTI-based regimen consisting of zidovudine + lamivudine + abacavir should be used only in special circumstances when a preferred or alternative NNRTI-based or PI-based regimen cannot be used as first-line therapy in treatment-naïve children (e.g., due to significant drug interactions or adherence concerns) (BI*).***

The Panel does not recommend any other triple-NRTI regimens as initial therapy in children due to inferior virologic potency or lack of comparative data (AIII).

Summary: Triple-NRTI Regimens

Triple-NRTI regimens are attractive for use in HIV-infected pediatric patients as initial therapy because of the ease of administration, availability of palatable liquid formulations, demonstrated tolerance, and avoidance of many drug interactions. Data on the efficacy of triple-NRTI regimens for treatment of antiretroviral-naïve children are limited; in small observational studies, response rates of 47%–50% have been reported *[98-99]*. In adult trials, these regimens have shown less potent virologic activity when compared with NNRTI- or PI-based regimens. Based on the results of these clinical trials, the Panel recommends that a three-NRTI-based regimen consisting of zidovudine + lamivudine + abacavir should be used only in special circumstances when a preferred or alternative NNRTI-based or PI-based regimen cannot be used as first-line therapy in treatment-naïve children (e.g., due to significant drug interactions or concerns related to adherence).

Following is a discussion of findings in clinical trials of triple-NRTI regimens:

Zidovudine + lamivudine + abacavir: In a randomized trial, the triple-NRTI combination of zidovudine + lamivudine + abacavir was shown to reduce viral load to <400 copies/mL in 51% of treatment-naïve adults at 48 weeks of therapy, results equivalent to those of the PI-based comparison arm of zidovudine + lamivudine + indinavir *[100]*. In a study of this regimen in previously treated children, the combination showed evidence of only modest viral suppression, with only 10% of 102 children maintaining a viral load of <400 copies/mL at

48 weeks of treatment *[101]*. Additionally, a clinical trial (ACTG 5095) in antiretroviral-naïve adults that compared initial therapy with abacavir + zidovudine + lamivudine to efavirenz + zidovudine + lamivudine or efavirenz + abacavir + zidovudine + lamivudine found that the triple-NRTI regimen was inferior to the efavirenz-based regimens, with a higher incidence of and an earlier time to virologic failure; after 48 weeks of therapy, 74% of adults receiving the triple-NRTI regimen had HIV RNA <200 copies/mL, compared with 89% of patients receiving efavirenz-based regimens *[26, 102]*.

Other triple-NRTI regimens: Clinical trials in adults also have investigated triple-NRTI regimens consisting of stavudine + didanosine + lamivudine, stavudine + lamivudine + abacavir, and didanosine + stavudine + abacavir *[103-104]*. The virologic response to all these regimens was inferior to viral suppression achieved in comparator regimens. In addition, the M184V lamivudine drug-resistance mutation was seen more frequently in patients treated with triple-NRTI regimens containing lamivudine. Triple-NRTI regimens containing tenofovir have been studied in adults. Tenofovir + abacavir + lamivudine and tenofovir + didanosine + lamivudine demonstrate significantly increased rates of virologic failure and are not recommended *[105-107]*. Tenofovir + zidovudine + lamivudine combination demonstrated antiviral activity in adults but no comparative data are available and the regimen is not recommended *[108]*.

Selection of Dual-NRTI Backbone as Part of Initial Combination Therapy

Panel's Recommendations (listed alphabetically):

- ***Preferred two-NRTI backbone combinations:***
  - ***Abacavir + (lamivudine or emtricitabine) (AI).***
    - ***HLA-B*5701 genetic testing should be performed prior to initiating abacavir-based therapy, and abacavir should not be given to a child who tests positive for HLA-B*5701 (AII*).***
  - ***Didanosine + (lamivudine or emtricitabine) (BI*).***
  - ***Zidovudine + (lamivudine or emtricitabine) (AI*).***
  - ***For postpubertal or Tanner stage 4 adolescents only: tenofovir + (lamivudine or emtricitabine) (A-I*).***
- ***Alternative two-NRTI backbone combinations:***
  - ***Zidovudine + (abacavir or didanosine) (BII).***
- ***Use in special circumstances:***
  - ***Stavudine + (lamivudine or emtricitabine) (BII).***

The Panel does not recommend the following dual-NRTI backbones for initial therapy in children:

- ***Stavudine + didanosine due to increased toxicity (AII).***
- ***Abacavir + didanosine, abacavir + tenofovir, and didanosine + tenofovir due to insufficient data (BIII).***
- ***Tenofovir as part of any dual-NRTI backbone in children in Tanner stages 1–3 due to lack of pediatric dosing data and formulation and concerns related to bone toxicity (BII).***

Summary: Selection of Dual-NRTI Backbone Regimen

Currently, six NRTIs (zidovudine, didanosine, lamivudine, stavudine, abacavir, and emtricitabine) are FDA approved for use in children younger than 13 years of age. Dual-NRTI combinations form the "backbone" of combination regimens for both adults and children. Dual-NRTI combinations that have been studied in children include zidovudine in combination with abacavir, didanosine, or lamivudine; abacavir in combination with lamivudine, stavudine, or didanosine; and emtricitabine in combination with stavudine or didanosine *[6, 37, 85, 91, 109-110]*. Advantages and disadvantages of different dual-NRTI backbone options are delineated in **Table 10**.

The preferred dual-NRTI combinations for initial therapy in children consist of abacavir, didanosine, or zidovudine combined with either lamivudine or emtricitabine. The most extensive experience in children is with zidovudine in combination with lamivudine. This combination has extensive data on safety in children and is generally well tolerated. The major toxicities are bone marrow suppression, manifested as macrocytic anemia and neutropenia. Minor toxicities include gastrointestinal toxicity and fatigue. The combination of zidovudine and didanosine had the lowest rate of toxicities in a large retrospective study of children *[111]*.

Both lamivudine and emtricitabine are well tolerated with few side effects. Although there is less experience in children with emtricitabine than lamivudine, it is similar to lamivudine and can be substituted for lamivudine as one component of a preferred dual-NRTI backbone (i.e., emtricitabine in combination with abacavir, didanosine, or zidovudine). The advantages of emtricitabine are once-daily administration, ability to be coadministered with didanosine as a once-daily NRTI backbone option, and availability as an oral solution. Both lamivudine and emtricitabine select for the M184V resistance mutation, which is associated with high-level resistance to both drugs; a modest decrease in susceptibility to abacavir and didanosine; and improved susceptibility to zidovudine, stavudine, and tenofovir *[112-113]*.

Abacavir in combination with lamivudine has been shown to be as potent or possibly more potent than zidovudine in combination with lamivudine in both children and adults *[114-115]* but has the potential for abacavir-associated life-threatening hypersensitivity reactions in a small proportion of patients. In 5 years of follow-up, abacavir plus lamivudine maintained significantly better viral suppression and growth in children than did zidovudine plus lamivudine and zidovudine plus abacavir *[115]*. Abacavir hypersensitivity is more common in individuals with certain HLA genotypes, particularly HLA-B*5701 (see **Appendix B: Pediatric Antiretroviral Drug Information**); however the prevalence of HLA-B*5701 is much lower in African American and Hispanic than white individuals in the United States (2%–2.5% compared with 8%) *[116]*. Pretreatment screening for HLA-B*5701 prior to initiation of abacavir treatment resulted in a significant reduction in the rate of abacavir hypersensitivity reaction in HIV-infected adults (from 7.8% to 3.4%) *[117]*. Genetic screening for HLA-B*5701 should be performed for HIV-infected children prior to initiating abacavir-based therapy and abacavir should not be given to those who test positive for HLA-B*5701.

Didanosine in combination with lamivudine or emtricitabine are also preferred dual-NRTI combinations. The combination of didanosine and emtricitabine allows for once-daily dosing. In a study of 37 treatment-naïve children age 3 to 21 years, long-term virologic suppression was achieved with a once-daily regimen of didanosine, emtricitabine, and efavirenz; 72% of subjects maintained HIV RNA suppression to <50 copies/mL through 96 weeks of therapy *[37]*. Prescribing information for didanosine recommends administration on an empty stomach. However, this is impractical for infants who feed frequently and may decrease medication compliance in older children by increasing regimen complexity. A comparison of didanosine given with or without food in children found that systemic exposure was similar but with slower and more prolonged absorption with food *[118]*. To improve compliance, some practitioners recommend administration without regard to timing of meals for young children. However, data are inadequate to allow a strong recommendation at this time, and it is preferred that didanosine be administered under fasting conditions when possible.

Tenofovir has been studied in HIV-infected children in combination with other NRTIs and as an investigational oral sprinkle/granule formulation *[119-122]*. Tenofovir in combination with lamivudine or emtricitabine is a preferred dual-NRTI combination for use in adolescents in Tanner stage 4 or who are postpuberty. The fixed-dose combinations of tenofovir + emtricitabine and tenofovir + emtricitabine + efavirenz are both administered as 1 pill once daily and may be particularly useful to improve adherence in older adolescents. In studies in adults, tenofovir when used with lamivudine or emtricitabine in combination with efavirenz had potent viral suppression for up to 3 years and was superior to zidovudine/lamivudine/efavirenz in viral efficacy *[123-124]*. In ACTG 5202, adults were randomly assigned to tenofovir + emtricitabine versus abacavir + lamivudine in combination with boosted atazanavir versus efavirenz (in factorial design). Among those with screening HIV-1 RNA ≥100,000 copies per mL, the times to virologic failure and to first adverse event were both significantly shorter in patients randomly assigned to abacavir + lamivudine than in those assigned to tenofovir + emtricitabine. Results for patients with lower entry viral loads and for comparisons by assignment to efavirenz or boosted atazanavir are not yet available *[125]*. In other nonrandomized studies, 48-week virologic efficacy of tenofovir + emtricitabine in combination with

lopinavir/ritonavir was similar to that seen in trials with other dual-NRTI backbones in treatment-naïve adults *[126]*. However, decreases in bone mineral density have been shown in both adults and children taking tenofovir for 48 weeks in some, although not all, studies *[119-122, 127]*. At this time data are insufficient to recommend use of this drug for initial therapy in infected children in Tanner stages 1–3, in whom the risk of bone toxicity may be greatest *[119, 122]* (see **Appendix B: Pediatric Antiretroviral Drug Information** for more detailed pediatric information). Renal toxicity has been reported in children as well as adults receiving tenofovir; in 1 single-center study, the rate of beta-2-microglobulinuria was higher in children receiving tenofovir than children receiving other antiretroviral agents (12/44 compared with 2/48, respectively), although creatinine clearance did not differ between groups *[128]*. Because of potential bone toxicity and renal toxicity, the drug may have greater utility for treatment of children in whom other antiretroviral drugs have failed than for initial therapy of treatment-naïve children. There are numerous drug-drug interactions with tenofovir and other antiretroviral drugs, including didanosine, lopinavir/ritonavir, atazanavir, and tipranavir, that complicate appropriate dosing of this drug.

Alternative dual-NRTI combinations include zidovudine in combination with abacavir or didanosine. There is considerable experience with use of these dual-NRTI regimens in children *[111]*. However, both zidovudine + abacavir and zidovudine + lamivudine had lower rates of viral suppression and more toxicity leading to drug modification than did abacavir + lamivudine in one European pediatric study *[91, 115]*.

The dual-NRTI combination of stavudine with lamivudine or emtricitabine is recommended for use only in special circumstances because stavudine is associated with a higher risk of lipoatrophy and hyperlactatemia than other NRTI drugs *[129-131]*. Children receiving dual-NRTI combinations containing stavudine had higher rates of clinical and laboratory toxicities than those receiving zidovudine-containing combinations *[111]*. In children with anemia in whom there are concerns related to abacavir hypersensitivity and who are too young to receive tenofovir, stavudine may be preferred to zidovudine for initial therapy because of its lower incidence of hematologic toxicity.

Certain dual-NRTI drug combinations are not recommended. These include zidovudine + stavudine due to pharmacologic interactions that can result in potential virologic antagonism. The drug structure of emtricitabine is similar to lamivudine and the same single resistance mutation confers cross resistance, so these drugs should not be used in combination. The dual-NRTI combination of stavudine + didanosine is also not recommended for use as initial therapy. In small pediatric studies, stavudine + didanosine demonstrated virologic efficacy and was well tolerated *[109-110, 132]*. However, in studies in adults, stavudine + didanosine-based combination regimens were associated with greater rates of neurotoxicity, pancreatitis, hyperlactatemia and lactic acidosis, and lipodystrophy than therapies based on zidovudine + lamivudine *[133-134]*; additionally, cases of fatal and nonfatal lactic acidosis with pancreatitis/hepatic steatosis have been reported in women receiving this combination during pregnancy *[129, 135]*. Abacavir + didanosine, abacavir + tenofovir, and didanosine + tenofovir are not recommended as dual-NRTI backbones in initial therapy on the basis of insufficient data in children.

***Not* Recommended for *Initial* Therapy for Children Because of Insufficient Data**

Panel's Recommendations:

Because of insufficient data for use as initial therapy, the following regimens (in addition to those already discussed in previous sections) should not be offered to children for initial therapy (AIII):

- ***Triple-class regimens, including NRTI plus NNRTI plus PI***
- ***Maraviroc-containing regimens***
- ***Raltegravir-containing regimens***
- ***Enfuvirtide (T-20)-containing regimens***

A number of antiretroviral drugs and drug regimens are not recommended for initial therapy of antiretroviral-naïve children because of insufficient pediatric data. These are summarized below.

Regimens containing three drug classes: Data are insufficient to recommend initial regimens containing agents from three drug classes (e.g., NRTI plus NNRTI plus PI). Although efavirenz plus nelfinavir plus one or two NRTIs was shown to be safe and effective in HIV-infected children with prior NRTI therapy, this regimen was not studied as initial therapy in treatment-naïve children and has the potential for inducing resistance to three drug classes, which could severely limit future treatment options *[38-40]*.

New agents without sufficient pediatric data for use as initial therapy (Tables 13 and 14): At this time several new agents appear promising in adults but do not have sufficient pediatric pharmacokinetic and safety data to recommend their use as components of an initial therapeutic regimen in children. These include maraviroc (a CCR5 antagonist), raltegravir (an integrase inhibitor), tenofovir (in children Tanner stages 1–3), and etravirine (a new NNRTI). Raltegravir is being evaluated in treatment-experienced children, but pharmacokinetic, safety, and efficacy data are not yet available and no pediatric formulation is commercially available. Tipranavir boosted with ritonavir was approved (June 2008) by the FDA for use in treatment-experienced children age 2–18 years, but data are insufficient to address use as initial therapy.

Enfuvirtide (T-20), a fusion inhibitor, is approved for use in children age ≥6 years in combination with other antiretroviral drugs in treatment-experienced patients with evidence of HIV replication despite ongoing antiretroviral therapy. The drug must be administered subcutaneously twice daily and is associated with a high incidence of local injection site reactions (98%). Data are currently insufficient to recommend use of enfuvirtide for initial therapy of children.

Antiretroviral Drug Regimens that Should Never be Offered (Table 9)

Panel's Recommendations:

The following regimens or regimen components should never be offered to HIV-infected children:

- ***Monotherapy (AII)***
- ***Two NRTIs alone (AI)***
- ***Certain two-NRTI combinations as part of a combination regimen:***
  - ***Lamivudine + emtricitabine due to similar resistance pattern and no additive benefit (AIII)***
  - ***Zidovudine + stavudine due to virologic antagonism (AII)***
- ***Dual-NNRTI combinations (AI*)***
- ***Unboosted saquinavir, darunavir, or tipranavir (AII*)***
- ***Atazanavir + indinavir (AIII)***
- ***Certain NRTI-only regimens***
  - ***Tenofovir + didanosine + (lamivudine or emtricitabine) (AI*)***
  - ***Tenofovir + abacavir + (lamivudine or emtricitabine) (AI*)***

Several antiretroviral drugs and drug regimens are not recommended for use in therapy of children or adults. These are summarized below. Clinicians should be aware of the components of fixed-drug combinations so that patients do not inadvertently receive a double dose of a drug contained in such a combination.

Monotherapy: Therapy with a single antiretroviral drug is not recommended because it is unlikely to result in sustained viral suppression, leading to the development of viral resistance to the drug being used and cross resistance to other drugs within the same drug class. The exception is for prophylaxis for the newborn infant born to an HIV-infected mother, in which case 6 weeks of monotherapy with zidovudine is recommended for the infant (unless the infant is identified as HIV infected, in which case zidovudine should be discontinued and standard triple therapy instituted) *[24]*.

Dual-nucleoside regimens alone: Dual-NRTI therapy alone is not recommended for initial therapy because it is unlikely to result in sustained viral suppression, leading to the development of viral resistance to the drugs being used and cross resistance to other drugs within the same drug class. For children previously initiated on a

dual-NRTI regimen who have achieved viral suppression, it is reasonable to either continue on this therapy or to add a PI or NNRTI to the regimen. If a child is to stay on a two-NRTI regimen, the plan should be to change to a three or more drug combination if viral rebound should occur (see **Antiretroviral Treatment Failure in Infants, Children, and Adolescents**).

In special circumstances of children with treatment failure associated with drug resistance and persistent nonadherence, there may be a role for use of single- or dual-NRTI regimens as holding or bridging regimens, while intensively working on improving adherence in preparation for initiation of a new, suppressive combination antiretroviral regimen (see section on **Approach to the Management of Antiretroviral Treatment Failure**).

Certain dual-nucleoside backbone combinations: Certain dual-NRTI combinations (zidovudine + stavudine, emtricitabine + lamivudine) are not recommended for therapy at any time because of pharmacological antagonism or inferior virologic response. Emtricitabine should not be used in combination with lamivudine because the drug structure is similar and the same single resistance mutation (M184V) induces resistance to both drugs.

Dual non-nucleoside reverse transcriptase inhibitors (NNRTIs): An adult study (2NN) demonstrated increased toxicity with the combination of nevirapine plus efavirenz *[34]*.

Certain PIs: The combination of atazanavir + indinavir has the potential for additive hyperbilirubinemia. Unboosted saquinavir, darunavir, and tipranivir have low bioavailablity and do not achieve adequate drug levels, and therefore should not be used without ritonavir boosting.

Three-NRTI regimen of tenofovir + (didanosine or abacavir) + (lamivudine or emtricitabine): The triple-NRTI combinations of tenofovir with (didanosine or abacavir) plus (lamivudine or emtricitabine) have a high rate of early virologic nonresponse when used as initial therapy in treatment-naïve adults and are not recommended as combination therapy for children at any time *[105-107]*.

Table 8. Antiretroviral Regimens Recommended for Initial Therapy for Human Immunodeficiency Virus (HIV) Infection in Children

A combination antiretroviral regimen in treatment-naïve children generally contains 1 NNRTI plus a 2-NRTI backbone or 1 PI plus a 2-NRTI backbone. A 3-NRTI regimen consisting of zidovudine, abacavir, and lamivudine is recommended only if a PI or NNRTI regimen cannot be used. Regimens should be individualized based on advantages and disadvantages of each combination (see **Tables 11–13**).

Preferred Regimens	
Children <3 years of age:	Two NRTIs ***plus*** lopinavir/ritonavir[3]
	Two NRTIs ***plus*** nevirapine[1,3] (only if no peripartum nevirapine exposure)
Children ≥3 years of age:	Two NRTIs ***plus*** lopinavir/ritonavir[3]
	Two NRTIs ***plus*** efavirenz[1]
Alternative Regimens	
Children <3 years of age:	None
Children ≥3 to <6 years of age:	Two NRTIs ***plus*** nevirapine[1,3]
Children ≥6 years of age	Two NRTIs ***plus*** atazanavir ***plus*** low-dose ritonavir
	Two NRTIs ***plus*** darunavir ***plus*** low-dose ritonavir
	Two NRTIs ***plus*** fosamprenavir ***plus*** low-dose ritonavir
	Two NRTIs ***plus*** nevirapine[1,3]
Use in Special Circumstances	
	Two NRTIs ***plus*** atazanavir unboosted (for treatment-naïve adolescents ≥13 years of age and >39 kg)
	Two NRTIs ***plus*** fosamprenavir unboosted (children ≥2 years of age)
	Two NRTIs ***plus*** nelfinavir (children ≥2 years of age)
	Zidovudine ***plus*** lamivudine ***plus*** abacavir
2-NRTI Backbone Options (for use in combination with additional drugs) (alphabetical ordering)	
Preferred	Abacavir ***plus*** (lamivudine ***or*** emtricitabine)
	Didanosine ***plus*** (lamivudine ***or*** emtricitabine)
	Tenofovir ***plus*** (lamivudine ***or*** emtricitabine) (for Tanner stage 4 or postpubertal adolescents only)
	Zidovudine ***plus*** (lamivudine ***or*** emtricitabine)
Alternative	Zidovudine ***plus*** abacavir
	Zidovudine ***plus*** didanosine
Use in Special Circumstances	Stavudine ***plus*** (lamivudine ***or*** emtricitabine)

Not Recommended for Initial Therapy
Etravirine-containing regimens
Efavirenz-containing regimens for children <3 years of age
Tipranavir-containing regimens
Saquinavir-containing regimens
Indinavir-containing regimens
Dual (full-dose) PI regimens
Full-dose ritonavir or use of ritonavir as the sole PI
Unboosted atazanavir-containing regimens in children <13 years of age and/or <39 kg
Nelfinavir-containing regimens for children <2 years old
Unboosted darunavir regimens using once-daily dosing of lopinavir/ritonavir, boosted darunavir, or fosamprenavir (boosted or unboosted)
Triple-NRTI regimens other than abacavir + zidovudine + lamivudine
Triple-class regimens, including NRTI *plus* NNRTI *plus* PI
Regimens with dual-NRTI backbones of abacavir + didanosine, abacavir + tenofovir, didanosine + tenofovir , and didanosine + stavudine
Tenofovir-containing regimens in children in Tanner stages 1–3
Maraviroc-containing regimens
Raltegravir-containing regimens
Enfuvirtide (T-20)-containing regimens

[1] Efavirenz is currently available only in capsule form and should be used only in children ≥3 years of age with weight ≥10 kg; nevirapine would be the preferred NNRTI for children age <3 years of age (excluding infants who were exposed to nevirapine as part of maternal-infant peripartum prophylaxis) or who require a liquid formulation. Unless adequate contraception can be ensured, efavirenz-based therapy is not recommended for adolescent females who are sexually active and may become pregnant.

[2] With the exception of lopinavir/ritonavir at all ages and atazanavir/ritonavir, fosamprenavir/ritonavir, and darunavir/ritonavir in children ≥6 years of age, use of other boosted PIs as a component of initial therapy is not recommended, although such regimens have utility as secondary treatment regimens for children who have failed initial therapy.

[3] For children <3 years of age, nevirapine is the preferred NNRTI when NNRTI-based therapy is used. However, lopinavir/ritonavir is preferred to nevirapine by many experts. Nevirapine should not be used in infants who have been exposed to nevirapine as part of maternal-infant prophylaxis.

[4] Nevirapine should not be used in postpubertal girls with CD4 count >250/mm^3, unless the benefit clearly outweighs the risk.

Table 9. Antiretroviral Regimens or Components that Should Never Be Offered for Treatment of Human Immunodeficiency Virus (HIV) Infection in Children

	Rationale	Exceptions
Antiretroviral regimens never recommended for children		
Monotherapy	• Rapid development of resistance • Inferior antiviral activity compared with combination with ≥3 antiretroviral drugs	• HIV-exposed infants (with negative viral testing) during 6-week period of prophylaxis to prevent perinatal transmission
Two NRTIs alone	• Rapid development of resistance • Inferior antiviral activity compared with combination with ≥3 antiretroviral drugs	• Not recommended for initial therapy; for patients currently on this treatment, some clinicians may opt to continue if virologic goals are achieved
Tenofovir ***plus*** abacavir ***plus*** lamivudine ***or*** emtricitabine as a triple-NRTI regimen	• High rate of early viral failure when this triple-NRTI regimen used as initial therapy in treatment-naïve adults	• No exception
Tenofovir ***plus*** didanosine ***plus*** lamivudine ***or*** emtricitabine as a triple-NRTI regimen	• High rate of early viral failure when this triple-NRTI regimen used as initial therapy in treatment-naïve adults	• No exception
Antiretroviral components never recommended as part of an antiretroviral regimen for children		
Atazanavir ***plus*** indinavir	• Potential additive hyperbilirubinemia	• No exception
Dual-NNRTI combinations	• Enhanced toxicity	• No exception
Dual-NRTI combinations:		
• Lamivudine ***plus*** emtricitabine	• Similar resistance profile and no additive benefit	• No exception
• Stavudine ***plus*** zidovudine	• Antagonistic effect on HIV	• No exception
Efavirenz in first trimester of pregnancy or for sexually active adolescent girls of childbearing potential when reliable contraception cannot be ensured	• Potential for teratogenicity	• When no other antiretroviral option is available and potential benefits outweigh risks
Nevirapine initiation in adolescent girls with CD4 >250 cells/mm^3 or adolescent boys with CD4 >400 cells/mm^3	• Increased incidence of symptomatic (including serious and potentially fatal) hepatic events in these patient groups	• Only if benefit clearly outweighs the risk
Unboosted saquinavir, darunavir, or tipranavir	• Poor oral bioavailablity • Inferior virologic activity compared with other protease inhibitors	• No exception

Table 10. Advantages and Disadvantages of Different Nucleoside or Nucleotide Analogue Reverse Transcriptase Inhibitor (NRTI, NtRTI) Backbone Combinations for Use in Highly Active Antiretroviral Combination Regimens for Initial Therapy in Children

	Advantages	Disadvantages
Preferred Combinations		
Abacavir ***plus*** lamivudine ***or*** emtricitabine	• Palatable liquid formulations • Can give with food • Abacavir and lamivudine are coformulated as a single pill for older/larger patients	• Risk of abacavir hypersensitivity reaction; perform HLA-B*5701 screening prior to initiation of abacavir treatment
Didanosine ***plus*** lamivudine ***or*** emtricitabine	• Delayed-release capsules of didanosine may allow once-daily dosing in older children able to swallow pills and who can receive adult dosing along with once-daily emtricitabine • Emtricitabine available as a palatable liquid formulation administered once daily	• Food effect (didanosine is recommended to be taken 1 hour before or 2 hours after food) – some experts give didanosine without regard to food in infants or when compliance is an issue (but can be coadministered with emtricitabine or lamivudine) • Limited pediatric experience using delayed-release didanosine capsules in younger children • Pancreatitis, neurotoxicity with didanosine
Zidovudine ***plus*** lamivudine ***or*** emtricitabine	• Extensive pediatric experience • Zidovudine and lamivudine are coformulated as single pill for older/larger patients • Palatable liquid formulations • Can give with food • Emtricitabine available as a palatable liquid formulation administered once daily	• Bone marrow suppression with zidovudine • Lipoatrophy with zidovudine
Tenofovir ***plus*** lamivudine ***or*** emtricitabine for Tanner stage 4 or postpubertal adolescents only	• Resistance slow to develop • Once-daily dosing for tenofovir • Less mitochondrial toxicity than other NRTIs • Can give with food • Bone toxicity may be less in postpubertal children • Tenofovir and emtricitabine are coformulated as single pill for older/larger patients	• No pediatric formulation of tenofovir • Limited pediatric experience • Potential bone and renal toxicity • Numerous drug-drug interactions with other ARV agents including didanosine, lopinavir/ritonavir, atazanavir, and tipranavir complicate appropriate dosing
Alternate Combinations		
Zidovudine ***plus*** abacavir	• Palatable liquid formulations • Can give with food	• Risk of abacavir hypersensitivity reaction; perform HLA-B*5701 screening prior to initiation of abacavir treatment • Bone marrow suppression and lipoatrophy with zidovudine
Zidovudine ***plus*** didanosine	• Extensive pediatric experience • Delayed-release capsules of didanosine may allow once-daily dosing of didanosine in older children able to swallow pills and who can receive adult dosing	• Bone marrow suppression and lipoatrophy with zidovudine • Pancreatitis, neurotoxicity with didanosine • Didanosine liquid formulation less palatable than lamivudine or emtricitabine liquid formulation • Food effect (recommended to take didanosine 1 hour before or 2 hours after food); some experts give didanosine without regard to food in infants or when compliance is an issue

	Advantages	Disadvantages
Use in Special Circumstances		
Stavudine ***plus*** lamivudine ***or*** emtricitabine	• Moderate pediatric experience • Palatable liquid formulations • Can give with food • Emtricitabine available as a palatable liquid formulation administered once daily	• Stavudine associated with higher incidence of hyperlactatemia/lactic acidosis, lipoatrophy, peripheral neuropathy, hyperlipidemia • Limited pediatric experience with stavudine plus emtricitabine
Not Recommended		
Tenofovir-containing regimens in children in Tanner stages 1–3	• Resistance slow to develop • Once-daily dosing for tenofovir (adults) • Less mitochondrial toxicity than other NRTIs • Can give with food	• No pediatric formulation of tenofovir • Limited PK data for tenofovir in children • Limited pediatric experience • Potential bone and renal toxicity; bone toxicity appears to be more frequent in younger children • Numerous drug-drug interactions with other ARV agents including didanosine, lopinavir/ritonavir, atazanavir, and tipranavir complicate appropriate dosing
Zidovudine ***plus*** stavudine	• None	• Pharmacologic and antiviral antagonism
Lamivudine ***plus*** emtricitabine	• None	• Similar drug structure • Single mutation (M184V) associated with resistance to both drugs
Stavudine ***plus*** Didanosine	• Has shown antiviral activity in small studies in children • Although not recommended for initial therapy, it may be considered for use in antiretroviral-experienced children who require a change in therapy	• Significant toxicities including lipoatrophy, peripheral neuropathy, hyperlactatemia including symptomatic and life-threatening lactic acidosis, hepatic steatosis, and pancreatitis

Table 11. Advantages and Disadvantages of Different Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) for Use in Highly Active Antiretroviral Combination Regimens for Initial Therapy in Children

	Advantages	Disadvantages
General Issues		
NNRTI-Based Regimens	**NNRTI Class Advantages:** • Less dyslipidemia and fat maldistribution than protease inhibitors • Protease inhibitor sparing • Lower pill burden than protease inhibitors for those taking solid formulation; easier to use and adhere to than protease inhibitor-based regimens	**NNRTI Class Disadvantages:** • Single mutation can confer resistance, with cross resistance between efavirenz and nevirapine • Rare but serious and potentially life-threatening cases of skin rash, including Stevens-Johnson syndrome, and hepatic toxicity with all NNRTIs (but highest with nevirapine) • Potential for multiple drug interactions due to metabolism via hepatic enzymes (e.g., CYP3A4)
Preferred		
Efavirenz (for children ≥3 years of age and who can take capsules)	• Potent antiretroviral activity • Once-daily administration • Can give with food (but avoid high fat meals)	• Neuropsychiatric side effects (bedtime dosing to reduce central nervous system effects) • Rash (generally mild) • No commercially available liquid • No data on dosing for children age <3 years • Teratogenic in primates; use with caution in adolescent females of childbearing age
Nevirapine for children age <3 years who have not been exposed to nevirapine as part of maternal-infant prophylaxis or who require a liquid formulation	• Liquid formulation available • Dosing information for young infants available • Can give with food	• Higher incidence of rash/hypersensitivity reaction than other NNRTIs • Higher rates of serious hepatic toxicity than efavirenz • Decreased virologic response compared with efavirenz • Need to initiate therapy with a lower dose and increase in a stepwise fashion. This is to allow for auto-induction of nevirapine metabolism and is associated with a lower incidence of toxicity.
Alternative		
Nevirapine (for children age ≥3 years)	• Liquid formulation available • Dosing information for young infants available • Can give with food	• Higher incidence of rash/hypersensitivity reaction than other NNRTIs • Higher rates of serious hepatic toxicity than efavirenz • Decreased virologic response compared with efavirenz • Need to initiate therapy with a lower dose and increase in a stepwise fashion. This is to allow for auto-induction of nevirapine metabolism and is associated with a lower incidence of toxicity. • Twice-daily dosing

	Advantages	Disadvantages
Not Recommended		
Efavirenz (for children age <3 years)	• Potent antiretroviral activity • Once-daily administration • Can give with food (but avoid high fat meals)	• Neuropsychiatric side effects (bedtime dosing to reduce central nervous system effects) • Rash (generally mild) • No commercially available liquid • No data on dosing for children age <3 years • Teratogenic in primates; use with caution in adolescent females of childbearing age
Etravirine	• Three or more baseline NNRTI mutations result in a decreased virologic response • Patients with a history of NNRTI-related rash do not appear to be at increased risk of etravirine-related rash	• Limited data on pediatric dosing or safety • No pediatric formulation available • Food effect (should be given with food) • No data in treatment-naïve patients • Multiple drug interactions with PIs and other medications • Twice-daily dosing • Skin rash

Table 12. Advantages and Disadvantages of Different Protease Inhibitors (PIs) for Use in Highly Active Antiretroviral Combination Regimens for Initial Therapy in Children

	Advantages	Disadvantages
General Issues		
Protease Inhibitor-Based Regimens	**Protease Class Advantages:** • NNRTI sparing • Clinical, virologic, and immunologic efficacy well documented • Resistance to protease inhibitors requires multiple mutations • Targets HIV at 2 steps of viral replication (viral reverse transcriptase and protease enzymes)	**Protease Class Disadvantages:** • Metabolic complications including dyslipidemia, fat maldistribution, insulin resistance • Potential for multiple drug interactions due to metabolism via hepatic enzymes (e.g., CYP3A4) • Higher pill burden than NRTI- or NNRTI-based regimens for those taking solid formulations • Poor palatability of liquid preparations, which may affect adherence to treatment regimen
Preferred		
Lopinavir/ritonavir	• Coformulated liquid and tablet formulations • Tablets can be given without regard to food but may be better tolerated when taken with food or snack	• Poor palatability of liquid (bitter taste), although better than ritonavir alone • Food effect (liquid should be administered with food) • Ritonavir component associated with large number of drug interactions (see ritonavir) • Use with caution in patients with pre-existing conduction system defects (can prolong PR and QT interval of electrocardiogram)
Alternative		
Atazanavir in combination with low-dose ritonavir in children age ≥6 years	• Once-daily dosing • Atazanavir has less effect on triglyceride and total cholesterol levels than other PIs (but ritonavir boosting may be associated with elevations in these parameters)	• No liquid formulation • Food effect (should be administered with food) • Indirect hyperbilirubinemia common but asymptomatic • Use with caution in patients with pre-existing conduction system defects (can prolong PR interval of electrocardiogram)
Fosamprenavir in combination with low-dose ritonavir in children age ≥6 years	• Oral prodrug of amprenavir with lower pill burden • Pediatric formulation available • Can give with food	• Skin rash • More limited pediatric experience than preferred PI • Food effect (should be given with food) • Ritonavir component associated with large number of drug interactions (see ritonavir) • Contains sulfa moiety; potential for cross sensitivity between fosamprenavir and other drugs in sulfonamide class is unknown.
Darunavir in combination with low-dose ritonavir in children age ≥6 years	• Effective in PI-experienced children when given with low-dose ritonavir boosting	• Pediatric data limited to antiretroviral-experienced children • Pediatric pill burden high with current tablet dose formulations • No liquid formulation • Food effect (should be given with food) • Must be given with ritonavir boosting to achieve adequate plasma concentrations • Contains sulfa moiety; potential for cross sensitivity between darunavir and other drugs in sulfonamide class is unknown.

	Advantages	Disadvantages
Use in Special Circumstances		
Fosamprenavir (unboosted) in children age ≥2 years	• Oral prodrug of amprenavir with lower pill burden • Pediatric formulation available • Can give with food	• Skin rash • More limited pediatric experience than preferred PI • May require boosted regimen to achieve adequate plasma concentrations but pharmacokinetic data to define appropriate dosing not yet available
Atazanavir (unboosted) in treatment-naïve adolescents age ≥13 years and >39 kg who are unable to tolerate ritonavir	• Once-daily dosing • Less effect on triglyceride and total cholesterol levels than other PIs	• No liquid formulation • Food effect (should be administered with food) • Indirect hyperbilirubinemia common but asymptomatic • Use in caution in patients with pre-existing conduction system defects (can prolong PR interval of electrocardiogram) • May require ritonavir boosting in treatment-naïve adolescent patients to achieve adequate plasma concentrations • Unboosted atazanavir cannot be used with tenofovir
Nelfinavir in children age ≥2 years	• Powder formation (for liquid preparation or to be added to food) • Can give with food • Simplified 2 tablets (625 mg) twice-daily regimen has a reduced pill burden compared with other PI-containing regimens in older patients where the adult dose is appropriate	• Diarrhea • Powder formulation poorly tolerated • Food effect (should be administered with food) • Appropriate dosage for younger children not well defined • Need for 3 times daily dosing for younger children • Adolescents may require higher doses than adults • Less potent that boosted PIs
Not Recommended		
Atazanavir (unboosted) in children <13 years of age and/or <39 kg	• Once-daily dosing (>13 years) • Less effect on triglyceride and total cholesterol levels than other PIs	• Drug levels low if used without ritonavir boosting • No liquid formulation • Food effect (should be administered with food) • Indirect hyperbilirubinemia common but asymptomatic • Use in caution in patients with pre-existing conduction system defects (can prolong PR interval of electrocardiogram) • May require ritonavir boosting in treatment-naïve adolescent patients to achieve adequate plasma concentrations
Indinavir (unboosted or boosted)	• May be considered for use as component of a regimen in combination with low-dose ritonavir in postpubertal adolescents who weigh enough to receive adult dosing	• Only available in capsule • Possible higher incidence of nephrotoxicity in children • Requires 3 times daily dosing unless boosted with ritonavir • High fluid intake required to prevent nephrolithiasis • Food effect (should be taken 1 hour before or 2 hours after food) • Limited pediatric pharmacokinetic data
Tipranavir	• Effective in PI-experienced children and adults when given with low-dose ritonavir boosting • Liquid formulation	• Limited data in treatment-naïve patients • Food effect (should be administered with food) • Must be given with ritonavir boosting to achieve adequate plasma concentrations
Ritonavir (full dose)	• Liquid formulation • Can be given with food	• Poor palatability of liquid (bitter taste) • Gastrointestinal intolerance • Food effect (should be administered with food) • Largest number drug interactions (most potent inhibitor of CYP3A4)

Table 12: Advantages and Disadvantages of Different Protease Inhibitors (PIs) for Use in Highly Active Antiretroviral Combination Regimens for Initial Therapy in Children
Page 3 of 3

	Advantages	Disadvantages
Not Recommended (continued)		
Nelfinavir in children age <2 years	• Powder formation (for liquid preparation or to be added to food) • Can give with food • Simplified 2 tablets (625 mg) twice-daily regimen has a reduced pill burden compared with other PI-containing regimens in older patients where the adult dose is appropriate	• Diarrhea • Powder formulation poorly tolerated • Food effect (should be administered with food) • Appropriate dosage for younger children not well defined • Need for 3 times daily dosing for younger children • Adolescents may require higher doses than adults • Less potent that boosted PIs
Saquinavir (unboosted or boosted)		• Low bioavailability, should never be used as sole PI • Limited pediatric pharmacokinetic data; will require boosting with another PI (e.g., ritonavir) to achieve adequate concentrations • No liquid formulation • High pill burden • Must be taken with food • Photosensitivity reactions can occur

Table 13. Advantages and Disadvantages of Entry Inhibitors for Use in Highly Active Antiretroviral Combination Regimens

	Advantages	Disadvantages
General Issues		
Entry Inhibitors	**Entry Inhibitor Class Advantages:** • Susceptibility of HIV to a new class of ARVs	**Entry Inhibitor Class Disadvantages:** • Rapid development of resistance with enfuvirtide • CCR5 inhibitors ineffective against CXCR4 virus, mixed CCR5 and CXCR4 viral populations, or dual-tropic virus
Use in Special Circumstances		
Enfuvirtide	• Susceptibility of HIV to a new class of ARVs • Route of administration ensures adequate drug levels	• Twice-daily subcutaneous injections • 98%–100% incidence of local injection site reactions • Poor adherence and limited levels of success in adolescents due to local site reactions
Insufficient Data to Recommend		
Maraviroc	• Susceptibility of HIV to a new class of ARVs • Can give with food	• Ineffective against CXCR4 or mixed/dual-tropic viral populations • Limited data on pediatric dosing or safety • No pediatric formulation • Multiple drug interactions; different dosing depending on which NNRTI or PI is coadministered

Table 14. Advantages and Disadvantages of Integrase Inhibitors for Use in Highly Active Antiretroviral Combination Regimens

	Advantages	Disadvantages
General Issues		
Integrase Inhibitors	**Integrase Inhibitor Class Advantages:** • Susceptibility of HIV to a new class of ARVs	**Integrase Inhibitor Class Disadvantages:** • Limited data on pediatric dosing or safety
Insufficient Data to Recommend		
Raltegravir	• Susceptibility of HIV to a new class of ARVs • Can give with food	• Limited data on pediatric dosing or safety • No pediatric formulation • Rare systemic allergic reaction or hepatitis

References

1. Nachman SA, Stanley K, Yogev R, et al. Nucleoside analogs plus ritonavir in stable antiretroviral therapy-experienced HIV-infected children: a randomized controlled trial. Pediatric AIDS Clinical Trials Group 338 Study Team. *JAMA.* 2000;283(4):492-498.
2. Chiappini E, Galli L, Gabiano C, et al. Early triple therapy vs mono or dual therapy for children with perinatal HIV infection. *JAMA.* 2006;295(6):626-628.
3. de Martino M, Tovo PA, Balducci M, et al. Reduction in mortality with availability of antiretroviral therapy for children with perinatal HIV-1 infection. Italian Register for HIV Infection in Children and the Italian National AIDS Registry. *JAMA.* 2000;284(2):190-197.
4. Gortmaker SL, Hughes M, Cervia J, et al. Effect of combination therapy including protease inhibitors on mortality among children and adolescents infected with HIV-1. *N Engl J Med.* 2001;345(21):1522-1528.
5. Violari A, Cotton MF, Gibb DM, et al. Early antiretroviral therapy and mortality among HIV-infected infants. *N Engl J Med.* 2008;359(21):2233-2244.
6. McKinney RE, Jr., Johnson GM, Stanley K, et al. A randomized study of combined zidovudine-lamivudine versus didanosine monotherapy in children with symptomatic therapy-naive HIV-1 infection. The Pediatric AIDS Clinical Trials Group Protocol 300 Study Team. *J Pediatr.* 1998;133(4):500-508.
7. Cane P, Chrystie I, Dunn D, et al. Time trends in primary resistance to HIV drugs in the United Kingdom: multicentre observational study. *BMJ.* 2005;331(7529):1368.
8. Novak RM, Chen L, MacArthur RD, et al. Prevalence of antiretroviral drug resistance mutations in chronically HIV-infected, treatment-naive patients: implications for routine resistance screening before initiation of antiretroviral therapy. *Clin Infect Dis.* 2005;40(3):468-474.
9. Viani RM, Peralta L, Aldrovandi G, et al. Prevalence of primary HIV-1 drug resistance among recently infected adolescents: a multicenter adolescent medicine trials network for HIV/AIDS interventions study. *J Infect Dis.* 2006;194(11):1505-1509.
10. Weinstock HS, Zaidi I, Heneine W, et al. The epidemiology of antiretroviral drug resistance among drug-naive HIV-1-infected persons in 10 US cities. *J Infect Dis.* 2004;189(12):2174-2180.
11. Wensing AM, van de Vijver DA, Angarano G, et al. Prevalence of drug-resistant HIV-1 variants in untreated individuals in Europe: implications for clinical management. *J Infect Dis.* 2005;192(6):958-966.
12. Karchava M, Pulver W, Smith L, et al. Prevalence of drug-resistance mutations and non-subtype B strains among HIV-infected infants from New York State. *J Acquir Immune Defic Syndr.* 2006;42(5):614-619.
13. Parker MM, Wade N, Lloyd RM, Jr., et al. Prevalence of genotypic drug resistance among a cohort of HIV-infected newborns. *J Acquir Immune Defic Syndr.* 2003;32(3):292-297.
14. Persaud D, Palumbo P, Ziemniak C, et al. Early archiving and predominance of nonnucleoside reverse transcriptase inhibitor-resistant HIV-1 among recently infected infants born in the United States. *J Infect Dis.* 2007;195(10):1402-1410.
15. Palumbo P, Violari A, Lindsey J, et al. Nevirapine (NVP) vs lopinavir-ritonavir (LPV/r)-based antiretroviral therapy (ART) in single dose nevirapine (sdNVP)-exposed HIV-infected infants: preliminary results from the IMPAACT P1060 trial. Paper presented at: 5th International AIDS Society (IAS) Conference on HIV Pathogenesis, Treatment and Prevention; July 19-22, 2009; Capetown, South Africa. Abstract LBPEB12.
16. Fiscus SA, Kovacs A, Petch LA, et al. Baseline resistance to nucleoside reverse transcriptase inhibitors fails to predict virologic response to combination therapy in children (PACTG 338). *AIDS Res Ther.* 2007;4:2.
17. Hecht FM, Grant RM. Resistance testing in drug-naive HIV-infected patients: is it time? *Clin Infect Dis.* 2005;41(9):1324-1325.
18. MacLeod IJ, Rowley CF, Thior I, et al. Minor resistant variants in nevirapine-exposed infants may predict virologic failure on nevirapine-containing ART. *J Clin Virol.* 2010;48(3):162-167.
19. Lockman S, Shapiro RL, Smeaton LM, et al. Response to antiretroviral therapy after a single, peripartum dose of nevirapine. *N Engl J Med.* 2007;356(2):135-147.
20. Jaspan HB, Berrisford AE, Boulle AM. Two-year outcomes of children on non-nucleoside reverse transcriptase inhibitor and protease inhibitor regimens in a South African pediatric antiretroviral program. *Pediatr Infect Dis J.* 2008;27(11):993-998.
21. Muller AD, Myer L, Jaspan H. Virological suppression achieved with suboptimal adherence levels among South African children receiving boosted protease inhibitor-based antiretroviral therapy. *Clin Infect Dis.* 2009;48(1):e3-5.
22. Kamya MR, Mayanja-Kizza H, Kambugu A, et al. Predictors of long-term viral failure among ugandan children and adults treated with antiretroviral therapy. *J Acquir Immune Defic Syndr.* 2007;46(2):187-193.

23. Kontorinis N, Dieterich DT. Toxicity of non-nucleoside analogue reverse transcriptase inhibitors. *Semin Liver Dis.* 2003;23(2):173-182.
24. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. December 1, 2009:1-161. http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf.
25. Staszewski S, Morales-Ramirez J, Tashima KT, et al. Efavirenz plus zidovudine and lamivudine, efavirenz plus indinavir, and indinavir plus zidovudine and lamivudine in the treatment of HIV-1 infection in adults. Study 006 Team. *N Engl J Med.* 1999;341(25):1865-1873.
26. Gulick RM, Ribaudo HJ, Shikuma CM, et al. Triple-nucleoside regimens versus efavirenz-containing regimens for the initial treatment of HIV-1 infection. *N Engl J Med.* 2004;350(18):1850-1861.
27. Lucas GM, Chaisson RE, Moore RD. Comparison of initial combination antiretroviral therapy with a single protease inhibitor, ritonavir and saquinavir, or efavirenz. *AIDS.* 2001;15(13):1679-1686.
28. Pulido F, Arribas JR, Miro JM, et al. Clinical, virologic, and immunologic response to efavirenz-or protease inhibitor-based highly active antiretroviral therapy in a cohort of antiretroviral-naive patients with advanced HIV infection (EfaVIP 2 study). *J Acquir Immune Defic Syndr.* 2004;35(4):343-350.
29. Torti C, Maggiolo F, Patroni A, et al. Exploratory analysis for the evaluation of lopinavir/ritonavir-versus efavirenz-based HAART regimens in antiretroviral-naive HIV-positive patients: results from the Italian MASTER Cohort. *J Antimicrob Chemother.* 2005;56(1):190-195.
30. Carr A. Antiretroviral therapy for previously untreated HIV-1-infected adults: 2NN, or just one? *Lancet.* 2004;363(9417):1248-1250.
31. Cozzi-Lepri A, Phillips AN, d'Arminio Monforte A, et al. Virologic and immunologic response to regimens containing nevirapine or efavirenz in combination with 2 nucleoside analogues in the Italian Cohort Naive Antiretrovirals (I.Co.N.A.) study. *J Infect Dis.* 2002;185(8):1062-1069.
32. Manfredi R, Calza L, Chiodo F. Efavirenz versus nevirapine in current clinical practice: a prospective, open-label observational study. *J Acquir Immune Defic Syndr.* 2004;35(5):492-502.
33. Manosuthi W, Sungkanuparph S, Vibhagool A, et al. Nevirapine- versus efavirenz-based highly active antiretroviral therapy regimens in antiretroviral-naive patients with advanced HIV infection. *HIV Med.* 2004;5(2):105-109.
34. van Leth F, Phanuphak P, Ruxrungtham K, et al. Comparison of first-line antiretroviral therapy with regimens including nevirapine, efavirenz, or both drugs, plus stavudine and lamivudine: a randomised open-label trial, the 2NN Study. *Lancet.* 2004;363(9417):1253-1263.
35. Fraaij PL, Neubert J, Bergshoeff AS, et al. Safety and efficacy of a NRTI-sparing HAART regimen of efavirenz and lopinavir/ritonavir in HIV-1-infected children. *Antivir Ther.* 2004;9(2):297-299.
36. Funk MB, Notheis G, Schuster T, et al. Effect of first line therapy including efavirenz and two nucleoside reverse transcriptase inhibitors in HIV-infected children. *Eur J Med Res.* 2005;10(12):503-508.
37. McKinney RE, Jr., Rodman J, Hu C, et al. Long-term safety and efficacy of a once-daily regimen of emtricitabine, didanosine, and efavirenz in HIV-infected, therapy-naive children and adolescents: Pediatric AIDS Clinical Trials Group Protocol P1021. *Pediatrics.* 2007;120(2):e416-423.
38. Spector SA, Hsia K, Yong FH, et al. Patterns of plasma human immunodeficiency virus type 1 RNA response to highly active antiretroviral therapy in infected children. *J Infect Dis.* 2000;182(6):1769-1773.
39. Starr SE, Fletcher CV, Spector SA, et al. Combination therapy with efavirenz, nelfinavir, and nucleoside reverse-transcriptase inhibitors in children infected with human immunodeficiency virus type 1. Pediatric AIDS Clinical Trials Group 382 Team. *N Engl J Med.* 1999;341(25):1874-1881.
40. Starr SE, Fletcher CV, Spector SA, et al. Efavirenz liquid formulation in human immunodeficiency virus-infected children. *Pediatr Infect Dis J.* 2002;21(7):659-663.
41. Teglas JP, Quartier P, Treluyer JM, et al. Tolerance of efavirenz in children. *AIDS.* 2001;15(2):241-243.
42. Gutierrez F, Navarro A, Padilla S, et al. Prediction of neuropsychiatric adverse events associated with long-term efavirenz therapy, using plasma drug level monitoring. *Clin Infect Dis.* 2005;41(11):1648-1653.
43. Marzolini C, Telenti A, Decosterd LA, et al. Efavirenz plasma levels can predict treatment failure and central nervous system side effects in HIV-1-infected patients. *AIDS.* 2001;15(1):71-75.
44. Treisman GJ, Kaplin AI. Neurologic and psychiatric complications of antiretroviral agents. *AIDS.* 2002;16(9):1201-1215.
45. Zugar A. Studies disagree on frequency of late cns side effects from efavirenz. *AIDS Clin Care.* 2006;4(1).
46. Bardsley-Elliot A, Perry CM. Nevirapine: a review of its use in the prevention and treatment of paediatric HIV infection. *Paediatr Drugs.* 2000;2(5):373-407.
47. Luzuriaga K, Bryson Y, Krogstad P, et al. Combination treatment with zidovudine, didanosine, and nevirapine in infants with human immunodeficiency virus type 1 infection. *N Engl J Med.* 1997;336(19):1343-1349.

48. Luzuriaga K, McManus M, Mofenson L, et al. A trial of three antiretroviral regimens in HIV-1-infected children. *N Engl J Med.* 2004;350(24):2471-2480.
49. Verweel G, Sharland M, Lyall H, et al. Nevirapine use in HIV-1-infected children. *AIDS.* 2003;17(11):1639-1647.
50. Sulkowski MS, Thomas DL, Mehta SH, et al. Hepatotoxicity associated with nevirapine or efavirenz-containing antiretroviral therapy: role of hepatitis C and B infections. *Hepatology.* 2002;35(1):182-189.
51. Baylor M, Ayime O, Truffa M, et al. Hepatotoxicity associated with nevirapine use in HIV-infected children. Paper presented at: 12th Conference on Retroviruses and Opportunistic Infections; 2005; Boston, MA. Abstract 776.
52. Wiznia A, Stanley K, Krogstad P, et al. Combination nucleoside analog reverse transcriptase inhibitor(s) plus nevirapine, nelfinavir, or ritonavir in stable antiretroviral therapy-experienced HIV-infected children: week 24 results of a randomized controlled trial--PACTG 377. Pediatric AIDS Clinical Trials Group 377 Study Team. *AIDS Res Hum Retroviruses.* 2000;16(12):1113-1121.
53. Mehta U, Maartens G. Is it safe to switch between efavirenz and nevirapine in the event of toxicity? *Lancet Infect Dis.* 2007;7(11):733-738.
54. Chadwick EG, Capparelli EV, Yogev R, et al. Pharmacokinetics, safety and efficacy of lopinavir/ritonavir in infants less than 6 months of age: 24 week results. *AIDS.* 2008;22(2):249-255.
55. Gatell J, Salmon-Ceron D, Lazzarin A, et al. Efficacy and safety of atazanavir-based highly active antiretroviral therapy in patients with virologic suppression switched from a stable, boosted or unboosted protease inhibitor treatment regimen: the SWAN Study (AI424-097) 48-week results. *Clin Infect Dis.* 2007;44(11):1484-1492.
56. Walmsley S, Avihingsanon A, Slim J, et al. Gemini: a noninferiority study of saquinavir/ritonavir versus lopinavir/ritonavir as initial HIV-1 therapy in adults. *J Acquir Immune Defic Syndr.* 2009;50(4):367-374.
57. Fraaij PL, Verweel G, van Rossum AM, et al. Indinavir/low-dose ritonavir containing HAART in HIV-1 infected children has potent antiretroviral activity, but is associated with side effects and frequent discontinuation of treatment. *Infection.* 2007;35(3):186-189.
58. Jankelevich S, Mueller BU, Mackall CL, et al. Long-term virologic and immunologic responses in human immunodeficiency virus type 1-infected children treated with indinavir, zidovudine, and lamivudine. *J Infect Dis.* 2001;183(7):1116-1120.
59. van Rossum AM, Geelen SP, Hartwig NG, et al. Results of 2 years of treatment with protease-inhibitor--containing antiretroviral therapy in dutch children infected with human immunodeficiency virus type 1. *Clin Infect Dis.* 2002;34(7):1008-1016.
60. van Rossum AM, Dieleman JP, Fraaij PL, et al. Persistent sterile leukocyturia is associated with impaired renal function in human immunodeficiency virus type 1-infected children treated with indinavir. *Pediatrics.* 2002;110(2 Pt 1):e19.
61. Ananworanich J, Kosalaraksa P, Hill A, et al. Pharmacokinetics and 24-week efficacy/safety of dual boosted saquinavir/lopinavir/ritonavir in nucleoside-pretreated children. *Pediatr Infect Dis J.* 2005;24(10):874-879.
62. Kosalaraksa P, Bunupuradah T, Engchanil C, et al. Double boosted protease inhibitors, saquinavir, and lopinavir/ritonavir, in nucleoside pretreated children at 48 weeks. *Pediatr Infect Dis J.* 2008;27(7):623-628.
63. Robbins BL, Capparelli EV, Chadwick EG, et al. Pharmacokinetics of high-dose lopinavir-ritonavir with and without saquinavir or nonnucleoside reverse transcriptase inhibitors in human immunodeficiency virus-infected pediatric and adolescent patients previously treated with protease inhibitors. *Antimicrob Agents Chemother.* 2008;52(9):3276-3283.
64. Kempf DJ, King MS, Bernstein B, et al. Incidence of resistance in a double-blind study comparing lopinavir/ritonavir plus stavudine and lamivudine to nelfinavir plus stavudine and lamivudine. *J Infect Dis.* 2004;189(1):51-60.
65. Walmsley S, Bernstein B, King M, et al. Lopinavir-ritonavir versus nelfinavir for the initial treatment of HIV infection. *N Engl J Med.* 2002;346(26):2039-2046.
66. De Luca M, Miccinesi G, Chiappini E, et al. Different kinetics of immunologic recovery using nelfinavir or lopinavir/ritonavir-based regimens in children with perinatal HIV-1 infection. *Int J Immunopathol Pharmacol.* 2005;18(4):729-735.
67. Havens P, Frank M, Cuene B, et al. Pharmacokinetics and safety of lopinavir/ritonavir doses greater than 300 mg/m2/dose in children and adolescents with HIV infection. Paper presented at: 11th Conference on Retroviruses and Opportunistic Infections; February 8-11, 2004; San Francisco, CA. Abstract 937.
68. Saez-Llorens X, Violari A, Deetz CO, et al. Forty-eight-week evaluation of lopinavir/ritonavir, a new protease inhibitor, in human immunodeficiency virus-infected children. *Pediatr Infect Dis J.* 2003;22(3):216-224.

69. Chadwick EG, Pinto J, Yogev R, et al. Early initiation of lopinavir/ritonavir in infants less than 6 weeks of age: pharmacokinetics and 24-week safety and efficacy. *Pediatr Infect Dis J.* 2009;28(3):215-219.
70. la Porte C, van Heeswijk R, Mitchell CD, et al. Pharmacokinetics and tolerability of once- versus twice-daily lopinavir/ritonavir treatment in HIV-1-infected children. *Antivir Ther.* 2009;14(4):603-606.
71. van der Flier M, Verweel G, van der Knaap LC, et al. Pharmacokinetics of lopinavir in HIV type-1-infected children taking the new tablet formulation once daily. *Antivir Ther.* 2008;13(8):1087-1090.
72. Squires K, Lazzarin A, Gatell JM, et al. Comparison of once-daily atazanavir with efavirenz, each in combination with fixed-dose zidovudine and lamivudine, as initial therapy for patients infected with HIV. *J Acquir Immune Defic Syndr.* 2004;36(5):1011-1019.
73. Molina JM, Andrade-Villanueva J, Echevarria J, et al. Once-daily atazanavir/ritonavir versus twice-daily lopinavir/ritonavir, each in combination with tenofovir and emtricitabine, for management of antiretroviral-naive HIV-1-infected patients: 48 week efficacy and safety results of the CASTLE study. *Lancet.* 2008;372(9639):646-655.
74. Meyers T, Rutstein R, Samson P, et al. Treatment responses to atazanavir-containing HAART in a drug-naïve paediatric population in South Africa. Paper presented at: 15th Conference on Retroviruses and Opportunistic Infections (CROI); February 3-6, 2008; Boston, MA. Abstract 582.
75. Bristol-Myers Squibb. Reyataz Package Insert. 2010; http://packageinserts.bms.com/pi/pi_reyataz.pdf.
76. Kiser JJ, Fletcher CV, Flynn PM, et al. Pharmacokinetics of antiretroviral regimens containing tenofovir disoproxil fumarate and atazanavir-ritonavir in adolescents and young adults with human immunodeficiency virus infection. *Antimicrob Agents Chemother.* 2008;52(2):631-637.
77. Kiser J, Rutstein R, Aldrovandi G, et al. Pharmacokinetics of atazanavir/ritonavir in HIV-infected infants, children, and adolescents: PACTG 1020. Paper presented at: 12th Conference on Retroviruses and Opportunistic Infections (CROI); February 22-25 2005; Boston, MA. Abstract 767.
78. Stebbing J, Nathan B, Jones R, et al. Virological failure and subsequent resistance profiles in individuals exposed to atazanavir. *AIDS.* 2007;21(13):1826-1828.
79. Ortiz R, Dejesus E, Khanlou H, et al. Efficacy and safety of once-daily darunavir/ritonavir versus lopinavir/ritonavir in treatment-naive HIV-1-infected patients at week 48. *AIDS.* 2008;22(12):1389-1397.
80. Blanche S, Bologna R, Cahn P, et al. Pharmacokinetics, safety and efficacy of darunavir/ritonavir in treatment-experienced children and adolescents. *AIDS.* 2009;23(15):2005-2013.
81. Chadwick E, Borkowsky W, Fortuny C, et al. Safety and antiviral activity of fosamprenavir/ritonavir once daily regimens in HIV-infected pediatric subjects ages 2 to 18 years (48-week interim data, study apv20003). Paper presented at: 14th Conference on Retroviruses and Opportunistic Infections; February 25-28, 2007; Los Angeles, CA. Abstract 719.
82. Cunningham C, Freedman A, Read S, et al. Safety and antiviral activity of fosamprenavir-containing regmens in HIV-infected 2- to 18-year-old pediatric subjects (interim data, study apv29005). Paper presented at: 14th Conference on Retroviruses and Opportunistic Infections; February 25-28, 2007; Los Angeles, CA. Abstract 718.
83. Eron J, Jr., Yeni P, Gathe J, Jr., et al. The KLEAN study of fosamprenavir-ritonavir versus lopinavir-ritonavir, each in combination with abacavir-lamivudine, for initial treatment of HIV infection over 48 weeks: a randomised non-inferiority trial. *Lancet.* 2006;368(9534):476-482.
84. National Institute of Allergy and Infectious Diseases (NIAID). Bulletin monitoring board recommends stopping experimental treatment regimen in international study of patients new to HIV treatment. 2008; http://www.niaid.nih.gov/news/newsreleases/2008/Pages/ACTG_5175.aspx.
85. Scherpbier HJ, Bekker V, van Leth F, et al. Long-term experience with combination antiretroviral therapy that contains nelfinavir for up to 7 years in a pediatric cohort. *Pediatrics.* 2006;117(3):e528-536.
86. Burger DM, Bergshoeff AS, De Groot R, et al. Maintaining the nelfinavir trough concentration above 0.8 mg/L improves virologic response in HIV-1-infected children. *J Pediatr.* 2004;145(3):403-405.
87. Capparelli EV, Sullivan JL, Mofenson L, et al. Pharmacokinetics of nelfinavir in human immunodeficiency virus-infected infants. *Pediatr Infect Dis J.* 2001;20(8):746-751.
88. Floren LC, Wiznia A, Hayashi S, et al. Nelfinavir pharmacokinetics in stable human immunodeficiency virus-positive children: Pediatric AIDS Clinical Trials Group Protocol 377. *Pediatrics.* 2003;112(3 Pt 1):e220-227.
89. Hirt D, Urien S, Jullien V, et al. Age-related effects on nelfinavir and M8 pharmacokinetics: a population study with 182 children. *Antimicrob Agents Chemother.* 2006;50(3):910-916.
90. Litalien C, Faye A, Compagnucci A, et al. Pharmacokinetics of nelfinavir and its active metabolite, hydroxy-tert-butylamide, in infants perinatally infected with human immunodeficiency virus type 1. *Pediatr Infect Dis J.* 2003;22(1):48-55.

91. Paediatric European Network for Treatment of AIDS (PENTA). Comparison of dual nucleoside-analogue reverse-transcriptase inhibitor regimens with and without nelfinavir in children with HIV-1 who have not previously been treated: the PENTA 5 randomised trial. *Lancet.* 2002;359(9308):733-740.
92. van Heeswijk RP, Scherpbier HJ, de Koning LA, et al. The pharmacokinetics of nelfinavir in HIV-1-infected children. *Ther Drug Monit.* 2002;24(4):487-491.
93. Rodriguez-French A, Boghossian J, Gray GE, et al. The NEAT study: a 48-week open-label study to compare the antiviral efficacy and safety of GW433908 versus nelfinavir in antiretroviral therapy-naive HIV-1-infected patients. *J Acquir Immune Defic Syndr.* 2004;35(1):22-32.
94. Gathe JC, Jr., Ive P, Wood R, et al. SOLO: 48-week efficacy and safety comparison of once-daily fosamprenavir /ritonavir versus twice-daily nelfinavir in naive HIV-1-infected patients. *AIDS.* 2004;18(11):1529-1537.
95. Robbins GK, De Gruttola V, Shafer RW, et al. Comparison of sequential three-drug regimens as initial therapy for HIV-1 infection. *N Engl J Med.* 2003;349(24):2293-2303.
96. Resino S, Larru B, Maria Bellon J, et al. Effects of highly active antiretroviral therapy with nelfinavir in vertically HIV-1 infected children: 3 years of follow-up. Long-term response to nelfinavir in children. *BMC Infect Dis.* 2006;6:107.
97. Regazzi MB, Seminari E, Villani P, et al. Nelfinavir suspension obtained from nelfinavir tablets has equivalent pharmacokinetic profile. *J Chemother.* 2001;13(5):569-574.
98. Saavedra J, Mccoig C, Mallory M, et al. Clinical experience with triple nucleoside (NRTI) combination ZDV/3TC/abacavir (ABC) as initial therapy in HIV-infected children. Paper presented at: 41st Interscience Conference on Antimicrobial Agents and Chemotherapy; September 22-25, 2001; Chicago, IL. Abstract 1941.
99. Wells C, Sharland M, Smith C, et al. Triple nucleoside analogue therapy with zidovudine (AZT), lamivudine (3TC), and abacavir (ABC) in the paediatric HIV London south network (phils-net) cohort. Paper presented at: XIV International AIDS Conference; July 7-12, 2002; Barcelona, Spain. Abstract TuPeB4625.
100. Staszewski S, Keiser P, Montaner J, et al. Abacavir-lamivudine-zidovudine vs indinavir-lamivudine-zidovudine in antiretroviral-naive HIV-infected adults: A randomized equivalence trial. *JAMA.* 2001;285(9):1155-1163.
101. Saez-Llorens X, Nelson RP, Jr., Emmanuel P, et al. A randomized, double-blind study of triple nucleoside therapy of abacavir, lamivudine, and zidovudine versus lamivudine and zidovudine in previously treated human immunodeficiency virus type 1-infected children. The CNAA3006 Study Team. *Pediatrics.* 2001;107(1):E4.
102. Moyle GJ. Where now for Trizivir? Role of the triple-NRTI pill post-ACTG 5095. *AIDS Read.* 2003;13(5):223-224, 227, 244.
103. Gerstoft J, Kirk O, Obel N, et al. Low efficacy and high frequency of adverse events in a randomized trial of the triple nucleoside regimen abacavir, stavudine and didanosine. *AIDS.* 2003;17(14):2045-2052.
104. van Leeuwen R, Katlama C, Murphy RL, et al. A randomized trial to study first-line combination therapy with or without a protease inhibitor in HIV-1-infected patients. *AIDS.* 2003;17(7):987-999.
105. Balestre E, Dupon M, Capdepont S, et al. Virological response to HIV-1 nucleoside/nucleotide reverse transcriptase inhibitors-based, tenofovir DF-including regimens in the ANRS Aquitaine Cohort. *J Clin Virol.* 2006;36(2):95-99.
106. Gallant JE, Rodriguez AE, Weinberg WG, et al. Early virologic nonresponse to tenofovir, abacavir, and lamivudine in HIV-infected antiretroviral-naive subjects. *J Infect Dis.* 2005;192(11):1921-1930.
107. Jemsek J, Hutcherson P, Harper E. Poor virologic responses and early emergence of resistance in treatment naive, HIV-infected patients receiving a once daily triple nucleoside regimen of didanosine, lamivudine, and tenofovir DF. Paper presented at: 11th conference on retroviruses and opportunistic infections; February, 2004; San Francisco, CA.
108. DART Virology Group and Trial Team. Virological response to a triple nucleoside/nucleotide analogue regimen over 48 weeks in HIV-1-infected adults in Africa. *AIDS.* 2006;20(10):1391-1399.
109. Kline MW, Van Dyke RB, Lindsey JC, et al. A randomized comparative trial of stavudine (d4T) versus zidovudine (ZDV, AZT) in children with human immunodeficiency virus infection. AIDS Clinical Trials Group 240 Team. *Pediatrics.* 1998;101(2):214-220.
110. Kline MW, Van Dyke RB, Lindsey JC, et al. Combination therapy with stavudine (d4T) plus didanosine (ddI) in children with human immunodeficiency virus infection. The Pediatric AIDS Clinical Trials Group 327 Team. *Pediatrics.* 1999;103(5):e62.
111. Van Dyke RB, Wang L, Williams PL. Toxicities associated with dual nucleoside reverse-transcriptase inhibitor regimens in HIV-infected children. *J Infect Dis.* 2008;198(11):1599-1608.

112. Borroto-Esoda K, Vela JE, Myrick F, et al. In vitro evaluation of the anti-HIV activity and metabolic interactions of tenofovir and emtricitabine. *Antivir Ther.* 2006;11(3):377-384.
113. Ross L, Parkin N, Chappey C, et al. Phenotypic impact of HIV reverse transcriptase M184I/V mutations in combination with single thymidine analog mutations on nucleoside reverse transcriptase inhibitor resistance. *AIDS.* 2004;18(12):1691-1696.
114. DeJesus E, Herrera G, Teofilo E, et al. Abacavir versus zidovudine combined with lamivudine and efavirenz, for the treatment of antiretroviral-naive HIV-infected adults. *Clin Infect Dis.* 2004;39(7):1038-1046.
115. Green H, Gibb DM, Walker AS, et al. Lamivudine/abacavir maintains virological superiority over zidovudine/lamivudine and zidovudine/abacavir beyond 5 years in children. *AIDS.* 2007;21(8):947-955.
116. Phillips EJ. Genetic screening to prevent abacavir hypersensitivity reaction: are we there yet? *Clin Infect Dis.* 2006;43(1):103-105.
117. Mallal S, Phillips E, Carosi G, et al. HLA-B*5701 screening for hypersensitivity to abacavir. *N Engl J Med.* 2008;358(6):568-579.
118. Stevens RC, Rodman JH, Yong FH, et al. Effect of food and pharmacokinetic variability on didanosine systemic exposure in HIV-infected children. Pediatric AIDS Clinical Trials Group Protocol 144 Study Team. *AIDS Res Hum Retroviruses.* 2000;16(5):415-421.
119. Gafni RI, Hazra R, Reynolds JC, et al. Tenofovir disoproxil fumarate and an optimized background regimen of antiretroviral agents as salvage therapy: impact on bone mineral density in HIV-infected children. *Pediatrics.* 2006;118(3):e711-718.
120. Giacomet V, Mora S, Martelli L, et al. A 12-month treatment with tenofovir does not impair bone mineral accrual in HIV-infected children. *J Acquir Immune Defic Syndr.* 2005;40(4):448-450.
121. Hazra R, Balis FM, Tullio AN, et al. Single-dose and steady-state pharmacokinetics of tenofovir disoproxil fumarate in human immunodeficiency virus-infected children. *Antimicrob Agents Chemother.* 2004;48(1):124-129.
122. Hazra R, Gafni RI, Maldarelli F, et al. Tenofovir disoproxil fumarate and an optimized background regimen of antiretroviral agents as salvage therapy for pediatric HIV infection. *Pediatrics.* 2005;116(6):e846-854.
123. Arribas JR, Pozniak AL, Gallant JE, et al. Tenofovir disoproxil fumarate, emtricitabine, and efavirenz compared with zidovudine/lamivudine and efavirenz in treatment-naive patients: 144-week analysis. *J Acquir Immune Defic Syndr.* 2008;47(1):74-78.
124. Gallant JE, DeJesus E, Arribas JR, et al. Tenofovir DF, emtricitabine, and efavirenz vs. zidovudine, lamivudine, and efavirenz for HIV. *N Engl J Med.* 2006;354(3):251-260.
125. Sax PE, Tierney C, Collier AC, et al. Abacavir-lamivudine versus tenofovir-emtricitabine for initial HIV-1 therapy. *N Engl J Med.* 2009;361(23):2230-2240.
126. Loutfy MR, Ackad N, Antoniou T, et al. Randomized controlled trial of once-daily tenofovir, lamivudine, and lopinavir/ritonavir versus remaining on the same regimen in virologically suppressed HIV-infected patients on their first PI-containing HAART regimen. *HIV Clin Trials.* 2007;8(5):259-268.
127. Gallant JE, Staszewski S, Pozniak AL, et al. Efficacy and safety of tenofovir DF vs stavudine in combination therapy in antiretroviral-naive patients: a 3-year randomized trial. *JAMA.* 2004;292(2):191-201.
128. Papaleo A, Warszawski J, Salomon R, et al. Increased beta-2 microglobulinuria in human immunodeficiency virus-1-infected children and adolescents treated with tenofovir. *Pediatr Infect Dis J.* 2007;26(10):949-951.
129. Dieterich DT. Long-term complications of nucleoside reverse transcriptase inhibitor therapy. *AIDS Read.* 2003;13(4):176-184, 187.
130. Falco V, Rodriguez D, Ribera E, et al. Severe nucleoside-associated lactic acidosis in human immunodeficiency virus-infected patients: report of 12 cases and review of the literature. *Clin Infect Dis.* 2002;34(6):838-846.
131. Joly V, Flandre P, Meiffredy V, et al. Increased risk of lipoatrophy under stavudine in HIV-1-infected patients: results of a substudy from a comparative trial. *AIDS.* 2002;16(18):2447-2454.
132. de Mendoza C, Ramos JT, Ciria L, et al. Efficacy and safety of stavudine plus didanosine in asymptomatic HIV-infected children with plasma HIV RNA below 50,000 copies per milliliter. *HIV Clin Trials.* 2002;3(1):9-16.
133. Blanco F, Garcia-Benayas T, Jose de la Cruz J, et al. First-line therapy and mitochondrial damage: different nucleosides, different findings. *HIV Clin Trials.* 2003;4(1):11-19.
134. Shafer RW, Smeaton LM, Robbins GK, et al. Comparison of four-drug regimens and pairs of sequential three-drug regimens as initial therapy for HIV-1 infection. *N Engl J Med.* 2003;349(24):2304-2315.

135. Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission. Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States. May 24, 2010:1-117. http://aidsinfo.nih.gov/contentfiles/PerinatalGL.pdf.

Monitoring of Children on Antiretroviral Therapy (Updated August 16, 2010)

Panel's Recommendations:

- ***Children who start a new antiretroviral regimen should be evaluated in person or by phone within 1 to 2 weeks of starting medication to screen for clinical side effects and to ensure patient adherence to the regimen (AIII).***
- ***Children should be evaluated within 4 to 8 weeks to assess for possible side effects and to evaluate initial response to therapy (AIII). More frequent evaluation may be needed following initiation or change in therapy to support adherence to the regimen (AIII).***
- ***Subsequently, children should have a monitoring evaluation at least every 3 to 4 months to assess both efficacy and potential toxicity of their antiretroviral regimens (AII*).***

Children who start a new antiretroviral regimen or who change to a new regimen should be followed to assess effectiveness, adherence, tolerability, and side effects of the regimen. Frequent patient visits and intensive follow-up during the initial months after a new antiretroviral regimen is started are necessary to support and educate the family. The first few weeks of antiretroviral therapy can be particularly difficult for children and their caregivers. They must adjust their schedules to allow for consistent and routine administration of medication doses. Children may also experience side effects of medications, and the child and caregivers need assistance in determining whether the effects are temporary and can be tolerated or whether they are more serious or long-term and necessitate a visit to the clinician. Thus, it is prudent for the clinician to assess the child within 1–2 weeks of initiating therapy, either in person or with a phone call, to assure proper administration of medications and to evaluate clinical concerns. Many clinicians will plan additional contact (in person or by telephone) with the child and caregivers during the first few weeks of therapy to support adherence.

Baseline laboratory assessments should be done prior to initiation of therapy; these include CD4 count/percentage and HIV RNA level; complete blood count and differential; serum chemistries (including electrolytes, BUN, creatinine, glucose, hepatic transaminases, calcium, and phosphorus); pancreatic enzyme evaluations (amylase, lipase) if therapy is being initiated with a drug with potential pancreatic toxicity, such as didanosine; and serum lipid evaluation (cholesterol, triglycerides). The child should be seen within 4–8 weeks after initiating or changing therapy to obtain a clinical history, with a focus on potential adverse effects and to assess adherence to medications; perform a physical examination; evaluate efficacy of therapy (measurement of CD4 count/percentage and HIV RNA levels); and obtain a laboratory evaluation for toxicity. More frequent evaluation may be needed following a change in therapy to support adherence to the regimen. At a minimum, laboratory assessments should include a complete blood count and differential, serum chemistries, and assessment of renal and hepatic function. Assessment of initial virologic response to therapy is important because an initial decrease in HIV viral load in response to antiretroviral treatment should be observed after 4–8 weeks of therapy.

Subsequently, children taking antiretroviral medication should have assessments of adherence, toxicity, and efficacy at least every 3–4 months. **Table 15** provides one proposed monitoring schema, which will require adjustment based on the specific therapy the child is receiving. Assessments should include basic hematology, chemistry, CD4 count/percentage, and HIV viral load. Monitoring of drug toxicities should be tailored to the particular medications the child is taking; for example, periodic monitoring of pancreatic enzymes may be desirable in children receiving didanosine, or of serum glucose and lipids in patients receiving PIs. Children who develop symptoms of toxicity should have appropriate laboratory evaluations (e.g., evaluation of serum lactate in a child receiving NRTI drugs who develops symptoms suspicious for lactic acidosis) performed more frequently until the toxicity resolves. For further details of adverse effects associated with particular

antiretroviral medications, please see **Tables 17a–17h. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations**.

Table 15. Example of Minimum Schedule for Monitoring of Children on Antiretroviral Therapy

Time Schedule for Monitoring	Toxicity Monitoring[1]	Efficacy and Adherence Monitoring
Baseline (prior to initiation of therapy)	Clinical history, complete blood count and differential, chemistries[3]	CD4 cell count/percentage, HIV RNA
1–2 weeks[2]	Clinical history	Adherence screen
4–8 weeks	Clinical history, complete blood count and differential, chemistries[3]	CD4 cell count/percentage[4], HIV RNA, adherence screen
Every 3–4 months	Clinical history, complete blood count and differential, chemistries[3]	CD4 cell count/percentage, HIV RNA, adherence screen
Every 6–12 months	Lipid panel	

[1] For children receiving nevirapine, serum transaminase levels should be measured every 2 weeks for the first 4 weeks of therapy, then monthly for 3 months, followed by every 3 to 4 months.

[2] Children starting a new antiretroviral regimen should be evaluated in person or by phone within 1 to 2 weeks of starting medication to screen for clinical side effects and to ensure patient adherence to the regimen. Many clinicians will plan additional contacts (in person or by telephone) with the child and caregivers to support adherence during the first few weeks of therapy. Some clinicians also recommend an HIV RNA measurement within the initial weeks of therapy for an early assessment of response/adherence to therapy.

[3] Chemistries may include electrolytes, glucose, liver function tests (hepatic transaminases and bilirubin), renal function tests (BUN, creatinine), calcium, and phosphate. Additional evaluations should be tailored to the particular drugs the child is receiving; for example, pancreatic enzymes (amylase and lipase) may be considered if the child is starting drugs with potential pancreatic toxicity, such as didanosine.

[4] Some clinicians do not recommend a CD4 cell count/percentage at this time, considering it too early to expect an immunologic response.

Specific Issues in Antiretroviral Therapy for HIV-Infected Adolescents (Updated August 16, 2010)

***Panel's Recommendations*:**

- ***Antiretroviral therapy regimens must be individually tailored to the adolescent because those with perinatal exposure generally have a very different clinical course and treatment history than those who acquired HIV during adolescence (AIII).***
- ***Appropriate dosing of antiretroviral medications for adolescents is complex, not always predictable, and dependent upon multiple factors, including body mass and composition and chronologic age (AII).***
- ***Effective and appropriate contraceptive methods should be selected to reduce the likelihood of unintended pregnancy and prevent transmission of HIV (AI).***
- ***Providers should be aware of potential interactions between antiretroviral drugs and hormonal contraceptives, which could lower contraceptive efficacy (AII*).***
- ***Efavirenz should be avoided for the adolescent girl who desires to become pregnant or who does not use effective and consistent contraception (AII). Efavirenz also should be avoided throughout the first trimester of pregnancy (AII).***
- ***Pediatric and adolescent care providers should work with older adolescent patients to prepare them for transition into adult care settings (AIII).***

BACKGROUND

An increasing number of HIV-infected children who acquired HIV infection through perinatal transmission are now surviving into adolescence. They generally have had a long clinical course and extensive antiretroviral treatment history. Adolescents with behaviorally acquired infection (i.e., infection acquired via sexual activity or intravenous substance use) generally follow a clinical course that is similar to that of adults; they are in an earlier stage of infection, making them potential candidates for early intervention *[1]*.

DOSING OF ANTIRETROVIRAL THERAPY FOR HIV-INFECTED ADOLESCENTS

Puberty is a time of somatic growth and sexual maturation, with females developing more body fat and males more muscle mass. These physiologic changes may affect drug pharmacokinetics, which is especially important for drugs with a narrow therapeutic index that are used in combination with protein-bound medicines or hepatic enzyme inducers or inhibitors *[2]*. Dosages of medications for HIV infection and opportunistic infections traditionally have been prescribed according to Tanner staging of puberty *[3]* rather than strictly on the basis of age *[1]*. Using this method, adolescents in early puberty (Tanner stages I and II) are administered doses using pediatric schedules, whereas those in late puberty (Tanner stage V) are administered doses using adult schedules. However, Tanner stage and age are not necessarily directly predictive of drug pharmacokinetics. In addition, puberty may be delayed in perinatally HIV-infected children *[4]*, adding to discrepancies between Tanner stage-based dosing and age-based dosing.

Many antiretroviral medications (e.g., abacavir, emtricitabine, lamivudine, tenofovir, and some PIs) are administered to children at higher weight- or surface area-based doses than would be predicted by direct scaling of adult doses, based upon reported pharmacokinetic data indicating higher oral drug clearance in children. Continued use of these pediatric weight- or surface area-based doses as a child grows during adolescence can result in medication doses that are higher than the usual adult doses. Data suggesting optimal doses for every antiretroviral medication for adolescents are not available; **Appendix B: Pediatric Antiretroviral Drug Information** includes discussion of data relevant to adolescents for individual drugs and notes the age listed on the drug label for adult dosing, when available. Other factors, such as toxicity, pill

burden, adherence, and virologic and immunologic parameters, may also help determine when to transition adolescents from pediatric to adult doses.

ADOLESCENT CONTRACEPTION, PREGNANCY, AND ANTIRETROVIRAL THERAPY

Adolescents with HIV infection, regardless of mode of acquisition, may be sexually active. Contraception methods and safer sex techniques for prevention of HIV transmission should be discussed with them regularly (see **Incorporating HIV Prevention into the Medical Care of Persons Living with HIV**) *[5]*.

The possibility of planned or unplanned pregnancy should be a consideration when selecting an antiretroviral regimen for the adolescent girl. The most vulnerable period in fetal organogenesis is early in gestation, often before pregnancy is recognized. Sexual activity, reproductive plans, and use of effective contraception should be discussed with the patient. Efavirenz-containing regimens should be avoided in adolescent girls who are trying to conceive or are not using effective and consistent contraception because of the potential for teratogenicity with fetal exposure to efavirenz in the first trimester.

Contraceptive-Antiretroviral Drug Interactions

Several PI and NNRTI drugs are known to interact with oral contraceptives, resulting in possible decreases in ethinyl estradiol or increases in estradiol or norethindrone levels (see the ***Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents)*** available at **http://aidsinfo.nih.gov** *[6]*. These changes may decrease the effectiveness of the oral contraceptives or potentially increase the risk of estrogen- or progestin-related side effects. Providers should be aware of these drug interactions and an alternative or additional contraceptive method should be considered in cases in which there are documented interactions. It is unknown whether the contraceptive effectiveness of progestogen-only injectable contraceptives (such as depot methoxyprogesterone acetate [DMPA]) would be compromised because these methods produce higher blood hormone levels than other progestogen-only oral contraceptives and combined oral contraceptives. In one study, the efficacy of DMPA was not altered among women receiving concomitant nelfinavir-, efavirenz-, or nevirapine-based treatment, with no evidence of ovulation during concomitant administration for 3 months, no additional side effects, and no clinically significant changes in antiretroviral drug levels *[7-8]*. There is minimal information about drug interactions with use of newer hormonal contraceptive methods (e.g., patch, vaginal ring). Adolescents who express a desire to become pregnant should be referred for preconception counseling and care, including discussion of special considerations with antiretroviral therapy use during pregnancy (see Health and Human Services [HHS] ***Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States*** available at **http://aidsinfo.nih.gov** *[9]*).

Pregnant Adolescents

Pregnancy should not preclude the use of optimal therapeutic regimens. However, because of considerations related to prevention of mother-to-child transmission and to maternal and fetal safety, timing of initiation of treatment and selection of regimens may be different for pregnant women than for nonpregnant adults or adolescents. Details regarding choice of antiretroviral regimen in pregnant HIV-infected women, including adolescents, are provided in HHS ***Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States*** available at **http://aidsinfo.nih.gov** *[9]*.

TRANSITION OF ADOLESCENTS INTO ADULT HIV CARE SETTINGS

Facilitating a smooth transition for adolescents with any chronic health condition from the child or adolescent health system to one devoted to the care of adults can be difficult and is especially so for adolescents infected with HIV. Transition is described as “a multifaceted, active process that attends to the medical, psychosocial,

and educational or vocational needs of adolescents as they move from the child-focused to the adult-focused health-care system" *[10]*. HIV care models for children and perinatally infected adolescents tend to be family centered, with input from members of a multidisciplinary team that often includes pediatric or adolescent physicians, nurses, social workers, and mental health professionals. These providers generally have long-standing relationships with patients and their families, and care is rendered in discreet, more intimate settings. Although expert care is also provided in the adult HIV care medical model, the adolescent may feel unfamiliar with the more individual-centered, busier clinics typical of adult medical providers and uncomfortable with providers who often do not have a long-standing relationship with the adolescent. Providing support and guidance to the adolescent and to the adult medical care provider as to what is expected from each may be helpful. Some general guidelines about transitional plans and who might best benefit from them are available *[11-12]*. Pediatric and adolescent programs may benefit from the establishment of formal programs to introduce adolescents to the adult care setting.

References

1. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. December 1, 2009:1-161. http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf.
2. Rogers A. Pharmacokinetics and pharmacodynamics in adolescents. January 20-21, 1994. Proceedings. *J Adolesc Health.* 1994;15(8):605-678.
3. Schneider MB. Physical examination. In: Friedman SB, Fisher MM, Schoenberg SK, Alderman EM, eds. Comprehensive adolescent health care. 2nd ed. St. Louis, MO: Mosby-Year Book, Inc.1998:69-80.
4. Buchacz K, Rogol AD, Lindsey JC, et al. Delayed onset of pubertal development in children and adolescents with perinatally acquired HIV infection. *J Acquir Immune Defic Syndr.* 2003;33(1):56-65.
5. Centers for Disease Control and Prevention (CDC). Incorporating HIV prevention into the medical care of persons living with HIV. Recommendations of CDC, the Health Resources and Services Administration, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. *MMWR Recomm Rep.* 2003;52(RR-12):1-24.
6. El-Ibiary SY, Cocohoba JM. Effects of HIV antiretrovirals on the pharmacokinetics of hormonal contraceptives. *Eur J Contracept Reprod Health Care.* 2008;13(2):123-132.
7. Watts DH, Park JG, Cohn SE, et al. Safety and tolerability of depot medroxyprogesterone acetate among HIV-infected women on antiretroviral therapy: ACTG A5093. *Contraception.* 2008;77(2):84-90.
8. Cohn SE, Park JG, Watts DH, et al. Depo-medroxyprogesterone in women on antiretroviral therapy: effective contraception and lack of clinically significant interactions. *Clin Pharmacol Ther*. 2007;81(2):222-227.
9. Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission. Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States. May 24, 2010:1-117. http://aidsinfo.nih.gov/contentfiles/PerinatalGL.pdf.
10. Reiss JG, Gibson RW, Walker LR. Health care transition: youth, family, and provider perspectives. *Pediatrics.* 2005;115(1):112-120.
11. American Academy of Pediatrics, American Academy of Family Physicians, American College of Physicians-American Society of Internal Medicine. A consensus statement on health care transitions for young adults with special health care needs. *Pediatrics.* 2002;110(6 Pt 2):1304-1306.
12. Rosen DS, Blum RW, Britto M, et al. Transition to adult health care for adolescents and young adults with chronic conditions: position paper of the Society for Adolescent Medicine. *J Adolesc Health.* 2003;33(4):309-311.

Adherence to Antiretroviral Therapy in HIV-Infected Children and Adolescents (Updated August 16, 2010)

Panel's Recommendations:

- ***Strategies to maximize adherence should be discussed prior to initiation of antiretroviral therapy and again when changing regimens (AIII).***
- ***Adherence to therapy must be stressed at each visit, along with continued exploration of strategies to maintain and/or improve adherence (AIII).***
- ***At least one method of measuring adherence to antiretroviral therapy (e.g., quantitative and/or qualitative self-report, pharmacy refill checks, pill counts) should be used in addition to monitoring viral load (AII).***
- ***When feasible, once-daily antiretroviral regimens should be prescribed (AI*).***
- ***Maintain a nonjudgmental attitude, establish trust, and identify mutually acceptable goals for care (AII*).***

BACKGROUND

Medication adherence is fundamental to successful antiretroviral therapy. Adherence is a major factor in determining the degree of viral suppression achieved in response to antiretroviral therapy *[1-4]*. Poor adherence can lead to virologic failure. Prospective adult and pediatric studies have shown the risk of virologic failure to increase as the proportion of missed doses increases *[2, 5-7]*. Subtherapeutic antiretroviral drug levels resulting from poor adherence may facilitate the development of drug resistance to one or more drugs in a given regimen as well as possible cross resistance to other drugs in the same class. Therefore, in addition to compromising the efficacy of the current regimen, suboptimal adherence has implications for limiting future effective drug regimens for patients who develop drug-resistant viral strains.

Evidence indicates that adherence problems occur frequently in children and adolescents. Multiple studies have reported that fewer than 50% of children and/or caretakers reported full adherence to their regimens. Rates of adherence varied with method of ascertainment (parent/child report, pharmacy records), antiretroviral regimens, and study characteristics *[3-4, 8-11]*. A variety of factors, including medication formulation, frequency of dosing, child age, and psychosocial characteristics of the child and parent, have been associated with adherence, but no clear predictors of either good or poor adherence in children have been consistently identified *[7-8, 10, 12-16]*. These findings illustrate the difficulty of maintaining high levels of adherence and underscore the need to work in partnership with families to make adherence education, support, and assessment integral components of care.

SPECIFIC ADHERENCE ISSUES IN CHILDREN

Adherence is a complex health behavior that is influenced by the regimen prescribed, patient factors, and characteristics of health care providers *[14-15]*. Limited availability of palatable formulations for young children is especially problematic *[5, 17]*. Furthermore, infants and children are dependent on others for administration of medication; thus, assessment of the capacity for adherence to a complex multidrug regimen requires evaluation of the caregivers and their environments as well as the ability and willingness of the child to take the drug. Barriers faced by adult caregivers that can contribute to nonadherence in children include forgetting doses, changes in routine, being too busy, and child refusal *[18]*. Some caregivers may place too much responsibility on older children for managing medications before they are developmentally able to take on such tasks *[19]*. Many other barriers to adherence exist for children with HIV infection. For example, caregivers' unwillingness to disclose the child's HIV infection status to others may create specific problems, including reluctance of caregivers to fill prescriptions locally, hiding or relabeling medications to maintain

secrecy within the household, reduction of social support, and a tendency to skip doses when the parent is away from the home or when the child is at school.

SPECIFIC ADHERENCE ISSUES FOR ADOLESCENTS

HIV-infected adolescents also face specific adherence challenges *[7, 20-22]*. Several studies have identified pill burden as well as lifestyle issues (not carrying medication, change in schedule) as barriers to complete adherence *[7, 20]*. Denial and fear of their HIV infection is common, especially in recently diagnosed youth; this may lead to refusal to initiate or continue antiretroviral therapy. Distrust of the medical establishment, misinformation about HIV, and a lack of knowledge about the availability and effectiveness of antiretroviral treatments can all be barriers to linking adolescents to care and maintaining successful antiretroviral therapy. Perinatally infected youth are familiar with the challenges of taking complex drug regimens and with the routine of chronic medical care; nevertheless, they may have long histories of inadequate adherence. Regimen fatigue has also been identified as a barrier to adherence in adolescents *[23]*. Regardless of the mode of acquisition of HIV infection, HIV-infected adolescents may suffer from low self-esteem, may have unstructured and chaotic lifestyles and concomitant mental illnesses, or may cope poorly with their illness due to a lack of familial and social support. Depression, alcohol or substance abuse, poor school attendance, and advanced HIV disease stage all correlate with nonadherence *[21, 24]*. In a study of 833 HIV-infected Medicaid beneficiaries age 12–17 years, youth diagnosed with a psychiatric comorbidity (substance abuse, conduct disorder, or emotional disorder) were less likely to be receiving combination therapy; however, for those on therapy, only a conduct disorder diagnosis was associated with lower adherence *[25]*. A review of published papers on adherence among HIV-infected youth, however, suggests that depression and anxiety have been consistently associated with poorer adherence *[24]*. Adherence to complex regimens is particularly challenging at a time of life when adolescents do not want to be different from their peers. Further difficulties face adolescents who live with parents or partners to whom they have not yet disclosed their HIV status and those who are homeless and have no place to store medicine. Treatment regimens for adolescents must balance the goal of prescribing a maximally potent antiretroviral regimen with realistic assessment of existing and potential support systems to facilitate adherence.

Interventions to promote long-term adherence to antiretroviral treatment have not been rigorously evaluated in adolescents. In clinical practice, reminder systems, such as beepers and alarm devices, are well accepted by some youth. Small, discreet pillboxes in which to store medications in an organized fashion may be useful *[26]*. In a pilot study evaluating peer support and pager messaging in an adult population, peer support was associated with greater self-reported adherence post intervention but the effect was not sustained at follow-up. Pager messaging was not associated with reported adherence but improved biologic outcomes were measured *[27]*. Another study evaluating the efficacy of a 4-session, individual, clinic-based motivational interviewing intervention targeting multiple risk behaviors in HIV-infected youth demonstrated an association with lower viral load at 6 months among youth taking antiretroviral therapy at 6 months. However, reduction in viral load was not maintained at 9 months *[28]*.

ADHERENCE ASSESSMENT AND MONITORING

The process of adherence preparation and assessment should begin before therapy is initiated or changed, and a routine adherence assessment should be incorporated into every clinic visit. A comprehensive assessment should be instituted for all children in whom antiretroviral treatment initiation or change is considered. Evaluations should include nursing, social, and behavioral assessments of factors that may affect adherence by the child and family and can be used to identify individual needs for intervention. Adherence preparation should focus on establishing a dialogue and a partnership in medication management. Specific, open-ended questions should be used to elicit information about past experience as well as concerns and expectations about treatment. When assessing readiness and preparing to begin treatment, it is important to obtain explicit agreement with the treatment plan, including strategies to support adherence.

Adherence is difficult to assess accurately; different methods of assessment have been shown to yield different results, and each approach has limitations *[29-31]*. Both caregivers and health care providers often

overestimate adherence. Use of multiple methods to assess adherence is recommended. Viral load response to a new regimen is often the most accurate indication of adherence, but it may be a less valuable measure in children with long treatment histories and multidrug-resistant virus. Other measures include quantitative self-report of missed doses by caregivers and children or adolescents (focusing on recent missed doses during a 3-day or 1-week period), descriptions of the medication regimens, and reports of barriers to administration of medications. Caregivers may report number of doses taken more accurately than doses missed *[32]*. Also, targeted questions about stress, pill burden, and daily routine are recommended *[7-8, 29]*. Pharmacy refill checks and pill counts can identify adherence problems not evident from self-reports *[33]*. Electronic monitoring devices, such as Medication Event Monitoring System (MEMS) caps, which record opening of medication bottles on a computer chip in the cap *[34]*, have been shown to be useful tools to measure adherence in some settings *[33, 35-36]*. Home visits can play an important role in assessing adherence and, in some cases, suspected nonadherence is confirmed only when dramatic clinical responses to antiretroviral therapy occur during hospitalizations or in other supervised settings *[37-40]*. Preliminary studies suggest that monitoring plasma concentrations of PIs, or therapeutic drug monitoring, may be a useful method to identify nonadherence *[41]*.

It is important for clinicians to recognize that nonadherence is a common problem and that it can be difficult for patients to share information about missed doses or difficulties adhering to treatment. Furthermore, adherence can change over time. An adolescent who was able to strictly adhere to treatment upon initiation of a regimen may not be able to maintain complete adherence over time. A nonjudgmental attitude and trusting relationship foster open communication and facilitate assessment. To obtain information on adherence in older children, it is often helpful to ask both the HIV-infected child and caregivers about missed doses and problems. Their reports may differ significantly; therefore, clinical judgment is required to best interpret adherence information obtained from the multiple sources *[42-43]*.

STRATEGIES TO IMPROVE AND SUPPORT ADHERENCE

Intensive follow-up is required, particularly during the critical first few months after therapy is started; patients should be seen frequently to assess adherence and determine the need for strategies to improve and support adherence. Strategies include development of patient-focused treatment plans to accommodate specific patient needs, integration of medication administration into the daily routines of life (e.g., associating medication administration with daily activities such as brushing teeth), and use of social and community support services. Multifaceted approaches that include regimen-related strategies; educational, behavioral, and supportive strategies focused on children and families; and strategies that focus on health care providers—rather than one specific intervention—may be most effective *[44-47]*. Although quite labor intensive, programs designed to administer directly observed combination therapy to adults in either the clinic or at home have demonstrated successful results in both the United States and in international, resource-poor settings *[48-52]*. In particular, modified directly observed therapy (m-DOT) when one dose is administered in a supervised setting and the remaining portions are self-administered appears to be both feasible and acceptable *[47]*. **Table 16** summarizes some of the strategies that can be used to support and improve adherence to antiretroviral medications.

Regimen-Related Strategies

Highly active antiretroviral regimens often require the administration of large numbers of pills or unpalatable liquids, each with potential side effects and drug interactions, in multiple daily doses. To the extent possible, regimens should be simplified with respect to the number of pills or volume of liquid prescribed, as well as frequency of therapy, and chosen to minimize drug interactions and side effects *[53]*. When nonadherence is a problem, addressing medication-related issues, such as side effects, may result in improvement. If a regimen is overly complex, it may be simplified. For example, when the burden of pills is great, one or more drugs can be changed to result in a regimen containing fewer pills and potentially greater adherence. Several studies in adults have demonstrated better adherence in once-daily compared with twice-daily antiretroviral regimens *[54-56]*. When nonadherence is related to poor palatability of a liquid formulation or crushed pills, the offending taste may be masked by a small amount of flavoring syrups or food, as long as the medication is not

one with contraindications to simultaneous administration of food (see **Appendix B: Pediatric Antiretroviral Drug Information**), or the child may be taught to swallow pills in order to overcome medication aversion *[57]*.

Child/Family-Related Strategies

The primary approach taken by the clinical team to promote medication adherence in children is patient/caregiver education. Educating families about adherence should begin before antiretroviral medications are initiated or changed and should include a discussion of the goals of therapy, the reasons for making adherence a priority, and the specific plans for supporting and maintaining the child's medication adherence. Caregivers should understand that the first antiretroviral regimen has the best chance of long-term success. Caregiver adherence education strategies should include the provision of both information and adherence tools, such as written and visual materials; a daily schedule illustrating times and doses of medications; and demonstration of the use of syringes, medication cups, and pillboxes.

A number of behavioral tools can be used to integrate taking medications into the HIV-infected child's daily routine. The use of behavior modification techniques, especially the application of positive reinforcements and the use of small incentives for taking medications, can be effective tools to promote adherence *[58-60]*. Training children on swallowing pills has been associated with improved adherence at 6 months post-training in a small study of children age 4 to 21 *[61]*. Availability of mental health services and treatment of mental health disorders may also facilitate adherence to complex antiretroviral regimens. For nonadherent children who are at risk of disease progression and for whom aversion to taking medications is severe and persistent, a gastrostomy tube may be considered *[62]*. Home nursing interventions may also be beneficial where adequate resources are available *[63]*. Directly observed dosing of antiretroviral medications has been implemented in adults and pediatrics with promising results *[48-52, 64]*, and such an approach has been implemented in some pediatric HIV programs, using home nursing services as well as daily medication administration in the clinic setting. Other strategies to support adherence that have been employed in the clinical setting include setting patient cell phones to alarm when medications are due to be taken, providing pill boxes and other adherence support tools, and weekly filling of pill boxes by nursing or pharmacy staff particularly for patients with complex regimens.

Health Care Provider-Related Strategies

Providers have the ability to improve adherence through their relationships with the families. This process begins early in the provider's relationship with the family, when the clinician obtains explicit agreement about the medication and treatment plan and any further strategies to support adherence. Fostering a trusting relationship and engaging in open communication are particularly important *[65-67]*. Provider characteristics that have been associated with improved patient adherence in adults include consistency, giving information, asking questions, technical expertise, and commitment to follow-up. Creating an environment in the health care setting that is child centered and includes caregivers in adherence support has also been shown to improve treatment outcomes *[68]*.

Table 16. Strategies to Improve Adherence with Antiretroviral Medications

Initial Intervention Strategies
• Establish trust and identify mutually acceptable goals for care. • Obtain explicit agreement on need for treatment and adherence. • Identify depression, low self-esteem, drug use, or other mental health issues for the child/adolescent and/or caregiver that may decrease adherence. Treat prior to starting antiretroviral drugs, if possible. • Identify family, friends, health team members, or others who can help with adherence support. • Educate patient and family about the critical role of adherence in therapy outcome. • Specify the adherence target: ≥95% of prescribed doses. • Educate patient and family about the relationship between partial adherence and resistance. • Educate patient and family about resistance and constraint of later choices of antiretroviral drug (i.e., explain that although a failure of adherence may be temporary, the effects on treatment choice may be permanent). • Develop a treatment plan that the patient and family understand and to which they feel committed. • Establish readiness to take medication by practice sessions or other means. • Consider a brief period of hospitalization at start of therapy in selected circumstances for patient education and to assess tolerability of medications chosen.
Medication Strategies
• Choose the simplest regimen possible, reducing dosing frequency and number of pills. • Choose a regimen with dosing requirements that best conform to the daily and weekly routines and variations in patient and family activities. • Choose the most palatable medicine possible (pharmacists may be able to add syrups or flavoring agents to increase palatability). • Choose drugs with the fewest side effects; provide anticipatory guidance for management of side effects. • Simplify food requirements for medication administration. • Prescribe drugs carefully to avoid adverse drug-drug interactions. • Assess pill swallowing capacity and offer pill swallowing training.
Follow-up Intervention Strategies
• Monitor adherence at each visit and in between visits by telephone or letter as needed. • Provide ongoing support, encouragement, and understanding of the difficulties of the demands of attaining ≥95% adherence with medication doses. • Use patient education aids including pictures, calendars, and stickers. • Use pill boxes, reminders, alarms, pagers, and timers. • Provide follow-up clinic visits or telephone calls to support and assess adherence. • Provide access to support groups, peer groups, or one-on-one counseling for caregivers and patients, especially for those with known depression or drug use issues that are known to decrease adherence. • Provide pharmacist-based adherence support. • Consider gastrostomy tube use in selected circumstances. • Consider a brief period of hospitalization for selected circumstances of apparent virologic failure to assess adherence and reinforce that medication adherence is fundamental to successful antiretroviral therapy. • Consider directly observed therapy at home, in the clinic, or during a brief inpatient hospitalization.

References

1. Flynn PM, Rudy BJ, Douglas SD, et al. Virologic and immunologic outcomes after 24 weeks in HIV type 1-infected adolescents receiving highly active antiretroviral therapy. *J Infect Dis.* 2004;190(2):271-279.
2. Paterson DL, Swindells S, Mohr J, et al. Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. *Ann Intern Med.* 2000;133(1):21-30.
3. Van Dyke RB, Lee S, Johnson GM, et al. Reported adherence as a determinant of response to highly active antiretroviral therapy in children who have human immunodeficiency virus infection. *Pediatrics.* 2002;109(4):e61.
4. Watson DC, Farley JJ. Efficacy of and adherence to highly active antiretroviral therapy in children infected with human immunodeficiency virus type 1. *Pediatr Infect Dis J.* 1999;18(8):682-689.
5. Chadwick EG, Rodman JH, Britto P, et al. Ritonavir-based highly active antiretroviral therapy in human immunodeficiency virus type 1-infected infants younger than 24 months of age. *Pediatr Infect Dis J.* 2005;24(9):793-800.
6. Howard AA, Arnsten JH, Lo Y, et al. A prospective study of adherence and viral load in a large multi-center cohort of HIV-infected women. *AIDS.* 2002;16(16):2175-2182.
7. Murphy DA, Sarr M, Durako SJ, et al. Barriers to HAART adherence among human immunodeficiency virus-infected adolescents. *Arch Pediatr Adolesc Med.* 2003;157(3):249-255.
8. French T, Weiss L, Waters M, et al. Correlation of a brief perceived stress measure with nonadherence to antiretroviral therapy over time. *J Acquir Immune Defic Syndr.* 2005;38(5):590-597.
9. Katko E, Johnson GM, Fowler SL, et al. Assessment of adherence with medications in human immunodeficiency virus-infected children. *Pediatr Infect Dis J.* 2001;20(12):1174-1176.
10. Mellins CA, Brackis-Cott E, Dolezal C, et al. The role of psychosocial and family factors in adherence to antiretroviral treatment in human immunodeficiency virus-infected children. *Pediatr Infect Dis J.* 2004;23(11):1035-1041.
11. Reddington C, Cohen J, Baldillo A, et al. Adherence to medication regimens among children with human immunodeficiency virus infection. *Pediatr Infect Dis J.* 2000;19(12):1148-1153.
12. Williams PL, Storm D, Montepiedra G, et al. Predictors of adherence to antiretroviral medications in children and adolescents with HIV infection. *Pediatrics.* 2006;118(6):e1745-1757.
13. Malee K, Williams PL, Montepiedra G, et al. The role of cognitive functioning in medication adherence of children and adolescents with HIV infection. *J Pediatr Psychol.* 2009;34(2):164-175.
14. Haberer J, Mellins C. Pediatric adherence to HIV antiretroviral therapy. *Curr HIV/AIDS Rep.* 2009;6(4):194-200.
15. Marón G, Herr M, Gaur A, et al. Adherence rates in adolescents prescribed once daily and twice daily doses of highly active antiretroviral therapy (HAART). Paper presented at: St. Jude/PIDS Research Conference; 2008; Memphis, TN.
16. Filho LF, Nogueira SA, Machado ES, et al. Factors associated with lack of antiretroviral adherence among adolescents in a reference centre in Rio de Janeiro, Brazil. *Int J STD AIDS.* 2008;19(10):685-688.
17. Gibb DM, Goodall RL, Giacomet V, et al. Adherence to prescribed antiretroviral therapy in human immunodeficiency virus-infected children in the PENTA 5 trial. *Pediatr Infect Dis J.* 2003;22(1):56-62.
18. Marhefka SL, Koenig LJ, Allison S, et al. Family experiences with pediatric antiretroviral therapy: responsibilities, barriers, and strategies for remembering medications. *AIDS Patient Care STDS.* 2008;22(8):637-647.
19. Naar-King S, Montepiedra G, Nichols S, et al. Allocation of family responsibility for illness management in pediatric HIV. *J Pediatr Psychol.* 2009;34(2):187-194.
20. Belzer ME, Fuchs DN, Luftman GS, et al. Antiretroviral adherence issues among HIV-positive adolescents and young adults. *J Adolesc Health.* 1999;25(5):316-319.
21. Murphy DA, Belzer M, Durako SJ, et al. Longitudinal antiretroviral adherence among adolescents infected with human immunodeficiency virus. *Arch Pediatr Adolesc Med.* 2005;159(8):764-770.
22. Rudy BJ, Murphy DA, Harris DR, et al. Patient-related risks for nonadherence to antiretroviral therapy among HIV-infected youth in the United States: a study of prevalence and interactions. *AIDS Patient Care STDS.* 2009;23(3):185-194.
23. Merzel C, Vandevanter N, Irvine M. Adherence to antiretroviral therapy among older children and adolescents with HIV: a qualitative study of psychosocial contexts. *AIDS Patient Care STDS.* 2008;22(12):977-987.
24. Reisner SL, Mimiaga MJ, Skeer M, et al. A review of HIV antiretroviral adherence and intervention studies among HIV-infected youth. *Top HIV Med.* 2009;17(1):14-25.

25. Walkup J, Akincigil A, Bilder S, et al. Psychiatric diagnosis and antiretroviral adherence among adolescent Medicaid beneficiaries diagnosed with human immunodeficiency virus/acquired immunodeficiency syndrome. *J Nerv Ment Dis.* 2009;197(5):354-361.
26. AIDS Institute New York State Department of Health. Supportive care issues for children with HIV infection. 2001; www.hivguidelines.org/GuidelineDocuments/p-suppcare.pdf.
27. Simoni JM, Huh D, Frick PA, et al. Peer support and pager messaging to promote antiretroviral modifying therapy in Seattle: a randomized controlled trial. *J Acquir Immune Defic Syndr.* 2009;52(4):465-473.
28. Naar-King S, Parsons JT, Murphy DA, et al. Improving health outcomes for youth living with the human immunodeficiency virus: a multisite randomized trial of a motivational intervention targeting multiple risk behaviors. *Arch Pediatr Adolesc Med.* 2009;163(12):1092-1098.
29. Wiener L, Riekert K, Ryder C, et al. Assessing medication adherence in adolescents with HIV when electronic monitoring is not feasible. *AIDS Patient Care STDS.* 2004;18(9):527-538.
30. Davies MA, Boulle A, Fakir T, et al. Adherence to antiretroviral therapy in young children in Cape Town, South Africa, measured by medication return and caregiver self-report: a prospective cohort study. *BMC Pediatr.* 2008;8:34.
31. Farley JJ, Montepiedra G, Storm D, et al. Assessment of adherence to antiretroviral therapy in perinatally HIV-infected children and youth using self-report measures and pill count. *J Dev Behav Pediatr.* 2008;29(5):377-384.
32. Allison SM, Koenig LJ, Marhefka SL, et al. Assessing medication adherence of perinatally HIV-infected children using caregiver interviews. *J Assoc Nurses AIDS Care.* 2010.
33. Farley J, Hines S, Musk A, et al. Assessment of adherence to antiviral therapy in HIV-infected children using the Medication Event Monitoring System, pharmacy refill, provider assessment, caregiver self-report, and appointment keeping. *J Acquir Immune Defic Syndr.* 2003;33(2):211-218.
34. Bond WS, Hussar DA. Detection methods and strategies for improving medication compliance. *Am J Hosp Pharm.* 1991;48(9):1978-1988.
35. Bova CA, Fennie KP, Knafl GJ, et al. Use of electronic monitoring devices to measure antiretroviral adherence: practical considerations. *AIDS Behav.* 2005;9(1):103-110.
36. Muller AD, Bode S, Myer L, et al. Electronic measurement of adherence to pediatric antiretroviral therapy in South Africa. *Pediatr Infect Dis J.* 2008;27(3):257-262.
37. Gigliotti F, Murante BL, Weinberg GA. Short course directly observed therapy to monitor compliance with antiretroviral therapy in human immunodeficiency virus-infected children. *Pediatr Infect Dis J.* 2001;20(7):716-718.
38. Parsons GN, Siberry GK, Parsons JK, et al. Multidisciplinary, inpatient directly observed therapy for HIV-1-infected children and adolescents failing HAART: A retrospective study. *AIDS Patient Care STDS.* 2006;20(4):275-284.
39. Roberts GM, Wheeler JG, Tucker NC, et al. Nonadherence with pediatric human immunodeficiency virus therapy as medical neglect. *Pediatrics.* 2004;114(3):e346-353.
40. Glikman D, Walsh L, Valkenburg J, et al. Hospital-based directly observed therapy for HIV-infected children and adolescents to assess adherence to antiretroviral medications. *Pediatrics.* 2007;119(5):e1142-1148.
41. van Rossum AM, Bergshoeff AS, Fraaij PL, et al. Therapeutic drug monitoring of indinavir and nelfinavir to assess adherence to therapy in human immunodeficiency virus-infected children. *Pediatr Infect Dis J.* 2002;21(8):743-747.
42. Dolezal C, Mellins C, Brackis-Cott E, et al. The reliability of reports of medical adherence from children with HIV and their adult caregivers. *J Pediatr Psychol.* 2003;28(5):355-361.
43. Podsadecki TJ, Vrijens BC, Tousset EP, et al. "White coat compliance" limits the reliability of therapeutic drug monitoring in HIV-1-infected patients. *HIV Clin Trials.* 2008;9(4):238-246.
44. Haynes RB, McKibbon KA, Kanani R. Systematic review of randomised trials of interventions to assist patients to follow prescriptions for medications. *Lancet.* 1996;348(9024):383-386.
45. Winnick S, Lucas DO, Hartman AL, et al. How do you improve compliance? *Pediatrics.* 2005;115(6):e718-724.
46. Wu AW, Ammassari A, Antinori A. Adherence to antiretroviral therapy: where are we, and where do we go from here? *J Acquir Immune Defic Syndr.* 2002;31 Suppl 3:S95-97.
47. Simoni JM, Amico KR, Pearson CR, et al. Strategies for promoting adherence to antiretroviral therapy: a review of the literature. *Curr Infect Dis Rep.* 2008;10(6):515-521.
48. Behforouz HL, Farmer PE, Mukherjee JS. From directly observed therapy to accompagnateurs: enhancing AIDS treatment outcomes in Haiti and in Boston. *Clin Infect Dis.* 2004;38 Suppl 5:S429-436.

49. Jack C, Lalloo U, Karim QA, et al. A pilot study of once-daily antiretroviral therapy integrated with tuberculosis directly observed therapy in a resource-limited setting. *J Acquir Immune Defic Syndr.* 2004;36(4):929-934.
50. Jayaweera DT, Kolber MA, Brill M, et al. Effectiveness and tolerability of a once-daily amprenavir/ritonavir-containing highly active antiretroviral therapy regimen in antiretroviral-naive patients at risk for nonadherence: 48-week results after 24 weeks of directly observed therapy. *HIV Med.* 2004;5(5):364-370.
51. Williams AB, Fennie KP, Bova CA, et al. Home visits to improve adherence to highly active antiretroviral therapy: a randomized controlled trial. *J Acquir Immune Defic Syndr.* 2006;42(3):314-321.
52. Myung P, Pugatch D, Brady MF, et al. Directly observed highly active antiretroviral therapy for HIV-infected children in Cambodia. *Am J Public Health.* 2007;97(6):974-977.
53. Pham PA. Antiretroviral adherence and pharmacokinetics: review of their roles in sustained virologic suppression. *AIDS Patient Care STDS.* 2009;23(10):803-807.
54. Boyle BA, Jayaweera D, Witt MD, et al. Randomization to once-daily stavudine extended release/lamivudine/efavirenz versus a more frequent regimen improves adherence while maintaining viral suppression. *HIV Clin Trials.* 2008;9(3):164-176.
55. Molina JM, Podsadecki TJ, Johnson MA, et al. A lopinavir/ritonavir-based once-daily regimen results in better compliance and is non-inferior to a twice-daily regimen through 96 weeks. *AIDS Res Hum Retroviruses.* 2007;23(12):1505-1514.
56. Parienti JJ, Bangsberg DR, Verdon R, et al. Better adherence with once-daily antiretroviral regimens: a meta-analysis. *Clin Infect Dis.* 2009;48(4):484-488.
57. Czyzewski D, Runyan D, Lopez M, et al. Teaching and maintaining pill swallowing in HIV-infected children. *The AIDS Reader.* 2000;10(2):88-94.
58. AIDS Institute New York State Department of Health. Promoting adherence to antiretroviral therapy. 2001; http://www.hivguidelines.org/quality-of-care/best-practices/promoting-adherence-to-antiretroviral-therapy/.
59. DiIorio C, Resnicow K, McDonnell M, et al. Using motivational interviewing to promote adherence to antiretroviral medications: a pilot study. *J Assoc Nurses AIDS Care.* 2003;14(2):52-62.
60. Hammami N, Nostlinger C, Hoeree T, et al. Integrating adherence to highly active antiretroviral therapy into children's daily lives: a qualitative study. *Pediatrics.* 2004;114(5):e591-597.
61. Garvie PA, Lensing S, Rai SN. Efficacy of a pill-swallowing training intervention to improve antiretroviral medication adherence in pediatric patients with HIV/AIDS. *Pediatrics.* 2007;119(4):e893-899.
62. Shingadia D, Viani RM, Yogev R, et al. Gastrostomy tube insertion for improvement of adherence to highly active antiretroviral therapy in pediatric patients with human immunodeficiency virus. *Pediatrics.* 2000;105(6):E80.
63. Berrien VM, Salazar JC, Reynolds E, et al. Adherence to antiretroviral therapy in HIV-infected pediatric patients improves with home-based intensive nursing intervention. *AIDS Patient Care STDS.* 2004;18(6):355-363.
64. Mitty JA, Stone VE, Sands M, et al. Directly observed therapy for the treatment of people with human immunodeficiency virus infection: a work in progress. *Clin Infect Dis.* 2002;34(7):984-990.
65. Tugenberg T, Ware NC, Wyatt MA. Paradoxical effects of clinician emphasis on adherence to combination antiretroviral therapy for HIV/AIDS. *AIDS Patient Care STDS.* 2006;20(4):269-274.
66. Wang X, Wu Z. Factors associated with adherence to antiretroviral therapy among HIV/AIDS patients in rural China. *AIDS.* 2007;21 Suppl 8:S149-155.
67. Molassiotis A, Morris K, Trueman I. The importance of the patient-clinician relationship in adherence to antiretroviral medication. *Int J Nurs Pract.* 2007;13(6):370-376.
68. Van Winghem J, Telfer B, Reid T, et al. Implementation of a comprehensive program including psycho-social and treatment literacy activities to improve adherence to HIV care and treatment for a pediatric population in Kenya. *BMC Pediatr.* 2008;8:52.

Management of Medication Toxicity or Intolerance (Updated August 16, 2010)

Panel's Recommendations:

- ***If a child has severe or life-threatening toxicity, all components of the drug regimen should be stopped immediately (AIII). Once the symptoms of toxicity have resolved, antiretroviral therapy should be resumed with substitution of a different antiretroviral drug or drugs for the offending agent(s) (AII*).***
- ***When changing therapy because of toxicity or intolerance to a specific drug in a virally suppressed individual, changing a single drug in a multi-drug regimen is permissible; if possible, an agent with a different toxicity and side effect profile should be chosen (AI*).***
- ***The toxicity and the medication presumed responsible should be documented in the medical record and the caregiver and patient advised of the drug-related toxicity to facilitate future medication choices if care is transferred (AIII).***
- ***Dose reduction is not a recommended option in the setting of antiretroviral toxicity except when therapeutic drug monitoring indicates a drug concentration above the normal therapeutic range (AII*).***

Side effects or intolerance of antiretroviral agents occur with moderate frequency and should prompt a re-evaluation of the antiretroviral regimen. Drug-related toxicity may be acute, occurring soon after a drug has been administered; subacute, occurring within 1−2 days of administration; or late, occurring after prolonged drug administration. Such adverse events may vary in severity from mild to severe and life threatening (see **Tables 17a–17h. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations**).

Identification of the responsible agent may allow for substitution of a similar agent to which the patient's virus is sensitive. Knowledge of the patient's prior antiretroviral history and, if possible, viral resistance profile prior to the current course of antiretroviral therapy is essential. Any new agent used should be assessed for likely effectiveness against the patient's virus and for possible interactions with the other medications the patient will take.

Experience with antiretroviral drugs has led to the recognition of several types of distinct adverse drug effects that may be most common with certain antiretroviral drugs or drug classes (see **Tables 17a–17h. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations**).

The physician, patient, and caregiver should discuss the response to a medication-related toxicity, taking into account the severity of toxicity, the relative need for viral suppression, and the available antiretroviral options. In general, mild and moderate toxicities do not require discontinuation of therapy or drug substitution; symptomatic treatment may be given, such as antihistamines for a mild rash. For some moderate toxicities, substituting the toxicity-associated antiretroviral drug with a drug in the same drug class but with a different toxicity profile may be sufficient and discontinuation of all therapy may not be required. Severe, life-threatening toxicity requires discontinuation of all antiretroviral drugs and the initiation of appropriate supportive therapy (depending on the type of toxicity). Another drug can be substituted for the drug associated with the toxicity once the patient is stabilized and the toxicity is resolved.

When a patient experiences an unacceptable adverse effect from antiretroviral therapy every attempt should be made to identify the offending agent and replace the drug with another effective agent to minimize the amount of time a patient is on suboptimal therapy. For example, if therapy needs to be stopped due to a severe or life-threatening side effect, all antiretroviral drugs should be stopped. Once the offending drug or alternative cause for the adverse event has been determined, planning can begin for resumption of therapy with a new antiretroviral drug regimen that does not contain the offending drug or with the original regimen if the event is attributable to another cause. All drugs in the antiretroviral regimen should then be started simultaneously, rather than starting them one at a time and observing for adverse effects. Many experts recommend stopping

efavirenz or nevirapine several days before stopping other drugs, if possible, because these drugs have a significantly longer half-life than NRTI antiretroviral drugs. However, if a patient has a severe or life-threatening toxicity, all components of the drug regimen should be stopped simultaneously, regardless of drug half-life.

When therapy is changed because of toxicity or intolerance in the context of virologic suppression, agents with different toxicity and side-effect profiles should be chosen, when possible. Clinicians should have comprehensive knowledge of the toxicity profile of each agent before selecting a new regimen. In the event of drug intolerance, changing a single drug in a multi-drug regimen is a permissible option. For a patient who is not virally suppressed, a single drug substitution with an active agent is generally not recommended due to concern for development of resistance (see **Approach to the Management of Antiretroviral Treatment Failure**).

Therapeutic drug monitoring (TDM) is not available on a routine basis to most clinicians, and the settings in which TDM is useful are unclear, especially in children. One such setting, however, may be in the context of a child with mild or moderate toxicity possibly attributable to a particular antiretroviral agent (see **Role of Therapeutic Drug Monitoring in Management of Treatment Failure**). In this situation, it is reasonable for the clinician to use TDM (if available) to determine if the toxicity is due to a concentration of drug exceeding the normal therapeutic range. This is the only setting in which dose reduction would be considered appropriate management of drug toxicity, and even then it should be used with caution.

Management strategies for drug intolerance include:

- Symptomatic treatment of mild-to-moderate transient side effects.
- If necessary, change from one drug to another drug to which the patient's virus is sensitive (e.g., change to stavudine for zidovudine-related anemia or to nevirapine for efavirenz-related central nervous system symptoms).
- Change in drug class, if necessary (e.g., from a PI to an NNRTI or vice versa) and if the patient's virus is sensitive to a drug in that class.
- Dose reduction only when drug levels are determined excessive.

Tables 17a–17h. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations describe specific adverse drug effects observed in children, including lactic acidosis, hepatic toxicity, fat maldistribution and body habitus changes, hyperlipidemia, hyperglycemia, osteopenia, hematological complications, and hypersensitivity reactions and skin rashes. The tables include information on common causative drugs, estimated frequency of occurrence, timing of symptoms, risk factors, potential preventive measures, and suggested clinical management strategies and provide selected references regarding these toxicities in pediatric patients.

Table 17a. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations – Hematologic Effects

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Hematologic Effects:						
Anemia*	Principally ZDV	Onset: Variable, weeks to months Presentation: • Most commonly asymptomatic or mild fatigue, pallor, tachypnea • Rarely, congestive heart failure	HIV-exposed newborns: • Uncommon but coincident with physiologic Hgb nadir HIV-infected children on ARVs: • 2–3 times more common with ZDV-containing regimens • Less frequent in recent studies, possibly due to lower dosing of ZDV	HIV-exposed newborns: • Premature birth • *In utero* exposure to ARVs • Advanced maternal HIV disease • Neonatal blood loss HIV-infected children on ARVs: • Underlying hemoglobinopathy (sickle cell disease, G6PD deficiency) • Poorly controlled HIV • Marrow-toxic drugs (e.g., trimethoprim-sulfamethoxazole, rifabutin) • Iron deficiency	HIV-exposed newborns: • Monitor CBC at birth. • Consider repeat CBC at 4 weeks for higher risk babies (exposed to ARVs *in utero* or as neonates, premature birth, or low birth Hgb). HIV-infected children on ARVs: • Avoid ZDV in children with anemia when alternative agents are available. • Monitor CBC 3–4 times per year as part of routine care.	HIV-exposed newborns: • Rarely require intervention unless Hgb is <7.0 gm/dL or anemia is associated with symptoms. • Consider discontinuing ZDV if ≥4 weeks of 6-week ZDV prophylaxis regimen are already completed. (see **Perinatal Guidelines**†). HIV-infected children on ARVs: • Discontinue non-ARV marrow-toxic drugs if feasible. • Treat coexisting iron deficiency, OIs, malignancies. • Rarely necessary to discontinue ARV therapy. • For persistent anemia thought to be associated with ARVs: o change to a non-ZDV-containing regimen; o give erythropoietin 50–200 IU/kg/dose 3 times weekly.

Table 17a. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations – Hematologic Effects

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Neutropenia*	Principally ZDV	Onset: Variable Presentation: • Most commonly asymptomatic with ANC >500 cells/mm^3 • Associated with increased bacterial infections if ANC persistently <500 cells/mm^3	HIV-exposed newborns: • Rare HIV-infected children on ARVs: • 9.9%–26.8% of children on ARVs, depending upon the ARV regimen • Higher with ZDV-containing regimens	HIV-exposed newborns: • *In utero* exposure to ARVs HIV-infected children on ARVs: • Poorly controlled HIV infection • Marrow-toxic drugs (e.g., trimethoprim-sulfamethoxazole, ganciclovir, hydroxyurea, rifabutin)	HIV-infected children on ARVs: • Monitor CBC 3–4 times per year as part of routine care.	HIV-infected children on ARVs: • Intervention typically not necessary unless ANC <500 cells/mm^3 for prolonged periods or if associated with recurrent infections. • Discontinue non-ARV marrow-toxic drugs if feasible. • Treat coexisting OIs, malignancies. • Rarely necessary to discontinue ARV therapy. • For persistent neutropenia thought to be associated with ARVs: o change to a non-ZDV-containing regimen o give G-CSF 5–10 mcg/kg once daily (doses up to 20 mcg/kg have been used).

* HIV infection itself, opportunistic infections, and medications used to prevent OIs, such as trimethroprim-sulfamethoxazole, may all contribute to anemia, neutropenia, and thrombocytopenia.

† Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States

Key to Abbreviations: ANC = absolute neutrophil count; ARVs = antiretrovirals; CBC = complete blood count; G6PD = glucose-6-phosphate dehydrogenase; G-CSF = granulocyte colony-stimulating factor; Hgb = hemoglobin; IU = International Unit; OIs = opportunistic infections; ZDV = zidovudine

References

1. Englund JA, Baker CJ, Raskino C, et al. Zidovudine, didanosine, or both as the initial treatment for symptomatic HIV-infected children. AIDS Clinical Trials Group (ACTG) Study 152 Team. *N Engl J Med*. 1997;336(24):1704-12.
2. Starr SE, Fletcher CV, Spector SA, et al. Combination therapy with efavirenz, nelfinavir, and nucleoside reverse- transcriptase inhibitors in children infected with human immunodeficiency virus type 1. Pediatric AIDS Clinical Trials Group 382 Team. *N Engl J Med*. 1999;341(25):1874-81.
3. Connor EM, Sperling RS, Gelber R, et al. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. Pediatric AIDS Clinical Trials Group Protocol 076 Study Group. *N Engl J Med*. 1994;331(18):1173-80.
4. Krogstad P, Lee S, Johnson G, et al. Nucleoside-analogue reverse-transcriptase inhibitors plus nevirapine, nelfinavir, or ritonavir for pretreated children infected with human immunodeficiency virus type 1. *Clin Infect Dis*. 2002;34(7):991-1001.
5. McKinney RE Jr, Johnson GM, Stanley K, et al. A randomized study of combined zidovudine-lamivudine versus didanosine monotherapy in children with symptomatic therapy-naive HIV-1 infection. The Pediatric AIDS Clinical Trials Group Protocol 300 Study Team. *J Pediatr*. 1998;133(4):500-8.
6. Najean Y, Rain JD. The mechanism of thrombocytopenia in patients with HIV infection. *J Lab Clin Med*. 1994;123(3):415-20.
7. Caselli D, Maccabruni A, Zuccotti GV, et al. Recombinant erythropoietin for treatment of anaemia in HIV-infected children. *AIDS*. 1996;10(8):929-31.
8. Allen UD, Kirby MA, Goeree R. Cost-effectiveness of recombinant human erythropoietin versus transfusions in the treatment of zidovudine-related anemia in HIV-infected children. *Pediatr AIDS HIV Infect*. 1997;8(1):4-11.
9. Mueller BU, Jacobsen F, Butler KM, et al. Combination treatment with azidothymidine and granulocyte colony-stimulating factor in children with human immunodeficiency virus infection. *J Pediatr*. 1992;121(5 Pt 1):792-802.
10. Bussel JB, Graziano JN, Kimberly RP, et al. Intravenous anti-D treatment of immune thrombocytopenic purpura: analysis of efficacy, toxicity, and mechanism of effect. *Blood*. 1991;77(9):1884-93.
11. Scaradavou A, Woo B, Woloski BM, et al. Intravenous anti-D treatment of immune thrombocytopenic purpura: experience in 272 patients. *Blood*. 1997;89(8):2689-700.

Table 17b. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations – Hepatic Events

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Hepatic Events:						
Hepatic toxicity (elevated AST, ALT, clinical hepatitis)	All ARVs	Onset: • *NNRTI and PI therapy*: Within 12 weeks of initiation. • *NRTI therapy*: Within months to years of initiation. • *Any antiretroviral combination regimen*: Early due to immune reconstitution inflammatory syndrome. Presentation: • Asymptomatic elevation of AST, ALT. • May be associated with symptoms of clinical hepatitis including nausea, fatigue, and jaundice. • NRTIs, especially ZDV, ddI, d4T, may be associated with lactic acidosis and hepatic steatosis. • Rarely, prolonged exposure to ddI is associated with non-cirrhotic portal hypertension with esophageal varicies.	• Uncommon in children. • Frequency varies with different agents and drug combinations (NVP, TPV of particular concern).	• HBV or HCV coinfection • Elevated baseline ALT, AST • Other hepatotoxic medications • Alcohol use • Underlying liver disease • For NVP-associated hepatic events in adults: o female with pre-NVP CD4 >250 cells/mm^3 o male with pre-NVP CD4 >400 cells/mm^3 • Higher drug concentrations for PIs, particularly TPV	Prevention: Avoid concomitant use of hepatotoxic medications. Monitoring: *For ARVs other than NVP*: Obtain AST, ALT at baseline and at least every 3–4 months or more frequently in at-risk patients (e.g., HBV or HCV coinfected, elevated baseline AST, ALT). *For NVP*: Obtain AST, ALT at baseline, at 2 and 4 weeks, then every 3 months.	• In asymptomatic patients with ALT or AST >5–10 times ULN, some may consider discontinuing ARVs, others may continue therapy with close monitoring. • If hepatic enzymes elevated >5–10 times ULN, most clinicians would avoid NVP. • In symptomatic patients, discontinue all ARVs and other potential hepatotoxic agents and avoid restart of the offending agent. • If a symptomatic hepatic event occurs on NVP, permanently discontinue NVP (see also NVP hypersensitivity). • When clinical hepatitis is associated with lactic acidosis, avoid restart of the most likely agent, NRTIs, ZDV, d4T,

Table 17b. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations – Hepatic Events

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
		• AST, ALT elevations while on NVP or ABC may be associated with a hypersensitivity reaction. • HBV-coinfected patients may develop severe hepatic flare with initiation, withdrawal, or when resistance develops with 3TC, FTC, TDF.				ddI in particular (see also lactic acidosis). • Rule out coinfection with HAV, HBV, HCV, EBV, and CMV.
Indirect hyperbilirubinemia	IDV, ATV	Onset: Early in therapy. Presentation: • Jaundice. • Asymptomatic elevation of indirect bilirubin levels.	HIV-infected children receiving ATV: 49% developed increased total bilirubin levels (≥3.2 mg/dL); 13% had jaundice/scleral icterus.	Not associated with HBV or HCV.	Monitoring: Assess bilirubin levels periodically, especially in first few months on regimen.	Not necessary to discontinue the offending agent except for cosmetic reasons (hyperbilirubinemia may improve over time).

Key to Abbreviations: 3TC = lamivudine; ABC = abacavir; ALT = alanine transaminase; ARVs = antiretrovirals; AST = aspartate aminotransferase; ATV = atazanavir; CMV = cytomegalovirus; d4T = stavudine; ddI = didanosine; EBV = Epstein-Barr virus; FTC = emtricitabine; HAV = hepatitis A virus; HBV = hepatitis B virus; HCV = hepatitis C virus; IDV = indinavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; TDF = tenofovir disoproxil fumarate; TPV = tipranavir; ULN = upper limit of normal; ZDV = zidovudine

References

1. Aceti A, Pasquazzi C, Zechini B, et al. Hepatotoxicity development during antiretroviral therapy containing protease inhibitors in patients with hiv: The role of hepatitis b and c virus infection. *J Acquir Immune Defic Syndr*. 2002;29(1)**,** 41-8.
2. Baylor MS, Johann-Liang R. Hepatotoxicity associated with nevirapine use. *J Acquir Immune Defic Syndr*. 2004;35(5)**,** 538-9.
3. Busti AJ, Hall RgandMargolis DM. Atazanavir for the treatment of human immunodeficiency virus infection. *Pharmcotherapy*. 2004;24(12)**,** 1732-47.
4. Dieterich DT, Robinson PA, Love J, Stern JO. Drug-induced liver injury associated with the use of nonnucleoside reverse-transcriptase inhibitors. *Clin Infect Dis*. 2004;38(Suppl 2)**,** S80-9.

5. Kontorinis N, Dieterich DT. Toxicity of non-nucleoside analogue reverse transcriptase inhibitors. *Semin Liver Dis*. 2003;23(2)**,** 173-82.
6. Kovari H, Ledergerber B, Battegay M, et al. Incidence and risk factors for chronic elevation of alanine aminotransferase levels in HIV-infected persons without hepatitis B or C virus co-infection. *Clin Infect Dis*. 2010;50:502-11.
7. Kovari H, Ledergerber B, Peter U et al. Association of noncirrhotic portal hypertension in HIV-infected persons and antiretroviral therapy with didanosine: a nested case-control study. *Clin Infect Dis*. 2009;49(4):626-635.
8. Levy V, Grant RM. Antiretroviral therapy for hepatitis b virus-hiv-coinfected patients: Promises and pitfalls. *Clin Infect Dis*. 2006;43(7)**,** 904-10.
9. Montessori V, Harris M, Montaner JS. Hepatotoxicity of nucleoside reverse transcriptase inhibitors. *Semin Liver Dis*. 2003;23(2)**,** 167-72.
10. Nunez M, Lana R, Mendoza JL, et al. Risk factors for severe hepatic injury after introduction of highly active antiretroviral therapy. *J Acquir Immune Defic Syndr*. 2001;27(5)**,** 426-31.
11. Pol S, Lebray P, Vallet-Pichard A. HIV infection and hepatic enzyme abnormalities: Intricacies of the pathogenic mechanisms. *Clin Infect Dis*. 2004;38(Suppl 2)**,** S65-72.
12. Puoti M, Torti C, Ripamonti D, et al. Severe hepatotoxicity during combination antiretroviral treatment: Incidence, liver histology, and outcome. *J Acquir Immune Defic Syndr*. 2003;32(3)**,** 259-67.
13. Stern JO, Robinson PA, Love J, et al. A comprehensive hepatic safety analysis of nevirapine in different populations of hiv infected patients. *J Acquir Immune Defic Syndr*. 2003;34(Suppl 1)**,** S21-33.
14. Sulkowski MS (2004) Drug-induced liver injury associated with antiretroviral therapy that includes hiv-1 protease inhibitors. *Clin Infect Dis,* 38(Suppl 2)**,** S90-7.
15. Van Dyke RB, Wang L, Williams PL. Toxicities associated with dual nucleoside reverse-transcriptase inhibitor regimens in HIV-infected children. *J Infect Dis.* 2008;198:1599-608.
16. Wit FW, Weverling GJ, Weel J, et al. Incidence of and risk factors for severe hepatotoxicity associated with antiretroviral combination therapy. *J Infect Dis*. 2002;186(1)**,** 23-31.

Table 17c. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations – Insulin Resistance, Asymptomatic Hyperglycemia, Diabetes Mellitus

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Insulin resistance, asymptomatic hyperglycemia, diabetes mellitus (DM)*	• Thymidine analogue NRTIs (d4T > ZDV) • Some PIs but unclear if class effect	Onset: Weeks to months after beginning therapy; median = 60 days (adult data) Presentation: • *Most commonly*: Asymptomatic fasting hyperglycemia, possibly in the setting of lipodystrophy, metabolic syndrome, or growth delay • *Also possible*: Frank DM (polyuria, polydipsia, polyphagia, fatigue, hyperglycemia)	Impaired fasting glucose: • *ARV-treated adults*: 3%–25% • *ARV-treated children*: 0%–7% Impaired glucose tolerance: • *ARV-treated adults*: 16%–35% • *ARV-treated children*: 3%–4% DM: • *ARV-treated adults*: 1.2–4.7 per 100 person-years (2–4-fold greater than that for non-HIV-infected adults) • *ARV-treated children*: Very rare in HIV-infected children	Risk factors for Type 2 DM: • Lipodystrophy, metabolic syndrome • Family history of DM • Overweight, obesity	Prevention: • Lifestyle modification (see Management). • Although uncertain, avoiding use of d4T, PI-containing regimens might reduce risk. Monitoring: • Monitor for polydipsia, polyuria, polyphagia, change in body habitus, acanthosis nigricans. • Obtain random plasma glucose (RPG) levels at: o initiation of ARV therapy; o 3–6 months later; and o annually thereafter. • For RPG ≥140 mg/dL, obtain fasting plasma glucose (FPG) performed after 8-hour fast and consider referral to endocrinologist.	• Counsel lifestyle modification (low fat diet, exercise, no smoking). • Consider changing from thymidine analogue NRTI (d4T or ZDV)-containing regimen. • *For either RPG ≥200 mg/dL plus symptoms of DM or FPG ≥126 mg/dL*: Diagnostic criteria for DM are met; consult endocrinologist. • *FPG 100–125 mg/dL*: Impaired FPG is suggestive of insulin resistance; consult endocrinologist. • *FPG <100 mg/dL*: Suggests no current insulin resistance; recheck in 6–12 months.

***** Insulin resistance, asymptomatic hyperglycemia, and diabetes mellitus form a spectrum of increasing severity. *Insulin resistance* is often defined as elevated insulin levels for the level of glucose observed; *impaired fasting plasma glucose* (impaired FPG) as an FPG of 100–125 mg/dL; *impaired glucose tolerance* is an elevated 2-hour PG of 140–199 mg/dL in a standard oral glucose tolerance test (OGTT); and *diabetes mellitus* as either a FPG ≥126 mg/dL, a random PG ≥200 mg/dL in a patient with hyperglycemia symptoms, a HgbA1C of ≥6.5%, or a 2-hour PG after OGTT ≥200 mg/dL. However, the Panel does not recommend routine determinations of insulin levels, glycosylated hemoglobin A1C, or glucose tolerance without consultation with an endocrinologist; these guidelines are instead based on the readily available random and fasting plasma glucose levels.

Key to Abbreviations: ARV = antiretroviral; d4T = stavudine; DM = diabetes mellitus; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; ZDV = zidovudine

References

Clinical features of hyperglycemia, insulin resistance, and diabetes mellitus

1. Amaya RA, Kozinetz CA, Mcmeans A, et al. Lipodystrophy syndrome in human immunodeficiency virus-infected children. *Pediatr Infect Dis J*. 2002;21(5)**,** 405-10.
2. Arpadi SM, Cuff PA, Horlick M, et al. Lipodystrophy in HIV-infected children is associated with high viral load and low CD4+ -lymphocyte count and CD4+ -lymphocyte percentage at baseline and use of protease inhibitors and stavudine. *J Acquir Immune Defic Syndr*. 2001;27(1)**,** 30-4.
3. Beregszaszi M, Dollfus C, Levine M, et al. Longitudinal evaluation and risk factors of lipodystrophy and associated metabolic changes in HIV-infected children. *J Acquir Immune Defic Syndr*. 2005;40(2)**,** 161-8.
4. Bitnun A, Sochett E, Babyn P, et al. Serum lipids, glucose homeostasis and abdominal adipose tissue distribution in protease inhibitor-treated and naive HIV-infected children. *AIDS*. 2003;17(9)**,** 1319-27.
5. Bitnun A, Sochett E, Dick PT, et al. Insulin sensitivity and beta-cell function in protease inhibitor-treated and -naive human immunodeficiency virus-infected children. *J Clin Endocrinol Metab*. 2005;90(1)**,** 168-74.
6. Bockhorst JL, Ksseiry I, Toye M, et al. Evidence of human immunodeficiency virus-associated lipodystrophy syndrome in children treated with protease inhibitors. *Pediatr Infect Dis J*. 2003;22(5)**,** 463-5.
7. Hadigan C. Insulin resistance among HIV-infected patients: Unraveling the mechanism. *Clin Infect Dis*. 2005;41(9)**,** 1341-2.
8. Leonard EG, McComsey GA. Antiretroviral therapy in HIV-infected children: The metabolic cost of improved survival. *Infect Dis Clin North Am*. 2005;19(3)**,** 713-29.
9. McComsey GA, Leonard E. Metabolic complications of HIV therapy in children. *AIDS*. 2004;18(13)**,** 1753-68.
10. Mulligan K, Grunfeld C, Tai VW, et al. Hyperlipidemia and insulin resistance are induced by protease inhibitors independent of changes in body composition in patients with HIV infection. *J Acquir Immune Defic Syndr*. 2000;23(1)**,** 35-43.
11. Morse CG, Kovacs JA. Metabolic and skeletal complications of HIV infection: The price of success. *JAMA*. 2006;296(7)**,** 844-54.
12. Brown TT, Cole SR, Li X, et al. Antiretroviral therapy and the prevalence and incidence of diabetes mellitus in the multicenter aids cohort study. *Arch Intern Med*. 2006;165(10)**,** 1179-84.
13. Justman JE, Benning L, Danoff A, et al. Protease inhibitor use and the incidence of diabetes mellitus in a large cohort of HIV-infected women. *J Acquir Immune Defic Syndr*. 2003;32(3)**,** 298-302.

14. Abdel-Khalek I, Moallem HJ, Fikrig S, Castells S. New onset diabetes mellitus in an HIV-positive adolescent. *AIDS Patient Care STDS*. 1998;12(3)**,** 167-9.

15. Aldrovandi GM, Lindsey JC, Jacobson DL, et al. Morphologic and metabolic abnormalities in vertically HIV-infected children and youth. *AIDS*. 2009;23(6):661-72.

16. Chantry CJ, Hughes MD, Alvero C, et al. Lipid and glucose alterations in HIV-infected children beginning or changing antiretroviral therapy. *Pediatrics*. 2008;122(1):e129-38.

17. Blümer RM, van Vonderen MG, Sutinen J, et al. Zidovudine/lamivudine contributes to insulin resistance within 3 months of starting combination antiretroviral therapy. *AIDS*. 2008;22(2):227-36.

18. Lee GA, Rao M, Mulligan K, et al. Effects of ritonavir and amprenavir on insulin sensitivity in healthy volunteers. *AIDS*. 2007;21(16):2183-90.

19. Tien PC, Schneider MF, Cole SR, et al. Antiretroviral therapy exposure and insulin resistance in the Women's Interagency HIV study. *J Acquir Immune Defic Syndr*. 2008;49(4):369-76.

Management of hyperglycemia, insulin resistance, and diabetes mellitus

20. American Diabetes Association. Type 2 diabetes in children and adolescents (consensus statement). *Diabetes Care***.** 2000;23:381-9.

21. American Diabetes Association. Screening for type 2 diabetes (position statement). *Diabetes Care*. 2004;27(Suppl 1)**,** S11-S14.

22. American Diabetes Association. Standards of medical care in diabetes—2010 (position statement). *Diabetes Care*. 2010;33(Suppl 1):S11-61.

23. Nathan DM, Buse JB, Davidson MB, et al. Medical management of hyperglycemia in type 2 diabetes: A consensus algorithm for the initiation and adjustment of therapy: A consensus statement from the American Diabetes Association; European Association for Study of Diabetes. *Diabetes Care*. 2009;32(1):193-203.

24. Nathan DM, Davidson MB, DeFronzo RA, et al. (2007) Impaired fasting glucose and impaired glucose tolerance: implications for care. *Diabetes Care*, 30(3):753-759.

25. Schambelan M, Benson CA, Carr A, et al. Management of metabolic complications associated with antiretroviral therapy for HIV-1 infection: Recommendations of an International AIDS Society-USA panel. *J Acquir Immune Defic Syndr* 2002;31(3)**,** 257-75.

26. Wohl DA, McComsey G, Tebas P, et al. Current concepts in the diagnosis and management of metabolic complications of HIV infection and its therapy. *Clin Infect Dis*. 2006;43(5)**,** 645-53.

Table 17d. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations – Dyslipidemia

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
Dyslipidemia	PIs: All PIs; lower incidence with ATV NRTIs: Especially d4T	Onset: Weeks to months after beginning therapy Presentation: *PIs*: ↑LDL-C, TC, and TG *NNRTIs*: ↑LDL-C, TC, and HDL-C *NRTIs*: ↑LDL-C, TC, and TG	20%–50% of children receiving combination antiretroviral therapy will have lipoprotein abnormalities.	• HIV infection • Poor diet • Lack of exercise • Obesity • Hypertension • Smoking • Family history of dyslipidemia or premature CVD • Metabolic syndrome	Prevention: Low fat diet, exercise, no smoking. Monitoring: *Adolescents and adults*: Obtain fasting (12-hour) TC, HDL-C, TG, LDL-C prior to initiating or changing ARV therapy, 3–6 months thereafter, then every 6–12 months. *Children without lipid abnormalities or risk factors*: Obtain nonfasting screening lipid profiles prior to initiating or changing therapy and every 6–12 months if stable. If TG or LDL-C is elevated, obtain fasting blood tests. *Children with lipid abnormalities and/or additional risk factors*: Obtain fasting (12-hour) TC, HDL-C, TG, LDL-C prior to initiating or changing therapy and every 6 months (or more often if indicated). *Children receiving lipid-lowering therapy with statins or fibrates*: Obtain fasting (12-hour) lipid profiles, liver function tests (LFTs), and creatine kinase (CK) prior to initiating lipid therapy and at 4 weeks and 8 weeks after starting lipid therapy. If minimal	• Counsel lifestyle modification (low fat diet, exercise, smoking cessation) for adequate trial period (3–6 months). • Switch to a new ARV regimen less likely to cause lipid abnormalities.* Pharmacologic Management: • Prompt intervention is required in patients with TG ≥500 mg/dL (high risk of pancreatitis). • Statins such as pravastatin or atorvastatin† • Fibrates such as gemfibrozil and fenofibrate may be used as alternative agents for adults with ↑TG but are not approved for use in children. • N-3 polyunsaturated fatty acids (PUFAs) derived from fish oils • No consensus as to what LDL-C should prompt treatment in children receiving ARVs ‡ o *High-risk patients*:

Table 17d. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations – Dyslipidemia

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
					alterations in AST, ALT, and CK, then every 3 months. Whenever doses of antihyperlipidemic agents are increased, repeat at 4 weeks.	Goal LDL-C ≤100 mg/dL o *Moderate-risk patients*: Goal LDL-C ≤130 mg/dL o *At-risk patients*: Goal LDL-C ≤160 mg/dL.

[*] The risks of new treatment-related toxicities and virologic failure that could occur with changes in therapy must be weighed against the potential risk of drug interactions and toxicities associated with the use of lipid-lowering agents.

[†]Statins are teratogenic and should not be used in female patients who may become pregnant. Serious toxicities include hepatotoxicity, skeletal muscle toxicity, and rhabdomyolysis. Experience with statins limited to children >6 years of age. Multiple drug interactions with lipid-lowering agents and ARVs.

Pravastatin (Pravachol)
8–13 years of age: 20 mg once daily; 14–18 years of age: 40 mg once daily

Atorvastatin (Lipitor)
>6 years of age: 10–20 mg once daily

[‡]It is unclear what the long-term risks of lipid abnormalities are in children receiving combination antiretroviral therapy. However, persistent dyslipidemia in children is likely to lead to premature cardiovascular disease.

Key to Abbreviations: ALT = alanine transaminase; ARV = antiretroviral; AST = aspartate aminotransferase; CVD = cardiovascular disease; d4T = stavudine; HDL-C = high-density lipoprotein cholesterol; LDL-C = low density lipoprotein cholesterol; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; TC = total cholesterol; TG = triglycerides; ZDV = zidovudine

References

1. Cheseaux JJ, Jotterand V, Aebi C, et al. Hyperlipidemia in HIV-infected children treated with protease inhibitors: relevance for cardiovascular diseases. *J Acquir Immune Defic Syndr*. 2002;30(3):288-93.
2. McCrindle BW, Urbina EM, Dennison BA, et al. Drug therapy of high-risk lipid abnormalities in children and adolescents: A scientific statement from the American Heart Association Atherosclerosis, Hypertension, and Obesity in Youth Committee, Council of Cardiovascular Disease in the Young, With the Council on Cardiovascular Nursing. *Circulation*. 2007;115:1948-1967.
3. Lainka E, Oezbek S, Falck M, et al. Marked dyslipidemia in human immunodeficiency virus-infected children on protease inhibitor-containing antiretroviral therapy. *Pediatrics*. 2002;110;e56.
4. Kavey RE, Allada V, Daniels SR, et al. Cardiovascular risk reduction in high-risk pediatric patients: a scientific statement from the American Heart Association Expert Panel on Population and Prevention Science; the Councils on Cardiovascular Disease in the Young, Epidemiology and Prevention, Nutrition, Physical Activity and Metabolism, High Blood Pressure Research, Cardiovascular Nursing, and the Kidney in Heart Disease; and the Interdisciplinary Working Group on Quality of Care and Outcomes Research: Endorsed by the American Academy of Pediatrics. *Circulation*. 2006;114: 2710-2738.

5. Kavey RE, Daniels SR, Lauer RM, et al. American Heart Association Guidelines for Primary Prevention of Atherosclerotic Cardiovascular Disease Beginning in Childhood. *Circulation*. 2003;107:1562-1566.
6. Belay B, Belamarich PF, Tom-Revzon C. The use of statins in pediatrics: knowledge base, limitations, and future directions. *Pediatrics*. 2007;119:370-0787.
7. Farley J, Gona P, Crain M, Cervia J, Oleske J, Seage III G, Lindsey J for the Pediatric AIDS Clinical Trials Study 219C Team. Prevalence of elevated cholesterol and associated risk factors among perinatally HIV-infected children (4-19 years) in PACTG 219C. *J Acquir Immune Defic Syndr*. 2004;38:480-487.
8. McComsey G, Bhumbra N, Ma JF, et al. Impact of protease inhibitor substitution with efavirenz in HIV-infected children: results of the First Pediatric Switch Study. *Pediatrics*. 2003;111(3):e275-81.
9. De Truchis P, Kirkstetter M, Perier A, et al. Reduction in triglyceride level with N-3 polyunsaturated fatty acids in HIV-infected patients taking potent antiretroviral therapy. A randomized prospective trial. *J Acquir Immune Defic Syndr*. 2007;44:278-285.
10. Engler MM, Engler MB, Malloy MJ, et al. Effect of docosahexaenoic acid on lipoprotein subclasses in hyperlipidemic children (the EARLY study). *Am J Cardiol*. 2005;95:869-871.
11. Gerber JG, Kitch DW, Fictenbaum CJ, et al. Fish oil and fenofibrate for the treatment of hypertriglyceridemia in HIV-infected subjects on antiretroviral therapy. Results of ACTG A5186. *J Acquir Immune Defic Syndr*. 2008;47:459-466.
12. The Strategies for Management of Antiretroviral Therapy (SMART) Study Group. CD4+ count-guided interruption of antiretroviral treatment. *New Engl J Med*. 2006;355:2283-96.
13. The D:A:D Study Group. Class of antiretroviral drugs and the risk of myocardial infarction. *New Engl J Med*. 2007;356:1723-35.
14. Vigano A, Adrovandi GM, Giacomet V, et al. Improvement in dyslipidemia after switching stavudine to tenofovir and replacing protease inhibitor with efavirenz in HIV-infected children. *Antiviral Therapy*. 2005;10:917-924.
15. European Paediatric Lipodystrophy Group. Antiretroviral therapy, fat redistribution, and hyperlipidemia in HIV-infected children in Europe. *AIDS*. 2004; 18:1443-1451.
16. Rhoads MP, Smith CJ, Tudor-Williams G, et al. Effects of HAART on pediatric metabolite levels. *HIV Med*. 2006; 7(1):16-24.
17. Carter RJ, Wiener J, Abrams EJ, et al. Dyslipidemia among perinatally HIV-infected children enrolled in the PACTS-HOPE cohort, 1999-2004: A longitudinal analysis. *J Acquir Immune Defic Syndr*. 2006; 41:453-460.
18. Tassiopoulos K, Williams PL, Seage GR, et al. Association of hypercholesterolemia incidence with antiretroviral treatment, including protease inhibitors, among perinatally HIV-infected children. *J Acquir Immune Defic Syndr*. 2008; 47:607-614.
19. Daniels SR, Greer FR, and the committee on nutrition. Lipid screening and cardiovascular health in childhood. *Pediatrics*. 2008; 122:198-208.
20. Kwiterovich PO. Recognition and management of dyslipidemia in children and adolescents. *J Clin Endocrinol Metab*. 2008; 93:4200-4209.
21. Currier JS. Update on cardiovascular complications in HIV infection. *Topics in HIV Medicine*. 2009;17: 98-103.
22. Dube M, Fenton M. Lipid abnornalities. *Clin Infect Dis*. 2003;36(Suppl 2):S79-83.

Table 17e. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations – Skin Rash, SJS/EM/TEN, HSR

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Skin rash	NVP, EFV, ETR, FPV, ATV, FTC ABC, DRV, TPV, TDF, LPV/r, RAL, MVC	Onset: The first few days to weeks after starting therapy. Presentation: Most rashes are mild-to-moderate, diffuse maculopapular eruptions. Some rashes are a manifestation of systemic hypersensitivity (see also hypersensitivity reaction).	Common (>10% adults and/or children): NVP, EFV, ETR, FPV, ATV, FTC Less common (5%–10%): ABC, DRV, TPV, TDF Unusual (2%–4%): LPV/r, RAL, MVC	• Rash with a sulfonamide is a risk factor for rash with NNRTIs and the PIs containing a sulfonamide moiety (FPV, APV, DRV, TPV). • Possible association of the HLA-DRB 101 allele with rash with NVP or EFV.	When starting NVP or restarting after interruptions ≥7 days: • Once-daily dosing for 2 weeks (50% of total daily dose), then escalation to target dose with twice-daily dosing is associated with fewer rashes.* • Avoid the use of corticosteroids during NVP dose escalation. • Assess patient for rash severity and presence of systemic signs and symptoms (see also hypersensitivity reaction).	Mild-to-moderate rash: • Prescribe antihistamine as needed; the antiretroviral medication can be continued.* Severe rash (accompanied by blisters, fever, involvement of the oral/anal mucous membranes, conjunctivitis, edema, arthralgias): • Discontinue all ARVs and other possible causative agents such as cotrimoxazole. Do not restart the offending medication. (See SJS/EM/TEN.) • In case of SJS/EM/TEN with one NNRTI, many experts would avoid use of other NNRTIs. • Measure hepatic transaminases if rash develops with NVP treatment. If hepatic transaminases are

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
						elevated, NVP should be discontinued and not restarted (see NVP hypersensitivity).
	ENF	Onset: The first few days to weeks after starting therapy. Presentation: Local injection site reactions with pain, erythema, induration, nodules and cysts, pruritis, ecchymosis. Often multiple reactions at the same time.	Adults: >90% (resulted in ENF discontinuation in 7%)	Unknown,	• During routine visits assess patient for local reactions. • Rotate injection sites. • Massage area after injection.	• Continue the agent as tolerated by the patient, adjust injection technique, and rotate injection sites.
Stevens-Johnson syndrome (SJS)/ erythema multiforme major (EM)/toxic epidermal necrolysis (TEN)	NVP, EFV, ETR, FPV, ABC, DRV, ZDV, ddI, IDV, LPV/r, ATV	Onset: The first few days to weeks after initiating therapy. Presentation: Skin eruption occurs with mucous membrane ulceration, conjunctivitis. Can evolve into blister/bullae formation and can progress to skin necrosis. Systemic symptoms may include fever, tachycardia, malaise, myalgia, arthralgia.	Infrequent: NVP (0.3%), EFV (0.1%), ETR (<0.1%) Case reports: FPV, ABC, DRV, ZDV, ddI, IDV, LPV/r, ATV	Adults: • Female • Black • Asian • Hispanic.	• For NVP, 2-week lead-in period for start or restart for interruptions ≥7 days with once-daily dosing then dose escalation to twice daily as recommended may prevent the rash.* • Counsel families to report symptoms as soon as they appear.	• Discontinue all ARVs and other possible causative agents such as cotrimoxazole. • May need intensive care support, intravenous hydration, aggressive wound care, pain management, antipyretics, parenteral nutrition, and antibiotics in case of superinfection. • Corticosteroids and/or IVIG are sometimes used but use of each is controversial. • Do not reintroduce the offending

Table 17e. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations – Skin Rash, SJS/EM/TEN, HSR

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
						medication. • In case of SJS/EM/TEN with one NNRTI, many experts would avoid use of other NNRTIs.
Systemic hypersensitivity reaction (HSR) (with or without skin involvement)	ABC	Onset: Within the first 6 weeks with first use; within hours with reintroduction. Presentation: Symptoms include high fever, diffuse skin rash, malaise, nausea, headache, myalgia, arthralgia, diarrhea, vomiting, abdominal pain, pharyngitis, respiratory symptoms such as dyspnea. Symptoms worsen to include hypertension and vascular collapse with continuation. Symptoms can mimic anaphylaxis with rechallenge.	2.3%–9% (varies by racial/ethnic group)	• HLA-B*5701 (HSR very uncommon in people who are HLA-B*5701 negative); also HLA-DR7, HLA-DQ3. • Whites are at much greater risk of HSR than blacks or Asians.	• Screen for HLA-B*5701. • ABC should not be prescribed if HLA-B*5701 is positive. The patient should be labeled as ABC allergic in the medical record. • Counsel families about the signs and symptoms of HSR to ensure prompt reporting of reactions.	• Discontinue ARVs and investigate for other causes of the symptoms such as an intercurrent viral illness. Treat symptoms as necessary. • Most symptoms resolve by 48 hours after discontinuation of ABC. • Do not rechallenge with ABC even if the patient is HLA-B*5701 negative.
	NVP	Onset: Most frequent in the first few weeks of therapy but can occur through 18 weeks. Presentation: Flu-like symptoms (including nausea, vomiting, myalgia, fatigue, fever, abdominal pain, jaundice) with or	4% (2.5%–11%)	For adults: • Treatment naïve with higher CD4 count (>250 cells/mm^3 in women; >400 cells/mm3 in men) • Females 3-fold higher risk than males • NVP	• 2-week lead-in period for start or restart for interruptions ≥7 days with once-daily dosing then dose escalation to twice daily as recommended may reduce rash and hepatic events.*	• Discontinue ARVs. • Consider other causes for hepatitis and discontinue all hepatotoxic medications. • Provide supportive care as indicated and close monitoring. • Do not reintroduce NVP. The safety of other NNRTIs is

Table 17e. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations – Skin Rash, SJS/EM/TEN, HSR

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
		without skin rash that may progress to hepatic failure with encephalopathy. DRESS syndrome (drug rash with eosinophilia and systemic symptoms) has also been described.		hepatoxicitiy and hypersensitivity may be less common in prepubertal children than in adults.	• Counsel families about signs and symptoms of HSR to ensure prompt reporting of reactions. • Obtain AST and ALT in patients with rash. • Obtain AST and ALT at baseline, prior to dose escalation, 2 weeks post dose escalation, and at 3-month intervals thereafter. • Avoid use in women with CD4 >250 cells/mm^3 and in men with CD4 >400 cells/mm^3 unless benefits outweigh risks. • Do not use NVP in postexposure prophylaxis.	unknown following symptomatic hepatitis due to NVP, and many experts would avoid the NNRTI drug class when restarting treatment.
	ENF	Onset: Any time during therapy. Presentation: Symptoms may include rash, fever, nausea, vomiting, rigors, hypertension, elevated hepatic transaminases.	<1%	Unknown.	• Evaluate for hypersensitivity if the patient is symptomatic.	• Discontinue ARVs. • Rechallenge with ENF is not recommended.

* The prescribing information for nevirapine states that patients experiencing rash during the 14-day lead-in period should not have the nevirapine dose increased until the rash has resolved. However, prolonging the lead-in phase beyond 14 days may increase the risk of nevirapine resistance due to subtherapeutic drug levels. Management of children who have persistent mild or moderate rash after the lead-in period should be individualized and consultation with an expert in HIV care should be obtained. Nevirapine should be stopped if the rash is severe or is worsening or progressing.

Key to Abbreviations: ABC = abacavir; ALT = alanine transaminase; APV = amprenavir; ARVs = antiretrovirals; AST = aspartate aminotransferase; ATV = atazanavir; ddI = didanosine; DRV = darunavir; EFV = efavirenz; EM = erythema multiforme; ENF = enfuvirtide; ETR = etravirine; FTC = emtricitabine; FPV = fosamprenavir; HSR = hypersensitiviy reaction; IDV = indinavir; IVIG = intravenous immune globulin; LPV/r = lopinavir/ritonavir; MVC = maraviroc; NNRTI = non-nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; RAL = raltegravir; SJS = Stevens Johnson syndrome; TDF = tenofovir disoproxil fumarate; TEN = toxic epidermal necrolysis; TPV = tipranavir; ZDV = zidovudine

References

1. Baylor M, Ayime O, Truffa M, et al. Hepatotoxicity associated with nevirapine use in HIV-infected children. 12th Conference on Retrovirues and Opportunistic Infections; February 22-25, 2005; Boston, MA. Abstract 776.
2. Borras-Blasco J, Navarro-Ruiz A, Borras C, Castera E. Adverse cutaneous reactions associated with the newest antiretroviral drugs in patients with human immunodeficiency virus infection. *J Antimicrob Chem*. 2008;62,879-888.
3. Carr A, Cooper DA. Adverse effects of antiretroviral therapy. *Lancet*. 2000;356,1423-1430.
4. Davis CM, Shearer WT. Diagnosis and management of HIV drug hypersensitivity. *J Allergy Clin Immunol*. 2008;121,826-32.
5. Mallal S, Nolan D, Witt C, et al. Association between presence of HLA-B*5701, HLA-DR7 and HLA-DQ3 and hypersensitivity to HIV-1 reverse-transcriptase inhibitor abacavir. *Lancet*. 2002;359,727-732.
6. Mallal S, Phillips E, Carosi G, et al. HLA_B*5701 screening for hypersensitivity to abacavir. *N Engl J Med*. 2008;358,568-579.
7. Mirochnick M, Clarke DF, Dorenbaum A. Nevirapine: pharmacokinetic considerations in children and pregnant women. *Clin Pharmacokinet*. 2000;39,281-293.
8. Stern JO, Robinson PA, Love J, et al. A comprehensive hepatic safety analysis of nevirapine in different populations of HIV-infected patients. *J Acquir Immune Defic Syndr*. 2003;35,538-539.
9. Tas S, Simonart T. Management of drug rash with eosinophilia and systemic symptoms (DRESS syndrome): an update. *Dermatol*. 2003;206,353-6.
10. Trottier, B, Walmsley S, Reynes J, et al. Safety of enfuvirtide in combination with an optimized background of antiretrovirals in treatment-experienced HIV-1-infected adults over 48 weeks. *J Acquir Immune Defic Syndr*. 2005;40(4):413-21.
11. Vitezica ZG, Milpied B, Lonjou C, et el. HLA-DRB1*01 associated with cutaneous hypersensitivity induced by nevirapine and efavirenz. *AIDS*. 2008;22(4):540-1.

Table 17f. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations – Lipodystrophy, Lipohypertrophy, Lipoatrophy

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Lipodystrophy—General information		Onset: Trunk and limb fat initially increases within a few months of start of ART; however, peripheral fat wasting may not begin to appear for 12–24 months.	Adults: 2%–84% Children: 1%–33%, perhaps more common in adolescents than prepubertal children	• Genetic predisposition • Puberty • HIV-associated inflammation		
Central lipohypertrophy	• Most associated with PIs and EFV • Can occur in the absence of ART	Presentation: Central fat accumulation with increased abdominal girth, which may include dorsocervical fat pad (buffalo hump) and/or gynecomastia. The appearance of central lipohypertrophy is accentuated in the presence of peripheral fat wasting (lipoatrophy). In adults, waist circumference >102 cm (men) or >88 cm (women) is associated with increased risk of metabolic syndrome. For children and adolescents, waist circumference above the 75% percentile for age is associated with increased risk of metabolic syndrome.	See above	• PIs • EFV	Prevention: Diet and exercise. Monitoring: Measure waist circumference, waist to height ratio, and/or BMI (increase of each associated with development of metabolic syndrome).	• Diet and exercise, especially strength training. • Liposuction (Lipohypertrophy may reoccur after this cosmetic procedure; liposuction is not recommended for children.) • Recombinant human growth hormone or growth hormone-releasing hormone (investigational). • Metformin and rosiglitazone are not useful for treatment.

Facial/peripheral lipoatrophy	Most associated with thymidine analogue NRTI (d4T > ZDV)	Presentation: Thinning of subcutaneous fat in face, buttocks, and extremities, measured as decrease in trunk/limb fat by DXA or triceps skinfold thickness. Preservation of lean body mass distinguishes lipoatrophy from HIV-associated wasting.	Risk low in patients not treated with d4T or ZDV	• d4T and ZDV • Obesity prior to ART	Prevention: Avoid use of d4T and ZDV. Monitoring: Patient self-report and physical exam are the most sensitive methods of monitoring lipoatrophy.	• Switch from d4T or ZDV to other NRTIs if possible without loss of virologic control. • Poly-L-lactic acid is FDA approved for injection into areas of facial lipoatrophy in adults but difficult to use. Use is not reported for children. • Recombinant human leptin (investigational).

Key to Abbreviations: ART = antiretroviral therapy; ARVs = antiretrovirals; BMI = body mass index; d4T = stavudine; DXA = dual energy x-ray absorptiometry; EFV = efavirenz; FDA = Food and Drug Administration; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; ZDV = zidovudine

References

(See the archived version of Supplement III, February 23, 2009 Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection, (**http://www.aidsinfo.nih.gov**) for a more complete discussion and reference list.)

General Reviews

1. Fernández JR, Redden DT, Pietrobelli A, Allison DB. Waist circumference percentiles in nationally representative samples of African-American, European-American, and Mexican-American children and adolescents. *J Pediatr*. 2004;145:439-44.
2. Lee JM, Davis MM, Woolford SJ, Gurney JG. Waist circumference percentile thresholds for identifying adolescents with insulin resistance in clinical practice. *Pediatr Diabetes*. 2009;10:336-42.
3. Carr A and A Carr. Treatment strategies for HIV lipodystrophy. *Current Opinion in HIV & AIDS*. 2007;2(4):332-8.
4. Phillips DR, Hay P et al. Current perspectives on the management and prevention of antiretroviral-associated lipoatrophy. *Journal of Antimicrobial Chemotherapy*. 2008;62(5):866-71.
5. Wohl DA, McComsey G, et al. Current concepts in the diagnosis and management of metabolic complications of HIV infection and its therapy. *Clinical Infectious Diseases*. 2006;43(5):645-53

Associated ARVs/Etiology

6. Chang E, Sekhar R, et al. Dysregulated energy expenditure in HIV-infected patients: a mechanistic review. *Clinical Infectious Diseases*. 2007;44(11):1509-17.

7. Dube MP, Komarow L, et al. Long-term body fat outcomes in antiretroviral-naive participants randomized to nelfinavir or efavirenz or both plus dual nucleosides. Dual X-ray absorptiometry results from A5005s, a substudy of Adult Clinical Trials Group 384. *Journal of Acquired Immune Deficiency Syndromes: JAIDS*. 2007;45(5):508-14.
8. Haubrich RH, Riddler SA, et al. Metabolic outcomes in a randomized trial of nucleoside, nonnucleoside and protease inhibitor-sparing regimens for initial HIV treatment. *AIDS*. 2009;23(9):1109-18.
9. Hulgan T, Tebas P , et al. Hemochromatosis gene polymorphisms, mitochondrial haplogroups, and peripheral lipoatrophy during antiretroviral therapy [erratum appears in *J Infect Dis*. 2008;Jun 1;197(11):1630.*Journal of Infectious Diseases*. 2008;197(6):858-66.
10. McComseyGA, Libutti DE, et al. Mitochondrial RNA and DNA alterations in HIV lipoatrophy are linked to antiretroviral therapy and not to HIV infection. *Antiviral Therapy*. 2008;13(5):715-22.
11. Tien PC, Benson C, et al. The study of fat redistribution and metabolic change in HIV infection (FRAM): methods, design, and sample characteristics. *American Journal of Epidemiology*. 2006;163(9):860-9.
12. Van Dyke RB, Wang L, et al. Toxicities associated with dual nucleoside reverse-transcriptase inhibitor regimens in HIV-infected children. *Journal of Infectious Diseases*. 2008;198(11):1599-608.
13. Mulligan K, Parker RA, et al. Mixed patterns of changes in central and peripheral fat following initiation of antiretroviral therapy in a randomized trial. *Journal of Acquired Immune Deficiency Syndromes: JAIDS*. 2006;41(5):590-7.
14. Scherzer R, Shen W, et al. Comparison of dual-energy X-ray absorptiometry and magnetic resonance imaging-measured adipose tissue depots in HIV-infected and control subjects. *American Journal of Clinical Nutrition*. 2008;88(4):1088-96.

Management

15. Wohl DA, Brown TT. Management of morphologic changes associated with antiretroviral use in HIV-infected patients. J Acquir Immune Defic Syndr. 2008;49(Suppl 2):S93-S100.
16. Carey DL, Baker D, et al. A randomized, multicenter, open-label study of poly-L-lactic acid for HIV-1 facial lipoatrophy. *Journal of Acquired Immune Deficiency Syndromes: JAIDS*. 2007;46(5):581-9.
17. Cavalcanti RB, Raboud J, et al. A randomized, placebo-controlled trial of rosiglitazone for HIV-related lipoatrophy. *Journal of Infectious Diseases*. 2007;195(12):1754-61.
18. Falutz J, Allas S, et al. Metabolic effects of a growth hormone-releasing factor in patients with HIV. *New England Journal of Medicine*. 2007;357(23):2359-70.
19. Gerschenson M, Kim C, et al. Mitochondrial function, morphology and metabolic parameters improve after switching from stavudine to a tenofovir-containing regimen. *Journal of Antimicrobial Chemotherapy*. 2009;63(6):1244-50
20. Hadigan C. and C Hadigan. Peroxisome proliferator-activated receptor gamma agonists and the treatment of HIV-associated lipoatrophy: unraveling the molecular mechanism of their shortcomings [comment]. *Journal of Infectious Diseases*. 2008;198(12):1729-31.
21. Lindegaard B, Hansen T, et al. The effect of strength and endurance training on insulin sensitivity and fat distribution in human immunodeficiency virus-infected patients with lipodystrophy. *Journal of Clinical Endocrinology & Metabolism*. 2008;93(10):3860-9.
22. Lo J, You SM, et al. Low-dose physiological growth hormone in patients with HIV and abdominal fat accumulation: a randomized controlled trial. *JAMA*. 2008;300(5):509-19.
23. Mulligan K, Khatami H, et al. The effects of recombinant human leptin on visceral fat, dyslipidemia, and insulin resistance in patients with human immunodeficiency virus-associated lipoatrophy and hypoleptinemia. *Journal of Clinical Endocrinology & Metabolism*. 2009;94(4):1137-44.

24. Tebas P, Zhang J, et al. Peripheral and visceral fat changes following a treatment switch to a non-thymidine analogue or a nucleoside-sparing regimen in HIV-infected subjects with peripheral lipoatrophy: results of ACTG A5110. *Journal of Antimicrobial Chemotherapy*. 2009;63(5):998-1005.

25. Tebas P, Zhang J, et al. Switching to a protease inhibitor-containing, nucleoside-sparing regimen (lopinavir/ritonavir plus efavirenz) increases limb fat but raises serum lipid levels: results of a prospective randomized trial (AIDS clinical trial group 5125s). *Journal of Acquired Immune Deficiency Syndromes: JAIDS*. 2007;45(2):193-200.

Table 17g. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations – Lactic Acidosis

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Lactic acidosis	NRTIs, in particular, d4T and ddI (each and in combination)	Onset: 1–20 months after starting therapy (median onset 4 months in one case series). Presentation: • Usually insidious onset of a combination of signs and symptoms: o Generalized fatigue, weakness, and myalgias o Vague abdominal pain, sudden weight loss, unexplained nausea or vomiting o Dyspnea o Peripheral neuropathy. • Patients may present with acute multi-organ failure (e.g., fulminant hepatic, pancreatic, and respiratory failure).	Chronic, asymptomatic mild hyperlactatemia (2.1–5.0 mmol/L): • *Adults*: 15%–35% of those receiving NRTI therapy longer than 6 months • *Children*: 29%–32% Symptomatic severe hyperlactatemia (>5.0 mmol/L): • *Adults*: 0.2%–2.5% Symptomatic lactic acidosis/hepatic steatosis: • Rare, but associated with a high fatality rate (33%–57%)	Adult risk factors: • Female gender • High BMI • Chronic HCV infection • African-American race • Prolonged NRTI use (particularly d4T and ddI) • Coadministration of ddI with other agents (e.g., d4T, TDF, ribavirin, or tetracycline) • CD4 count <350 cells/mm^3 • Acquired riboflavin or thiamine deficiency • Possibly pregnancy	Prevention: • Avoidance of d4T and ddI in combination. • Early recognition of clinical manifestations and adjustment of therapy. Monitoring: • *Asymptomatic*: Measurement of serum lactate is not recommended. • *Clinical signs or symptoms consistent with lactic acidosis*: Obtain blood lactate level*; additional diagnostic evaluations should include serum bicarbonate and anion gap and/or arterial blood gas, amylase and lipase, serum albumin, and hepatic transaminases.	Lactate 2.1–5.0 mmol/L (confirmed with second test): • Consider replacing ddI and d4T with other ARVs. • As alternative, temporarily discontinue all ARVs while conducting additional diagnostic work-up. Lactate >5.0 mmol/L (confirmed with second test)† or >10.0 mmol/L (any one test): • Discontinue all ARVs. • Provide supportive therapy (intravenous fluids; some patients may require sedation and respiratory support to reduce oxygen demand and ensure adequate oxygenation of tissues). • Anecdotal (unproven) supportive therapies: bicarbonate infusions, tris–hydroxymethyl-aminomethane (THAM), high-dose thiamine and riboflavin, oral antioxidants (e.g., L-carnitine, co-enzyme Q, vitamin C). • Following resolution of

Table 17g. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations – Lactic Acidosis

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
						clinical and laboratory abnormalities, therapy can be resumed, either with: o an NRTI-sparing regimen; or o a revised NRTI-containing regimen instituted with caution, using NRTIs less likely to inhibit mitochondria (ABC or TDF preferred; possibly FTC or 3TC); and o monthly monitoring of lactate for at least 3 months.

* Blood for lactate determination should be collected without prolonged tourniquet application or fist clenching into a prechilled, gray-top, fluoride-oxalate-containing tube and transported on ice to the laboratory to be processed within 4 hours of collection.

† Management may be initiated before the results of the confirmatory test.

Key to Abbreviations: 3TC = lamivudine; ABC = abacavir; ARVs = antiretrovirals; BMI = body mass index; d4T = stavudine; ddI = didanosine; FTC = emtricitabine; HCV = hepatitis C virus; NRTI = nucleoside reverse transcriptase inhibitor; TDF = tenofovir disoproxil fumarate

References

General Reviews

1. Falco V, Rodriguez D, Ribera E, et al. Severe nucleoside-associated lactic acidosis in human immunodeficiency virus-infected patients: Report of *12 cases and revie*w of the literature. *Clin Infect Dis*. 2002;34(6): 838-46.
2. Birkus G, Hitchcock MJ, Cihlar T. Assessment of mitochondrial toxicity in human cells treated with tenofovir: Comparison with other nucleoside reverse transcriptase inhibitors. *Antimicrob Agents Chemother*. 2002;46(3):716-23.
3. Carr A. Lactic acidemia in infection with human immunodeficiency virus. *Clin Infect Dis*. 2003;36(Suppl 2):S96-S100.
4. Fichtenbaum CJ. Metabolic abnormalities associated with HIV infection and antiretroviral therapy. *Curr Infect Dis Rep*. 2009;11(1):84-92.
5. Desai N, Mathur M, Weedon J. Lactate levels in children with HIV/AIDS on highly active antiretroviral therapy. *AIDS*. 2003;17(10):1565-8.
6. Foster C, Lyall H. HIV and mitochondrial toxicity in children. *J Antimicrob Chemother*. 2008;61(1):8-12.

7. Noguera A, Fortuny C, Sanchez E, et al. Hyperlactatemia in human immunodeficiency virus-infected children receiving antiretroviral treatment. *Pediatr Infect Dis J*. 22(9):778-82.

Risk Factors

8. Datta D, Moyle G, Mandalia S, Gazzard B. Matched case-control study to evaluate risk factors for hyperlactataemia in HIV patients on antiretroviral therapy. *HIV Med*. 2003;4(4):311-4.
9. Imhof A, Ledergerber B, Günthard HF, et al. Risk factors for and outcome of hyperlactatemia in HIV-infected persons: Is there a need for routine lactate monitoring? *Clin Infect Dis*. 2005;41(5):721-8.
10. Lactic Acidosis International Study Group. Risk factors for lactic acidosis and severe hyperlactataemia in HIV-1-infected adults exposed to antiretroviral therapy. *AIDS*. 2007;21(18):2455-64.
11. Osler M, Stead D, Rebe K, et al. Risk factors for and clinical characteristics of severe hyperlactataemia in patients receiving antiretroviral therapy: a case-control study. *HIV Med*. 2009;Aug 20.

Monitoring and Management

12. Brinkman K. Management of hyperlactatemia: No need for routine lactate measurements. *AIDS*. 2001;15(6):795-7.
13. Carter RW, Singh J, Archambault C, et al. Severe lactic acidosis in association with reverse transcriptase inhibitors with potential response to l-carnitine in a pediatric HIV-positive patient. *AIDS Patient Care STDs*. 2004;18(3):131-4.
14. Claessens YE, Cariou A, Monchi M, et al. Detecting life-threatening lactic acidosis related to nucleoside-analog treatment of human immunodeficiency virus-infected patients, and treatment with l-carnitine. *Crit Care Med*. 2003;31(4):1042-7.
15. Delgado J, Harris M, Tesiorowski A, Montaner JS. Symptomatic elevations of lactic acid and their response to treatment manipulation in human immunodeficiency virus-infected persons: A case series. *Clin Infect Dis*. 2001;33(12):2072-4.
16. Lonergan JT, Barber RE, Mathews WC. Safety and efficacy of switching to alternative nucleoside analogues following symptomatic hyperlactatemia and lactic acidosis. *AIDS*. 2003;17(17):2495-9.
17. Mccomsey G, Lonergan JT. Mitochondrial dysfunction: Patient monitoring and toxicity management. *J Acquir Immune Defic Syndr*. 2004;37(Suppl 1):S30-5.
18. Schambelan M, Benson CA, Carr A, et al. Management of metabolic complications associated with antiretroviral therapy for HIV-1 infection: Recommendations of an international AIDS society-USA panel. *J Acquir Immune Defic Syndr*. 2002;31(3):257-75.
19. Wohl DA, Mccomsey G, Tebas P, et al. Current concepts in the diagnosis and management of metabolic complications of HIV infection and its therapy. *Clin Infect Dis*. 2006;43(5):645-53.

Table 17h. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations – Osteopenia, Osteoporosis, Osteonecrosis

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Osteopenia and osteoporosis	Following initiation of combination therapy, regardless of regimen. Specific agents of possible concern: TDF, d4T, or PIs.	Onset: Any age; greatest risk in months after initiation of associated ARV Presentation: Most commonly asymptomatic; fracture (rare) Note: Osteoporosis diagnosis in children requires clinical evidence of bone fragility and cannot rely solely on measured low bone density.	Low bone density: 20% of children treated with combination ARV therapy had BMD z score <-1.5	• Longer duration of HIV infection • Greater severity of HIV disease • Growth delay, pubertal delay • Low BMI • Lipodystrophy • Nonblack race • Smoking • Steroid use, medroxyprogesterone	Prevention: • Ensure calcium and vitamin D sufficiency. • Encourage weight-bearing exercise. • Minimize modifiable risk factors (smoking, low BMI, steroid use). Monitoring: • Assess nutritional intake (calcium, vitamin D, and total calories). • Serum 25-OH-Vitamin D.* • DXA.†	• Ensure calcium and vitamin D sufficiency. • Encourage weight-bearing exercise. • Reduce modifiable risk factors (smoking, low BMI, steroids, medroxyprogesterone). • Role of bisphosphonates not established in children. • Consider change in ARV regimen.
Osteonecrosis	No specific ARV identified. May be related to HIV infection itself.	Onset: Any age Presentation: • Limp; hip or other periarticular pain • Asymptomatic reported in adults	Prevalence: 0.2% in children Incidence: 0.03% per year in children	Children: Unknown Adults: • Steroid use • Alcohol abuse • Hemoglobinopathies • Hyperlipidemia • Pancreatitis • Osteopenia, osteoporosis • Hypercoagulable states	Prevention: Minimize steroid and alcohol use. Monitoring: Consider diagnostic evaluation in patients with unexplained limp, hip or other periarticular pain.	Confirm diagnosis: Plain radiographs and MRI; bone scan or CT if negative x-ray/MRI but clinical suspicion high. Treatment: • *Early stages*: decreased weight bearing on affected joint and use of analgesic. • *Later stages*: surgical intervention.

*Some experts would periodically measure 25-OH-Vitamin D, especially in HIV-infected urban youth because of high prevalence of vitamin D insufficiency.

† Until more data are available about the long-term effects of tenofovir on bone mineral acquisition in childhood, some experts would obtain a DXA at baseline and every 6 to 12 months for children in early puberty who are initiating treatment with tenofovir.

Key to Abbreviations: ARVs = antiretrovirals; BMI = body mass index; CT = computed tomography; d4T = stavudine; DXA = dual energy x-ray absorptiometry; MRI = magnetic resonance imaging; PIs = protease inhibitors; TDF = tenofovir disoproxil fumarate

References

Osteopenia and Osteoporosis

1. Mora S, Sala N, Bricalli D, et al. Bone mineral loss through increased bone turnover in hiv-infected children treated with highly active antiretroviral therapy. *AIDS*. 2001;15(14):1823-9.
2. Mora S, Zamproni I, Beccio S, et al. Longitudinal changes of bone mineral density and metabolism in antiretroviral-treated human immunodeficiency virus-infected children. *J Clin Endocrinol Metab*. 2004;89(1):24-8.
3. Arpadi SM, Horlick M, Thornton J, et al. Bone mineral content is lower in prepubertal HIV-infected children. *J Acquir Immune Defic Syndr*. 2002;29(5):450-4.
4. Hazra R, Gafni RI, Maldarelli F, et al. Tenofovir disoproxil fumarate and an optimized background regimen of antiretroviral agents as salvage therapy for pediatric HIV infection. *Pediatrics*. 2005;116(6):e846-54.
5. Gafni RI, Hazra R, Reynolds JC, et al. Tenofovir disoproxil fumarate and an optimized background regimen of antiretroviral agents as salvage therapy: Impact on bone mineral density in HIV-infected children. *Pediatrics*. 2006;118(3):e711-8.
6. Purdy JB, Gafni RI, Reynolds JC, Zeichner S, Hazra R. Decreased bone mineral density with off-label use of tenofovir in children and adolescents infected with human immunodeficiency virus. *J Pediatr*. 2008;152(4):582-4.
7. Jacobson D, Huang J, Shevitz A, et al. Duration of ART and change in bone mineral density over time. 12th Conference on Retroviruses and Opportunistic Infections (Boston). Foundation For Retrovirology and Human Health; 2005; Alexandria, Va. Abstract 825.
8. Jacobson DL, Spiegelman D, Duggan C, et al. Predictors of bone mineral density in human immunodeficiency virus-1 infected children. *J Pediatr Gastroenterol Nutr*. 2005;41(3):339-46.
9. Kalkwarf HJ, Zemel BS, Gilsanz V, et al. The bone mineral density in childhood study: Bone mineral content and density according to age, sex, and race. *J Clin Endocrinol Metab*. 2007;92(6):2087-99.

Osteonecrosis

10. Gaughan DM, Mofenson LM, Hughes MD, et al. Osteonecrosis of the hip (Legg-Calve-Perthes disease) in human immunodeficiency virus-infected children. *Pediatrics*. 2002;109(5):E74-4.
11. Glesby MJ. Bone disorders in human immunodeficiency virus infection. *Clin Infect Dis*. 2003;37(Suppl 2):S91-5.
12. Morse CG, Mican JM, Jones EC, et al. The incidence and natural history of osteonecrosis in HIV-infected adults. *Clin Infect Dis*. 2007;44(5):739-48.
13. Allison GT, Bostrom MP, Glesby MJ. Osteonecrosis in HIV disease: Epidemiology, etiologies, and clinical management. *AIDS*. 2003; 17(1), 1-9.

Antiretroviral Treatment Failure in Infants, Children, and Adolescents (Updated August 16, 2010)

OVERVIEW

Panel's Recommendations:

- ***The goal of therapy following treatment failure is to achieve and maintain virologic suppression, as measured by a plasma viral load below the limits of detection using the most sensitive assay (AI*).***
- ***When complete virologic suppression cannot be achieved, the goals of therapy are to preserve or restore immunologic function (as measured by CD4 lymphocyte values), prevent clinical disease progression, and preserve future antiretroviral options (AII).***
- ***Not all instances of treatment failure require an immediate change in therapy; careful assessment, especially of adherence, is required to evaluate the etiology of the treatment failure and determine an appropriate management strategy (AII).***
- ***Children who experience treatment failure should be managed in collaboration with a pediatric HIV specialist (AI*).***

Although many children can remain on stable antiretroviral therapy for several years *[1-4]*, at some point reassessment of a therapeutic regimen will become necessary. This section will discuss the definitions, causes, assessment, and management of antiretroviral treatment failure and specific issues to consider when changing a drug regimen. Treatment failure is defined as suboptimal response or a lack of sustained response to therapy using virologic, immunologic, and clinical criteria. It is important to recognize that not all instances of treatment failure require an immediate change in antiretroviral therapy, and a careful assessment is required to evaluate the etiology of treatment failure and determine the appropriate management strategy.

Although the approach to treatment failure is generally straightforward after failure of the first regimen, it is typically more complex for children who have received more than one antiretroviral regimen. However, with the recent development of new antiretroviral agents, including those directed at new viral targets, the goal of treatment regimens for all patients—whether on initial, second, or subsequent regimen—is complete virologic suppression, combined with the recovery or maintenance of immunologic parameters and improvement in baseline clinical condition (or maintenance of clinical condition if asymptomatic). (See **Assessment of Patients with Antiretroviral Treatment Failure** and **Management of Medication Toxicity or Intolerance**). Decisions regarding changing antiretroviral therapy may need to be individualized and should take into consideration the child's treatment history and toxicities; prior and current detection of drug-resistant virus; current virologic, immunologic, and clinical status; ability to adhere to a new regimen; and available treatment options. In the context of these complexities it is recommended that all children being evaluated for treatment failure be managed in collaboration with a pediatric HIV specialist.

Developmental as well as behavioral characteristics distinguish adolescents from adults and affect decisions around management of treatment failure (see **Specific Issues in Antiretroviral Therapy for HIV-Infected Adolescents**). Drug metabolism may vary during puberty, necessitating a reassessment of medication dosing throughout adolescence. In some instances, young adults may require larger doses by weight or by surface area than older adults. In addition, dosing recommendations for adolescents have not been established for a number of new antiretroviral medications now used in adults. Dosing guidance for children and adolescents for all antiretroviral agents can be found in **Appendix B: Pediatric Antiretroviral Drug Information**. The ***Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*** can provide additional information to help inform management of antiretroviral treatment failure in adolescents.

Definition of Treatment Failure (see Table 12):

Treatment failure is categorized as virologic, immunologic, and clinical failure. Laboratory results must be confirmed with repeat testing before making a final assessment of virologic or immunologic treatment failure.

Virologic Failure: Virologic failure occurs as an incomplete response to therapy or a viral rebound after achieving virologic suppression.

- **Incomplete viral response to therapy:** Incomplete virologic response to therapy is defined for all children as a <1.0 $\log_{10}$ decrease in HIV RNA copy number from baseline after 8–12 weeks of therapy, HIV RNA >400 copies/mL after 6 months of therapy, or repeated HIV RNA greater than the level of detection using the most sensitive assay after 12 months of therapy. Children with higher HIV RNA levels at initiation of therapy, especially infants, may take longer to reach undetectable viral load.
- **Viral rebound:** For children who have previously achieved undetectable plasma viral load in response to therapy, viral rebound is defined as subsequent, repeated detection of plasma HIV RNA on ultrasensitive PCR assays. Infrequent episodes of low level viremia (<1,000 copies/mL) are common and not generally reflective of virologic failure, whereas repeated or persistent viremia (especially if >1,000 copies/mL) more likely represents viral rebound.

Immunologic Failure: Evaluation of immune response in children is complicated by the normal age-related changes in CD4 cell count discussed previously (see **Immunologic Monitoring in Children**). Thus, the normal decline in CD4 values with age needs to be taken into account when evaluating declines in CD4 parameters. CD4 percentage tends to vary less with age; absolute CD4 count values in children approach those of adults at about 5 years of age. Consequently, changes in absolute count may be used in children ≥5 years of age.

- **Incomplete immunologic response to therapy:** This is defined as a failure to improve CD4 values by ≥5 percentage points in a child <5 years of age with severe immune suppression (CD4 percentage <15%) or as a failure to improve CD4 values by ≥50 cells/mm^3 above baseline within the first year of therapy in a child age 5 years old or older with severe immune suppression (CD4 <200 cells/mm^3).
- **Immunologic decline:** This is defined as a sustained decline of 5 percentage points in CD4 percentage below pretherapy baseline at any age or decline to below pretherapy baseline in absolute CD4 cell count in children who are ≥5 years of age. Declines that represent a change to a more advanced category of immunosuppression compared with baseline (e.g., from CD4 percentage of 28% to 23% or from CD4 count of 250 cells/mm^3 to 150 cells/mm^3) or to more severe immunosuppression in those already suppressed at baseline (e.g., from CD4 percentage of 14% to 9% or from CD4 count of 150 cells/mm^3 to 100 cells/mm^3) are of particular concern.

Clinical Failure: The occurrence of new opportunistic infections and/or general clinical disease progression represents the most urgent and concerning type of treatment failure and should prompt an immediate evaluation. Clinical findings should be viewed in the context of virologic and immunologic response to therapy; in patients with stable virologic and immunologic parameters, development of clinical symptoms may not represent treatment failure. For example, development of a new opportunistic infection in a patient who had severe immune suppression at the time of recent initiation of therapy may not reflect failure of virologic suppression, but rather persistence of immune dysfunction despite adequate virologic response. Additionally, immune reconstitution inflammatory syndrome (IRIS) should be excluded as a possible cause of clinical symptoms before it is concluded that there is suboptimal clinical response to therapy. Although clinical events occurring in the first several months after antiretroviral initiation should not necessarily be construed as antiretroviral treatment failure, the occurrence of significant clinical disease progression, such as noted below, requires strong consideration that the current treatment regimen is failing:

- **Progressive neurodevelopmental deterioration:** The presence of two or more of the following findings documented on repeated assessments: impairment in brain growth, decline of cognitive function documented by psychometric testing, or clinical motor dysfunction.

- **Growth failure:** Persistent decline in weight-growth velocity despite adequate nutritional support and without other explanation.
- **Severe or recurrent infection or illness:** Recurrence or persistence of AIDS-defining conditions or other serious infections.

Children who experience treatment failure do not always require an immediate change in therapy; careful assessment is required to evaluate the etiology of the treatment failure and determine an appropriate management strategy (see **Assessment of Patients with Antiretroviral Treatment Failure**).

Discordance between Viral, Immune, and Clinical Responses

In general, effective combination antiretroviral therapy that results in virologic suppression also leads to immune restoration or preservation as well as to prevention of new or recurrent HIV-related illnesses. Similarly, ineffective antiretroviral therapy that fails to achieve virologic suppression is commonly accompanied by concordant immunologic and clinical failure *[5]*. However, clinicians may also be presented with patients in whom antiretroviral therapy is associated with failure in one domain (e.g., virologic failure) but a good response in the other domains (e.g., immunologic and clinical response). In fact, the discordance in responses to antiretroviral therapy may occur in any of these three domains in relation to the other two. It is essential to consider potential alternative causes of discordant responses before concluding that antiretroviral treatment failure has truly occurred.

Adequate Clinical and Immunologic Responses despite Incomplete Virologic Response: Some patients who are maintained on combination antiretroviral therapy may maintain immunologic and clinical benefit despite detectable viral replication for up to 3 years *[6-15]*. This observation is the rationale for continuing nonsuppressive antiretroviral therapy for immunologic and clinical benefit in selected patients for whom a completely suppressive regimen is not available or practicable. The risks and benefits as well as the indications for this approach are discussed in **Approach to the Management of Antiretroviral Treatment Failure** and **Choice of Next Antiretroviral Regimen for Treatment Failure with Evidence of Drug Resistance**. The proposed mechanisms for immunologic and clinical benefit without complete virologic suppression are the maintenance of a lower viral load or the selection for strains harboring drug-resistance mutations that impair viral replication or virulence. Another potential explanation is that some of these children may have host genetic and/or virologic characteristics that would have allowed them to be either “slow-progressors” or “long-term nonprogressors” without therapy.

Poor Immunologic Response despite Virologic Suppression Regardless of Clinical Response: Poor immunologic response despite virologic suppression can occur in the context of adequate or poor clinical response. The first considerations in cases of poor immunologic response despite virologic suppression are to exclude laboratory error in CD4 or viral load measurements and to ensure that CD4 values have been interpreted correctly in relation to the natural decline in CD4 count over the first 5–6 years of life. Another laboratory consideration is that some viral load assays may not amplify all HIV groups and subtypes (e.g., HIV-1 non-M groups or non-B subtypes, HIV-2), resulting in falsely low or negative viral load results (see **Diagnosis of HIV Infection in Infants** and **Laboratory Monitoring of Pediatric HIV Infection**). Once lab results are confirmed, evaluation for adverse drug effects, medical conditions, and other factors that can result in lower CD4 values is necessary.

Additionally, in patients with baseline severe immunosuppression, it is common to achieve virologic suppression weeks to months before achieving immunologic recovery, resulting in a transient early treatment period of persistent immunosuppression during which additional clinical disease progression can occur. Patients who have very low baseline CD4 values prior to initiating combination therapy are at higher risk of an impaired CD4 lymphocyte response to antiretroviral therapy and may be at higher risk of death and AIDS-defining illnesses, despite virologic suppression *[3, 12, 16-20]*.

Certain antiretroviral regimens may be associated with a blunted CD4 response. Treatment with a regimen containing tenofovir and didanosine can blunt the CD4 response, especially if the didanosine dose is not adjusted downward *[21]*. In adults, antiretroviral regimens containing zidovudine may also impair rise in CD4 count but not CD4 percentage, perhaps through the myelosuppressive effects of zidovudine; fortunately, this suboptimal CD4 count response to therapy does not seem to confer an increased risk of clinical events *[22]*.

Several drugs (e.g., corticosteroids, chemotherapeutic agents) and other conditions (e.g., hepatitis C, tuberculosis, malnutrition, Sjogren's syndrome, sarcoidosis) are independently associated with low CD4 values. Occasional cases of idiopathic CD4 lymphocytopenia have also been reported in adults without HIV infection *[23]*.

Differential Diagnosis of Poor Immunologic Response despite Virologic Suppression:

Poor Immunologic Response despite Virologic Suppression and Good Clinical Response

- Lab error
- Normal age-related CD4 lymphocyte decline
- Low pretreatment CD4 lymphocyte count or percentage
- Adverse effects of use of zidovudine or the combination of tenofovir + didanosine
- Use of systemic corticosteroids or chemotherapeutic agents
- Conditions that can cause low CD4 values: hepatitis C coinfection, Sjogren's syndrome, tuberculosis, sarcoidosis

Poor Immunologic and Clinical Responses despite Virologic Suppression

- Lab error, including HIV strain/type not detected by VL assay (HIV-1 non-M groups, non-B subtypes; HIV-2)
- Persistent immunodeficiency soon after initiation of antiretroviral therapy but prior to antiretroviral-related reconstitution
- Primary protein-calorie malnutrition
- Untreated tuberculosis
- Malignancy
- Loss of immunologic (CD4) reserve

Poor Clinical Response despite Adequate Virologic and Immunologic Responses: Clinicians must carefully evaluate patients who experience clinical disease progression despite favorable immunological and virological responses to antiretroviral therapy. Not all cases represent antiretroviral treatment failure. One of the most important reasons for new or recurrent opportunistic conditions despite achieving virologic suppression and immunologic restoration/preservation within the first months of antiretroviral treatment is immune reconstitution inflammatory syndrome (IRIS), which does not represent antiretroviral treatment failure and does not generally require discontinuation of antiretroviral treatment. Children who have suffered irreversible damage to their lungs, brain, or other organs, especially during prolonged and profound pretreatment immunosuppression, may continue to have recurrent infections or symptoms in those damaged organs because the damage may not be reversed by immunologic improvement *[24]*. Such cases do not represent antiretroviral treatment failure and would not be expected to benefit from a change in antiretroviral regimen. Evaluation for and treatment of other causes or conditions that can occur with or without HIV-related immunosuppression, such as pulmonary tuberculosis, malnutrition, and malignancy, should also be undertaken before drawing a conclusion of antiretroviral treatment failure. Occasionally, however, children will develop new HIV-related opportunistic conditions (e.g., *Pneumocystis jiroveci* pneumonia [PCP] or esophageal candidiasis occurring more than 6 months after achieving markedly improved CD4 values and virologic suppression) not explained by IRIS, pre-existing organ damage, or another reason. Such cases may be antiretroviral treatment failure and suggest that improvement in CD4 values may not necessarily represent return of complete immunologic function.

Differential Diagnosis of Poor Clinical Response despite Adequate Virologic and Immunologic Responses:

- IRIS
- Previously unrecognized pre-existing infection or condition (tuberculosis, malignancy)
- Malnutrition
- Clinical manifestations of previous organ damage: brain (strokes, vasculopathy), lungs (bronchiectasis)
- Clinical event due to non-HIV illness or condition
- New, otherwise unexplained HIV-related clinical event (treatment failure)

Table 18. Considerations for Changing Antiretroviral Therapy for Human Immunodeficiency Virus (HIV)-Infected Children

Virologic Considerations*	• **Incomplete viral response to therapy:** Incomplete virologic response to therapy is defined for all children as a <1.0 $\log_{10}$ decrease in HIV RNA copy number from baseline after 8–12 weeks of therapy, HIV RNA >400 copies/mL after 6 months of therapy, or repeated HIV RNA above the level of detection using the most sensitive assay after 12 months of therapy.† • **Viral rebound:** For children who have previously achieved undetectable plasma viral load in response to therapy, viral rebound is defined as subsequent, repeated detection of plasma HIV RNA on ultrasensitive PCR assays. Infrequent episodes of low level viremia (<1,000 copies/mL) are common and not generally reflective of virologic failure, whereas repeated or persistent viremia (especially if >1,000 copies/mL) more likely represents viral rebound.‡
Immunologic Considerations*	• **Incomplete immunologic response to therapy:** Failure in a child <5 years of age with severe immune suppression (CD4 percentage <15%) to improve CD4 values by ≥5 percentage points or failure in a child ≥5 years of age with severe immune suppression (CD4 <200 cells/mm^3) to improve CD4 values by ≥50 cells/mm^3 above baseline within the first year of therapy. • **Immunologic decline:** Sustained decline of 5 percentage points in CD4 percentage below pretherapy baseline at any age or decline to below pretherapy baseline in absolute CD4 cell count in children who are ≥5 years of age.§
Clinical Considerations	• **Progressive neurodevelopmental deterioration:** Two or more of the following on repeated assessments: impairment in brain growth, decline of cognitive function documented by psychometric testing, or clinical motor dysfunction. • **Growth failure:** Persistent decline in weight-growth velocity despite adequate nutritional support and without other explanation. • **Severe or recurrent infection or illness:** Recurrence or persistence of AIDS-defining conditions or other serious infections.

* At least two measurements (taken 1 week apart) should be performed before considering a change in therapy.

† The initial HIV RNA level of the child at the start of therapy and the level achieved with therapy should be considered when contemplating potential drug changes. For example, an immediate change in therapy may not be warranted if there is a sustained 1.5–2.0 $\log_{10}$ decrease in HIV RNA copy number, even if RNA remains detectable at low levels. Additionally, virologic suppression may take longer in young children given their higher viral load at the time of initiation of therapy than in older children or adults.

‡ Continued observation with more frequent evaluation of HIV RNA levels should be considered if the HIV RNA increase is limited (i.e., <5,000 copies/mL), especially in children with limited treatment options. The presence of repeatedly detectable or increasing RNA levels suggests the development of resistance mutations and/or nonadherence.

§ Declines that represent a change to a more advanced category of immunosuppression compared with baseline (e.g., from CD4 percentage of 28% to 23% or from CD4 count of 250 cells/mm^3 to 150 cells/mm^3) or to more severe immunosuppression in those already suppressed at baseline (e.g., from CD4 percentage of 14% to 9% or from CD4 count of 150 cells/mm^3 to 100 cells/mm^3) are of particular concern.

References

1. Fraaij PL, Verweel G, van Rossum AM, et al. Sustained viral suppression and immune recovery in HIV type 1-infected children after 4 years of highly active antiretroviral therapy. *Clin Infect Dis.* 2005;40(4):604-608.
2. Luzuriaga K, McManus M, Mofenson L, et al. A trial of three antiretroviral regimens in HIV-1-infected children. *N Engl J Med.* 2004;350(24):2471-2480.
3. Resino S, Resino R, Micheloud D, et al. Long-term effects of highly active antiretroviral therapy in pretreated, vertically HIV type 1-infected children: 6 years of follow-up. *Clin Infect Dis.* 2006;42(6):862-869.
4. Scherpbier HJ, Bekker V, van Leth F, et al. Long-term experience with combination antiretroviral therapy that contains nelfinavir for up to 7 years in a pediatric cohort. *Pediatrics.* 2006;117(3):e528-536.
5. Oliveira R, Krauss M, Essama-Bibi S, et al. HIV viral load predicts World Health Organization (WHO) Stage 3 and 4 events among children in Latin America independent of CD4 level. Paper presented at: (Oral Presentation) 1st International Workshop on HIV Pediatrics; July 16-18 2009; Cape Town, Africa. Abstract O_11.
6. Chiappini E, Galli L, Gabiano C, et al. Early triple therapy vs mono or dual therapy for children with perinatal HIV infection. *JAMA.* 2006;295(6):626-628.
7. Chiappini E, Galli L, Tovo PA, et al. Virologic, immunologic, and clinical benefits from early combined antiretroviral therapy in infants with perinatal HIV-1 infection. *AIDS.* 2006;20(2):207-215.
8. de Martino M, Galli L, Moriondo M, et al. Dissociation of responses to highly active antiretroviral therapy: Notwithstanding virologic failure and virus drug resistance, both CD4+ and CD8+ T lymphocytes recover in HIV-1 perinatally infected children. *J Acquir Immune Defic Syndr.* 2001;26(2):196-197.
9. Deeks SG, Barbour JD, Martin JN, et al. Sustained CD4+ T cell response after virologic failure of protease inhibitor-based regimens in patients with human immunodeficiency virus infection. *J Infect Dis.* 2000;181(3):946-953.
10. Flynn PM, Rudy BJ, Douglas SD, et al. Virologic and immunologic outcomes after 24 weeks in HIV type 1-infected adolescents receiving highly active antiretroviral therapy. *J Infect Dis.* 2004;190(2):271-279.
11. Kovacs A, Montepiedra G, Carey V, et al. Immune reconstitution after receipt of highly active antiretroviral therapy in children with advanced or progressive HIV disease and complete or partial viral load response. *J Infect Dis.* 2005;192(2):296-302.
12. Nikolic-Djokic D, Essajee S, Rigaud M, et al. Immunoreconstitution in children receiving highly active antiretroviral therapy depends on the CD4 cell percentage at baseline. *J Infect Dis.* 2002;185(3):290-298.
13. Piketty C, Weiss L, Thomas F, et al. Long-term clinical outcome of human immunodeficiency virus-infected patients with discordant immunologic and virologic responses to a protease inhibitor-containing regimen. *J Infect Dis.* 2001;183(9):1328-1335.
14. Rutstein RM, Gebo KA, Flynn PM, et al. Immunologic function and virologic suppression among children with perinatally acquired HIV infection on highly active antiretroviral therapy. *Med Care.* 2005;43(9 Suppl):III15-22.
15. Sufka SA, Ferrari G, Gryszowka VE, et al. Prolonged CD4+ cell/virus load discordance during treatment with protease inhibitor-based highly active antiretroviral therapy: immune response and viral control. *J Infect Dis.* 2003;187(7):1027-1037.
16. Moore DM, Hogg RS, Chan K, et al. Disease progression in patients with virological suppression in response to HAART is associated with the degree of immunological response. *AIDS.* 2006;20(3):371-377.
17. Moore RD, Keruly JC. CD4+ cell count 6 years after commencement of highly active antiretroviral therapy in persons with sustained virologic suppression. *Clin Infect Dis.* 2007;44(3):441-446.
18. Newell ML, Patel D, Goetghebuer T, et al. CD4 cell response to antiretroviral therapy in children with vertically acquired HIV infection: is it associated with age at initiation? *J Infect Dis.* 2006;193(7):954-962.
19. Resino S, Alvaro-Meca A, de Jose MI, et al. Low immunologic response to highly active antiretroviral therapy in naive vertically human immunodeficiency virus type 1-infected children with severe immunodeficiency. *Pediatr Infect Dis J.* 2006;25(4):365-368.
20. Soh CH, Oleske JM, Brady MT, et al. Long-term effects of protease-inhibitor-based combination therapy on CD4 T-cell recovery in HIV-1-infected children and adolescents. *Lancet.* 2003;362(9401):2045-2051.
21. Negredo E, Bonjoch A, Paredes R, et al. Compromised immunologic recovery in treatment-experienced patients with HIV infection receiving both tenofovir disoproxil fumarate and didanosine in the TORO studies. *Clin Infect Dis.* 2005;41(6):901-905.
22. Huttner AC, Kaufmann GR, Battegay M, et al. Treatment initiation with zidovudine-containing potent antiretroviral therapy impairs CD4 cell count recovery but not clinical efficacy. *AIDS.* 2007;21(8):939-946.

23. Smith DK, Neal JJ, Holmberg SD. Unexplained opportunistic infections and CD4+ T-lymphocytopenia without HIV infection. An investigation of cases in the United States. The Centers for Disease Control Idiopathic CD4+ T-lymphocytopenia Task Force. *N Engl J Med.* 1993;328(6):373-379.
24. Graham SM. Non-tuberculosis opportunistic infections and other lung diseases in HIV-infected infants and children. *Int J Tuberc Lung Dis.* 2005;9(6):592-602.

ASSESSMENT OF PATIENTS WITH ANTIRETROVIRAL TREATMENT FAILURE

Panel's Recommendations:

- ***Assess adherence to therapy and barriers and interventions to improve adherence because inadequate adherence is the most common cause of antiretroviral treatment failure (AII).***
- ***Assess medication intolerance (AIII).***
- ***Assess issues related to pharmacokinetics because developmental and individual differences in drug absorption, distribution, metabolism, and elimination can cause inadequate antiretroviral drug exposure that results in antiretroviral treatment failure (AII).***
- ***Perform antiretroviral drug-resistance testing when virologic failure occurs and prior to changing to a new regimen (AI*).***
- ***Perform assessment in collaboration with a pediatric HIV specialist (AI*).***

Each patient with an incomplete response to therapy should be assessed to determine the cause of treatment failure because the approach to management and subsequent treatment may differ depending on the etiology of the problem. In most instances, treatment failure is multifactorial. The assessment of a child with suspicion of treatment failure should include evaluation of adherence to therapy; medication intolerance; issues related to pharmacokinetics that could result in low drug levels or elevated, potentially toxic levels; and evaluation of suspected drug resistance. The main challenge to long-term maintenance of undetectable plasma viral load in adults and children is incomplete adherence to medication regimens, with the subsequent emergence of viral mutations conferring partial or complete resistance to one or more of the components of the antiretroviral regimen.

Table 13 outlines a comprehensive approach to evaluating causes of treatment failure in children, with particular attention to adherence. An extensive history should focus on the details of drug administration as well as changes in the social and psychological circumstances of the family likely to impact the child's ability to adhere to therapy. In some situations, it may be necessary to directly observe drug-taking behaviors either in the clinic, at home, or within the hospital because history alone may not fully identify the barriers to complete adherence *[1-2]*.

Adherence Issues (For more details, see **Adherence to Antiretroviral Therapy in HIV-Infected Children and Adolescents** and **Table 11**.)

When treatment failure is observed, clinicians need to assess the likely contribution of adherence problems to the failure of the current regimen. In patients on initial therapy, poor virologic response or widely fluctuating viral loads are commonly an indication of poor adherence, particularly in the presence of susceptible virus. Even small lapses in adherence can lead to antiretroviral treatment failure *[3-7]*. Although adherence should be addressed at each medical visit for all children receiving antiretroviral therapy, suspicion of treatment failure warrants increased scrutiny. Patterns of adherence can change over time and may be influenced by a large number of factors related to the drugs themselves as well social and psychological issues of the child and the family.

Evaluation of whether adherence problems are related to drug formulation, number of pills, drug dose timing and frequency, food or fasting requirements, or drug side effects is important for determining what changes would be best suited to the individual requirements of the child and family. Intensive family education, training in the administration of prescribed medications, and discussion of the importance of adherence to the drug regimen should be reinforced. If competing family needs are identified as impediments to adherence, social issues may need to be addressed before adherence can be improved. Issues to be addressed may include achieving financial or housing security, assessing concomitant mental health problems, accessing substance abuse treatment, and

initiating a discussion around HIV disclosure. In some situations, clinicians may need to involve outside agencies such as child protective services to ensure support of the child's treatment. Various interventions should be considered if problems within the household are extreme and unlikely to resolve in favor of successfully supporting the child's treatment. Frequent patient visits and intensive follow-up may be necessary to support new adherence interventions and efforts by the child and family to improve adherence to the current or new regimen. Directly observed therapy (DOT) may be used to identify additional factors impeding adherence as well as to confirm drug administration.

Pharmacokinetic Issues

In addition to poor adherence, inadequate drug exposure can result in treatment failure *[8]*. Children consistently require higher weight-based dosing of antiretroviral drugs compared with adults because of developmental differences in absorption, body composition, and metabolic activity through the pediatric age range *[9]*. Causes of subtherapeutic drug levels may include failure to increase dosing for rapid growth of the child or impaired absorption because of gastrointestinal symptoms, such as vomiting or diarrhea. Drug exposure may be enhanced or reduced by administering medications with food; the clinician should review the food/fasting requirements of the regimen with the patient and caregiver. Drug interactions can alter drug metabolism; all concomitant medications, including over-the-counter medications and nutritional and herbal supplements, should be reviewed to evaluate whether they may be contributing to poor treatment response. (See the ***Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents***.) Several recent studies suggest that genetic polymorphisms may influence pharmacokinetics and therapeutic response for a number of antiretroviral medications *[10-11]*. In some circumstances, therapeutic drug monitoring can be considered for children receiving selected drugs (see **Role of Therapeutic Drug Monitoring in Management of Treatment Failure**).

Suspected Drug-Resistance Issues (See **Antiretroviral Drug-Resistance Testing**.)

Antiretroviral drug resistance may develop in children with inadequate viral suppression. Genotypic resistance testing can help assess adherence to therapy. If testing reveals no resistance-associated mutations to the drugs of the current regimen, it is unlikely that the child is taking these medications. The presence of mutations supports inadequate drug exposure and failure to fully suppress viral replication. Antiretroviral resistance testing should be performed while the patient is still taking the failing regimen or within 4 weeks of its discontinuation. In the absence of the selective pressure of antiretroviral drugs, virus variants harboring resistance mutations may decrease in frequency to below the limits of detection of standard resistance assays. Resistance testing can be used to guide current management as well as to identify active antiretroviral medications for future regimens. Other laboratory tests such as tropism assays may be indicated as well if CCR5 inhibitors are being considered for treatment in the subsequent regimen.

Table 19. Assessment of Antiretroviral Treatment Failure

Assessment	Method	Intervention
Adherence	1. Interview child and caretaker • Take 24-hour or 7-day recall • Get description of: o *WHO* gives medication o *WHAT* is given (names, doses) o *WHERE* medications are kept, administered o *WHEN* they are taken/given • Have open-ended discussion of experiences taking/giving medications and barriers/challenges 2. Review pharmacy records • Assess timeliness of refills 3. Observe medication administration • Observe dosing/administration in clinic • Conduct home-based observation by visiting health professional • Admit to hospital for trial of therapy o Observe administration/tolerance o Monitor treatment response 4. Conduct psychosocial assessment • Make a comprehensive family-focused assessment of factors likely to impact adherence with particular attention to recent changes: o Status of caregiver, financial stability, housing, intimate relationships o School and achievement o Substance abuse (child, caretaker, family members) o Mental health and behavior o Child/youth and caretaker beliefs about antiretroviral therapy o Disclosure status (to child and others)	Identify or re-engage family members to support/supervise adherence. Establish fixed daily times and routines for medication administration. Avoid confusion with drug names by explaining that drug therapies have generic names and trade names, and many agents are coformulated under a third or fourth name. Explore opportunities for facility or home-based directly observed therapy. Simplify medication regimen if feasible. Substitute new agents if single ARV is poorly tolerated. Consider gastric tube placement to facilitate adherence. Consider directly observed therapy (DOT). Use tools to simplify administration (pill boxes, reminders including alarms, integrated medication packaging for AM or PM dosing, others). Suggest relaxation techniques. Address competing needs through appropriate social services. Address and treat concomitant mental illness and behavioral disorders. Initiate disclosure discussions with family/child. Consider need for child protection services and alternate care settings when necessary.
Pharmaco-kinetics and Dosing	1. Recalculate doses for individual medications using weight or body surface area. 2. Identify concomitant medications including prescription, over-the-counter, and recreational substances; assess for drug-drug interactions. 3. Consider drug levels for specific antiretroviral drugs (see **Role of Therapeutic Drug Monitoring in Management of Treatment Failure**).	Adjust drug doses. Discontinue or substitute competing medications. Reinforce applicable food restrictions.
Resistance Testing	1. Perform genotypic and phenotypic resistance assays (see **Antiretroviral Drug-Resistance Testing**). 2. Perform tropism assay, as appropriate.	

References

1. Gigliotti F, Murante BL, Weinberg GA. Short course directly observed therapy to monitor compliance with antiretroviral therapy in human immunodeficiency virus-infected children. *Pediatr Infect Dis J.* 2001;20(7):716-718.
2. Parsons GN, Siberry GK, Parsons JK, et al. Multidisciplinary, inpatient directly observed therapy for HIV-1-infected children and adolescents failing HAART: A retrospective study. *AIDS Patient Care STDS.* 2006;20(4):275-284.
3. Gibb DM, Goodall RL, Giacomet V, et al. Adherence to prescribed antiretroviral therapy in human immunodeficiency virus-infected children in the PENTA 5 trial. *Pediatr Infect Dis J.* 2003;22(1):56-62.
4. Katko E, Johnson GM, Fowler SL, et al. Assessment of adherence with medications in human immunodeficiency virus-infected children. *Pediatr Infect Dis J.* 2001;20(12):1174-1176.
5. Van Dyke RB, Lee S, Johnson GM, et al. Reported adherence as a determinant of response to highly active antiretroviral therapy in children who have human immunodeficiency virus infection. *Pediatrics.* 2002;109(4):e61.
6. van Rossum AM, Bergshoeff AS, Fraaij PL, et al. Therapeutic drug monitoring of indinavir and nelfinavir to assess adherence to therapy in human immunodeficiency virus-infected children. *Pediatr Infect Dis J.* 2002;21(8):743-747.
7. Watson DC, Farley JJ. Efficacy of and adherence to highly active antiretroviral therapy in children infected with human immunodeficiency virus type 1. *Pediatr Infect Dis J.* 1999;18(8):682-689.
8. Menson EN, Walker AS, Sharland M, et al. Underdosing of antiretrovirals in UK and Irish children with HIV as an example of problems in prescribing medicines to children, 1997-2005: cohort study. *BMJ.* 2006;332(7551):1183-1187.
9. Kearns GL, Abdel-Rahman SM, Alander SW, et al. Developmental pharmacology--drug disposition, action, and therapy in infants and children. *N Engl J Med.* 2003;349(12):1157-1167.
10. Saitoh A, Fletcher CV, Brundage R, et al. Efavirenz pharmacokinetics in HIV-1-infected children are associated with CYP2B6-G516T polymorphism. *J Acquir Immune Defic Syndr.* 2007;45(3):280-285.
11. Saitoh A, Sarles E, Capparelli E, et al. CYP2B6 genetic variants are associated with nevirapine pharmacokinetics and clinical response in HIV-1-infected children. *AIDS.* 2007;21(16):2191-2199.

APPROACH TO THE MANAGEMENT OF ANTIRETROVIRAL TREATMENT FAILURE

Panel Recommendations:

- ***The causes of treatment failure, which include drug resistance, poor absorption of medications, poor adherence, inadequate dosing, and drug-drug interactions, should be assessed and addressed (AII).***
- ***When deciding how to treat a child with treatment failure, the probability of achieving durable suppression based on the prior treatment history, drug resistance, drug potency, and likelihood of adherence should be considered as well as the future options available should durable suppression not be achieved; in addition, the future availability and timing of novel agents should be considered (AII).***
- ***Children who experience treatment failure should be managed in collaboration with a pediatric HIV specialist (AI*).***

General

Once the causes of failure have been identified and addressed, the child should be assessed to determine whether a change in the antiretroviral regimen is necessary. This will depend on the urgency and likelihood of achieving and sustaining an undetectable plasma viral load. The immediacy of implementing a more effective treatment regimen depends on the immunologic status of the child, with the greatest urgency for patients with clinical disease progression or clinical failure. The likelihood of achieving and maintaining undetectable plasma viral load depends on the extent of drug resistance, the number and quality of available agents that are active against the child's virus, and the likelihood of adherence to the new regimen.

Timing of Initiation of a New Regimen: Relative Importance of Virologic Suppression and Immunologic Improvement

Because immunologic improvement typically results from achieving undetectable plasma viral load *[1]*, the urgency of re-establishing virologic suppression depends on the clinical and immunologic status of a child. For example, for older children or adolescents with very low CD4 cell counts (e.g., <200 cells/mm^3), a change in therapy may be critical to prevent further immunologic decline or clinical disease progression and is strongly recommended. A patient with less immunosuppression may not be at significant risk of clinical disease progression in the near future, so an immediate change in therapy is less urgent. However, continued treatment of a child with persistently detectable viremia increases the risk of immunologic or clinical disease progression and leads to further accumulation of resistance mutations, possibly further limiting future treatment options *[2]*.

Likelihood of Viral Suppression below the Limit of Detection Using the Most Sensitive Assay

When deciding whether to change a child's antiretroviral regimen, a clinician must assess whether such a change is likely to achieve significantly better virologic control than the current regimen. Although complete virologic suppression should be the goal, this may not always be achievable in HIV-infected children. Clinical benefit may be observed with decrements in HIV RNA levels that do not result in undetectable levels *[1]*. However, failure to maximally suppress plasma viral load is associated with an increased probability of acquiring mutations associated with resistance. Anticipating and minimizing toxicities is central to the clinician-patient discussion. The likelihood of adherence to a new regimen plays a significant role in determining whether to change an antiretroviral regimen; if a child is unlikely to adhere to a new regimen, resistance will develop and sustainable virologic suppression will not be achieved. Although studies differ on the exact predictors of adherence, several contributing factors have been noted. These include medication characteristics *[3]*, psychosocial stressors *[4-5]*, health beliefs *[6]*, and prior adherence to medication (see **Adherence to Antiretroviral Therapy in HIV-Infected Children and Adolescents** for more detail). Importantly, the pediatric patient's adherence to antiretroviral therapy may change over time as the child moves through progressive developmental stages, and any changes in these risk factors can occur rapidly and unexpectedly. Thus, a clinician may choose to target a new antiretroviral regimen to start at a time when the child is most likely to adhere to this regimen for a sustained period.

Categories of Children with Treatment Failure and Approaches to Consider

No Viral Resistance Identified

Persistent viremia in the absence of detectable viral resistance to current medications suggests that the virus is not being exposed to the antiretroviral agents. This lack of antiretroviral drug exposure is usually due to nonadherence, but it is important to exclude other factors such as poor drug absorption, incorrect dosing, and drug interactions. If adequate drug exposure can be assured, then resuming the existing current regimen should result in undetectable plasma levels. Resistance testing should take place while the child is on therapy, because predominant plasma viral strains may quickly revert to wild-type and fail to reveal the drug-resistant virus that would have been detectable while the patient was receiving therapy (see **Antiretroviral Drug-Resistance Testing**). Thus, if a child with prior therapy develops resistant virus and then stops therapy, sensitive virus will dominate in the absence of therapy. In this situation, resuming the prior therapy would fail to suppress the virus because the resistant virus would again emerge. An approach to identify resistance in this situation is to restart the prior medications while emphasizing adherence and repeating the resistance testing in 4 weeks (unless undetectable plasma viral load has already been achieved). If plasma virus is undetectable by ultrasensitive assays, it is likely that the virus is susceptible to the current therapy.

Viral Resistance to Current Therapy

The goal in this situation is to start a new regimen in order to fully suppress and sustain plasma viral load below the limits of detection and prevent the emergence of virus with additional resistance mutations. This requires a regimen that includes at least two, and preferably three, fully active agents. The choice of new agents should be based on current and past resistance testing (see **Antiretroviral Drug-Resistance Testing**), the antiretroviral history, availability of new drugs and classes of agents, and consideration of potential toxicities. Some antiretroviral drugs (e.g., NRTIs) may contribute partial antiretroviral activity to an antiretroviral regimen, despite drug resistance. Because of the potential for cross resistance of some drugs within a single class, substituting a new drug from the same previously used class does not assure that the replacement drug will be fully active. This is particularly true for the NNRTIs nevirapine and efavirenz, for which cross resistance with drug mutations is uniformly seen.

The availability of multiple new antiretroviral drugs, including some with new viral targets, makes complete virologic suppression achievable for many adult patients with treatment failure. Unfortunately, the lack of pediatric formulations and dosing information for many of these agents limits the number of options available for children. Thus, it remains difficult to identify a new, active regimen for many children with extensive prior therapy. (See **The Use of Antiretroviral Agents Not Approved for Use in Children**.)

If there is evidence of poor adherence to the current regimen and an assessment that good adherence to a new regimen would also be difficult, the emphasis and effort should be placed on addressing barriers to adherence. In such cases, some clinicians may choose to continue a nonsuppressive regimen that may provide some clinical and immunologic benefit while preserving future antiretroviral choices (see **Choice of Next Antiretroviral Regimen for Treatment Failure with Evidence of Drug Resistance**). Treating with the same nonsuppressive regimen in such situations should be regarded as an acceptable but not ideal short-term strategy. These patients should be followed more closely than patients with stable virologic status, and the potential to successfully initiate a fully suppressive antiretroviral regimen should be reassessed at every opportunity.

Extensive Drug Resistance Such That Two Fully Active Agents cannot be Identified or Administered

In the case of children for whom undetectable plasma virus is not achievable because two or more fully active agents cannot be identified, the goal is to preserve immunologic function and prevent clinical disease progression while preserving future options for new agents that are not yet available. Adult cohort studies suggest that there may be ongoing immunologic and clinical benefit if the HIV viral load can be maintained lower than 10,000–20,000 copies/mL *[7-8]*. Several cohort studies show a clinical benefit of remaining on antiretroviral therapy whether this leads to a decrease in the viral load. The principal risk associated with continuing a failing regimen is the development of additional resistance mutations that can limit future treatment options. Interrupting therapy completely, on the other hand, may cause a rapid increase in viral load, a decrease in CD4 cell count that is frequently persistent, and an increased risk of clinical disease progression *[4]*. This approach should only be considered in special circumstances when there is a low risk that therapy interruption will quickly lead to severe immunosuppression (i.e., CD4 values at the time of therapy interruption are high). The goal of continued treatment with an incompletely suppressive regimen is to select for resistant virus with reduced viral fitness that will cause slower disease progression while reducing the risk of drug toxicity and the development of new resistance mutations to multiple classes of drugs. The overall goal of these alternative strategies is to prevent clinical and immunological progression until additional active drugs are available that can be used to design a regimen that is expected to achieve undetectable plasma viral load *[1, 9-17]*. This approach should be regarded as acceptable but not ideal, these patients should be followed more closely than patients with stable virologic status, and the potential to successfully initiate a fully suppressive antiretroviral regimen should be reassessed at every opportunity.

When managing disease progression in a patient with advanced disease and extensive resistance, the patient's quality of life must be considered. The relative benefits (e.g., reduced viral fitness, continued clinical benefit

despite resistance, etc.) and burdens of continuing a failing antiretroviral regimen should be discussed. Decisions to continue, discontinue, or simplify antiretroviral therapy should be made collaboratively with patients, families, and clinicians and should be consistent with the patients'/families' stated values and goals for care.

References

1. Kovacs A, Montepiedra G, Carey V, et al. Immune reconstitution after receipt of highly active antiretroviral therapy in children with advanced or progressive HIV disease and complete or partial viral load response. *J Infect Dis.* 2005;192(2):296-302.
2. Eshleman SH, Krogstad P, Jackson JB, et al. Analysis of human immunodeficiency virus type 1 drug resistance in children receiving nucleoside analogue reverse-transcriptase inhibitors plus nevirapine, nelfinavir, or ritonavir (Pediatric AIDS Clinical Trials Group 377). *J Infect Dis.* 2001;183(12):1732-1738.
3. Boni S, Pontali E, De Gol P, et al. Compliance to combination antiretroviral therapy in HIV-1 infected children. *Int J Antimicrob Agents.* 2000;16(3):371-372.
4. Gibb DM, Duong T, Leclezio VA, et al. Immunologic changes during unplanned treatment interruptions of highly active antiretroviral therapy in children with human immunodeficiency virus type 1 infection. *Pediatr Infect Dis J.* 2004;23(5):446-450.
5. Mellins CA, Brackis-Cott E, Dolezal C, et al. The role of psychosocial and family factors in adherence to antiretroviral treatment in human immunodeficiency virus-infected children. *Pediatr Infect Dis J.* 2004;23(11):1035-1041.
6. Reddington C, Cohen J, Baldillo A, et al. Adherence to medication regimens among children with human immunodeficiency virus infection. *Pediatr Infect Dis J.* 2000;19(12):1148-1153.
7. Ledergerber B, Lundgren JD, Walker AS, et al. Predictors of trend in CD4-positive T-cell count and mortality among HIV-1-infected individuals with virological failure to all three antiretroviral-drug classes. *Lancet.* 2004;364(9428):51-62.
8. Raffanti SP, Fusco JS, Sherrill BH, et al. Effect of persistent moderate viremia on disease progression during HIV therapy. *J Acquir Immune Defic Syndr.* 2004;37(1):1147-1154.
9. Abadi J, Sprecher E, Rosenberg MG, et al. Partial treatment interruption of protease inhibitor-based highly active antiretroviral therapy regimens in HIV-infected children. *J Acquir Immune Defic Syndr.* 2006;41(3):298-303.
10. de Martino M, Galli L, Moriondo M, et al. Dissociation of responses to highly active antiretroviral therapy: Notwithstanding virologic failure and virus drug resistance, both CD4+ and CD8+ T lymphocytes recover in HIV-1 perinatally infected children. *J Acquir Immune Defic Syndr.* 2001;26(2):196-197.
11. Deeks SG, Barbour JD, Martin JN, et al. Sustained CD4+ T cell response after virologic failure of protease inhibitor-based regimens in patients with human immunodeficiency virus infection. *J Infect Dis.* 2000;181(3):946-953.
12. Deeks SG, Martin JN, Sinclair E, et al. Strong cell-mediated immune responses are associated with the maintenance of low-level viremia in antiretroviral-treated individuals with drug-resistant human immunodeficiency virus type 1. *J Infect Dis.* 2004;189(2):312-321.
13. Devereux HL, Emery VC, Johnson MA, et al. Replicative fitness in vivo of HIV-1 variants with multiple drug resistance-associated mutations. *J Med Virol.* 2001;65(2):218-224.
14. Eron JJ, Jr., Bartlett JA, Santana JL, et al. Persistent antiretroviral activity of nucleoside analogues after prolonged zidovudine and lamivudine therapy as demonstrated by rapid loss of activity after discontinuation. *J Acquir Immune Defic Syndr.* 2004;37(5):1581-1583.
15. Nikolic-Djokic D, Essajee S, Rigaud M, et al. Immunoreconstitution in children receiving highly active antiretroviral therapy depends on the CD4 cell percentage at baseline. *J Infect Dis.* 2002;185(3):290-298.
16. Piketty C, Weiss L, Thomas F, et al. Long-term clinical outcome of human immunodeficiency virus-infected patients with discordant immunologic and virologic responses to a protease inhibitor-containing regimen. *J Infect Dis.* 2001;183(9):1328-1335.
17. Rutstein RM, Gebo KA, Flynn PM, et al. Immunologic function and virologic suppression among children with perinatally acquired HIV infection on highly active antiretroviral therapy. *Med Care.* 2005;43(9 Suppl):III15-22.

CHOICE OF NEXT ANTIRETROVIRAL REGIMEN FOR TREATMENT FAILURE WITH EVIDENCE OF DRUG RESISTANCE

Panel's Recommendations:

- ***Antiretroviral regimens should be chosen based on treatment history and drug-resistance testing, including past and current resistance test results (AI*).***
- ***Ideally, use three fully active antiretroviral medications in the new regimen, assessing anticipated antiretroviral activity based on past treatment history and resistance test results (AII*).***
- ***Interpretation of resistance test results showing complex combinations of mutations and assessment of future treatment options should be made in collaboration with a pediatric HIV specialist (AI*).***
- ***Use of novel agents with limited available pharmacokinetic and/or safety data in pediatric populations should be undertaken only in collaboration with a pediatric HIV specialist (AIII).***

General

After carefully reaching a decision that a change in therapy is needed, the clinician should attempt to identify at least two but preferably three fully active antiretroviral agents on the basis of resistance testing, prior antiretroviral exposure, acceptability to the patient, and likely adherence *[1-5]*. This often requires the use of one or more new drug classes. Substitution or addition of a single drug to a failing regimen should be avoided because this approach is unlikely to achieve and sustain an undetectable plasma viral load and frequently will result in additional drug resistance. A drug may be "new" to the patient but have diminished antiviral potency due to the presence of drug mutations that confer cross resistance within a drug class. In children who are changing therapy due to occurrence or progression of abnormal neurodevelopment, the new treatment regimen should include agents (such as zidovudine) that are known to achieve higher levels within the central nervous system *[6-9]*.

A change to a new regimen must include an extensive discussion of treatment adherence and potential toxicity with the patient in an age- and development-appropriate manner and with the patient's caregivers. The clinician must recognize that conflicting requirements of some medications with respect to food and concomitant medication restrictions may complicate coordination of a regimen. Timing of medication administration is particularly important to ensure adequate antiretroviral drug exposures throughout the day. Palatability, pill size, pill number, and dosing frequency all need to be considered when choosing a new regimen.

Choice of Therapy with Viral Resistance to Current Therapy: Goal of Complete Virologic Suppression

Determination of a new regimen with the best chance for complete virologic suppression in children who have already experienced treatment failure should be made in collaboration with a pediatric HIV specialist. Antiretroviral regimens should be chosen based on treatment history and drug-resistance testing to optimize antiretroviral drug potency in the new regimen. A general strategy for regimen change is shown in **Table 14**, although as additional agents are licensed and studied for use in children, newer strategies that are better tailored to the needs of each patient may be constructed.

If a child has received initial therapy with an NNRTI-based regimen, a change to a PI-based regimen is recommended; if a child received initial therapy with a PI-based regimen, a change to an NNRTI-based regimen is recommended. Resistance to the NNRTI nevirapine results in cross resistance to the NNRTI efavirenz and vice versa; however, the newer NNRTI etravirine retains activity against nevirapine- or efavirenz-resistant virus in the presence of a limited number of NNRTI resistance-associated mutations. Etravirine is currently approved for use only in adults; pediatric studies are under way.

Choice of the new dual-NRTI component is particularly important when constructing a regimen because the choice of an insufficiently potent NRTI may result in the selection of additional NRTI-related drug mutations.

Resistance testing is essential to properly select a potent NRTI combination, and interpretation of these results should take place in collaboration with an expert in pediatric HIV infection (see **Antiretroviral Drug-Resistance Testing**). In this case, use of a triple-class regimen or a novel agent may be necessary.

If a patient has substantial pre-existing resistance or if the initial regimen contained drugs from all three major classes (NRTI, NNRTI, and PI), the drug-resistance profile and management approach is likely to resemble that of a patient who has had multiple antiretroviral regimen failures (see **Choice of Therapy with Extensive Drug Resistance Such That Two Fully Active Agents Cannot Be Identified or Administered**). In this situation, a new regimen with only two fully active agents may be the best available option. Lopinavir/ritonavir-based regimens have shown durable antiretroviral activity in antiretroviral treatment-experienced children, including children with prior PI therapy *[10-12]*. Adult studies of treatment-experienced patients have shown that using one or more new class(es) of drug (e.g., integrase inhibitors, entry inhibitors), possibly coupled with a ritonavir-boosted PI (e.g., darunavir) in PI-experienced, multiresistant patients is associated with better virologic responses *[13-14]*. **Appendix B: Pediatric Antiretroviral Drug Information** provides more detailed information on drug formulation, pediatric and adult dosing, and toxicity as well as discussion of available pediatric data for the approved antiretroviral drugs, including new drugs in existing classes such as darunavir and new classes of drugs such as CCR5 antagonists and integrase inhibitors. Maraviroc (CCR5 inhibitor) and raltegravir (integrase inhibitor) are approved for use in adolescents 16 years or older and can be considered for management of older adolescents with multidrug failure; pediatric trials are under way or in development.

Previously prescribed drugs discontinued due to poor tolerance or poor adherence may sometimes be reintroduced. Reintroduction of the drugs is particularly possible if antiretroviral resistance did not develop and if prior difficulties with tolerance and adherence can be overcome (e.g., by switching from a liquid to pill formulation). Limited data in adults suggest that continuation of lamivudine can contribute to suppression of HIV replication despite the presence of lamivudine resistance mutations and can maintain lamivudine mutations (184V) that can partially reverse the effect of other mutations conferring resistance to zidovudine, stavudine, and tenofovir *[15-17]*. The use of new drugs that have been evaluated in adults but have not been fully evaluated in children might be justified and is ideally done in the framework of a clinical trial (see **The Use of Antiretroviral Agents Not Approved for Use in Children**). Expanded access programs or clinical trials may be available. New drugs should be used in combination with at least one, and ideally two, additional active agents.

The HIV entry inhibitor enfuvirtide (T-20) has been approved for use in heavily treatment experienced patients based on potent antiretroviral activity in heavily treatment experienced adults and has been approved for use in children age ≥6 years *[18-19]*. Studies have helped establish safety, appropriate dosing, and efficacy of enfuvirtide in treatment-experienced children ≥6 years of age; this therapy has the disadvantage of administration by subcutaneous injection twice daily *[20-21]*. Enfuvirtide adherence in adolescent populations remains a unique challenge when compared with younger children. However, this agent should be considered as an option when designing a new regimen for pediatric populations who have failed treatment with multiple classes of antiretroviral medications.

Pharmacokinetic studies of certain dual-boosted PI regimens (lopinavir/ritonavir with saquinavir and lopinavir/ritonavir with atazanavir/ritonavir) suggest that pharmacokinetic targets for both PIs can be achieved or exceeded when used in combination in adults *[22-24]* and in children *[25-27]*. Pharmacokinetic studies of other dual-boosted PI combinations are limited but suggest inadequate drug levels of one or both PIs *[28-29]*. A study in Thailand of 50 PI-naïve but NRTI+/-NNRTI experienced children treated with a combination of lopinavir/ritonavir (230/57.5 mg/m^2 twice daily) and saquinavir (50 mg/kg twice daily, maximum dose 1,000 mg) demonstrated trough levels of both PIs at or above therapeutic targets and complete viral suppression at 48 weeks for ≥50% of patients. The regimen was well tolerated but hyperlipidemia was common. The use of multidrug regimens, sometimes including up to 3 PIs and/or 2 NNRTIs, has shown efficacy in a pediatric case series *[30]* but should be used cautiously due to its complexity, poor tolerability, and unfavorable drug-drug interactions. Therapeutic drug monitoring (TDM) may be helpful for confirming therapeutic PI levels when using PIs in combinations that result in complex drug interactions or when there is partially reduced PI activity

due to the presence of drug-resistance mutations (see **Role of Therapeutic Drug Monitoring in Management of Treatment Failure**).

When searching for at least two fully active agents in cases of extensive drug resistance, the clinician should consider the potential availability and future use of newer therapeutic agents that may not be studied or approved in children or may be in clinical development (see **The Use of Antiretroviral Agents Not Approved for Use in Children**). Information concerning potential clinical trials can be found at **http://aidsinfo.nih.gov/clinical_trials** and through collaboration with a pediatric HIV specialist. Children should be enrolled in clinical trials of new drugs whenever possible.

Choice of Therapy with Extensive Drug Resistance Such That Two Fully Active Agents Cannot Be Identified or Administered

The creation of an effective and sustainable therapeutic regimen may not be possible with currently available agents due to lack of potency in the face of extensive drug resistance or the patient's inability to adhere to or tolerate combination antiretroviral therapy. In such cases, nonsuppressive regimens (or "holding regimens") are sometimes used with the overall objective of preventing clinical and immunological deterioration pending availability of additional active drugs that can be used to design a regimen that is expected to achieve undetectable plasma viral load. This approach should be regarded as acceptable but not ideal. These patients should be followed more closely than patients with stable virologic status, and the potential to successfully initiate a fully suppressive antiretroviral regimen should be reassessed at every opportunity.

Even when NRTI drug-resistance mutations are present, there can be immunologic and clinical benefit despite persistent viremia when patients are treated with lamivudine monotherapy or when they are treated with lamivudine or emtricitabine in combination with one or more other NRTIs, such as zidovudine, stavudine, abacavir, or tenofovir *[31-32]*.

Because the newer NNRTI etravirine retains activity against nevirapine- or efavirenz-resistant virus in the presence of a limited number of NNRTI resistance-associated mutations, efavirenz or nevirapine should not be continued as part of a failing regimen if NNRTI resistance is documented.

Continued use of a PI in the face of persistent viremia can lead to accumulation of additional mutations conferring resistance to that PI as well as other, newer PIs. Such acquisition of additional PI drug resistance occurs slowly, especially if the viral load is relatively low *[33-35]*. However, continued PI use, in the presence of resistance, may limit viral replication and be beneficial to some patients.

In general, every effort should be made to avoid adding a single, new, fully active agent to these "holding" nonsuppressive regimens because such use of a single fully active agent will quickly lead to diminished activity of that agent. When clinical or immunologic deterioration occurs in such cases, it is often appropriate to use investigational agents or agents approved for older age groups as a second fully active drug in the new regimen (see **The Use of Antiretroviral Agents Not Approved for Use in Children**).

Table 20. Options for Regimens with at Least Two Fully Active Agents Following Failure of Antiretroviral Regimen with Evidence for Viral Resistance to Therapy with Goal of Virologic Suppression*

Prior Regimen	Recommended Change
2 NRTIs + NNRTI	• 2 NRTIs (based on resistance testing) + PI
2 NRTIs + PI	• 2 NRTIs (based on resistance testing) + NNRTI • 2 NRTIs (based on resistance testing) + alternative PI (with low-dose ritonavir boosting, based on resistance testing) • NRTI(s) (based on resistance testing) + NNRTI + alternative PI (with low-dose ritonavir boosting, based on resistance testing)
3 NRTIs	• 2 NRTIs (based on resistance testing) + (NNRTI *or* PI) • NRTI(s) (based on resistance testing) + (NNRTI + PI)
Failed regimens including NRTI, NNRTI, PI	• >1 NRTI (based on resistance testing) + a newer PI (with low-dose ritonavir boosting, based on resistance testing) • >1 NRTI + dual-boosted PI (LPV/r + SQV, LPV/r + ATV) (consider adding either one or more of T-20, ETR, or an integrase inhibitor) • NRTI(s) + ritonavir-boosted, potent PI (based upon resistance testing) + ETR • NRTI(s) + ritonavir-boosted, potent PI (based upon resistance testing) + T-20 and/or CCR5 antagonist and/or integrase inhibitor • If patient refuses PI and/or ritonavir boosting: NRTI(s) + T-20 and/or integrase inhibitor and/or CCR5 antagonist

* Antiretroviral regimens should be chosen based on treatment history and drug-resistance testing to optimize antiretroviral drug effectiveness in the second regimen. This is particularly important in selecting NRTI components of an NNRTI-based regimen where drug resistance may occur rapidly to the NNRTI if the virus is not sufficiently sensitive to the NRTIs. Regimens should contain at least two, but preferably three, fully active drugs for durable, potent virologic suppression.

Key to Abbreviations: T-20 = enfuvirtide, ATV = atazanavir, ETR = etravirine, LPV/r = lopinavir/ritonavir, NRTI = nucleoside reverse transcriptase inhibitor, NNRTI = non-nucleoside reverse transcriptase inhibitor, PI = protease inhibitor, SQV = saquinavir

References

1. Katlama C, Haubrich R, Lalezari J, et al. Efficacy and safety of etravirine in treatment-experienced, HIV-1 patients: pooled 48 week analysis of two randomized, controlled trials. *AIDS.* 2009;23(17):2289-2300.
2. Steigbigel RT, Cooper DA, Teppler H, et al. Long-term efficacy and safety of Raltegravir combined with optimized background therapy in treatment-experienced patients with drug-resistant HIV infection: week 96 results of the BENCHMRK 1 and 2 Phase III trials. *Clin Infect Dis.* 2010;50(4):605-612.
3. De Luca A, Di Giambenedetto S, Cingolani A, et al. Three-year clinical outcomes of resistance genotyping and expert advice: extended follow-up of the Argenta trial. *Antivir Ther.* 2006;11(3):321-327.
4. Baxter JD, Mayers DL, Wentworth DN, et al. A randomized study of antiretroviral management based on plasma genotypic antiretroviral resistance testing in patients failing therapy. CPCRA 046 Study Team for the Terry Beirn Community Programs for Clinical Research on AIDS. *AIDS.* 2000;14(9):F83-93.
5. Tural C, Ruiz L, Holtzer C, et al. Clinical utility of HIV-1 genotyping and expert advice: the Havana trial. *AIDS.* 2002;16(2):209-218.
6. Antinori A, Giancola ML, Grisetti S, et al. Factors influencing virological response to antiretroviral drugs in cerebrospinal fluid of advanced HIV-1-infected patients. *AIDS.* 2002;16(14):1867-1876.
7. Antinori A, Perno CF, Giancola ML, et al. Efficacy of cerebrospinal fluid (CSF)-penetrating antiretroviral drugs against HIV in the neurological compartment: different patterns of phenotypic resistance in CSF and plasma. *Clin Infect Dis.* 2005;41(12):1787-1793.
8. Capparelli EV, Letendre SL, Ellis RJ, et al. Population pharmacokinetics of abacavir in plasma and cerebrospinal fluid. *Antimicrob Agents Chemother.* 2005;49(6):2504-2506.
9. Letendre S, Marquie-Beck J, Capparelli E, et al. Validation of the CNS Penetration-Effectiveness rank for quantifying antiretroviral penetration into the central nervous system. *Arch Neurol.* 2008;65(1):65-70.
10. Galan I, Jimenez JL, Gonzalez-Rivera M, et al. Virological phenotype switches under salvage therapy with lopinavir-ritonavir in heavily pretreated HIV-1 vertically infected children. *AIDS.* 2004;18(2):247-255.
11. Ramos JT, De Jose MI, Duenas J, et al. Safety and antiviral response at 12 months of lopinavir/ritonavir therapy in human immunodeficiency virus-1-infected children experienced with three classes of antiretrovirals. *Pediatr Infect Dis J.* 2005;24(10):867-873.
12. Resino S, Bellon JM, Munoz-Fernandez MA. Antiretroviral activity and safety of lopinavir/ritonavir in protease inhibitor-experienced HIV-infected children with severe-moderate immunodeficiency. *J Antimicrob Chemother.* 2006;57(3):579-582.
13. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. December 1, 2009:1-161. http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf.
14. Temesgen Z, Cainelli F, Poeschla EM, et al. Approach to salvage antiretroviral therapy in heavily antiretroviral-experienced HIV-positive adults. *Lancet Infect Dis.* 2006;6(8):496-507.
15. Campbell TB, Shulman NS, Johnson SC, et al. Antiviral activity of lamivudine in salvage therapy for multidrug-resistant HIV-1 infection. *Clin Infect Dis.* 2005;41(2):236-242.
16. Nijhuis M, Schuurman R, de Jong D, et al. Lamivudine-resistant human immunodeficiency virus type 1 variants (184V) require multiple amino acid changes to become co-resistant to zidovudine in vivo. *J Infect Dis.* 1997;176(2):398-405.
17. Ross L, Parkin N, Chappey C, et al. Phenotypic impact of HIV reverse transcriptase M184I/V mutations in combination with single thymidine analog mutations on nucleoside reverse transcriptase inhibitor resistance. *AIDS.* 2004;18(12):1691-1696.
18. Church JA, Cunningham C, Hughes M, et al. Safety and antiretroviral activity of chronic subcutaneous administration of T-20 in human immunodeficiency virus 1-infected children. *Pediatr Infect Dis J.* 2002;21(7):653-659.
19. Church JA, Hughes M, Chen J, et al. Long term tolerability and safety of enfuvirtide for human immunodeficiency virus 1-infected children. *Pediatr Infect Dis J.* 2004;23(8):713-718.
20. Wiznia A, Church J, Emmanuel P, et al. Safety and efficacy of enfuvirtide for 48 weeks as part of an optimized antiretroviral regimen in pediatric human immunodeficiency virus 1-infected patients. *Pediatr Infect Dis J.* 2007;26(9):799-805.
21. Zhang X, Lin T, Bertasso A, et al. Population pharmacokinetics of enfuvirtide in HIV-1-infected pediatric patients over 48 weeks of treatment. *J Clin Pharmacol.* 2007;47(4):510-517.
22. Ribera E, Azuaje C, Lopez RM, et al. Atazanavir and lopinavir/ritonavir: pharmacokinetics, safety and efficacy of a promising double-boosted protease inhibitor regimen. *AIDS.* 2006;20(8):1131-1139.
23. Stephan C, von Hentig N, Kourbeti I, et al. Saquinavir drug exposure is not impaired by the boosted double protease inhibitor combination of lopinavir/ritonavir. *AIDS.* 2004;18(3):503-508.

24. van der Lugt J, Autar RS, Ubolyam S, et al. Pharmacokinetics and short-term efficacy of a double-boosted protease inhibitor regimen in treatment-naive HIV-1-infected adults. *J Antimicrob Chemother.* 2008;61(5):1145-1153.
25. Ananworanich J, Kosalaraksa P, Hill A, et al. Pharmacokinetics and 24-week efficacy/safety of dual boosted saquinavir/lopinavir/ritonavir in nucleoside-pretreated children. *Pediatr Infect Dis J.* 2005;24(10):874-879.
26. Kosalaraksa P, Bunupuradah T, Engchanil C, et al. Double boosted protease inhibitors, saquinavir, and lopinavir/ritonavir, in nucleoside pretreated children at 48 weeks. *Pediatr Infect Dis J.* 2008;27(7):623-628.
27. Robbins BL, Capparelli EV, Chadwick EG, et al. Pharmacokinetics of high-dose lopinavir-ritonavir with and without saquinavir or nonnucleoside reverse transcriptase inhibitors in human immunodeficiency virus-infected pediatric and adolescent patients previously treated with protease inhibitors. *Antimicrob Agents Chemother.* 2008;52(9):3276-3283.
28. Collier AC, Tierney C, Downey GF, et al. Randomized study of dual versus single ritonavir-enhanced protease inhibitors for protease inhibitor-experienced patients with HIV. *HIV Clin Trials.* 2008;9(2):91-102.
29. Walmsley SL, Katlama C, Lazzarin A, et al. Pharmacokinetics, safety, and efficacy of tipranavir boosted with ritonavir alone or in combination with other boosted protease inhibitors as part of optimized combination antiretroviral therapy in highly treatment-experienced patients (BI Study 1182.51). *J Acquir Immune Defic Syndr.* 2008;47(4):429-440.
30. King JR, Acosta EP, Chadwick E, et al. Evaluation of multiple drug therapy in human immunodeficiency virus-infected pediatric patients. *Pediatr Infect Dis J.* 2003;22(3):239-244.
31. Castagna A, Danise A, Menzo S, et al. Lamivudine monotherapy in HIV-1-infected patients harbouring a lamivudine-resistant virus: a randomized pilot study (E-184V study). *AIDS.* 2006;20(6):795-803.
32. Deeks SG, Hoh R, Neilands TB, et al. Interruption of treatment with individual therapeutic drug classes in adults with multidrug-resistant HIV-1 infection. *J Infect Dis.* 2005;192(9):1537-1544.
33. Garcia-Gasco P, Maida I, Blanco F, et al. Episodes of low-level viral rebound in HIV-infected patients on antiretroviral therapy: frequency, predictors and outcome. *J Antimicrob Chemother.* 2008;61(3):699-704.
34. Napravnik S, Edwards D, Stewart P, et al. HIV-1 drug resistance evolution among patients on potent combination antiretroviral therapy with detectable viremia. *J Acquir Immune Defic Syndr.* 2005;40(1):34-40.
35. Nettles RE, Kieffer TL, Kwon P, et al. Intermittent HIV-1 viremia (Blips) and drug resistance in patients receiving HAART. *JAMA.* 2005;293(7):817-829.

THE USE OF ANTIRETROVIRAL AGENTS NOT APPROVED FOR USE IN CHILDREN

Panel's Recommendations:

- ***Some children with HIV need to use antiretrovirals that are not yet approved for their age range because many of the recently approved, more convenient, and potent agents are approved for adults before pharmacokinetic, safety, and efficacy data are available in children (AII).***
- ***This "off-label" use of antiretrovirals can be risky because dosing recommendations have not yet been made and often cannot be inferred from a simple calculation using the adult dose and the child's weight (AII).***
- ***Off-label use of antiretrovirals should always be done in collaboration with a pediatric HIV specialist, who may have access to unpublished data about safety and pharmacokinetics of these agents (AI*).***
- ***Whenever possible, use of antiretrovirals that are not yet FDA approved for children should be done in the context of clinical trials that can generate the data needed for pediatric approval (AIII).***

It has long been practice for physicians, especially pediatricians, to prescribe medications in "off-label" situations, meaning for indications or populations that do not fall within the FDA's official indication *[1]*. The relatively small market for pediatric antiretroviral drugs and few children available for clinical trials have delayed or prevented studies to obtain an FDA pediatric label indication for some antiretroviral drugs at the same time they are approved in adults. Pediatric HIV specialists may need to prescribe these agents because of

high levels of resistance seen in heavily treated children and adolescents and improvements in tolerability and ease of adherence with newer agents with less frequent dosing.

One distinct advantage of some of the newer medications is improved tolerability. Examples include a reduction in the number or severity of side effects with newer PIs and the ability to create simpler regimens using fixed-dose combination tablets or once-daily preparations. The incentive to use these drugs in such instances is that these regimens will lead to improved adherence and thus better long-term outcomes.

Another major factor leading to the off-label use of antiretrovirals has been the development of new drugs belonging to novel classes of agents effective against resistant virus. In the United States, many older perinatally infected children have extensive drug resistance resulting from incomplete viral suppression due to treatment with multiple nonsuppressive regimens. Cross resistance between fully approved antiretrovirals within a class complicates finding an array of agents likely to fully suppress the virus. In an effort to find a regimen likely to achieve complete virologic suppression in an individual patient, providers must find at least two and preferably three drugs with demonstrated activity against the patient's virus. Success is almost impossible in heavily treatment experienced children using only drugs with approved pediatric label indications; thus providers may use drugs not yet approved for children in order to provide optimal virologic response. The recent FDA approvals for adults of raltegravir and maraviroc (the first integrase inhibitor and CCR5 inhibitor, respectively) have provided new options for therapy to achieve virologic suppression in patients experiencing treatment failure with extensive antiretroviral resistance.

However, the use of agents not yet approved for pediatric use causes some difficulties, and one of the major issues is lack of data on appropriate dosing in children. Agents are approved for adult use prior to pediatric use because safety and pharmacokinetic studies in children have not yet been completed. Sometimes these studies are ongoing and some data are available, but other times these studies have not yet begun. It is essential for providers prescribing agents for off-label use to consult with pediatric HIV experts to avail themselves of the latest information from ongoing studies.

The possibility of age-related side effects is another concern when initiating off-label antiretroviral use. To date no antiretroviral has been found to have adverse effects that uniquely preclude use in children, but until an agent has been tested in children it cannot be considered to be free of such an effect. Additionally, adverse effects noted in adults may be of more substantial concern in the growing and developing child.

Even more difficult than the potential for adverse effects has been the difficulty of dosing of antiretrovirals in pediatric patients. As absorption, hepatic metabolism and excretion change with age, so will drug levels change in children *[2]*. The difficulty in dosing children as they increase in weight is exacerbated by changing pharmacokinetics. The direct extrapolation of the adult dose to a pediatric dose, based either on body weight or body surface area, has been shown in clinical trials of several antiretroviral agents to underestimate the appropriate pediatric dose *[3]*.

In summary, the use of antiretroviral agents without a pediatric indication is an absolute necessity for the treatment of some children with HIV, but it must be done with care. **It is essential that the provider consult with a pediatric HIV specialist to identify any particular concerns with each agent, to access any available data from clinical trials or other limited off-label pediatric use, and to investigate the availability of suitable clinical trials.**

References

1. Riordan A, Judd A, Boyd K, et al. Tenofovir use in human immunodeficiency virus-1-infected children in the United kingdom and Ireland. *Pediatr Infect Dis J*. 2009;28(3):204-209.
2. Kearns GL, Abdel-Rahman SM, Alander SW, et al. Developmental pharmacology--drug disposition, action, and therapy in infants and children. *N Engl J Med*. 2003;349(12):1157-1167.
3. Fletcher CV, Brundage RC, Fenton T, et al. Pharmacokinetics and pharmacodynamics of efavirenz and nelfinavir in HIV-infected children participating in an area-under-the-curve controlled trial. *Clin Pharmacol Ther*. 2008;83(2):300-306.

ROLE OF THERAPEUTIC DRUG MONITORING IN MANAGEMENT OF TREATMENT FAILURE

Therapeutic drug monitoring (TDM) is the use of plasma drug concentration measurements as part of a strategy to optimize drug dosing to minimize toxicity and maximize treatment benefit. TDM can be considered for use in antiretroviral treatment because *[1]*:

- There is high interpatient variability in antiretroviral exposure (plasma drug concentrations) using standard recommended doses;
- Low drug exposure can lead to suboptimal virologic response to therapy; and
- High plasma concentrations can be associated with increased risk of drug toxicity.

Developmental pharmacokinetic differences contribute to greater variability and a greater frequency of suboptimal antiretroviral exposure in pediatric patients than in adults *[2]*. Pediatric dosing is designed to mimic adult exposure and rarely reflects the maximum tolerated antiretroviral drug dose. Even when using dose recommendations from published pediatric guidelines, children frequently receive inadequate antiretroviral doses *[3]*.

There are two main situations in which TDM might be useful in a child who is failing therapy. First, TDM can be used to rule out subtherapeutic drug levels as a cause of failure. Such inadequate drug levels could result from malabsorption, drug interactions, poor adherence, or increased drug metabolism or clearance. Second, drug levels can be used to optimize the dose of a drug when changing to a new regimen in a patient whose virus has a reduced susceptibility to that drug.

For TDM to be useful there needs to be a clearly defined relationship between antiretroviral concentrations and anti-HIV effects *[4-6]*. This association is strongest with PI and NNRTI drugs *[7]*, but maintaining adequate NRTI serum concentrations has also been shown to be important for maximal anti-HIV activity *[8]*. The exposure-toxicity response relationship is less well defined for NRTI drugs but has been determined for some agents *[6]*. Concentration-response relationships have been established with minimum plasma concentrations (C_{min} or C_{trough}) or area under the curve (AUC), but the optimal measure is not defined for all antiretroviral drugs *[9]*.

Table 15 presents recommendations for the minimum target trough concentrations of PIs and NNRTIs in patients with wild-type virus. In antiretroviral-experienced patients, the choice of minimum target trough concentration should be based on results of resistance testing *[10-12]*. Although it is intrinsically difficult to demonstrate benefit of TDM using double-blind studies, limited data suggest targeted concentrations can be achieved with TDM, clinical responses can be improved with increased or modified doses, and TDM information can be helpful in decision making *[7, 13-17]*. The clinician should consult with a pediatric HIV specialist or pharmacologist in making these decisions.

TDM is not recommended for routine use but may be considered in the following circumstances in which it is potentially useful:

- Patients in whom clinical response is different from that expected;

- Treatment-experienced patients infected with virus with reduced drug susceptibility, where a comparison of the drug susceptibility of the virus and the achieved drug concentrations may be useful;
- Patients with potential drug administration difficulties, including suboptimal dietary intake, malabsorption, incorrect dose, caregiver measuring errors, or adherence concerns; and
- Patients who experience drug or food interactions, including alteration of drug formulations by crushing or mixing with various foods and liquids.

Current limitations for pediatric antiretroviral TDM include:

- Prolonged time for laboratory processing in the face of potentially diminishing benefit the longer the patient is on inadequate therapy;
- Difficulties in coordinating sample collections at appropriate times make determination of true C_{min} or AUC difficult;
- High intrapatient variability from single drug concentration measurements may complicate interpretation of results *[18-19]*;
- Single trough measurements within the target range do not guarantee consistent adequacy of drug exposure or therapeutic success;
- Inadequate information on safety and effectiveness of dose adjustment strategies in children and adolescents;
- Limited availability of certified laboratories capable of assaying drug concentrations; and
- Lack of third party reimbursement of costs associated with TDM.

Table 21. Suggested Minimum Target Trough Concentrations*

Drug	Concentration (ng/mL)
Fosamprenavir	400 (measured as amprenavir concentration)
Atazanavir	150
Indinavir	100
Lopinavir	1,000
Nelfinavir (Measurable active [M8] metabolite)	800
Saquinavir	100–250
Efavirenz	1,000
Nevirapine	3,000
Recommendations applicable only to treatment-experienced persons who have resistant HIV-1 strains	
Maraviroc	>50
Tipranavir	20,500

* Reprinted from: Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. December 1, 2009:1-161. **http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf**.

References

1. Fraaij PL, Rakhmanina N, Burger DM, et al. Therapeutic drug monitoring in children with HIV/AIDS. *Ther Drug Monit.* 2004;26(2):122-126.
2. Kearns GL, Abdel-Rahman SM, Alander SW, et al. Developmental pharmacology--drug disposition, action, and therapy in infants and children. *N Engl J Med.* 2003;349(12):1157-1167.
3. Menson EN, Walker AS, Sharland M, et al. Underdosing of antiretrovirals in UK and Irish children with HIV as an example of problems in prescribing medicines to children, 1997-2005: cohort study. *BMJ.* 2006;332(7551):1183-1187.
4. Acosta EP, Gerber JG. Position paper on therapeutic drug monitoring of antiretroviral agents. *AIDS Res Hum Retroviruses.* 2002;18(12):825-834.
5. Anderson PL, Fletcher CV. Updated clinical pharmacologic considerations for HIV-1 protease inhibitors. *Curr HIV/AIDS Rep.* 2004;1(1):33-39.
6. Morse GD, Catanzaro LM, Acosta EP. Clinical pharmacodynamics of HIV-1 protease inhibitors: use of inhibitory quotients to optimise pharmacotherapy. *Lancet Infect Dis.* 2006;6(4):215-225.
7. Burger D, Hugen P, Reiss P, et al. Therapeutic drug monitoring of nelfinavir and indinavir in treatment-naive HIV-1-infected individuals. *AIDS.* 2003;17(8):1157-1165.
8. Fletcher CV, Acosta EP, Henry K, et al. Concentration-controlled zidovudine therapy. *Clin Pharmacol Ther.* 1998;64(3):331-338.
9. Back D, Gatti G, Fletcher C, et al. Therapeutic drug monitoring in HIV infection: current status and future directions. *AIDS.* 2002;16 Suppl 1:S5-37.
10. Acosta EP, King JR. Methods for integration of pharmacokinetic and phenotypic information in the treatment of infection with human immunodeficiency virus. *Clin Infect Dis.* 2003;36(3):373-377.
11. Ellner PD, Neu HC. The inhibitory quotient. A method for interpreting minimum inhibitory concentration data. *JAMA.* 1981;246(14):1575-1578.
12. Hsu A, Isaacson J, Brun S, et al. Pharmacokinetic-pharmacodynamic analysis of lopinavir-ritonavir in combination with efavirenz and two nucleoside reverse transcriptase inhibitors in extensively pretreated human immunodeficiency virus-infected patients. *Antimicrob Agents Chemother.* 2003;47(1):350-359.
13. Best B, Witt M, Goicoechea M, et al. Improved antiretroviral exposure with therapeutic drug monitoring. Paper presented at: 13th Conference on Retroviruses and Opportunistic Infections; February 5-8, 2006; Denver, CO. Abstract 589.

14. Bossi P, Peytavin G, Ait-Mohand H, et al. GENOPHAR: a randomized study of plasma drug measurements in association with genotypic resistance testing and expert advice to optimize therapy in patients failing antiretroviral therapy. *HIV Med.* 2004;5(5):352-359.
15. Clevenbergh P, Garraffo R, Durant J, et al. PharmAdapt: a randomized prospective study to evaluate the benefit of therapeutic monitoring of protease inhibitors: 12 week results. *AIDS.* 2002;16(17):2311-2315.
16. de Requena DG, Nunez M, Gallego O, et al. Does an increase in nevirapine plasma levels cause complete virologic suppression in patients experiencing early virologic failure? *HIV Clin Trials.* 2002;3(6):463-467.
17. Fletcher CV, Anderson PL, Kakuda TN, et al. Concentration-controlled compared with conventional antiretroviral therapy for HIV infection. *AIDS.* 2002;16(4):551-560.
18. Haas DW. Can responses to antiretroviral therapy be improved by therapeutic drug monitoring? *Clin Infect Dis.* 2006;42(8):1197-1199.
19. Nettles RE, Kieffer TL, Parsons T, et al. Marked intraindividual variability in antiretroviral concentrations may limit the utility of therapeutic drug monitoring. *Clin Infect Dis.* 2006;42(8):1189-1196.

DISCONTINUATION OR INTERRUPTION OF THERAPY

General

Discontinuation of antiretroviral therapy may be indicated in some situations, including serious treatment-related toxicity, acute illnesses or planned surgeries that preclude oral intake, lack of available medication, or patient or parent request. Although these events are usually unplanned, purposeful discontinuation of therapy has been widely used in the adult population to reduce toxicity, costs, and drug-related failure associated with antiretroviral therapy. At this time, there are minimal data in infants, children, and adolescents about planned structured treatment interruptions (STI). Thus, STI should not be attempted in children or adults outside of a clinical trial setting. The discussion below provides general guidance for the interruption of antiretroviral therapy and the risks and benefits in specific situations.

Short-Term Therapy Interruption

In the pediatric patient, short-term therapy interruptions are most often necessitated by acute illnesses that limit oral intake. These illnesses are often infectious diseases that result in vomiting and/or diarrhea. The clinician has no choice but to stop all therapy at the same time. Planned short-term interruption of therapy may also be required in the event of surgery or sedation for procedures, but when possible, the patient should be allowed to continue regular antiretroviral therapy with minimal fluid intake. If the period of restricted oral intake will be prolonged, then all therapy should be stopped at the same time if the medications have similar half-lives. In the case of serious or life-threatening antiretroviral therapy toxicity, all drugs should be stopped immediately.

When a short-term therapy interruption is indicated, all antiretroviral therapy should be stopped at the same time in most cases. This can be problematic with agents with a long half-life. Stopping agents with different half-lives at the same time can result in functional monotherapy with the drug with the longest half-life. This is particularly concerning in the case of the NNRTIs efavirenz and nevirapine.

Efavirenz and nevirapine have very long half-lives and can be detected for 21 days or longer after discontinuation *[1-4]*. As the other drugs with shorter half-lives are cleared, only nevirapine or efavirenz may persist, resulting in functional monotherapy, which can increase the risk of selection of NNRTI-resistant mutations. In addition, it is known that certain genetic polymorphisms may result in a slower rate of drug clearance. These polymorphisms may be more common among some ethnic groups, such as in African Americans and Hispanics *[3-4]*. To prevent this functional monotherapy, some experts recommend stopping the NNRTI first and continuing the other antiretroviral drugs (i.e., NRTI backbone or PI) for a period of time *[2]*. However, the optimal interval between stopping an NNRTI and the other antiretroviral drugs is not known. Detectable levels of NNRTIs may be present from less than 1 week to greater than 3 weeks after discontinuation *[4]*. An alternative is to substitute a PI for up to 4 weeks prior to the interruption of all drugs; however, there are no data to support this practice. Studies are ongoing in adults to help determine an effective

strategy. There is no information in children and, because the pharmacokinetics of these agents are different in children, the recommendations for adults may not be applicable *[5-7]*.

An additional consideration is reintroduction of nevirapine. Currently, a 2-week, half-dose escalation is recommended in patients who are started on nevirapine. Dose escalation is necessary because nevirapine induces its own metabolism by inducing CYP3A4 metabolic liver enzymes; thus, initial administration of the full therapeutic dose will result in elevated drug levels until metabolic enzyme induction has occurred. Lower rates of rash toxicity have been observed with the 2-week dose escalation *[5]*. In cases where nevirapine has been discontinued for more than 2 weeks, it is recommended that another 2-week dose escalation be used when the drug is reintroduced.

Long-Term Structured Treatment Interruptions

Long-term STIs have been proposed to reduce toxicities and costs associated with long-term antiretroviral therapy. STIs have also been proposed in patients who have limited treatment options to allow a return to their wild-type virus, which may be more susceptible to treatment. At this time, there is only minimal information about STI in children. In 1 study, children with controlled viral load (HIV RNA <400 copies/mL for $\geq$12 months) were subjected to increasing intervals of treatment interruption. Of 14 children studied, 4 maintained undetectable viral loads with interruptions of up to 27 days. It has been hypothesized that enhanced HIV-specific immune responses may play a role in the viral suppression *[8]*. However, new drug-resistance mutations were detected in 3 of 14 children in the STI study.

Recently, the results of two large, randomized clinical trials in adults have demonstrated inferior responses when CD4 cell count was used as an indication to stop and start therapy. The Strategies for Management of Antiretroviral Therapy stopped antiretroviral therapy when the CD4 cell count was >350 cells/mm^3 and reintroduced therapy when the count was <250 cells/mm^3. In comparison to the group receiving continuous antiretroviral therapy, the STI group had an increased risk of disease progression and death *[9]*. Similarly, in the Trivican trials, which used the same CD4 cell count triggers to stop and restart therapy, STI was shown to be inferior *[10]*. However, in studies in adults using a CD4 count <350 cells/mm^3 as a trigger to restart therapy, no significant difference in serious disease progression or death was seen *[11-12]*. A large cohort study in Italy showed an increased risk of disease progression after interruption of first-line therapy *[13]*. Several additional trials are currently ongoing in adults.

Many questions remain about STI in children and adolescents. In the United States and other developed countries, the majority of HIV-infected children began antiretroviral therapy during infancy *[14-15]*. Many of these children have had controlled viral replication for many years and are growing and developing normally. It is unclear if these children could discontinue therapy at some point and reinitiate based on CD4 cell decline. Although this has been speculated as plausible, there are no data to support this strategy and it should not be attempted outside of a clinical trial setting.

An additional scenario that is often raised is the patient who has limited treatment options and who, despite aggressive antiretroviral therapy, cannot reach an undetectable viral load. In these cases, interruption of therapy is generally not recommended because, despite detectable viral replication, immunologic benefit has been well documented *[16-19]*.

With either unplanned or STI therapy, the clinician should discuss the reasons and plans with the parent or guardian and, if applicable, the patient prior to proceeding. The parent and child should be made aware of the possibility of viral rebound resulting in a worsening of clinical symptoms, the risk of developing drug resistance, and the need for protection against opportunistic pathogens. The timelines and criteria for restarting therapy should be clear.

References

1. Cressey TR, Jourdain G, Lallemant MJ, et al. Persistence of nevirapine exposure during the postpartum period after intrapartum single-dose nevirapine in addition to zidovudine prophylaxis for the prevention of mother-to-child transmission of HIV-1. *J Acquir Immune Defic Syndr.* 2005;38(3):283-288.
2. Mackie NE, Fidler S, Tamm N, et al. Clinical implications of stopping nevirapine-based antiretroviral therapy: relative pharmacokinetics and avoidance of drug resistance. *HIV Med.* 2004;5(3):180-184.
3. Nolan D, Phillips E, Mallal S. Efavirenz and CYP2B6 polymorphism: implications for drug toxicity and resistance. *Clin Infect Dis.* 2006;42(3):408-410.
4. Ribaudo HJ, Haas DW, Tierney C, et al. Pharmacogenetics of plasma efavirenz exposure after treatment discontinuation: an Adult AIDS Clinical Trials Group Study. *Clin Infect Dis.* 2006;42(3):401-407.
5. Luzuriaga K, Bryson Y, McSherry G, et al. Pharmacokinetics, safety, and activity of nevirapine in human immunodeficiency virus type 1-infected children. *J Infect Dis.* 1996;174(4):713-721.
6. Starr SE, Fletcher CV, Spector SA, et al. Combination therapy with efavirenz, nelfinavir, and nucleoside reverse-transcriptase inhibitors in children infected with human immunodeficiency virus type 1. Pediatric AIDS Clinical Trials Group 382 Team. *N Engl J Med.* 1999;341(25):1874-1881.
7. Starr SE, Fletcher CV, Spector SA, et al. Efavirenz liquid formulation in human immunodeficiency virus-infected children. *Pediatr Infect Dis J.* 2002;21(7):659-663.
8. Borkowsky W, Mcfarland E, Yogev R, et al. Repeated supervised treatment interruption with progressive increases in "Off treatment" Duration results in enhanced virologic control in a subset of pediatric individuals. Paper presented at: 13th Conference on Retroviruses and Opportunistic Infections; February 5-8, 2006; Denver, CO. Abstract 19.
9. El-Sadr WM, Lundgren JD, Neaton JD, et al. CD4+ count-guided interruption of antiretroviral treatment. *N Engl J Med.* 2006;355(22):2283-2296.
10. Danel C, Moh R, Minga A, et al. CD4-guided structured antiretroviral treatment interruption strategy in HIV-infected adults in West Africa (Trivacan ANRS 1269 trial): a randomised trial. *Lancet.* 2006;367(9527):1981-1989.
11. Ananworanich J, Gayet-Ageron A, Le Braz M, et al. CD4 guided scheduled treatment interruptions compared to continuous therapy: Results of the staccato trial. Paper presented at: 13th Conference on Retroviruses and Opportunistic Infections; February 5-8, 2006; Denver, CO. Abstract 102.
12. Marchou B, Tangre P, Charreau I, et al. Structured treatment interruptions in HIV-infected patients with high CD4 cell counts and virologic suppression: Results of a prospective, randomized, open-lable trial (window-anrs 106). Paper presented at: 13th Conference on Retroviruses and Opportunistic Infections; February 5-8, 2006; Denver, CO. Abstract 104.
13. d'arminio Monforte A, Cozzi-Lepri A, Phillips A, et al. Interruption of highly active antiretroviral therapy in HIV clinical practice: results from the Italian Cohort of Antiretroviral-Naive Patients. *J Acquir Immune Defic Syndr.* 2005;38(4):407-416.
14. Brogly S, Williams P, Seage GR, 3rd, et al. Antiretroviral treatment in pediatric HIV infection in the United States: from clinical trials to clinical practice. *JAMA.* 2005;293(18):2213-2220.
15. Liu KL, Peters V, Weedon J, et al. Sex differences in morbidity and mortality among children with perinatally acquired human immunodeficiency virus infection in New York City. *Arch Pediatr Adolesc Med.* 2004;158(12):1187-1188.
16. Deeks SG, Barbour JD, Martin JN, et al. Sustained CD4+ T cell response after virologic failure of protease inhibitor-based regimens in patients with human immunodeficiency virus infection. *J Infect Dis.* 2000;181(3):946-953.
17. Flynn PM, Rudy BJ, Douglas SD, et al. Virologic and immunologic outcomes after 24 weeks in HIV type 1-infected adolescents receiving highly active antiretroviral therapy. *J Infect Dis.* 2004;190(2):271-279.
18. Piketty C, Weiss L, Thomas F, et al. Long-term clinical outcome of human immunodeficiency virus-infected patients with discordant immunologic and virologic responses to a protease inhibitor-containing regimen. *J Infect Dis.* 2001;183(9):1328-1335.
19. Sufka SA, Ferrari G, Gryszowka VE, et al. Prolonged CD4+ cell/virus load discordance during treatment with protease inhibitor-based highly active antiretroviral therapy: immune response and viral control. *J Infect Dis.* 2003;187(7):1027-1037.

Antiretroviral Drug-Resistance Testing

(Updated August 16, 2010)

Panel's Recommendations:

- ***Antiretroviral drug-resistance testing is recommended prior to initiation of therapy in all treatment-naïve children (AII).***
- ***Antiretroviral drug-resistance testing is recommended prior to changing therapy for treatment failure (AI*).***
- ***Resistance testing in the setting of virological failure should be obtained while the patient is still on the failing regimen or within 4 weeks of discontinuing the regimen (AII*).***
- ***The absence of detectable resistance to a drug does not ensure that use of the drug will be successful, especially if the antiretroviral agent shares cross resistance with drugs previously used. In addition, current resistance assays are not sensitive enough to fully exclude the presence of resistant virus. Thus, previously used antiretroviral agents and previous resistance tests should be reviewed when making decisions regarding the choice of new agents for patients with virologic failure (AII).***
- ***Viral coreceptor (tropism) assays should be used whenever the use of a CCR5 antagonist is being considered (AI*). Tropism assays should also be considered for patients who demonstrate virologic failure while receiving therapy that contains a CCR5 antagonist (AI*).***
- ***Consultation with a specialist in pediatric HIV infection is recommended for interpretation of resistance assays when considering starting or changing an antiretroviral regimen in a pediatric patient (AI*).***

OVERVIEW OF HIV DRUG-RESISTANCE AND RESISTANCE ASSAYS

HIV replication is a continuous process in most untreated patients, leading to the daily production of billions of viral particles. The goal of antiretroviral therapy is to suppress HIV replication as rapidly and fully as possible, indicated by a reduction in plasma HIV RNA to below the limit of detection of the most sensitive assays available (<50–70 copies/mL). Unfortunately, mutations in HIV RNA readily arise during viral replication because HIV reverse transcriptase is a highly error-prone enzyme. Consequently, ongoing replication in the presence of antiretroviral drugs readily and progressively selects for strains of HIV with mutations that confer drug resistance.

Drug-resistance detection methods vary depending on the class of antiretroviral agents. Both genotypic assays and phenotypic assays are used to detect the presence of virus that is resistant to inhibitors of the HIV reverse transcriptase (RT), integrase, or protease (PR). Viral coreceptor (tropism) assays, a form of phenotypic assay, have been successfully employed in detecting the presence of virus with tropism that will (R5 tropism) or will not (X4 or mixed tropism) respond to CCR5 antagonists. Clinical experience with testing for viral resistance to other agents is more limited, but genetic mutations associated with resistance to integrase strand transfer inhibitors have been identified, and a commercial phenotypic assay is available for evaluation of resistance to the fusion inhibitor enfuvirtide (T20). Experience is also limited with the use of commercially available genotypic and phenotypic assays in the evaluation of drug resistance in patients infected with non-B subtypes of HIV *[1]*.

Genotypic Assays

Genotypic assays for resistance to RT, PR, and integrase strand transfer inhibitors are based on polymerase chain reaction (PCR) amplification and analysis of the RT, PR, and integrase coding sequences present in HIV RNA extracted from plasma. Genotypic assays can detect resistance-associated mutations in plasma samples containing approximately 1,000 copies/mL or more of HIV RNA, and results are generally available within 1–2 weeks of sample collection *[2]*. Interpretation of test results requires knowledge of the mutations selected by different antiretroviral drugs and of the potential for cross resistance to other drugs conferred by certain

mutations. For some drugs, there is a low genetic barrier to the development of resistance, and a single nucleotide mutation is enough to confer high-level resistance sufficient to remove any clinical utility. This is exemplified by resistance to nevirapine resulting from mutations in the HIV reverse transcriptase. Other mutations lead to drug resistance but simultaneously impair HIV replication. Clinically useful activity of the antiretroviral agent may therefore remain, as demonstrated by evidence of continued clinical benefit from lamivudine in individuals with evidence of the high-level resistance engendered by the M184V reverse transcriptase mutation *[3]*. Other mutations have little direct effect on resistance but arise during HIV evolution to high-level resistance or improve the replication of virus-bearing mutations that confer high-level resistance to an antiretroviral agent.

The International AIDS Society-USA (IAS-USA), the Los Alamos HIV Drug Resistance Database, and the Stanford University HIV Drug Resistance Database maintain lists of significant resistance-associated mutations relevant to currently available antiretroviral drugs (see **http://www.iasusa.org/resistance_mutations**, **http://hiv-web.lanl.gov** or **http://hivdb.stanford.edu**). A variety of online tools that take into account the ability of some mutations selected by one drug to cause partial or full cross resistance with other drugs are now available to assist the provider in interpreting genotypic test results. Although the response to antiretroviral therapy in children and adolescents is not always predicted by the results of genotypic resistance assays, clinical trials in adults have demonstrated the benefit of resistance testing combined with consultation with specialists in HIV drug resistance in improving virologic outcomes *[2, 4-10]*. Given the potential complexity of interpretation of genotypic resistance, it is recommended that clinicians consult with a specialist in pediatric HIV infection for assistance in the interpretation of genotypic results and design of an optimal new regimen.

Phenotypic Assays

Phenotypic resistance assays provide a more direct assessment of the impact of mutations acquired by mixture of virus strains present in an individual. As they are most often performed, phenotypic assays involve PCR amplification of the reverse transcriptase, integrase, protease, or other HIV gene sequences from patient plasma and insertion of those amplified patient sequences into the backbone of a laboratory strain of HIV. Replication of this recombinant virus at different drug concentrations is monitored by expression of a reporter gene and is compared with replication of a reference HIV strain. The drug concentration that inhibits viral replication by 50% (i.e., the median inhibitory concentration, or IC50) is calculated, and the ratio of the IC50 of test and reference viruses is reported as the fold increase in IC50 (i.e., fold resistance change). Automated, recombinant phenotypic assays are commercially available with results available in 2–3 weeks but are more costly than genotypic assays. In addition, interpretation of phenotypic assay results is sometimes complicated by the paucity of information about outcomes with specific levels of resistance.

Analytic techniques have also been developed to use the genotype to predict the likelihood of a drug-resistant phenotype. This bioinformatic approach, currently applicable for reverse transcriptase and protease inhibitor resistance only, matches the pattern of mutations obtained from the patient sample with a large database of samples for which both genotype and phenotype are known. Thus, the sample is assigned a predicted phenotype susceptibility (or "virtual phenotype") based on the data from specimens matching the patient's genotype. The primary limitation of this approach is that predictive power depends upon the number of matched phenotypic and genotypic assays, which may be limited for newer drugs.

Tropism (Viral Coreceptor Use) Assays

HIV enters cells by a complex multistep process that involves sequential interactions between the HIV envelope protein molecules and the CD4 receptor, then with either the CCR5 or CXCR4 coreceptor molecules, culminating in the fusion of the viral and cellular membranes. Viruses in the majority of untreated individuals, including infants and children infected by mother-to-child transmission of HIV, are initially CCR5 tropic. However, a shift in coreceptor tropism often occurs over time, from CCR5 usage to either CXCR4 or both CCR5 and CXCR4 tropism (dual- or mixed-tropic; D/M-tropic). Antiretroviral-treated patients with extensive drug resistance are more likely to harbor detectable X4- or D/M-tropic virus than untreated patients with comparable CD4 T-cell counts *[11]*.

Resistance to CCR5 antagonists is currently detected using the specialized phenotypic assay methods Phenoscript (VIRalliance, Paris, France) and Trofile (Monogram Biosciences, Inc). These assays involve the generation of recombinant viruses bearing patient-derived envelope proteins (gp120 and gp41). The relative capacity of these pseudoviruses to infect cells bearing the cell surface proteins CCR5 or CXCR4 is quantified based on the expression of a reporter gene. The Trofile assay takes about 2 weeks to perform and requires a plasma viral load ≥1,000 copies/mL. The initial version of the Trofile assay used during the clinical trials that led to the licensure of maraviroc was able to detect X4-tropic virus with 100% sensitivity when present at a frequency of 10% of the plasma virus population but only 83% sensitivity when the variant was present at a frequency of 5%. In initial clinical trials of CCR5 antagonist drugs, this sensitivity threshold was not always sufficient to exclude the presence of clinically meaningful levels of X4- or D/M-tropic virus in patients initiating a CCR5 inhibitor-based regimen. A newer version of the Trofile assay with improved sensitivity able to detect X4- or D/M-tropic virus representing as little as 0.3% of the plasma virus is now available *[12-13]*. Genotypic assays that may also prove useful in detection of X4 or D/M tropism are also under development. The detection of any usage of CXCR4 is a contraindication to the use of the CCR5 antagonists as part of a therapeutic regimen. Coreceptor use assays should be performed prior to the use of a CCR5 inhibitor and may be considered in patients exhibiting virologic failure on a CCR5 inhibitor such as maraviroc.

Use of Resistance Assays in Determining Initial Treatment

Mother-to-child transmission and horizontal transmission of drug-resistant HIV strains have been well documented and are associated with suboptimal virologic response to initial antiretroviral therapy *[14-18]*. Drug-resistant variants of HIV may persist for months after birth in infected infants *[19]* and impair the response to antiretroviral therapy *[20]*. Consequently, antiretroviral drug-resistance testing is recommended prior to initiation of therapy in all treatment-naïve children.

Use of Resistance Assays in the Event of Virologic Failure

Several studies *[2, 4-10]* have been performed in adults indicating that early virologic responses to salvage regimens were improved when results of resistance testing were available to guide changes in therapy, compared with responses observed when changes in therapy were guided only by clinical judgment. Although not yet confirmed in children *[21]*, resistance testing appears to be a useful tool in selecting active drugs when changing antiretroviral regimens in cases of virologic failure. Resistance testing also can help guide treatment decisions for patients with suboptimal viral load reduction because virologic failure in the setting of combination antiretroviral therapy may be associated with resistance to only one component of the regimen *[1]*. Poor adherence should be suspected when no evidence of resistance to a failing regimen is identified.

Limitations of Current Resistance and Tropism Assays

Limitations of the genotypic, phenotypic, and phenotype-prediction assay approaches include lack of uniform quality assurance testing and high cost. In addition, drug-resistant viruses that constitute <10%–20% of the circulating virus population may not be detected by any of the currently available assays. Consequently, a review of the past use of antiretroviral agents is important in making decisions regarding the choice of new agents for patients with virologic failure.

Although drug resistance may be detected in infants, children, and adults who are not receiving therapy at the time of the assay, loss of detectable resistance and reversion to predominantly wild-type virus often occur in the first 4–6 weeks after antiretroviral drugs are stopped *[22-24]*. As a result, resistance testing is of greatest value when performed before or within 4 weeks after drugs are discontinued. The absence of detectable resistance to a drug at the time of testing does not ensure that future use of the drug will be successful *[25]*, especially if the agent shares cross resistance with drugs previously used. It may be prudent to repeat resistance testing if an incomplete virological response to a new treatment regimen is observed in an individual with prior treatment failure(s) (see **Antiretroviral Treatment Failure in Infants, Children, and Adolescents**).

References

1. Hirsch MS, Gunthard HF, Schapiro JM, et al. Antiretroviral drug resistance testing in adult HIV-1 infection: 2008 recommendations of an International AIDS Society-USA panel. *Clin Infect Dis.* 2008;47(2):266-285.
2. Durant J, Clevenbergh P, Halfon P, et al. Drug-resistance genotyping in HIV-1 therapy: the VIRADAPT randomised controlled trial. *Lancet.* 1999;353(9171):2195-2199.
3. Campbell TB, Shulman NS, Johnson SC, et al. Antiviral activity of lamivudine in salvage therapy for multidrug-resistant HIV-1 infection. *Clin Infect Dis.* 2005;41(2):236-242.
4. Baxter JD, Mayers DL, Wentworth DN, et al. A randomized study of antiretroviral management based on plasma genotypic antiretroviral resistance testing in patients failing therapy. CPCRA 046 Study Team for the Terry Beirn Community Programs for Clinical Research on AIDS. *AIDS.* 2000;14(9):F83-93.
5. Cingolani A, Antinori A, Rizzo MG, et al. Usefulness of monitoring HIV drug resistance and adherence in individuals failing highly active antiretroviral therapy: a randomized study (ARGENTA). *AIDS.* 2002;16(3):369-379.
6. Cohen CJ, Hunt S, Sension M, et al. A randomized trial assessing the impact of phenotypic resistance testing on antiretroviral therapy. *AIDS.* 2002;16(4):579-588.
7. Meynard JL, Vray M, Morand-Joubert L, et al. Phenotypic or genotypic resistance testing for choosing antiretroviral therapy after treatment failure: a randomized trial. *AIDS.* 2002;16(5):727-736.
8. Vray M, Meynard JL, Dalban C, et al. Predictors of the virological response to a change in the antiretroviral treatment regimen in HIV-1-infected patients enrolled in a randomized trial comparing genotyping, phenotyping and standard of care (Narval trial, ANRS 088). *Antivir Ther.* 2003;8(5):427-434.
9. Wegner SA, Wallace MR, Aronson NE, et al. Long-term efficacy of routine access to antiretroviral-resistance testing in HIV type 1-infected patients: results of the clinical efficacy of resistance testing trial. *Clin Infect Dis.* 2004;38(5):723-730.
10. Tural C, Ruiz L, Holtzer C, et al. Clinical utility of HIV-1 genotyping and expert advice: the Havana trial. *AIDS.* 2002;16(2):209-218.
11. Hunt PW, Harrigan PR, Huang W, et al. Prevalence of CXCR4 tropism among antiretroviral-treated HIV-1-infected patients with detectable viremia. *J Infect Dis.* 2006;194(7):926-930.
12. Su Z, Gulick RM, Krambrink A, et al. Response to vicriviroc in treatment-experienced subjects, as determined by an enhanced-sensitivity coreceptor tropism assay: reanalysis of AIDS clinical trials group A5211. *J Infect Dis.* 2009;200(11):1724-1728.
13. Cooper DA, Heera J, Goodrich J, et al. Maraviroc versus efavirenz, both in combination with zidovudine-lamivudine, for the treatment of antiretroviral-naive subjects with CCR5-tropic HIV-1 infection. *J Infect Dis.* 2010;201(6):803-813.
14. Borroto-Esoda K, Waters JM, Bae AS, et al. Baseline genotype as a predictor of virological failure to emtricitabine or stavudine in combination with didanosine and efavirenz. *AIDS Res Hum Retroviruses.* 2007;23(8):988-995.
15. Jourdain G, Ngo-Giang-Huong N, Le Coeur S, et al. Intrapartum exposure to nevirapine and subsequent maternal responses to nevirapine-based antiretroviral therapy. *N Engl J Med.* 2004;351(3):229-240.
16. Kuritzkes DR, Lalama CM, Ribaudo HJ, et al. Preexisting resistance to nonnucleoside reverse-transcriptase inhibitors predicts virologic failure of an efavirenz-based regimen in treatment-naive HIV-1-infected subjects. *J Infect Dis.* 2008;197(6):867-870.
17. Little SJ, Holte S, Routy JP, et al. Antiretroviral-drug resistance among patients recently infected with HIV. *N Engl J Med.* 2002;347(6):385-394.
18. Pozniak AL, Gallant JE, DeJesus E, et al. Tenofovir disoproxil fumarate, emtricitabine, and efavirenz versus fixed-dose zidovudine/lamivudine and efavirenz in antiretroviral-naive patients: virologic, immunologic, and morphologic changes--a 96-week analysis. *J Acquir Immune Defic Syndr.* 2006;43(5):535-540.
19. Persaud D, Palumbo P, Ziemniak C, et al. Early archiving and predominance of nonnucleoside reverse transcriptase inhibitor-resistant HIV-1 among recently infected infants born in the United States. *J Infect Dis.* 2007;195(10):1402-1410.
20. Lockman S, Shapiro RL, Smeaton LM, et al. Response to antiretroviral therapy after a single, peripartum dose of nevirapine. *N Engl J Med.* 2007;356(2):135-147.
21. Green H, Gibb DM, Compagnucci A, et al. A randomized controlled trial of genotypic HIV drug resistance testing in HIV-1-infected children: the PERA (PENTA 8) trial. *Antivir Ther.* 2006;11(7):857-867.
22. Devereux HL, Youle M, Johnson MA, et al. Rapid decline in detectability of HIV-1 drug resistance mutations after stopping therapy. *AIDS.* 1999;13(18):F123-127.

23. Miller V, Sabin C, Hertogs K, et al. Virological and immunological effects of treatment interruptions in HIV-1 infected patients with treatment failure. *AIDS.* 2000;14(18):2857-2867.
24. Verhofstede C, Wanzeele FV, Van Der Gucht B, et al. Interruption of reverse transcriptase inhibitors or a switch from reverse transcriptase to protease inhibitors resulted in a fast reappearance of virus strains with a reverse transcriptase inhibitor-sensitive genotype. *AIDS.* 1999;13(18):2541-2546.
25. Benson CA, Vaida F, Havlir DV, et al. A randomized trial of treatment interruption before optimized antiretroviral therapy for persons with drug-resistant HIV: 48-week virologic results of ACTG A5086. *J Infect Dis.* 2006;194(9):1309-1318.

Conclusion

The care of HIV-infected children is complex and evolving rapidly as results of new research are reported and new antiretroviral drugs and newer classes of drugs are approved. Clinical trials to define appropriate drug dosing and toxicity in children ranging in age from infancy to adolescence are critical as new drugs become available. As additional antiretroviral drugs become approved and optimal use of these drugs in children becomes better understood, the Panel will modify these guidelines. It should be noted that guidelines are only a starting point for medical decision making and are not meant to supersede the judgment of clinicians experienced in the care of HIV-infected children. Because of the complexity of caring for HIV-infected children, health care providers with limited experience in the care of these patients should consult with a pediatric HIV specialist.

The Centers for Disease Control and Prevention, the National Institutes of Health, the HIV Medicine Association of the Infectious Disease Society of America, the Pediatric Infectious Disease Society, and the American Academy of Pediatrics jointly developed and published guidelines for the prevention and treatment of opportunistic infections in HIV-exposed and -infected children; these guidelines are available at **http://aidsinfo.nih.gov** *[1]*. Similar guidelines for adults are also available at the same Web site *[2]*.

References

1. Centers for Disease Control and Prevention (CDC). Guidelines for the prevention and treatment of opportunistic infections among HIV-exposed and HIV-infected children. *MMWR.* 2009;58(RR-11):1-176.
2. Centers for Disease Control and Prevention (CDC). Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. *MMWR Recomm Rep.* 2009;58(RR-4):1-207; quiz CE201-204.

Appendix A: Financial Disclosure for Members of HHS Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children – January 2010

Name	Panel Status	Company	Relationship
Elaine S. Abrams	M	NONE	N/A
Edmund Capparelli	M	Cadence Pharmaceuticals Bristol-Myers Squibb Pharmaceuticals GlaxoSmithKline Pharmaceuticals Arpida Pharmaceuticals Johnson & Johnson	• Consultant • Consultant • Travel Support • Consultant • Consultant
Diana Clarke	M	NONE	N/A
Kenneth L. Dominguez	HHS	NONE	N/A
Brian Feit	HHS	NONE	N/A
Patricia M. Flynn	M	Tibotec	• Clinical TrialsAgreement
Marc D. Foca	M	Cellestis	• Honoraria (Participated in an expert panel discussion and received a single honorarium.)
Edward Handelsman	HHS	NONE	N/A
Peter Havens	C	Roche Gilead Biotech Pharmaceuticals National Institute of Child Health and Human Development (NICHD) HHS	• Consultant • Other: Research Collaboration • Other: Research Collaboration • Research Support: Adolescent Trials Network • Advisory Board • Other: Pediatric Guidelines
Rohan Hazra	HHS	NONE	N/A
Nancy Hutton	M	NONE	N/A
Patrick Jean-Philippe	HHS	NONE	N/A

Name	Panel Status	Company	Relationship
Ebony Johnson	M	NONE	N/A
Paul A. Krogstad	M	NONE	N/A
Linda Lewis	HHS	NONE	N/A
James McAuley	M	NONE	N/A
Mark Mirochnick	M	NONE	N/A
Lynne Mofenson	ES	NONE	N/A
Paul Palumbo	M	NONE	N/A
Mary E. Paul	M	NONE	N/A
Vicki Peters	M	NONE	N/A
Richard M. Rutstein	M	Bristol-Myers Squib Pharmaceuticals Tibotec	• Advisory Board • Research Support
Dorothy Shaw	M	NONE	N/A
George Siberry	HHS	NONE	N/A
Russell Van Dyke	C	NONE	N/A
Geoffrey A. Weinberg	C	MedImmune, Inc. Merck Vaccines Sanofi Pasteur Vaccines GlaxoSmithKline Vaccines	• Advisory Board • Speakers' Bureau • Speakers' Bureau • Speakers' Bureau
Andrew Wiznia	M	Gilead Sciences Argos Therapeutics	• Consultant • Advisory Board

Key to Abbreviations: C = Co-Chair; ES = Executive Secretary; M = Member; HHS = Member from HHS; N/A = Not applicable

Appendix B: Pediatric Antiretroviral Drug Information

NUCLEOSIDE AND NUCLEOTIDE ANALOGUE REVERSE TRANSCRIPTASE INHIBITORS

Abacavir (ABC, Ziagen)

For additional information see Drugs@FDA: **http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm**

Formulations

Pediatric oral solution: 20 mg/mL
Tablets: 300 mg (scored)
Combination tablets:
- *with lamivudine (3TC)*: 600 mg ABC + 300 mg 3TC (Epzicom)
- *with zidovudine (ZDV) and lamivudine (3TC)*: 300 mg ABC + 300 mg ZDV + 150 mg 3TC (Trizivir)

Dosing Recommendations

Neonate/Infant dose:
Not approved for infants <3 months of age.

Pediatric dose:
Oral solution (≥3 months):
8 mg/kg (maximum 300 mg) twice daily

Scored 150 mg tablet (≥14 kg):

Weight (kg)	Twice-Daily Dosage Regimen		
	AM Dose	PM Dose	Total Daily Dose
14–21 kg	½ tablet (150 mg)	½ tablet (150 mg)	300 mg
>21–<30 kg	½ tablet (150 mg)	1 tablet (300 mg)	450 mg
≥30 kg	1 tablet (300 mg)	1 tablet (300 mg)	600 mg

Adolescent (≥16 years)/Adult dose:
300 mg twice daily or 600 mg once daily

Dosing Recommendations for Combination Formulations

Trizivir
Adolescent (≥40 kg)/Adult dose:
One tablet twice daily

Epzicom
Adolescent (>16 years)/Adult:
One tablet once daily

Selected Adverse Events

- Hypersensitivity reaction that may be fatal; symptoms may include fever, rash, nausea, vomiting, malaise or fatigue, loss of appetite, respiratory symptoms such as sore throat, cough, shortness of breath.
- Several observational cohort studies suggest increased risk of myocardial infarction in adults with recent or current use of ABC; however, other studies have not substantiated this finding, and there are no data in children.

Special Instructions

- Can be given without regard to food.
- Caution patients and parents about the risk of serious hypersensitivity reaction that can be fatal. Do not rechallenge.
- Test patients for the HLA-B*5701 allele prior to starting therapy to predict risk of hypersensitivity; patients with the HLA-B*5701 allele should not be given ABC. Patients with no prior HLA-B+5701 testing who are tolerating ABC do not need to be tested.

Metabolism

- Metabolized by alcohol dehydrogenase and glucuronyl transferase; renal excretion of metabolites 82%.
- ABC requires dosage adjustment in hepatic insufficiency. Do not use Trizivir and Epzicom (fixed-dose combination products) in patients with CrCl <50 mL/min, patients on dialysis, or patients with impaired hepatic function.

Drug Interactions (See also the ***Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents***.):
- Abacavir does not inhibit, nor is it metabolized by, hepatic cytochrome P450 enzymes. Thus, it should not cause changes in clearance of agents metabolized through these pathways, such as PIs and NNRTIs.
- Abacavir is metabolized by alcohol dehydrogenase and glucuronyltransferase. Alcohol increases abacavir levels by 41%.

Major Toxicities:
- *More common:* Nausea, vomiting, fever, headache, diarrhea, rash, and anorexia.
- *Less common (more severe):* Serious and sometimes fatal hypersensitivity reactions observed in approximately 5% of adults and children (rate varies by race/ethnicity) receiving abacavir. Hypersensitivity to abacavir is a multi-organ clinical syndrome usually characterized by rash or by signs or symptoms in two or more of the following groups: (1) fever; (2)

constitutional, including malaise, fatigue, or achiness; (3) gastrointestinal, including nausea, vomiting, diarrhea, or abdominal pain; or (4) respiratory, including dyspnea, cough, or pharnygitis. Laboratory and imaging abnormalities include elevated liver function tests, elevated creatine phosphokinase, elevated creatinine, lymphopenia, and pulmonary infiltrates. This reaction generally occurs in the first 6 weeks of therapy and has occurred after a single dose. If a hypersensitivity reaction is suspected, abacavir should be stopped and **not restarted because hypotension and death have occurred upon rechallenge**. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported. Pancreatitis may occur.

- *Rare:* Increased liver enzymes, elevated blood glucose, elevated triglycerides, and possible increased risk of myocardial infarction (in observational studies in adults).

Resistance: The International AIDS Society-USA (IAS-USA) maintains a list of updated resistance mutations (see **http://www.iasusa.org/resistance_mutations/index.html**) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see **http://hivdb.stanford.edu/pages/GRIP/ABC.html**).

Pediatric Experience: Abacavir has been studied in HIV-infected children both separately and in combination with other antiretroviral drugs *[1-11]*. In the PENTA-5 trial, 130 HIV-infected antiretroviral-naïve children were randomly assigned to 1 of 3 different nucleoside analogue regimens: zidovudine/lamivudine, abacavir/zidovudine, and abacavir/lamivudine, with and without nelfinavir *[10]*. The 2 abacavir-containing regimens were associated with greater mean viral load decreases after 48 weeks of therapy than the zidovudine/lamivudine regimen (-1.71, -2.17, and -2.63 log copies/mL with zidovudine/lamivudine, abacavir/zidovudine, and abacavir/lamivudine, respectively). In this study, 4 children (3%) stopped abacavir due to a possible hypersensitivity reaction. After 5 years of follow-up in the PENTA-5 study, children who were treated with abacavir/lamivudine were significantly more likely to have HIV RNA levels <50 copies/mL than children treated with zidovudine/lamivudine or abacavir/ zidovudine (63% vs. 25 % or 32%, p = 0.003) and had significantly better improvement in height for age and weight for age *[5]*.

Pharmacokinetic studies of abacavir in children <12 years of age have demonstrated that children have more rapid clearance than adults and that pediatric doses approximately twice the directly scaled adult dose are necessary to achieve similar systemic exposure *[4, 6]*. Adolescents and young adults (ages 13 to 25) have clearance that is slower than younger children but still more rapid than that found in adults *[12]*. The PENTA-13 trial studied once-daily versus twice-daily dosing of abacavir in combination with lamivudine in 24 children age 2–13 years, with undetectable or low, stable virus load at the time of starting once-daily therapy, showing equivalent $AUC_{0\text{-}24}$ for both drugs and improved acceptability in the once-daily dosing arm *[1, 8]*. However, trough concentrations were lower for both abacavir and lamivudine in younger children (ages 2–6 years) receiving the once-daily regimen *[1]*. More long-term clinical trials with viral efficacy endpoints are needed to confirm that once-daily dosing of abacavir and lamivudine can be effectively used in children.

In pediatric populations, triple-NRTI-only combinations should be used only in special circumstances. In 1 study of 205 treatment-experienced children ranging in age from 0.7 to 13 years, only 10% of 102 children receiving abacavir/ zidovudine/lamivudine had HIV RNA concentrations <400 copies/mL after 48 weeks of therapy *[11]*. Several studies of abacavir as part of a PI-sparing 3-drug NRTI regimen (zidovudine, lamivudine, and abacavir) have been done in adults and show decreased antiretroviral potency of the triple-NRTI-only regimens *[13-17]*.

References

1. Bergshoeff AS, Fraaij PL, Ndagijimana J, et al. Increased dose of lopinavir/ritonavir compensates for efavirenz-induced drug-drug interaction in HIV-1-infected children. *J Acquir Immune Defic Syndr.* 2005;39(1):63-68.
2. Bergshoeff A, Burger D, Verweij C, et al. Plasma pharmacokinetics of once- versus twice-daily lamivudine and abacavir: simplification of combination treatment in HIV-1-infected children (PENTA-13). *Antivir Ther.* 2005;10(2):239-246.
3. Capparelli EV, Letendre SL, Ellis RJ, et al. Population pharmacokinetics of abacavir in plasma and cerebrospinal fluid. *Antimicrob Agents Chemother.* 2005;49(6):2504-2506.
4. Cross SJ, Rodman JH, Lindsey JC, et al. Abacavir and metabolite pharmacokinetics in HIV-1-infected children and adolescents. *J Acquir Immune Defic Syndr.* 2009;51(1):54-59.
5. Green H, Gibb DM, Walker AS, et al. Lamivudine/abacavir maintains virological superiority over zidovudine/lamivudine and zidovudine/abacavir beyond 5 years in children. *AIDS.* 2007;21(8):947-955.
6. Hughes W, McDowell JA, Shenep J, et al. Safety and single-dose pharmacokinetics of abacavir (1592U89) in human immunodeficiency virus type 1-infected children. *Antimicrobial Agents Chemother.* 1999;43(3):609-615.

7. Kline MW, Blanchard S, Fletcher CV, et al. A phase I study of abacavir (1592U89) alone and in combination with other antiretroviral agents in infants and children with human immunodeficiency virus infection. AIDS Clinical Trials Group 330 Team. *Pediatrics.* 1999;103(4):e47.
8. LePrevost M, Green H, Flynn J, et al. Adherence and acceptability of once daily lamivudine and abacavir in human immunodeficiency virus type-1 infected children. *Pediatr Infect Dis J.* 2006;25(6):533-537.
9. McKinney RE Jr, Rodman J, Hu C, et al. Long-term safety and efficacy of a once-daily regimen of emtricitabine, didanosine, and efavirenz in HIV-infected, therapy-naive children and adolescents: Pediatric AIDS Clinical Trials Group Protocol P1021. *Pediatrics.* 2007;120(2):e416-423.
10. Paediatric European Network for Treatment of AIDS (PENTA). Comparison of dual nucleoside-analogue reverse-transcriptase inhibitor regimens with and without nelfinavir in children with HIV-1 who have not previously been treated: the PENTA 5 randomised trial. *Lancet.* 2002;359(9308):733-740.
11. Saez-Llorens X, Nelson RP Jr, Emmanuel P, et al. A randomized, double-blind study of triple nucleoside therapy of abacavir, lamivudine, and zidovudine versus lamivudine and zidovudine in previously treated human immunodeficiency virus type 1-infected children. The CNAA3006 Study Team. *Pediatrics.* 2001;107(1):E4.
12. Sleasman JW, Robbins BL, Cross SJ, et al. Abacavir pharmacokinetics during chronic therapy in HIV-1-infected adolescents and young adults. *Clin Pharmacol Ther.* 2009;85(4):394-401.
13. Gallant JE, Rodriguez AE, Weinberg WG, et al. Early virologic nonresponse to tenofovir, abacavir, and lamivudine in HIV-infected antiretroviral-naive subjects. *J Infect Dis.* 2005;192(11):1921-1930.
14. Gerstoft J, Kirk O, Obel N, et al. Low efficacy and high frequency of adverse events in a randomized trial of the triple nucleoside regimen abacavir, stavudine and didanosine. *AIDS.* 2003;17(14):2045-2052.
15. Khanlou H, Yeh V, Guyer B, Farthing C. Early virologic failure in a pilot study evaluating the efficacy of therapy containing once-daily abacavir, lamivudine, and tenofovir DF in treatment-naive HIV-infected patients. *AIDS Patient Care STDS.* 2005;19(3):135-140.
16. Kumar PN, Salvato P, Lamarca A, et al. A randomized, controlled trial of initial anti-retroviral therapy with abacavir/lamivudine/zidovudine twice-daily compared to atazanavir once-daily with lamivudine/zidovudine twice-daily in HIV-infected patients over 48 weeks (ESS100327, the ACTION Study). *AIDS Res Ther.* 2009;6:3.
17. Gulick RM, Ribaudo HJ, Shikuma CM, et al. Triple-nucleoside regimens versus efavirenz-containing regimens for the initial treatment of HIV-1 infection. *N Engl J Med.* 2004;350(18):1850-1861.

Didanosine (ddI, Videx)

For additional information see Drugs@FDA: **http://www.accessdata.fda.gov/scripts/cder/drugsatfda/**

Formulations

Videx pediatric powder for oral solution: reconstituted 10 mg/ml
Videx EC delayed-release capsules (enteric-coated beadlets): 125 mg, 200 mg, 250 mg, and 400 mg
Generic ddI delayed-release capsules: 200 mg, 250 mg, and 400 mg

Dosing Recommendations

Neonate/Infant dose (2 weeks to <3 months):
50 mg/m^2 of body surface area every 12 hours
(Manufacturer recommends 100 mg/m^2 of body surface area every 12 hours in this age range. Panel members interpret PK data as suggesting potential increased toxicity at that dose in this age group and many would use 50 mg/m^2 of body surface area every 12 hours.)

Infant dose (>3 months to 8 months):
100 mg/m^2 of body surface area every 12 hours

Pediatric usual dose of oral solution (>8 months):
120 mg/m^2 of body surface area every 12 hours
(Dose range: 90–150 mg/m^2 of body surface area every 12 hours)

Pediatric dose of Videx EC or generic capsules (6–18 years and ≥20 kg):

Body Weight (kg)	Dose
20 kg to <25 kg	200 mg once daily
25 kg to <60 kg	250 mg once daily
≥60 kg	400 mg once daily

In treatment-naïve children 3–21 years of age, 240 mg/m^2 of body surface area once daily (oral solution or capsules) has been used with good viral suppression.

Adolescent/Adult dose:
<60 kg: 250 mg once daily
≥60 kg: 400 mg once daily

Dosing Recommendations for Coadministration with Other Antiretroviral Drugs

ddI in combination with tenofovir (TDF)

Pediatric/Adolescent dose:
No data on combination in children or adolescents <18 years of age.

Adult dose:
<60 kg (limited data in adults): 200 mg once daily
≥60 kg: 250 mg once daily

Selected Adverse Events

- Peripheral neuropathy (dose related)
- Electrolyte abnormalities and hyperuricemia
- Diarrhea, abdominal pain, nausea, and vomiting
- Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases have been reported (increased risk when used in combination with stavudine [d4T])
- Pancreatitis (dose related, less common in children than adults, more common in adults when used in combination with TDF or d4T)
- Potential association with noncirrhotic portal hypertension

Special Instructions

- Food decreases absorption of all ddI preparations; administer ddI on an empty stomach (30 minutes before or 2 hours after a meal).
- ddI oral solution contains antacids that may interfere with the absorption of other medications.
- Shake oral solution well. Keep refrigerated; admixture is stable for 30 days.
- When coadministered, ddI delayed-release capsule formulation and TDF may be taken under fasted conditions or with a light meal.

Metabolism

- Renal excretion 50%.
- Dosing of ddI in patients with renal insufficiency: Decreased dosage should be used in patients with impaired renal function. Consult manufacturer's prescribing information for adjustment of dosage in accordance with creatinine clearance.

Drug Interactions (See also the ***Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents***.)*:*

- *Absorption:* The presence of antacids in the didanosine suspension has the potential to decrease the absorption of a number of medications if given at the same time. Many of these interactions can be avoided by the appropriate timing of doses.
- *Mechanism unknown:* Didanosine serum concentrations are increased when coadministered with tenofovir.
- *Renal elimination:* Drugs that decrease renal function could decrease clearance.
- *Enhanced toxicity:* Didanosine mitochondrial toxicity is enhanced by ribavirin.
- *Overlapping toxicities:* There is increased risk of pancreatitis and peripheral neuropathy with some NRTIs (e.g., stavudine). Combination of stavudine and didanosine is not recommended (unless the benefits clearly outweigh the risks) because of overlapping toxicities and reports of serious, even fatal, cases of lactic acidosis with hepatic steatosis with or without pancreatitis in pregnant women.

Major Toxicities:

- *More common:* Diarrhea, abdominal pain, nausea, and vomiting.
- *Less common (more severe):* Peripheral neuropathy (dose related), electrolyte abnormalities, and hyperuricemia. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported. Pancreatitis (dose related, less common in children than adults, more common in adults when used in combination with tenofovir), increased liver enzymes, and retinal depigmentation have been reported. The combination of stavudine with didanosine may result in enhanced toxicity (increased risk of fatal and nonfatal cases of lactic acidosis or pancreatitis); this combination should not be used unless the potential benefit clearly outweighs the potential risk.
- *Rare:* Noncirrhotic portal hypertension, with increased transaminases, increased alkaline phosphatase, and thrombocytopenia, has been associated with long-term didanosine use in adults [1].

Resistance: The International AIDS Society-USA (IAS-USA) maintains a list of updated resistance mutations (see **http://www.iasusa.org/resistance_mutations/index.html**) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see **http://hivdb.stanford.edu/pages/GRIP/ddI.html**).

Pediatric Experience: Didanosine has been studied in HIV-infected children as monotherapy and in combination with other antiretroviral drugs *[2-24]*. Recommended didanosine doses in children have traditionally been 90–150 mg per meter^2 body surface area per dose twice daily. Doses higher than 180 mg per meter^2 body surface area twice daily are associated with increased toxicity *[3]*. In a simulation based on didanosine concentration data from 16 children, a dose of 90 mg per meter^2 body surface area twice daily was predicted to result in adequate drug exposure in only 57% of pediatric patients, compared with a predicted 88% of patients at a dose of 120 mg per meter^2 body surface area *[6]*. This dose of 120 mg per meter^2 body surface area per dose twice daily has therefore become the "standard" dose of didanosine for older infants and children. Data from multiple pediatric studies of didanosine alone or in combination with other drugs, including a study of long-term didanosine use (median duration of almost 2 years), show that didanosine appears safe and is associated with clinical improvement, increase in CD4 count, and decrease in viral load *[5, 7-8, 11, 13, 15, 19]*.

Three major areas of controversy remain in the use of didanosine in the treatment of children with HIV infection: (1) the appropriate dose to use in infants 2 weeks to 4 months of age, (2) the need to dose didanosine on an empty stomach, and (3) the potential use of enteric-coated didanosine (Videx EC) once daily in children.

The "usual pediatric dose" of 120 mg per meter^2 body surface area per dose twice daily was used successfully in combination therapy in infants 2 to 16 months of age without significant toxicity *[18]*. Currently, the FDA recommends 100 mg per meter^2 body surface area per dose twice daily for infants from 2 weeks to 8 months of age, increasing to 120 mg per meter^2 body surface area per dose twice daily at age 8 months. However, two small studies suggest that higher AUCs are seen in infants <6 weeks of age and that a dose of 100 mg per meter^2 body surface area per day (either as 50 mg per meter^2 body surface area per dose twice daily or 100 mg per meter^2 body surface area once daily) achieves AUCs consistent with those of higher doses in older children *[9, 12]*. Therefore, because of pharmacokinetic differences in younger infants (2 weeks to 4 months) compared with older children, a dose of 50 mg per meter^2 of body surface area twice daily may be more appropriate in younger infants.

Although the prescribing information recommends taking didanosine on an empty stomach, this is impractical for infants who must be fed frequently and may decrease medication compliance by increasing regimen complexity. A comparison of didanosine given with or without food in children found that systemic exposure was similar, but with slower and more prolonged absorption *[20]*. To improve compliance, some practitioners recommend administration without regard to timing of

meals for young children. However, there are inadequate data to allow a strong recommendation at this time, and it is preferred that didanosine be administered under fasting conditions when possible.

Enteric-coated didanosine (Videx EC) administered as a single dose of 240 mg per meter^2 body surface area once daily has been shown to have similar plasma AUC (although lower peak plasma concentrations) compared with the equivalent dose of buffered didanosine *[9]*. The resultant intracellular (active) drug concentrations are unknown. In 24 children with HIV infection, didanosine at a dose of 180 mg per meter^2 body surface area once daily was compared with 90 mg per meter^2 body surface area twice daily, and the AUC was actually higher in the once-daily group than in the twice-daily group *[2]*. In fact, in 53 children with advanced symptomatic HIV infection, once- versus twice-daily didanosine at a dose of 270 mg per meter^2 body surface area per day showed no difference in surrogate marker or clinical endpoints, except that weight gain was poorer in the children given once-daily therapy *[14]*. A European trial of once-daily combination therapy in 36 children 3–11 years of age that included didanosine at a dose of 200–240 mg per meter^2 demonstrated safety and efficacy with 96 weeks of follow-up data *[25]*. Enteric-coated didanosine is currently approved for use in children ages 6 to 18 years who are able to swallow capsules whole and have a body weight of at least 20 kg.

In a study in the United States, long-term virologic suppression with a once daily regimen of efavirenz, emtricitabine, and didanosine (enteric-coated beadlet capsules) was reported in 37 treatment-naïve children, 3–21 years of age, participating in PACTG 1021 *[26]*. The didanosine dose used in that study was 240 mg/ meter^2/dose once daily, and pharmacokinetic analysis showed no dose changes were needed to reach PK targets *[26]*. Eighty-five percent of subjects were able to achieve HIV RNA <400 copies/mL and 72% maintained HIV RNA suppression to <50 copies/mL through 96 weeks of therapy.

References

1. Kovari H, Ledergerber B, Peter U, et al. Association of noncirrhotic portal hypertension in HIV-infected persons and antiretroviral therapy with didanosine: a nested case-control study. *Clin Infect Dis.* 2009;49(4):626-635.
2. Abreu T, Plaisance K, Rexroad V, et al. Bioavailability of once- and twice-daily regimens of didanosine in human immunodeficiency virus-infected children. *Antimicrob Agents Chemother.* 2000;44(5):1375-1376.
3. Butler KM, Husson RN, Balis FM, et al. Dideoxyinosine in children with symptomatic human immunodeficiency virus infection. *N Engl J Med.* 1991;324(3):137-144.
4. de Mendoza C, Ramos JT, Ciria L, et al. Efficacy and safety of stavudine plus didanosine in asymptomatic HIV-infected children with plasma HIV RNA below 50,000 copies per milliliter. *HIV Clin Trials.* 2002;3(1):9-16.
5. Englund JA, Baker CJ, Raskino C, et al. Zidovudine, didanosine, or both as the initial treatment for symptomatic HIV-infected children. AIDS Clinical Trials Group (ACTG) Study 152 Team. *N Engl J Med.* 1997;336(24):1704-1712.
6. Fletcher CV, Brundage RC, Remmel RP, et al. Pharmacologic characteristics of indinavir, didanosine, and stavudine in human immunodeficiency virus-infected children receiving combination therapy. *Antimicrob Agents Chemother.* 2000;44(4):1029-1034.
7. Funk MB, Linde R, Wintergerst U, et al. Preliminary experiences with triple therapy including nelfinavir and two reverse transcriptase inhibitors in previously untreated HIV-infected children. *AIDS.* 1999;13(13):1653-1658.
8. Gibb D, Barry M, Ormesher S, et al. Pharmacokinetics of zidovudine and dideoxyinosine alone and in combination in children with HIV infection. *Br J Clin Pharmacol.* 1995;39(5):527-530.
9. King JR, Nachman S, Yogev R, et al. Single-dose pharmacokinetics of enteric-coated didanosine in HIV-infected children. *Antivir Ther.* 2002;7(4):267-270.
10. King JR, Nachman S, Yogev R, et al. Efficacy, tolerability and pharmacokinetics of two nelfinavir-based regimens in human immunodeficiency virus-infected children and adolescents: pediatric AIDS clinical trials group protocol 403. *Pediatr Infect Dis J.* 2005;24(10):880-885.
11. Kline MW, Van Dyke RB, Lindsey JC, et al. Combination therapy with stavudine (d4T) plus didanosine (ddI) in children with human immunodeficiency virus infection. The Pediatric AIDS Clinical Trials Group 327 Team. *Pediatrics.* 1999;103(5):e62.
12. Kovacs A, Cowles MK, Britto P, et al. Pharmacokinetics of didanosine and drug resistance mutations in infants exposed to zidovudine during gestation or postnatally and treated with didanosine or zidovudine in the first three months of life. *Pediatr Infect Dis J.* 2005;24(6):503-509.
13. Luzuriaga K, Bryson Y, Krogstad P, et al. Combination treatment with zidovudine, didanosine, and nevirapine in infants with human immunodeficiency virus type 1 infection. *N Engl J Med.* 1997;336(19):1343-1349.
14. Marchisio P, Principi N, Gabiano C, et al. Once versus twice daily administration of didanosine in children with symptomatic HIV-associated disease who were intolerant to or clinically deteriorated on zidovudine. The Italian Pediatric Collaborative Study Group on Didanosine. *Antivir Ther.* 1997;2(1):47-55.

15. McKinney RE Jr, Johnson GM, Stanley K, et al. A randomized study of combined zidovudine-lamivudine versus didanosine monotherapy in children with symptomatic therapy-naive HIV-1 infection. The Pediatric AIDS Clinical Trials Group Protocol 300 Study Team. *J Pediatr.* 1998;133(4):500-508.
16. Mueller BU, Butler KM, Stocker VL, et al. Clinical and pharmacokinetic evaluation of long-term therapy with didanosine in children with HIV infection. *Pediatrics.* 1994;94(5):724-731.
17. Palacios GC, Palafox VL, Alvarez-Munoz MT, et al. Response to two consecutive protease inhibitor combination therapy regimens in a cohort of HIV-1-infected children. *Scand J Infect Dis.* 2002;34(1):41-44.
18. Rongkavilit C, Thaithumyanon P, Chuenyam T, et al. Pharmacokinetics of stavudine and didanosine coadministered with nelfinavir in human immunodeficiency virus-exposed neonates. *Antimicrob Agents Chemother.* 2001;45(12):3585-3590.
19. Mueller BU, Nelson RP, Jr., Sleasman J, et al. A phase I/II study of the protease inhibitor ritonavir in children with human immunodeficiency virus infection. *Pediatrics.* 1998;101(3 Pt 1):335-343.
20. Stevens RC, Rodman JH, Yong FH, et al. Effect of food and pharmacokinetic variability on didanosine systemic exposure in HIV-infected children. Pediatric AIDS Clinical Trials Group Protocol 144 Study Team. *AIDS Res Hum Retroviruses.* 2000;16(5):415-421.
21. Hirt D, Bardin C, Diagbouga S, et al. Didanosine population pharmacokinetics in West African human immunodeficiency virus-infected children administered once-daily tablets in relation to efficacy after one year of treatment. *Antimicrob Agents Chemother.* 2009;53(10):4399-4406.
22. Balis FM, Pizzo PA, Butler KM, et al. Clinical pharmacology of 2',3'-dideoxyinosine in human immunodeficiency virus-infected children. *J Infect Dis.* 1992;165(1):99-104.
23. Butler KM, Venzon D, Henry N, et al. Pancreatitis in human immunodeficiency virus-infected children receiving dideoxyinosine. *Pediatrics.* 1993;91(4):747-751.
24. Whitcup SM, Butler KM, Caruso R, et al. Retinal toxicity in human immunodeficiency virus-infected children treated with 2',3'-dideoxyinosine. *Am J Ophthalmol.* 1992;113(1):1-7.
25. Scherpbier HJ, Bekker V, Pajkrt D, et al. Once-daily highly active antiretroviral therapy for HIV-infected children: safety and efficacy of an efavirenz-containing regimen. *Pediatrics.* 2007;119(3):e705-715.
26. McKinney RE Jr, Rodman J, Hu C, et al. Long-term safety and efficacy of a once-daily regimen of emtricitabine, didanosine, and efavirenz in HIV-infected, therapy-naive children and adolescents: Pediatric AIDS Clinical Trials Group Protocol P1021. *Pediatrics.* 2007;120(2):e416-423.

Emtricitabine (FTC, Emtriva)

For additional information see Drugs@FDA: **http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm**

Formulations

Pediatric oral solution: 10 mg/mL
Capsules: 200 mg
Combination tablets
- *With tenofovir (TDF):* 200 mg FTC + 300 mg TDF (*Truvada*)
- *With TDF and efavirenz (EFV):* 200 mg FTC + 300 mg TDF + 600 mg EFV (*Atripla*)

Dosing Recommendations

Neonate/Infant Dose (0–3 months):
Oral solution: 3 mg/kg once daily

Pediatric Dose (3 months–17 years):
Oral solution: 6 mg/kg (maximum dose 240 mg) once daily
Capsules (>33 kg): 200 mg once daily

Adolescent (≥18 years)/Adult dose:
Oral solution: 240 mg (24 mL) once daily
Capsules: 200 mg once daily

Dosing Recommendations for Combination Formulations

Truvada
Adult dose:
1 tablet once daily

Atripla
Adult dose:
1 tablet once daily

Selected Adverse Events

- Nausea, diarrhea
- Hyperpigmentation/skin discoloration on palms and/or soles, predominantly observed in nonwhite patients

Special Instructions

- Can be given without regard to food. Because Atripla contains EFV, administer the drug on an empty stomach.
- Oral solution can be kept at room temperatures up to 77°F (25°C) if used within 3 months; refrigerate for longer term storage.
- Screen patients for hepatitis B virus prior to use of FTC. Severe acute exacerbation of hepatitis can occur when FTC is discontinued; monitor hepatic function for several months after therapy with FTC is stopped.

Metabolism

- Limited metabolism: No CYP450 interactions.
- Renal excretion 86%: Competition with other compounds that undergo renal elimination.
- Decrease dosage in patients with impaired renal function. Consult manufacturer's prescribing information.
- Do not use Atripla (fixed-dose combination) in patients with CrCl <50 mL/min or in patients requiring dialysis.
- Do not use Truvada (fixed-dose combination) in patients with CrCl <30 mL/min or in patients requiring dialysis.

Drug Interactions (See also the ***Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents***.)***:***
- *Other NRTIs:* Do not use in combination with lamivudine because of the similar resistance profiles and no additive benefit.
- *Renal elimination:* Competition with other compounds that undergo renal elimination (possible competition for renal tubular secretion). Drugs that decrease renal function could decrease clearance.

Major Toxicities:
- *More common:* Headache, insomnia, diarrhea, nausea, rash, and hyperpigmentation/skin discoloration (possibly more common in children).
- *Less common (more severe):* Neutropenia. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported. Exacerbations of hepatitis have occurred in HIV/HBV-coinfected patients changed from emtricitabine-containing to non-emtricitabine-containing regimens.

Resistance: The International AIDS Society-USA (IAS-USA) maintains a list of updated resistance mutations (see **http://www.iasusa.org/resistance_mutations/index.html**) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see **http://hivdb.stanford.edu/pages/GRIP/FTC.html**).

Pediatric Experience: A single-dose pharmacokinetic study of emtricitabine liquid solution and capsules was performed in 25 HIV-infected children 2–17 years of age *[1]*. Emtricitabine was found to be well absorbed following oral administration, with a

mean elimination half-life of 11 hours (range 9.7 to 11.6 hours). Plasma concentrations in children receiving the 6 mg/kg emtricitabine once-daily dose were approximately equivalent to those in adults receiving the standard 200-mg dose.

Based on this dose-finding study, emtricitabine was given at a dose of 6 mg/kg once daily in combination with other antiretroviral drugs *[2-3]*. In a pediatric Phase II study, 71 antiretroviral-naïve children received emtricitabine plus stavudine and lopinavir/ritonavir while 45 treatment-experienced children were maintained on their initial regimens, but changed from lamivudine to emtricitabine *[3]*. Pharmacokinetic results were similar to the preceding dose-finding study *[1]*. Follow-up data extending to Week 96 indicated that 89% of the antiretroviral-naïve and 76% of the antiretroviral-experienced children maintained suppression of plasma HIV RNA <400 copies/mL (74% and 62%, respectively, at <50 copies/mL). Grade 3 or 4 laboratory abnormalities were found in 2.9% of the study population, and serious adverse events possibly related to emtricitabine were found to be 1.2% after 164 weeks of follow-up.

Emtricitabine was studied in PACTG P1021 at a dose of 6 mg/kg (maximum 240 mg/day as liquid or 200 mg/day as capsules) in combination with didanosine and efavirenz, all given once daily, in 37 antiretroviral-naïve HIV-infected children age 3 months to 21 years *[2]*. This regimen was well tolerated, and emtricitabine and didanosine concentrations met the desired target study concentrations. Eighty-five percent of subjects achieved HIV RNA <400 copies/mL and 72% maintained HIV RNA suppression to <50 copies/mL through 96 weeks of therapy. The median CD4 count rose by 329 cells/mm^3 at week 96.

A study in South Africa evaluated the pharmacokinetics of emtricitabine in 20 HIV-exposed infants age <3 months, given as 3 mg/kg once daily for two 4-day courses, separated by an interval of ≥2 weeks *[4]*. Emtricitabine exposure (AUC) in neonates receiving 3 mg/kg emtricitabine once daily was in the range of pediatric patients age >3 months receiving the recommended dose of 6 mg/kg once daily and adults receiving the once-daily recommended 200 mg emtricitabine dose (AUC approximately 10 hr*ug/mL). Emtricitabine AUC decreased with increasing age over the first 3 months of life, correlating with an increase in total body clearance of the drug. No safety issues were identified in this short pharmacokinetics study; however, extensive safety data are lacking in this age group.

References

1. Wang LH, Wiznia AA, Rathore MH, et al. Pharmacokinetics and safety of single oral doses of emtricitabine in human immunodeficiency virus-infected children. *Antimicrob Agents Chemother.* 2004;48(1):183-191.
2. McKinney RE, Jr., Rodman J, Hu C, et al. Long-term safety and efficacy of a once-daily regimen of emtricitabine, didanosine, and efavirenz in HIV-infected, therapy-naive children and adolescents: Pediatric AIDS Clinical Trials Group Protocol P1021. *Pediatrics.* 2007;120(2):e416-423.
3. Saez-Llorens X, Violari A, Ndiweni D, et al. Long-term safety and efficacy results of once-daily emtricitabine-based highly active antiretroviral therapy regimens in human immunodeficiency virus-infected pediatric subjects. *Pediatrics.* 2008;121(4):e827-835.
4. Blum M, Ndiweni D, Chittick G, et al. Steady state pharmacokinetic evaluation of emtricitabine in neonates exposed to HIV in utero. Paper presented at: 13th Conference on Retroviruses and Opportunistic Infections (CROI); February 5-9, 2006; Denver, CO. Abstract 568.

Lamivudine (3TC/Epivir)

For additional information see Drugs@FDA: **http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm**

Formulations

Oral Solution: 10 mg/mL (Epivir); 5 mg/mL (Epivir HBV[1])
Tablets: 150 mg (scored) and 300 mg (Epivir); 100 mg (Epivir HBV[1])
Combination Tablets:

- *With zidovudine (ZDV):* 150 mg 3TC + 300 mg ZDV (Combivir)
- *With abacavir (ABC):* 300 mg 3TC + 600 mg ABC (Epzicom)
- *With ZDV and ABC:* 150 mg 3TC + 300 mg ZDV + 300 mg ABC (Trizivir)

[1] Epivir HBV oral solution and tablets contain a lower amount of 3TC than Epivir oral solution and tablets. The formulation and dosing of 3TC in Epivir HBV are not appropriate for patients coinfected with HIV and HBV. If Epivir HBV used in HIV-infected patients, the higher dosage indicated for HIV therapy should be used as part of an appropriate combination regimen. The Epivir HBV tablet could be used in a child who requires a 100-mg 3TC dose for treatment of HIV infection.

Dosing Recommendations

Epivir (Oral Solution and Tablets)

Neonate/infant dose (<4 weeks) for prevention of transmission or treatment: 2 mg/kg twice daily

Pediatric dose (>4 weeks): 4 mg/kg (up to 150 mg) twice daily

Pediatric dosing for scored 150-mg tablet (weight ≥14 kg):

Weight (kg)	AM dose	PM dose	Total Daily Dose
14–21	½ tablet (75 mg)	½ tablet (75 mg)	150 mg
>21–<30	½ tablet (75 mg)	1 tablet (150 mg)	225 mg
≥30	1 tablet (150 mg)	1 tablet (150 mg)	300 mg

Adolescent (≥16 years)/Adult dose:
Body weight ≥50 kg: 150 mg twice daily or 300 mg once daily
Body weight <50 kg: 4 mg/kg (up to 150 mg) twice daily

Dosing Recommendations for Combination Formulations

Combivir
Adolescent (weight ≥30 kg)/Adult dose:
1 tablet twice daily

Trizivir
Adolescent (weight >40 kg)/Adult dose:
1 tablet twice daily

Epzicom
Adolescent (age >16 years)/Adult dose:
1 tablet once daily

Selected Adverse Events

- Minimal toxicity

Special Instructions

- Can be given without regard to food.
- Store oral solution at room temperature.
- Screen patients for HBV infection before starting therapy; exacerbation of hepatitis has been reported after discontinuation of 3TC. HIV/HBV-coinfected patients should have close clinical and laboratory monitoring for at least several months after stopping therapy with 3TC.

Metabolism

- Renal excretion – dosage adjustment required in renal insufficiency.
- Combivir and Trizivir (fixed-dose combination products) should not be used in patients with CrCl <50 mL/min, patients on dialysis, or patients with impaired hepatic function.

Drug Interactions (see also the ***Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents***.):

- *Renal elimination*: Drugs that decrease renal function could decrease clearance of lamivudine.
- *Other NRTIs:* Do not use lamivudine in combination with emtricitabine because of the similar resistance profiles and no additive benefit *[1]*.

Major Toxicities:

- *More common:* Headache, nausea.
- *Less common (more severe):* Peripheral neuropathy, pancreatitis, lipodystrophy/lipoatrophy.
- *Rare:* Increased liver enzymes. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported.

Resistance: The International AIDS Society-USA (IAS-USA) maintains a list of updated resistance mutations (see **http://www.iasusa.org/resistance_mutations/index.html**) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see **http://hivdb.stanford.edu/pages/GRIP/3TC.html**).

Pediatric Experience: Lamivudine has been studied in HIV-infected children alone and in combination with other antiretroviral drugs, and extensive data demonstrate that lamivudine appears safe and is associated with clinical improvement and virologic response *[2-17]*. Lamivudine is commonly used in HIV-infected children as a component of a dual-NRTI backbone, most often with zidovudine, as part of a combination antiretroviral drug regimen *[3-4, 6-7, 11-12, 14, 16-17]*. In one study, the NRTI background components of lamivudine/abacavir were superior to zidovudine/lamivudine or zidovudine/abacavir in long-term virologic efficacy *[18]*. Because of its safety profile and availability in a liquid formulation, lamivudine has been given to infants during the first 6 weeks of life *[11]*. Recently, weight band dosing recommendations for lamivudine have been developed *[19-20]*.

Few data are available regarding once-daily administration of lamivudine in children. The pharmacokinetics of once-daily versus twice-daily dosing of lamivudine (8 mg/kg once daily vs. 4 mg/kg twice daily) and abacavir (16 mg/kg once daily vs. 8 mg/kg twice daily) were evaluated in 20 HIV-infected children age 2–13 years in the PENTA-13 trial (all were stable on twice-daily therapy prior to randomization). The plasma AUC_{0-24} for both drugs was similar with once- and twice-daily administration, but trough concentrations were lower for both abacavir and lamivudine in younger children (age 2–6 years) receiving the once-daily regimen, as were peak (C_{max}) concentrations for lamivudine *[2]*. No major toxicities were noted, and there was improved acceptability of the once-daily dosing regimen *[2]*. Lamivudine undergoes intracellular metabolism to its active form, lamivudine triphosphate. In adolescents, the mean half-life of intracellular lamivudine triphosphate (17.7 hours) is considerably longer than that of unmetabolized lamivudine in plasma (1.5–2 hours). Intracellular concentrations of lamivudine triphosphate have been shown to be equivalent with once-daily and twice-daily dosing in adults and adolescents, supporting a recommendation for once-daily lamivudine dosing in adolescents ≥16 years and ≥50 kg *[21-22]*. More studies are needed to confirm that once-daily dosing of abacavir and lamivudine can be safely used in children.

References

1. Anderson PL, Lamba J, Aquilante CL, et al. Pharmacogenetic characteristics of indinavir, zidovudine, and lamivudine therapy in HIV-infected adults: a pilot study. *J Acquir Immune Defic Syndr.* 2006;42(4):441-449.
2. Bergshoeff A, Burger D, Verweij C, et al. Plasma pharmacokinetics of once- versus twice-daily lamivudine and abacavir: simplification of combination treatment in HIV-1-infected children (PENTA-13). *Antivir Ther.* 2005;10(2):239-246.
3. Chadwick EG, Rodman JH, Britto P, et al. Ritonavir-based highly active antiretroviral therapy in human immunodeficiency virus type 1-infected infants younger than 24 months of age. *Pediatr Infect Dis J.* 2005;24(9):793-800.
4. Chaix ML, Rouet F, Kouakoussui KA, et al. Genotypic human immunodeficiency virus type 1 drug resistance in highly active antiretroviral therapy-treated children in Abidjan, Cote d'Ivoire. *Pediatr Infect Dis J.* 2005;24(12):1072-1076.
5. Horneff G, Adams O, Wahn V. Pilot study of zidovudine-lamivudine combination therapy in vertically HIV-infected antiretroviral-naive children. *AIDS.* 1998;12(5):489-494.
6. Jankelevich S, Mueller BU, Mackall CL, et al. Long-term virologic and immunologic responses in human immunodeficiency virus type 1-infected children treated with indinavir, zidovudine, and lamivudine. *J Infect Dis.* 2001;183(7):1116-1120.
7. Krogstad P, Lee S, Johnson G, et al; Pediatric AIDS Clinical Trials Group 377 Study Team. Nucleoside-analogue reverse-transcriptase inhibitors plus nevirapine, nelfinavir, or ritonavir for pretreated children infected with human immunodeficiency virus type 1. *Clin Infect Dis.* 2002;34(7):991-1001.

8. LePrevost M, Green H, Flynn J, et al. Adherence and acceptability of once daily Lamivudine and abacavir in human immunodeficiency virus type-1 infected children. *Pediatr Infect Dis J.* 2006;25(6):533-537.
9. Lewis LL, Venzon D, Church J, et al. Lamivudine in children with human immunodeficiency virus infection: a phase I/II study. The National Cancer Institute Pediatric Branch-Human Immunodeficiency Virus Working Group. *J Infect Dis.* 1996;174(1):16-25.
10. McKinney RE, Jr., Johnson GM, Stanley K, et al. A randomized study of combined zidovudine-lamivudine versus didanosine monotherapy in children with symptomatic therapy-naive HIV-1 infection. The Pediatric AIDS Clinical Trials Group Protocol 300 Study Team. *J Pediatr.* 1998;133(4):500-508.
11. Mirochnick M, Stek A, Acevedo M, et al. Safety and pharmacokinetics of nelfinavir coadministered with zidovudine and lamivudine in infants during the first 6 weeks of life. *J Acquir Immune Defic Syndr.* 2005;39(2):189-194.
12. Mueller BU, Lewis LL, Yuen GJ, et al. Serum and cerebrospinal fluid pharmacokinetics of intravenous and oral lamivudine in human immunodeficiency virus-infected children. *Antimicrob Agents Chemother.* 1998;42(12):3187-3192.
13. Mueller BU, Sleasman J, Nelson RP, et al. A phase I/II study of the protease inhibitor indinavir in children with HIV infection. *Pediatrics.* 1998;102(1 Pt 1):101-109.
14. Nachman SA, Stanley K, Yogev R, et al. Nucleoside analogs plus ritonavir in stable antiretroviral therapy-experienced HIV-infected children: a randomized controlled trial. Pediatric AIDS Clinical Trials Group 338 Study Team. *JAMA.* 2000;283(4):492-498.
15. PENTA. A randomized double-blind trial of the addition of lamivudine or matching placebo to current nucleoside analogue reverse transcriptase inhibitor therapy in HIV-infected children: the PENTA-4 trial. Paediatric European Network for Treatment of AIDS. *AIDS.* 1998;12(14):F151-160.
16. Scherpbier HJ, Bekker V, van Leth F, et al. Long-term experience with combination antiretroviral therapy that contains nelfinavir for up to 7 years in a pediatric cohort. *Pediatrics.* 2006;117(3):e528-536.
17. van Rossum AM, Geelen SP, Hartwig NG, et al. Results of 2 years of treatment with protease-inhibitor--containing antiretroviral therapy in dutch children infected with human immunodeficiency virus type 1. *Clin Infect Dis.* 2002;34(7):1008-1016.
18. Green H, Gibb DM, Walker AS, et al. Lamivudine/abacavir maintains virological superiority over zidovudine/lamivudine and zidovudine/abacavir beyond 5 years in children. *AIDS.* 2007;21(8):947-955.
19. World Health Organization (WHO). Preferred antiretroviral medicines for treating and preventing HIV infection in younger children: Report of the WHO paediatric antiretroviral working group. 2008; http://www.who.int/hiv/paediatric/Sum_WHO_ARV_Ped_ARV_dosing.pdf.
20. L'Homme R F, Kabamba D, Ewings FM, et al. Nevirapine, stavudine and lamivudine pharmacokinetics in African children on paediatric fixed-dose combination tablets. *AIDS.* 2008;22(5):557-565.
21. Yuen GJ, Lou Y, Bumgarner NF, et al. Equivalent steady-state pharmacokinetics of lamivudine in plasma and lamivudine triphosphate within cells following administration of lamivudine at 300 milligrams once daily and 150 milligrams twice daily. *Antimicrob Agents Chemother.* 2004;48(1):176-182.
22. Flynn PM, Rodman J, Lindsey JC, et al. Intracellular pharmacokinetics of once versus twice daily zidovudine and lamivudine in adolescents. *Antimicrob Agents Chemother.* 2007;51(10):3516-3522.

Stavudine (d4T, Zerit)

For additional information see Drugs@FDA: **http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm**

Formulations

Oral solution: 1 mg/mL
Capsules: 15 mg, 20 mg, 30 mg, and 40 mg
Generic: Stavudine capsules and solution have been approved by the FDA for manufacture and distribution in the United States.

Dosing Recommendations

Neonate/Infant dose (birth to 13 days):
0.5 mg/kg twice daily

Pediatric dose (14 days and up to 30 kg):
1 mg/kg twice daily

Adolescent (≥30 kg)/Adult dose:
30 to <60 kg: 30 mg twice daily
≥60 kg: 40 mg twice daily

Selected Adverse Events

- Peripheral neuropathy
- Fat maldistribution
- Pancreatitis
- Lactic acidosis with hepatic steatosis (higher incidence than with other NRTIs)
- Hyperlipidemia
- Rapidly progressive ascending neuromuscular weakness (rare)

Special Instructions

- Can be given without regard to food.
- Shake oral solution well. Keep refrigerated; will remain stable for 30 days.

Metabolism

- Renal excretion 50%. Decrease dose in renal dysfunction.

Drug Interactions (See also the ***Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents***.)***:***

- *Renal elimination:* Drugs that decrease renal function could decrease stavudine clearance.
- *Other NRTIs*: Stavudine should not be administered in combination with zidovudine due to virologic antagonism.
- *Overlapping toxicities*: Combination of stavudine and didanosine is not recommended for initial therapy because of overlapping toxicities. Reported toxicities are more often reported in adults and include serious, even fatal, cases of lactic acidosis with hepatic steatosis with or without pancreatitis in pregnant women.

Major Toxicities:

- *More common:* Headache, gastrointestinal disturbances, skin rashes, hyperlipidemia, and fat maldistribution.
- *Less common (more severe):* Peripheral neuropathy and pancreatitis. Lactic acidosis and severe hepatomegaly with hepatic steatosis, including fatal cases, have been reported. The combination of stavudine with didanosine may result in enhanced toxicity (increased risk of fatal and nonfatal cases of lactic acidosis or pancreatitis), particularly in adults including pregnant women. This combination should not be used for initial therapy.
- *Rare:* Increased liver enzymes, rapidly progressive ascending neuromuscular weakness.

Resistance: The International AIDS Society-USA (IAS-USA) maintains a list of updated resistance mutations (see **http://www.iasusa.org/resistance_mutations/index.html**) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see **http://hivdb.stanford.edu/pages/GRIP/d4T.html**).

Pediatric Experience: Stavudine has been studied in HIV-infected children as monotherapy and in combination with other antiretroviral drugs. Data from multiple pediatric studies of stavudine alone or in combination with other antiretrovirals demonstrate that stavudine appears safe and is associated with clinical and virologic response *[1-11]* In resource-limited countries, stavudine is frequently a component of initial HAART therapy in children in combination with nevirapine or efavirenz, often as a component of fixed-dose combinations not available in the United States. In this setting, reported outcomes from observational studies are good; data show substantial increases in the CD4 count and complete viral suppression in 50%–80% of treatment-naïve children *[12-15]*.

Early initiation of triple therapy with stavudine, didanosine, and nelfinavir was evaluated in 20 infants starting therapy at <3 months of age (median age at initiation, 2.5 months) *[1]*. Therapy was generally well tolerated; 7 infants (35%) experienced 11 events considered possibly related to study drugs, although only 3 such events (rash, diarrhea, and neutropenia) required drug modification. At least 1 episode of Grade 1 hypertriglyceridemia was observed in 19 of 20 (95%) infants; 9 of 12 (75%) infants with cholesterol measured after baseline had at least 1 episode of Grade 1 hypercholesterolemia. However, no infant had Grade 2 or higher triglyceride or cholesterol concentrations. Seventy percent of infants had incomplete viral suppression, which was associated with genotypic resistance mutations in 6 (30%) of these infants. However, only 2 infants developed resistance mutations to stavudine, and 1 of these infants had pre-existing TAMs present at baseline. Stavudine has been used as a component of a second regimen after treatment failure or as a replacement for zidovudine if the patient develops anemia. In a Phase II comparison study of stavudine and zidovudine, they were largely comparable in terms of safety and tolerability, although neutropenia occurred significantly less often among children receiving stavudine *[6]*. Stavudine is associated with a higher rate of adverse events than zidovudine in adults and children receiving combination therapy *[16-17]*. In a large pediatric natural history study (PACTG 219C), stavudine-containing regimens had a modest but significantly higher rate of clinical and laboratory toxicities than those containing zidovudine, with pancreatitis, peripheral neuropathy, and lipodystrophy/lipoatrophy (fat maldistribution) associated with stavudine *[17]*. Peripheral neuropathy is an important toxicity associated with stavudine but appears to be less common in children than in adults *[4, 6]*. Elevated hepatic transaminases are seen in about 11% and pancreatitis in 1% of adults enrolled in clinical trials of stavudine. In a small pediatric study of stavudine in combination with didanosine, no pharmacokinetic interactions were observed and there were no cases of peripheral neuropathy *[5]*. In PACTG 219C, peripheral neuropathy was recognized in 0.9% of children *[17]*. Lipodystrophy, and specifically lipoatrophy (loss of subcutaneous fat), are toxicities associated with the use of NRTIs, particularly stavudine, in adults and children *[18-20]*. Lipodystrophy developed in 28% of 39 children receiving stavudine, lamivudine, and nelfinavir after a median of 49 months of therapy with 9 demonstrating lipoatrophy *[10]*. Among 90 children receiving stavudine, lamivudine, and nevirapine or efavirenz, 65% developed lipodystrophy at 33 months *[21]*. Further research concerning body habitus changes associated with NRTI use in pediatric patients is ongoing. Lactic acidosis with hepatic steatosis, including fatal cases, has been reported with the use of nucleoside analogues, including stavudine, alone or in combination *[22-23]*. The combination of stavudine and didanosine in pregnant women has been associated with fatal lactic acidosis and should be used during pregnancy only if no other alternatives are available *[24]*. Many of these adverse events are believed to be due to mitochondrial toxicity resulting from inhibition of mitochondrial DNA polymerase gamma, with depletion of mitochondrial DNA demonstrated in fat, muscle, peripheral blood mononuclear cells, and other tissues *[22, 25-27]*. (For additional information on lactic acidosis see **Tables 17a–17h. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations**.)

Although the World Health Organization has chosen to limit the maximum dose of stavudine to 30 mg (WHO guidelines at www.who.int/hiv/art/ARTadultsaddendum.pdf), these guidelines support switching to another agent rather than lowering the dose of stavudine to reduce the risk of or to manage toxicity. This recommendation is based on the availability of alternative antiretroviral agents in the United States and concerns of some Panel members about suboptimal therapy with a lower dose of stavudine.

References

1. Aboulker JP, Babiker A, Chaix ML, et al. Highly active antiretroviral therapy started in infants under 3 months of age: 72-week follow-up for CD4 cell count, viral load and drug resistance outcome. *AIDS.* 2004;18(2):237-245.
2. de Mendoza C, Ramos JT, Ciria L, et al. Efficacy and safety of stavudine plus didanosine in asymptomatic HIV-infected children with plasma HIV RNA below 50,000 copies per milliliter. *HIV Clin Trials.* 2002;3(1):9-16.
3. King JR, Nachman S, Yogev R, et al. Efficacy, tolerability and pharmacokinetics of two nelfinavir-based regimens in human immunodeficiency virus-infected children and adolescents: pediatric AIDS clinical trials group protocol 403. *Pediatr Infect Dis J.* 2005;24(10):880-885.
4. Kline MW, Dunkle LM, Church JA, et al. A phase I/II evaluation of stavudine (d4T) in children with human immunodeficiency virus infection. *Pediatrics.* 1995;96(2 Pt 1 (Aug)):247-252.
5. Kline MW, Fletcher CV, Federici ME, et al. Combination therapy with stavudine and didanosine in children with advanced human immunodeficiency virus infection: pharmacokinetic properties, safety, and immunologic and virologic effects. *Pediatrics.* 1996;97(6 Pt 1):886-890.
6. Kline MW, Fletcher CV, Harris AT, et al. A pilot study of combination therapy with indinavir, stavudine (d4T), and didanosine (ddI) in children infected with the human immunodeficiency virus. *J Pediatr.* 1998;132(3 Pt 1):543-546.
7. Kline MW, Van Dyke RB, Lindsey JC, et al. Combination therapy with stavudine (d4T) plus didanosine (ddI) in children with human immunodeficiency virus infection. The Pediatric AIDS Clinical Trials Group 327 Team. *Pediatrics.* 1999;103(5):e62.

8. Krogstad P, Lee S, Johnson G, et al; Pediatric AIDS Clinical Trials Group 377 Study Team. Nucleoside-analogue reverse-transcriptase inhibitors plus nevirapine, nelfinavir, or ritonavir for pretreated children infected with human immunodeficiency virus type 1. *Clin Infect Dis.* 2002;34(7):991-1001.
9. Nachman SA, Stanley K, Yogev R, et al. Nucleoside analogs plus ritonavir in stable antiretroviral therapy-experienced HIV-infected children: a randomized controlled trial. Pediatric AIDS Clinical Trials Group 338 Study Team. *Journal of the American Medical Association.* 2000;283(4):492-498.
10. Scherpbier HJ, Bekker V, van Leth F, et al. Long-term experience with combination antiretroviral therapy that contains nelfinavir for up to 7 years in a pediatric cohort. *Pediatrics.* 2006;117(3):e528-536.
11. Yogev R, Lee S, Wiznia A, et al. for the Pediatric AIDS Clinical Trials Group 338 Study Team. Stavudine, nevirapine and ritonavir in stable antiretroviral therapy-experienced children with human immunodeficiency virus infection. *Pediatr Infect Dis J.* 2002;21(2):119-125.
12. Bolton-Moore C, Mubiana-Mbewe M, Cantrell RA, et al. Clinical outcomes and CD4 cell response in children receiving antiretroviral therapy at primary health care facilities in Zambia. *JAMA.* 2007;298(16):1888-1899.
13. Janssens B, Raleigh B, Soeung S, et al. Effectiveness of highly active antiretroviral therapy in HIV-positive children: evaluation at 12 months in a routine program in Cambodia. *Pediatrics.* 2007;120(5):e1134-1140.
14. Kamya MR, Mayanja-Kizza H, Kambugu A, et al. Predictors of long-term viral failure among ugandan children and adults treated with antiretroviral therapy. *J Acquir Immune Defic Syndr.* 2007;46(2):187-193.
15. Zhang F, Haberer JE, Zhao Y, et al. Chinese pediatric highly active antiretroviral therapy observational cohort: a 1-year analysis of clinical, immunologic, and virologic outcomes. *J Acquir Immune Defic Syndr.* 2007;46(5):594-598.
16. Robbins GK, De Gruttola V, Shafer RW, et al. Comparison of sequential three-drug regimens as initial therapy for HIV-1 infection. *N Engl J Med.* 2003;349(24):2293-2303.
17. Van Dyke RB, Wang L, Williams PL. Toxicities associated with dual nucleoside reverse-transcriptase inhibitor regimens in HIV-infected children. *J Infect Dis.* 2008;198(11):1599-1608.
18. Joly V, Flandre P, Meiffredy V, et al. Increased risk of lipoatrophy under stavudine in HIV-1-infected patients: results of a substudy from a comparative trial. *AIDS.* 2002;16(18):2447-2454.
19. European Paediatric Lipodystrophy Group. Antiretroviral therapy, fat redistribution and hyperlipidaemia in HIV-infected children in Europe. *AIDS.* 2004;18(10):1443-1451.
20. Ene L, Goetghebuer T, Hainaut M, et al. Prevalence of lipodystrophy in HIV-infected children: a cross-sectional study. *Eur J Pediatr.* 2007;166(1):13-21.
21. Aurpibul L, Puthanakit T, Lee B, et al. Lipodystrophy and metabolic changes in HIV-infected children on non-nucleoside reverse transcriptase inhibitor-based antiretroviral therapy. *Antivir Ther.* 2007;12(8):1247-1254.
22. Haugaard SB, Andersen O, Pedersen SB, et al. Depleted skeletal muscle mitochondrial DNA, hyperlactatemia, and decreased oxidative capacity in HIV-infected patients on highly active antiretroviral therapy. *J Med Virol.* 2005;77(1):29-38.
23. Koh MT. Unrecognized near-fatal hyperlactatemia in an HIV-infected infant exposed to nucleoside reverse transcriptase inhibitors. *Int J Infect Dis.* 2007;11(1):85-86.
24. Sarner L, Fakoya A. Acute onset lactic acidosis and pancreatitis in the third trimester of pregnancy in HIV-1 positive women taking antiretroviral medication. *Sex Transm Infect.* 2002;78(1):58-59.
25. Blanco F, Garcia-Benayas T, Jose de la Cruz J, et al. First-line therapy and mitochondrial damage: different nucleosides, different findings. *HIV Clin Trials.* 2003;4(1):11-19.
26. Cherry CL, Gahan ME, McArthur JC, et al. Exposure to dideoxynucleosides is reflected in lowered mitochondrial DNA in subcutaneous fat. *J Acquir Immune Defic Syndr.* 2002;30(3):271-277.
27. Sanchez-Conde M, de Mendoza C, Jimenez-Nacher I, et al. Reductions in stavudine dose might ameliorate mitochondrial-associated complications without compromising antiviral activity. *HIV Clin Trials.* 2005;6(4):197-202.

Tenofovir Disoproxil Fumarate (TDF, Viread)

For additional information see Drugs@FDA: **http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm**

Formulations

Tablet: 300 mg

Combination tablets:

- *With emtricitabine (FTC)*: 200 mg FTC + 300 mg TDF (Truvada)
- *With FTC + efavirenz (EFV)*: 200 mg FTC + 600 mg EFV + 300 mg TDF (Atripla)

Dosing Recommendations

Neonate/Infant dose:

Not approved for use in neonates/infants.

Pediatric dose:

Not approved for use in children <12 years of age; only commercially available preparation is 300-mg tablet. Investigational dose of 8 mg/kg of body weight once daily in children <12 years of age provided a lower exposure than was observed in adults.

Adolescent (≥12 years and >35 kg) dose:

300 mg once daily

See text for concerns about decreased bone mineral density, especially in prepubertal patients and those in early puberty (Tanner stages 1 and 2).

Dosing Recommendations for Combination Formulations

Truvada

Adult dose:

1 tablet once daily

Atripla

Adult dose:

1 tablet once daily

Dosing Recommendations for Coadministration with Other Antiretroviral Drugs

TDF in combination with didanosine (ddI)

ddI dose requires modification. See section on **ddI**.

TDF in combination with atazanavir (ATV)

Only ATV boosted with ritonavir (RTV) should be used in combination with TDF. See section on **ATV**.

Selected Adverse Events

- Asthenia, headache, diarrhea, nausea, vomiting, flatulence
- Renal insufficiency, Fanconi syndrome
- Decreased bone mineral density

Special Instructions

- TDF can be administered without regard to food, although absorption is enhanced when administered with a high-fat meal. It is recommended to administer Atripla on an empty stomach because it contains EFV.
- When coadministered, ddI delayed-release capsule formulation and TDF may be taken under fasted conditions or with a light meal.
- Screen patients for hepatitis B virus infection (HBV) prior to use of TDF. Severe acute exacerbation of HBV can occur when TDF is discontinued; monitor hepatic function for several months after therapy with TDF is stopped.

Metabolism

- Renal excretion.
- Dosing of TDF in patients with renal insufficiency: Decreased dosage should be used in patients with impaired renal function. Consult manufacturer's prescribing information for adjustment of dosage in accordance with creatinine clearance.
- Atripla (fixed-dose combination) should not be used in patients with CrCl <50 mL/min or in patients requiring dialysis.
- Truvada (fixed-dose combination) should not be used in patients with CrCl <30 mL/min or in patients requiring dialysis.

Drug Interactions (See also the ***Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents***):

- *Renal elimination:* Drugs that decrease renal function or compete for active tubular secretion could reduce clearance of tenofovir.
- *Other NRTIs:* Didanosine serum concentrations are increased when coadministered with tenofovir.
- *PIs:* Tenofovir decreases atazanavir plasma concentrations. In adults, the recommended dosing for atazanavir coadministered with tenofovir is atazanavir 300 mg with ritonavir 100 mg and tenofovir 300 mg, all as a single daily dose with food. Atazanavir without ritonavir should not be coadministered with tenofovir. In addition, atazanavir and lopinavir/ritonavir increase tenofovir concentrations and could potentiate tenofovir-associated toxicity.

Major Toxicities:

- *More common:* Nausea, diarrhea, vomiting, and flatulence.
- *Less common (more severe):* Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported. Tenofovir caused bone toxicity (osteomalacia and reduced bone density) in animals when given in high doses. Decreases in bone mineral density have been shown in both adults and children taking tenofovir for 48 weeks; the clinical significance of these changes is not yet known. Evidence of renal toxicity, including increases in serum creatinine, blood urea nitrogen, glycosuria, proteinuria, phosphaturia, and/or calciuria and decreases in serum phosphate has been observed. Numerous case reports of renal tubular dysfunction have been reported in patients receiving tenofovir; patients at increased risk of renal dysfunction should be closely monitored.

Resistance: The International AIDS Society-USA (IAS-USA) maintains a list of updated resistance mutations (see **http://www.iasusa.org/resistance_mutations/index.html**) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see **http://hivdb.stanford.edu/pages/GRIP/TDF.html**).

Pediatric Experience: In a Phase I/II study of tenofovir for salvage therapy using an investigational 75-mg formulation in 18 heavily pretreated children and adolescents at the National Institutes of Health (NIH) *[1]*, the major toxicity attributable to tenofovir was a >6% decrease in bone mineral density (BMD) measured by dual-energy x-ray absorptiometry (DXA) scan in 5 of 15 (33%) children evaluated at Week 48. Two of the 5 children discontinued tenofovir at 48 weeks as required by the protocol and experienced partial or complete recovery of BMD by 96 weeks *[2]*. Among children with BMD decreases, the median Tanner score was 1 (range 1–3) and mean age was 10.2 years; for children who had no BMD decreases, the median Tanner score was 2.5 (range 1–4) and median age was 13.2 years *[2-3]*. In a second study of 6 patients at NIH using the commercially available 300-mg formulation of tenofovir, 2 prepubertal children experienced >6% BMD decreases. One of the 2 children, the smallest child in the study, experienced a 27% decrease in BMD, necessitating withdrawal of tenofovir from her antiretroviral therapy regimen. The child continued therapy without tenofovir and subsequently her BMD recovered *[4]* The data from both of these small studies suggest that tenofovir-related bone loss may be greater in less mature children (e.g., Tanner 1–2) than in those with more advanced development (Tanner ≥3), and other studies offer further support for this conclusion *[5-6]*.

It is also possible that the bone loss seen in the patients in the NIH studies *[1-4]* may have been associated with higher tenofovir exposures. All participants were treated with regimens that also contained ritonavir, which increases tenofovir exposure *[7-8]*. Although the median initial dose in the Phase I/II studies was 208 mg/m^2 (= 7.1 mg/kg), the administered dose varied from 161 to 256 mg/m^2 (3.7 to 10 mg/kg) *[1]*. Loss of bone mineral density at 48 weeks was associated with higher drug exposure (AUC) *[3]*. However, in this heavily pretreated cohort, the group with the best virologic response had statistically significantly higher AUC, suggesting that in salvage therapy tenofovir may have a relatively small therapeutic window, especially in children in Tanner stages 1–2.

In contrast to the NIH studies, an Italian study showed no effect of tenofovir on BMD in pediatric patients on stable therapy with undetectable viral load who were switched from stavudine and PI-containing regimens to tenofovir/lamivudine/efavirenz *[9]*. The different results may be explained by different patient populations, differences in concurrent medication use, and tenofovir dosing. The patients in the Italian study *[9-11]* included older participants (up to age 18 years), had greater height and weight *z* scores, and the majority were in middle to late puberty or postpubertal. The NIH study involved heavily treatment experienced patients in need of salvage therapy while the Italian study evaluated BMD in a potentially healthier population of patients who were required to have long-lasting viral suppression prior to the switch in therapy. Finally, because the patients in the Italian study received tenofovir in the absence of ritonavir and were administered fractions of tenofovir pills to provide lower doses, the tenofovir concentrations experienced by the Italian patients may have been lower than those seen in the NIH patients. No BMD studies have been reported in treatment-naïve children who initiate therapy with tenofovir.

No significant renal disease was seen with tenofovir therapy in either of the 2 small NIH studies or in the Italian study. In 6/159 (3.7%) children with HIV-1 treated with tenofovir in the Collaborative HIV Pediatric Study (CHIPS) in the United Kingdom and Ireland, renal toxicity leading to discontinuation of tenofovir was reported *[12]*. All 6 of those patients were taking didanosine and lopinavir/ritonavir in addition to tenofovir, and the interaction of didanosine and tenofovir *[13]* or the boosting of tenofovir exposure by concurrent use of lopinavir/ritonavir *[7]* may have caused this toxicity. Possible tenofovir-associated nephrotoxicity manifest as Fanconi syndrome, reduced creatinine clearance, and diabetes insipidus has been reported in a child receiving tenofovir as a component of salvage therapy including lopinavir/ritonavir and didanosine for 1 year *[14]*, and irreversible renal failure has been reported in an adolescent treated with tenofovir without didanosine *[15]*. Increased urinary beta-2 microglobulin suggesting proximal renal tubular damage was identified in 12 of 44 (27%) children treated with tenofovir

compared with 2 of 48 (4%) children not treated with tenofovir *[16]*. An observational cohort study of 2,102 children with HIV in the United States suggested an increased risk of renal disease (increased creatinine or proteinuria) in children treated with tenofovir-containing combination antiretroviral therapy *[17]*. However, no significant decrease in calculated glomerular filtration rate was found in 27 HIV-infected children treated with tenofovir for 96 weeks *[10]*. Lipid profiles improved significantly after the switch from stavudine and PI-containing regimens to tenofovir/lamivudine/efavirenz *[11]*.

The NIH study, using a 75-mg tablet formulation of tenofovir in treatment-experienced children and adolescents 6–18 years of age, showed that a median dose of 208 mg/m^2 of body surface area (range 161–256 mg/m^2 body surface area) resulted in a median single dose AUC and C_{max} that were 34% and 27% lower, respectively, compared with values reported in adults administered a daily dose of 300 mg *[1, 18]*. Renal clearance of tenofovir was approximately 1.5-fold higher in children than previously reported in adults, possibly explaining the lower systemic exposure *[1]*. Steady-state tenofovir exposures were higher but still less than those seen in adults and may reflect the concomitant treatment with ritonavir, which boosts tenofovir plasma concentrations. Lower than anticipated tenofovir exposure was also found in young adults (median age 23 years) treated with atazanavir/ritonavir plus tenofovir *[19]*. The clinical impact of these low drug exposures is unknown, but in the NIH study, lower single-dose and steady-state AUC were associated with inferior virologic outcome *[3]*. The CHIPS cohort used a target dose of 8 mg/kg, but 18% were dosed at >120% of the target and 37% at less than 80%.

In the Italian study, which only enrolled patients with undetectable viral load on current therapy, all HIV-infected children remained clinically stable and virologically suppressed after the change to a tenofovir-containing regimen *[11]*. In the NIH "salvage" study, plasma HIV RNA concentrations ($\log_{10}$ copies/mL) decreased from a median pretreatment concentration of 5.4 $\log_{10}$ copies/mL to 4.21 $\log_{10}$ copies/mL after 48 weeks of therapy *[3]*. HIV RNA was <400 copies/mL in 6/16 (37.5%) participants and <50 copies/mL in 4/16 (25%) participants at 48 weeks. In the CHIPS cohort 115 patients had outcome data available *[12]*. Viral load decreased to <50 copies/mL at 12 months in 38% of patients starting tenofovir for the first time; in 50% on first-line therapy; 39% of those on second-line therapy; and 13% of patients on third-line or greater therapy *[12]*.

In March 2010, the FDA approved the use of tenofovir in adolescents ≥12 years of age and weighing ≥35 kg based upon data from Gilead study 321, a randomized, placebo-controlled trial of tenofovir or placebo plus an optimized background regimen in 87 treatment-experienced adolescents between 12 and <18 years of age in Brazil and Panama *[20-21]*. No difference in viral load response was seen between the 2 groups. Subgroup analyses suggest this lack of response may have been due to imbalances in viral susceptibility to the optimized background regimens between the 2 groups. Importantly, impaired bone accrual was seen in the tenofovir group, manifest by declining BMD *z* scores over 48 and 96 weeks. In addition, 6 of 33 (18%) participants in the tenofovir arm experienced a >4% decline in absolute lumbar spine BMD in 48 weeks compared with only 1 of 33 (3%) participants in the placebo arm *[20-21]*. Limited pharmacokinetic data were reported from 8 participants and suggested that tenofovir exposures were higher than those seen in the NIH study, but no data on correlation of tenofovir exposure with BMD loss were provided.

Given this potential for BMD loss, some experts recommend obtaining a DXA prior to the initiation of tenofovir therapy and approximately 6 months after start of tenofovir, especially in prepubertal patients and those early in puberty (Tanner stages 1 and 2). However, in view of the potential cost and difficulty in obtaining pediatric DXA in some settings, other experts try to avoid using tenofovir in prepubertal patients and those in early puberty, especially for initial therapy. Despite the ease of use of a once-daily drug and the efficacy of tenofovir, this potential for BMD loss during the important period of rapid bone accrual in adolescence is concerning and favors judicious use of tenofovir in this age group. There is still an urgent need for more research to develop appropriate pediatric formulations and to identify the safest uses of tenofovir in children and adolescents.

An investigational liquid formulation has been studied in children 2–8 years of age; a tenofovir dose of 8 mg/kg resulted in tenofovir exposure similar to that observed in adults receiving a tenofovir dose of 300 mg, but this formulation had poor palatability and was not developed further *[22]*. A powder formulation is also under investigation. An investigational dose of 8 mg/kg of body weight once daily in children <12 years of age provided a lower exposure than was observed in adults, and the FDA has recommended that a higher dose be evaluated in this age group *[21]*.

References

1. Hazra R, Balis FM, Tullio AN, et al. Single-dose and steady-state pharmacokinetics of tenofovir disoproxil fumarate in human immunodeficiency virus-infected children. *Antimicrob Agents Chemother.* 2004;48(1):124-129.

2. Gafni RI, Hazra R, Reynolds JC, et al. Tenofovir disoproxil fumarate and an optimized background regimen of antiretroviral agents as salvage therapy: impact on bone mineral density in HIV-infected children. *Pediatrics.* 2006;118(3):e711-718.
3. Hazra R, Gafni RI, Maldarelli F, et al. Tenofovir disoproxil fumarate and an optimized background regimen of antiretroviral agents as salvage therapy for pediatric HIV infection. *Pediatrics.* 2005;116(6):e846-854.
4. Purdy JB, Gafni RI, Reynolds JC, et al. Decreased bone mineral density with off-label use of tenofovir in children and adolescents infected with human immunodeficiency virus. *J Pediatr.* 2008;152(4):582-584.
5. Jacobson D, Dimeglio L, Hazra R, et al. Clinical determinants of bone mineral density in perinatally HIV-infected children. Paper presented at: 16th Conference on Retroviruses and Opportunistic Infections (CROI); February 8-11, 2009; Montreal, Canada. Abstract 911.
6. Thomas V, Purdy J, Reynolds J, et al. Bone mineral density in adolescents infected with HIV perinatally or childhood: Data from the NIH intramural program. Paper presented at: 16th Conference on Retroviruses and Opportunistic Infections (CROI); February 8-11, 2009; Montreal, Canada. Abstract 912.
7. Kiser JJ, Carten ML, Aquilante CL, et al. The effect of lopinavir/ritonavir on the renal clearance of tenofovir in HIV-infected patients. *Clin Pharmacol Ther.* 2008;83(2):265-272.
8. Kearney BP, Mathias A, Mittan A, et al. Pharmacokinetics and safety of tenofovir disoproxil fumarate on coadministration with lopinavir/ritonavir. *J Acquir Immune Defic Syndr.* 2006;43(3):278-283.
9. Giacomet V, Mora S, Martelli L, et al. A 12-month treatment with tenofovir does not impair bone mineral accrual in HIV-infected children. *J Acquir Immune Defic Syndr.* 2005;40(4):448-450.
10. Vigano A, Zuccotti GV, Martelli L, et al. Renal safety of tenofovir in HIV-infected children: a prospective, 96-week longitudinal study. *Clin Drug Investig.* 2007;27(8):573-581.
11. Vigano A, Aldrovandi GM, Giacomet V, et al. Improvement in dyslipidaemia after switching stavudine to tenofovir and replacing protease inhibitors with efavirenz in HIV-infected children. *Antivir Ther.* 2005;10(8):917-924.
12. Riordan A, Judd A, Boyd K, et al. Tenofovir use in human immunodeficiency virus-1-infected children in the United kingdom and Ireland. *Pediatr Infect Dis J.* 2009;28(3):204-209.
13. Crane HM, Kestenbaum B, Harrington RD, et al. Amprenavir and didanosine are associated with declining kidney function among patients receiving tenofovir. *AIDS.* 2007;21(11):1431-1439.
14. Hussain S, Khayat A, Tolaymat A, et al. Nephrotoxicity in a child with perinatal HIV on tenofovir, didanosine and lopinavir/ritonavir. *Pediatr Nephrol.* 2006;21(7):1034-1036.
15. Wood SM, Shah SS, Steenhoff AP, et al. Tenofovir-associated nephrotoxicity in two HIV-infected adolescent males. *AIDS Patient Care STDS.* 2009;23(1):1-4.
16. Papaleo A, Warszawski J, Salomon R, et al. Increased beta-2 microglobulinuria in human immunodeficiency virus-1-infected children and adolescents treated with tenofovir. *Pediatr Infect Dis J.* 2007;26(10):949-951.
17. Andiman WA, Chernoff MC, Mitchell C, et al. Incidence of persistent renal dysfunction in human immunodeficiency virus-infected children: associations with the use of antiretrovirals, and other nephrotoxic medications and risk factors. *Pediatr Infect Dis J.* 2009;28(7):619-625.
18. Barditch-Crovo P, Deeks SG, Collier A, et al. Phase i/ii trial of the pharmacokinetics, safety, and antiretroviral activity of tenofovir disoproxil fumarate in human immunodeficiency virus-infected adults. *Antimicrob Agents Chemother.* 2001;45(10):2733-2739.
19. Kiser JJ, Fletcher CV, Flynn PM, et al. Pharmacokinetics of antiretroviral regimens containing tenofovir disoproxil fumarate and atazanavir-ritonavir in adolescents and young adults with human immunodeficiency virus infection. *Antimicrob Agents Chemother.* 2008;52(2):631-637.
20. TDF FDA label. 2010; http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021356s033lbl.pdf.
21. Food and Drug Administration (FDA). FDA clinical review.
22. Kearney B, Abadi J, Rosenberg M, et al. Pharmacokinetics of tenofovir DF oral suspension in HIV-1-infected children between 2 and 8 years of age. 11th Conference on Retroviruses and Opportunistic Infections; Feb 8-11, 2004; San Francisco, CA. Abstract 935.

Zidovudine (ZDV, AZT, Retrovir)

For additional information see Drugs@FDA: **http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm**

Formulations

Capsules: 100 mg
Tablets: 300 mg
Syrup: 10 mg/mL
Concentrate for injection/for intravenous infusion: 10 mg/mL
Generic: ZDV capsules, tablets, and solution are approved by the FDA for manufacture and distribution in the United States.
Combination tablets:

- *With lamivudine (3TC)*: 300 mg ZDV + 150 mg 3TC (Combivir)
- *With 3TC + abacavir (ABC)*: 300 mg ZDV + 150 mg 3TC + 300 mg ABC (Trizivir)

Dosing Recommendations

Premature infant dose for prevention of transmission or treatment (standard neonate dose may be excessive in premature infants):
1.5 mg/kg of body weight (intravenous) or 2 mg/kg of body weight (oral) every 12 hours, increased to every 8 hours at 2 weeks of age (neonates ≥30 weeks gestational age) or at 4 weeks of age (neonates <30 weeks gestational age)

Neonate/Infant dose (<6 weeks) for prevention of transmission or treatment:
Oral: 2 mg/kg of body weight every 6 hours
Intravenous: 1.5 mg/kg of body weight every 6 hours

Pediatric dose (6 weeks to <18 years):
Body surface area dosing:
Oral: 180–240 mg/m^2 of body surface area every 12 hours or 160 mg/m^2 every 8 hours

Weight-based dosing:

Body Weight	Twice-Daily Dosing*
4 kg to <9 kg	12 mg/kg
9 kg to <30 kg	9 mg/kg
≥30 kg	300 mg

*Three times daily dosing is approved but rarely used in clinical practice.

Adolescent (≥18 years)/Adult dose:
200 mg three times a day or 300 mg twice daily

Dosing Recommendations for Combination Formulations

Combivir
Adolescent (weight ≥30 kg)/Adult dose:
1 tablet twice daily

Trizivir
Adolescent (weight ≥40 kg)/Adult dose:
1 tablet twice daily

Selected Adverse Events

- Bone marrow suppression: macrocytic anemia or neutropenia
- GI intolerance, headache, insomnia, asthenia
- Lactic acidosis with hepatic steatosis

Special Instructions

- Can be given without regard to food.
- Substantial granulocytopenia or anemia may necessitate interruption of therapy until marrow recovery is observed; use of erythropoietin, filgrastim, or transfusion may be necessary in some patients.

Metabolism

- Metabolized to AZT glucuronide (GAZT), which is renally excreted.
- Dosage adjustment required in renal insufficiency.
- Decreased dosing may be required in patients with hepatic impairment.
- Combivir and Trizivir (fixed-dose combination products) should not be used in patients with CrCl <50 mL/min, patients on dialysis, or patients with impaired hepatic function.

Drug Interactions (See also the ***Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents***.)**:**

- *Other NRTIs:* Should not be administered in combination with stavudine due to virologic antagonism.
- *Bone marrow suppressive/cytotoxic agents including ganciclovir, interferon alpha, and ribavirin:* May increase the hematologic toxicity of zidovudine.
- *Doxorubicin:* Use should be avoided.

Major Toxicities:

- *More common:* Hematologic toxicity, including granulocytopenia and anemia. Headache, malaise, nausea, vomiting, and anorexia.
- *Less common (more severe):* Myopathy (associated with prolonged use), myositis, and liver toxicity. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported. Fat maldistribution.
- *Rare:* Increased risk of hypospadias after first-trimester exposure to zidovudine observed in one cohort study.

Resistance: The International AIDS Society-USA (IAS-USA) maintains a list of updated resistance mutations (see **http://www.iasusa.org/resistance_mutations/index.html**) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see **http://hivdb.stanford.edu/pages/GRIP/ZDV.html**).

Pediatric Experience: Zidovudine was the first NRTI studied in adult and pediatric clinical trials and the first antiretroviral agent approved for treatment of HIV infection. Data from multiple pediatric studies of zidovudine alone or in combination with other antiretrovirals demonstrate that zidovudine appears safe and is associated with clinical improvement and virologic and immunologic effects *[1-16]*.

Perinatal trial PACTG 076 established that a zidovudine prophylactic regimen given during pregnancy, labor, and to the newborn reduced the risk of perinatal HIV transmission by nearly 70% *[17]*. Recommended neonatal zidovudine dosing for prevention of mother-to-child transmission of HIV is 2 mg/kg orally every 6 hours or 1.5 mg/kg intravenously every 6 hours for those unable to receive oral dosing. Although not FDA approved, twice-daily dosing (4 mg/kg every 12 hours) is sometimes prescribed when concerns about adherence exist, but the efficacy of this approach for prevention of mother-to-child transmission has not been evaluated. Pharmacokinetic studies, such as PACTG 331, have shown that dose adjustments are necessary for premature infants due to decreased zidovudine clearance compared with term newborns of similar postnatal ages *[2, 6]*. Resistance mutations were shown to be present in 5 of 17 (29%) newborns born to mothers who received zidovudine during pregnancy *[18]*.

Overall, zidovudine pharmacokinetics in pediatric patients >3 months of age are similar to those in adult patients. The manufacturer's recommended oral dose in pediatric patients 6 weeks to 12 years of age is 160 mg per meter^2 of body surface area every 8 hours or 240 mg per meter^2 of body surface area every 12 hours, in combination with other antiretroviral agents, although the recommended dose for adults is 300 mg twice daily. Recently, weight band dosing has also been approved *[19]*. Zidovudine undergoes intracellular metabolism to its active form, zidovudine triphosphate. Although the mean half-life of intracellular zidovudine triphosphate (9.1 hours) is considerably longer than that of unmetabolized zidovudine in plasma (1.5 hours), once-daily zidovudine dosing is not recommended because of low intracellular zidovudine triphosphate concentrations seen with 600-mg once-daily dosing in adolescents *[20]*. Zidovudine has good central nervous system (CNS) penetration (cerebrospinal fluid-to-plasma concentration ratio = 0.68) and has been used in children with HIV-related CNS disease *[1]*.

References

1. Balis FM, Pizzo PA, Murphy RF, et al. The pharmacokinetics of zidovudine administered by continuous infusion in children. *Ann Intern Med.* 1989;110(4):279-285.
2. Capparelli EV, Mirochnick M, Dankner WM, et al. Pharmacokinetics and tolerance of zidovudine in preterm infants. *J Pediatr.* 2003;142(1):47-52.
3. Chadwick EG, Rodman JH, Britto P, et al. Ritonavir-based highly active antiretroviral therapy in human immunodeficiency virus type 1-infected infants younger than 24 months of age. *Pediatr Infect Dis J.* 2005;24(9):793-800.
4. Englund JA, Baker CJ, Raskino C, et al. Zidovudine, didanosine, or both as the initial treatment for symptomatic HIV-infected children. AIDS Clinical Trials Group (ACTG) Study 152 Team. *N Engl J Med.* 1997;336(24):1704-1712.
5. Jankelevich S, Mueller BU, Mackall CL, et al. Long-term virologic and immunologic responses in human immunodeficiency virus type 1-infected children treated with indinavir, zidovudine, and lamivudine. *J Infect Dis.* 2001;183(7):1116-1120.
6. King JR, Kimberlin DW, Aldrovandi GM, Acosta EP. Antiretroviral pharmacokinetics in the paediatric population: a review. *Clin Pharmacokinet.* 2002;41(14):1115-1133.
7. Luzuriaga K, Bryson Y, Krogstad P, et al. Combination treatment with zidovudine, didanosine, and nevirapine in infants with human immunodeficiency virus type 1 infection. *N Engl J Med.* 1997;336(19):1343-1349.
8. McKinney RE, Jr., Maha MA, Connor EM, et al. A multicenter trial of oral zidovudine in children with advanced human immunodeficiency virus disease. The Protocol 043 Study Group. *N Engl J Med.* 1991;324(15):1018-1025.
9. McKinney RE, Jr., Johnson GM, Stanley K, et al. A randomized study of combined zidovudine-lamivudine versus didanosine monotherapy in children with symptomatic therapy-naive HIV-1 infection. The Pediatric AIDS Clinical Trials Group Protocol 300 Study Team. *J Pediatr.* 1998;133(4):500-508.
10. Mueller BU, Nelson RP, Jr., Sleasman J, et al. A phase I/II study of the protease inhibitor ritonavir in children with human immunodeficiency virus infection. *Pediatrics.* 1998;101(3 Pt 1):335-343.
11. Mueller BU, Sleasman J, Nelson RP, et al. A phase I/II study of the protease inhibitor indinavir in children with HIV infection. *Pediatrics.* 1998;102(1 Pt 1):101-109.
12. Nachman SA, Stanley K, Yogev R, et al. Nucleoside analogs plus ritonavir in stable antiretroviral therapy-experienced HIV-infected children: a randomized controlled trial. Pediatric AIDS Clinical Trials Group 338 Study Team. *JAMA.* 2000;283(4):492-498.
13. Palacios GC, Palafox VL, Alvarez-Munoz MT, et al. Response to two consecutive protease inhibitor combination therapy regimens in a cohort of HIV-1-infected children. *Scand J Infect Dis.* 2002;34(1):41-44.
14. Pizzo PA, Eddy J, Falloon J, et al. Effect of continuous intravenous infusion of zidovudine (AZT) in children with symptomatic HIV infection. *N Engl J Med.* 1988;319(14):889-896.
15. Saez-Llorens X, Nelson RP, Jr., Emmanuel P, et al. A randomized, double-blind study of triple nucleoside therapy of abacavir, lamivudine, and zidovudine versus lamivudine and zidovudine in previously treated human immunodeficiency virus type 1-infected children. The CNAA3006 Study Team. *Pediatrics.* 2001;107(1):E4.
16. van Rossum AM, Geelen SP, Hartwig NG, et al. Results of 2 years of treatment with protease-inhibitor--containing antiretroviral therapy in dutch children infected with human immunodeficiency virus type 1. *Clin Infect Dis.* 2002;34(7):1008-1016.
17. Connor EM, Sperling RS, Gelber R, et al. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. Pediatric AIDS Clinical Trials Group Protocol 076 Study Group. *N Engl J Med.* 1994;331(18):1173-1180.
18. Kovacs A, Cowles MK, Britto P, et al. Pharmacokinetics of didanosine and drug resistance mutations in infants exposed to zidovudine during gestation or postnatally and treated with didanosine or zidovudine in the first three months of life. *Pediatr Infect Dis J.* 2005;24(6):503-509.
19. World Health Organization (WHO). Preferred antiretroviral medicines for treating and preventing HIV infection in younger children: Report of the WHO paediatric antiretroviral working group. 2008; http://www.who.int/hiv/paediatric/Sum_WHO_ARV_Ped_ARV_dosing.pdf.
20. Flynn PM, Rodman J, Lindsey JC, et al. Intracellular pharmacokinetics of once versus twice daily zidovudine and lamivudine in adolescents. *Antimicrob Agents Chemother.* 2007;51(10):3516-3522.

NON-NUCLEOSIDE ANALOGUE REVERSE TRANSCRIPTASE INHIBITORS

Efavirenz (EFV, Sustiva)

For additional information see Drugs@FDA: **http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm**

Formulations

Capsules: 50 mg and 200 mg
Tablets: 600 mg
Combination tablets:
- *with emtricitabine (FTC) and tenofovir disoproxil fumarate (TDF)*:
  200 mg FTC + 300 mg TDF + 600 mg EFV (Atripla)

Dosing Recommendations

Neonate/Infant dose:
Not approved for use in neonates/infants.

Pediatric dose:
Children <3 years of age:
There are currently no data available on the appropriate dosage for children <3 years of age.

Children ≥3 years and ≥10 kg:
Administer EFV once daily:

Weight (kg)	EFV dose (mg)*
10–<15	200
15–<20	250
20–<25	300
25–<32.5	350
32.5–<40	400
≥40	600

***** The dose in mg could be dispensed in any combination of capsule strengths; dose represents the maximum recommended EFV dose for each weight band.

Adolescent (≥40 kg)/Adult dose:
600 mg once daily

Dosing Recommendations for Combination Formulations

Atripla
Atripla should not be used in pediatric patients <40 kg where the EFV dose would be excessive.

Adult dose:
One tablet once daily

Dosing Recommendations for Coadministration with Other Antiretroviral Drugs

Atazanavir (ATV), **fosamprenavir (FPV)**, **indinavir (IDV)**, **lopinavir/ritonavir (LPV/r)**, and **maraviroc (MVC)** used in combination with EFV may require dosage adjustment or addition of RTV. See appropriate drug section.

Selected Adverse Events

- Rash
- Central nervous system symptoms
- Increased transaminases
- False-positive with some cannabinoid and benzodiazepine tests
- Teratogenic
- Lipohypertrophy

Special Instructions

- Administer EFV on an empty stomach, preferably at bedtime. The relative bioavailability of EFV was increased by 50% (range 11%–126%) following a high fat meal. Because there is no information on the safety of EFV when given above the recommended dose, avoid administration with a high fat meal due to the potential for increased absorption.
- Administer Atripla on an empty stomach.
- Capsules may be opened and added to liquids or small amounts of food.
- Bedtime dosing is recommended, particularly during the first 2 to 4 weeks of therapy, to improve tolerability of central nervous system side effects.

Metabolism

- Metabolized by cytochrome P450, 2B6, and 3A4. CYP 3A4 inducer/inhibitor (more inducer than inhibitor).
- Dosing of EFV in patients with hepatic impairment: No recommendation is currently available; use with caution in patients with hepatic impairment.
- Adult dose of Atripla in patients with renal impairment: Because Atripla is a fixed-dose combination product, it should not be used in patients with creatinine clearance of <50 mL/minute or in patients on dialysis.

Drug Interactions (See also the ***Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents***.)***:***

- *Metabolism*: Mixed inducer/inhibitor of cytochrome P450 3A4 enzymes; concentrations of concomitant drugs can be increased or decreased depending on the specific enzyme pathway involved. There are multiple drug interactions.
- Before administration, the patient's medication profile should be carefully reviewed for potential drug interactions.

Major Toxicities:

- *More common:* Skin rash, increased transaminase levels. Central nervous system abnormalities (e.g., somnolence, insomnia, abnormal dreams, confusion, abnormal thinking, impaired concentration, amnesia, agitation, depersonalization, hallucinations, euphoria) primarily reported in adults.
- *Rare*: In cynomolgus monkeys, prenatal efavirenz exposure has been associated with central nervous system congenital abnormalities in infant monkeys. Based on these data and retrospective reports in humans of an unusual pattern of severe central nervous system defects in five infants after first-trimester exposure to efavirenz-containing regimens (three meningomyelocoeles and two Dandy-Walker malformations), efavirenz has been classified as FDA Pregnancy Class D (positive evidence of human fetal risk). Efavirenz use in the first trimester of pregnancy should be avoided. Women of childbearing potential should undergo pregnancy testing and be counseled about the risk of efavirenz to the fetus and need to avoid pregnancy before initiating and during efavirenz therapy.

Resistance: The International AIDS Society-USA (IAS-USA) maintains a list of updated resistance mutations (see **http://www.iasusa.org/resistance_mutations/index.html**) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see **http://hivdb.stanford.edu/pages/GRIP/EFV.html**).

Pediatric Experience: Efavirenz has been studied in HIV-infected children in combinations of efavirenz plus NRTIs or efavirenz plus NRTIs plus a PI (nelfinavir or lopinavir/ritonavir) *[1-17]*. An open label study (PACTG 382) of efavirenz combined with nelfinavir and 1 or 2 NRTIs was performed in 57 NNRTI- and PI-naïve pediatric patients, some as young as 3 years of age *[11]*. In an intent-to-treat analysis, 76% of children had plasma HIV RNA concentrations <400 copies/mL and 63% had HIV RNA concentrations <50 copies/mL at 48 weeks of therapy. The median times to achieve those concentrations were 4 and 20 weeks, respectively. Therefore, children with detectable HIV RNA (>50 copies/mL by the ultra-sensitive RNA assay) after 1 month of therapy continued to accrue some virologic benefit through 5 months of treatment with this regimen *[10]*. Long-term virologic suppression with once-daily efavirenz therapy in combination with emtricitabine and didanosine was reported in 37 treatment-naïve children, 3–18 years of age, participating in PACTG 1021 *[8]*. Eighty-five percent of subjects were able to achieve HIV-RNA <400 copies/mL and 72% maintained HIV-RNA suppression <50 copies/mL through 96 weeks of therapy.

A study of a liquid formulation of efavirenz in 19 HIV-infected children 3–9 years of age has been reported *[12]*. A 20% higher dose of efavirenz liquid formulation resulted in pharmacokinetic AUC values that were similar to those observed with efavirenz capsules. Limited pharmacokinetic data in children <3 years of age or who weigh <13 kg have shown that it is difficult to achieve target trough concentrations in this age group even with very high (>30 mg/kg) doses of this investigational liquid formulation *[18]*. Thus, efavirenz is not recommended for use in children <3 years of age at this time and no liquid formulation is commercially available. Additional studies are required to determine the appropriate dose of efavirenz in infants and young children.

Efavirenz metabolism is controlled by enzymes that are polymorphically expressed and result in large between patient variability in efavirenz exposure. CYP 2B6 is the primary enyzme for efavirenz metabolism and pediatric patients with the 516 T/T or G/T genotype have reduced metabolism and higher efavirenz levels compared with those with the G/G genotype *[19-20]*. Additional variant CYP 2B6 alleles and variant CYP 2A6 alleles have been found to influence efavirenz concentrations in adults *[21-22]*.

Long-term HIV RNA suppression has been associated with maintenance of trough efavirenz concentrations >1 mcg/mL in adults *[23]*. Early HIV RNA suppression in children has also been seen with higher drug concentrations. Higher efavirenz troughs of 1.9 mcg/mL were seen in subjects with HIV RNA ≤400 copies/mL versus efavirenz troughs of 1.3 mcg/mL in subjects with detectible virus (>400 copies/mL) *[3]*. In a West African pediatric study, ANRS 12103, early reduction in viral load (12 weeks) was greater in children with efavirenz C_{min} >1.1 mcg/mL or AUC >51 mcg*h/mL *[24]*. Even with the use of FDA-approved pediatric dosing, efavirenz concentrations can be suboptimal *[19, 24-25]*, so that some experts recommend therapeutic drug monitoring when using efavirenz and possibly using higher doses in young children, especially in select clinical situations such as virologic rebound or lack of response in an adherent patient. In 1 study that adjusted the efavirenz

dose in response to measurement of the AUC, the administered efavirenz dose median was 13 mg/kg (367 mg/m^2) and the range was from 3 to 23 mg/kg (69 to 559 mg/m^2) *[3]*. A pharmacokinetic study in 20 children age 10 to 16 years treated with the combination of lopinavir/ritonavir 300 mg/m^2 twice daily plus efavirenz 350 mg/m^2 once daily showed adequacy of the lopinavir trough values but suggested that the efavirenz trough was lower than pharmacokinetic targets, and the authors recommend that higher doses of efavirenz might be needed when these drugs are used together *[16]*. Therapeutic drug monitoring might be considered when using efavirenz in combinations with potentially complex drug interactions.

The toxicity profile for efavirenz differs for adults and children. In adults, a central nervous system (CNS) complex of confusion, agitation, sleep disturbance, nightmares, hallucinations, or other symptoms has been reported in >50% of patients *[26]*. These symptoms usually occur early in treatment and rarely require drug discontinuation but sometimes occur or persist for months. Bedtime efavirenz dosing appears to decrease the occurrence and severity of these neuropsychiatric side effects. In several studies, the incidence of such side effects was correlated with efavirenz plasma concentrations and occurred more frequently in patients with higher concentrations *[23, 27-30]*. In patients with pre-existing psychiatric conditions, efavirenz should be used cautiously for initial therapy. Adverse CNS effects occurred in 14% of children receiving efavirenz in clinical studies *[11]* and in 30% of children with efavirenz concentrations >4 mcg/mL *[20]*. The principal side effect of efavirenz in children is rash, which was seen in up to 40% of children, compared with 27% of adults. The rash is usually maculopapular, pruritic, and mild to moderate in severity and rarely requires drug discontinuation. Onset is typically in the first 2 weeks of treatment *[11]*. Although severe rash and Stevens-Johnson syndrome have been reported, this is rare. Other reported adverse events in adults and children include diarrhea, nausea, and increased transaminases including liver failure *[31]*. There are insufficient data to recommend substituting nevirapine for efavirenz following either rash or hepatotoxicity *[32]*.

Efavirenz should be used with caution in adolescent women of childbearing age because of the risk of teratogenicity *[33]*. See ***Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States*** *[34]*. Many clinicians choose alternative drugs for use in sexually active adolescent women in whom contraception use is sometimes erratic and the risk of unintended pregnancy is high.

References

1. Brundage RC, Yong FH, Fenton T, et al. Intrapatient variability of efavirenz concentrations as a predictor of virologic response to antiretroviral therapy. *Antimicrob Agents Chemother.* 2004;48(3):979-984.
2. Chaix ML, Rouet F, Kouakoussui KA, et al. Genotypic human immunodeficiency virus type 1 drug resistance in highly active antiretroviral therapy-treated children in Abidjan, Cote d'Ivoire. *Pediatr Infect Dis J.* 2005;24(12):1072-1076.
3. Fletcher CV, Brundage RC, Fenton T, et al. Pharmacokinetics and pharmacodynamics of efavirenz and nelfinavir in HIV-infected children participating in an area-under-the-curve controlled trial. *Clin Pharmacol Ther.* 2008;83(2):300-306.
4. Fraaij PL, Neubert J, Bergshoeff AS, et al. Safety and efficacy of a NRTI-sparing HAART regimen of efavirenz and lopinavir/ritonavir in HIV-1-infected children. *Antivir Ther.* 2004;9(2):297-299.
5. Funk MB, Notheis G, Schuster T, et al. Effect of first line therapy including efavirenz and two nucleoside reverse transcriptase inhibitors in HIV-infected children. *Eur J Med Res.* 2005;10(12):503-508.
6. King JR, Yogev R, Aldrovandi G, et al. Pharmacokinetics of antiretrovirals administered to HIV-infected children via gastrostomy tube. *HIV Clin Trials.* 2004;5(5):288-293.
7. McComsey G, Bhumbra N, Ma JF, et al. Impact of protease inhibitor substitution with efavirenz in HIV-infected children: results of the First Pediatric Switch Study. *Pediatrics.* 2003;111(3):e275-281.
8. McKinney RE, Jr., Rodman J, Hu C, et al. Long-term safety and efficacy of a once-daily regimen of emtricitabine, didanosine, and efavirenz in HIV-infected, therapy-naive children and adolescents: Pediatric AIDS Clinical Trials Group Protocol P1021. *Pediatrics.* 2007;120(2):e416-423.
9. Scherpbier HJ, Bekker V, Pajkrt D, et al. Once-daily highly active antiretroviral therapy for HIV-infected children: safety and efficacy of an efavirenz-containing regimen. *Pediatrics.* 2007;119(3):e705-715.
10. Spector SA, Hsia K, Yong FH, et al. Patterns of plasma human immunodeficiency virus type 1 RNA response to highly active antiretroviral therapy in infected children. *J Infect Dis.* 2000;182(6):1769-1773.
11. Starr SE, Fletcher CV, Spector SA, et al. Combination therapy with efavirenz, nelfinavir, and nucleoside reverse-transcriptase inhibitors in children infected with human immunodeficiency virus type 1. Pediatric AIDS Clinical Trials Group 382 Team. *N Engl J Med.* 1999;341(25):1874-1881.
12. Starr SE, Fletcher CV, Spector SA, et al. Efavirenz liquid formulation in human immunodeficiency virus-infected children. *Pediatr Infect Dis J.* 2002;21(7):659-663.
13. Teglas JP, Quartier P, Treluyer JM, et al. Tolerance of efavirenz in children. *AIDS.* 2001;15(2):241-243.

14. Vigano A, Aldrovandi GM, Giacomet V, et al. Improvement in dyslipidaemia after switching stavudine to tenofovir and replacing protease inhibitors with efavirenz in HIV-infected children. *Antivir Ther.* 2005;10(8):917-924.
15. Wintergerst U, Engelhorn C, Kurowski M, et al. Pharmacokinetic interaction of amprenavir in combination with efavirenz or delavirdine in HIV-infected children. *AIDS.* 2000;14(12):1866-1868.
16. King JR, Acosta EP, Yogev R, et al. Steady-state pharmacokinetics of lopinavir/ritonavir in combination with efavirenz in human immunodeficiency virus-infected pediatric patients. *Pediatr Infect Dis J.* 2009;28(2):159-161.
17. Schneider E, Whitmore S, Glynn KM, et al. Revised surveillance case definitions for HIV infection among adults, adolescents, and children aged <18 months and for HIV infection and AIDS among children aged 18 months to <13 years--United States, 2008. *MMWR Recomm Rep.* 2008;57(RR-10):1-12.
18. Capparelli E, Rochon-Duck M, Robbins B, et al. Age-related pharmacokinetics of efavirenz solution. Paper presented at: 16th Conference on Retroviruses and Opportunistic Infections (CROI); February 8-11, 2009; Montréal, Canada. Abstract 884.
19. Saitoh A, Fletcher CV, Brundage R, et al. Efavirenz pharmacokinetics in HIV-1-infected children are associated with CYP2B6-G516T polymorphism. *J Acquir Immune Defic Syndr.* 2007;45(3):280-285.
20. Puthanakit T, Tanpaiboon P, Aurpibul L, et al. Plasma efavirenz concentrations and the association with CYP2B6-516G >T polymorphism in HIV-infected Thai children. *Antivir Ther.* 2009;14(3):315-320.
21. di Iulio J, Fayet A, Arab-Alameddine M, et al. In vivo analysis of efavirenz metabolism in individuals with impaired CYP2A6 function. *Pharmacogenet Genomics.* 2009;19(4):300-309.
22. Arab-Alameddine M, Di Iulio J, Buclin T, et al. Pharmacogenetics-based population pharmacokinetic analysis of efavirenz in HIV-1-infected individuals. *Clin Pharmacol Ther.* 2009;85(5):485-494.
23. Marzolini C, Telenti A, Decosterd LA, et al. Efavirenz plasma levels can predict treatment failure and central nervous system side effects in HIV-1-infected patients. *AIDS.* 2001;15(1):71-75.
24. Hirt D, Urien S, Olivier M, et al. Is the recommended dose of efavirenz optimal in young West African human immunodeficiency virus-infected children? *Antimicrob Agents Chemother.* 2009;53(10):4407-4413.
25. Ren Y, Nuttall JJ, Egbers C, et al. High prevalence of subtherapeutic plasma concentrations of efavirenz in children. *J Acquir Immune Defic Syndr.* 2007;45(2):133-136.
26. Staszewski S, Morales-Ramirez J, Tashima KT, et al. Efavirenz plus zidovudine and lamivudine, efavirenz plus indinavir, and indinavir plus zidovudine and lamivudine in the treatment of HIV-1 infection in adults. Study 006 Team. *N Engl J Med.* 1999;341(25):1865-1873.
27. Gutierrez F, Navarro A, Padilla S, et al. Prediction of neuropsychiatric adverse events associated with long-term efavirenz therapy, using plasma drug level monitoring. *Clin Infect Dis.* 2005;41(11):1648-1653.
28. Zugar A. Studies disagree on frequency of late cns side effects from efavirenz. *AIDS Clin Care.* 2006;4(1).
29. Treisman GJ, Kaplin AI. Neurologic and psychiatric complications of antiretroviral agents. *AIDS.* 2002;16(9):1201-1215.
30. Wintergerst U, Hoffmann F, Jansson A, et al. Antiviral efficacy, tolerability and pharmacokinetics of efavirenz in an unselected cohort of HIV-infected children. *J Antimicrob Chemother.* 2008;61(6):1336-1339.
31. Turkova A, Ball C, Gilmour-White S, et al. A paediatric case of acute liver failure associated with efavirenz-based highly active antiretroviral therapy and effective use of raltegravir in combination antiretroviral treatment after liver transplantation. *J Antimicrob Chemother.* 2009;63(3):623-625.
32. Mehta U, Maartens G. Is it safe to switch between efavirenz and nevirapine in the event of toxicity? *Lancet Infect Dis.* 2007;7(11):733-738.
33. Saitoh A, Hull AD, Franklin P, et al. Myelomeningocele in an infant with intrauterine exposure to efavirenz. *J Perinatol.* 2005;25(8):555-556.
34. Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission. Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States. May 24, 2010:1-117. http://aidsinfo.nih.gov/contentfiles/PerinatalGL.pdf.

Etravirine (ETR, Intelence, TMC 125)

For additional information see Drugs@FDA: **http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm**

Formulations

Tablets: 100 mg

Dosing Recommendations

Neonate/Infant dose:
Not approved for use in neonates/infants.

Pediatric dose:
Not approved for use in children.

Adult dose (ARV-experienced patients):
200 mg (two 100 mg tablets) twice daily following a meal

Selected Adverse Events

- Nausea
- Rash including Stevens-Johnson syndrome
- Hypersensitivity reactions have been reported, characterized by rash, constitutional findings, and sometimes organ dysfunction, including hepatic failure

Special Instructions

- Always administer ETR following a meal; area under the curve (AUC) is decreased by about 50% when taken on an empty stomach.
- Tablets are sensitive to moisture; store at room temperature (59–86°F) in original container with desiccant.
- Patients unable to swallow tablets may disperse the tablets in a small amount of water. Once dispersed, instruct patients to stir the dispersion well and consume it immediately. The glass should be rinsed with water several times and each of the rinses completely swallowed to ensure that the entire dose is consumed.
- Dosing of ETR in patients with hepatic impairment: No dosage adjustment is necessary for patients with mild-to-moderate hepatic insufficiency. No dosing information is available for patients with severe hepatic impairment.
- Dosing of ETR in patients with renal impairment: No dose adjustments are required in patients with renal impairment.

Metabolism

- Metabolism by cytochrome P450: inducer of CYP3A4 and inhibitor of CYP2C9, CYP2C19. Substrate for CYP3A4, 2C9, and 2C19. Also inhibitor of P-glycoprotein.
- Multiple drug interactions (see below).

Drug Interactions (See also the ***Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents***.)***:***

- *Metabolism*: Etravirine is an inducer of CYP3A4; an inhibitor of CYP2C9 and CPY2C19; and a substrate for 3A4, 2C9, and 2C19. Etravirine is also an inhibitor of P-glycoprotein.
- There are multiple drug interactions.
- Before administration, the patient's medication profile should be carefully reviewed for potential drug interactions.
- Etravirine should not be coadministered with the following antiretrovirals: tipranavir/ritonavir, fosamprenavir/ritonavir, amprenavir/ritonavir, ritonavir, unboosted PIs, nevirapine, or efavirenz.

Major Toxicities:

- *More common:* Nausea, diarrhea, mild rash. Rash occurs most commonly in the first 6 weeks of therapy. Rash generally resolves after 1 to 2 weeks on continued therapy. A history of NNRTI-related rash does not appear to increase the risk of developing rash with etravirine. However, patients who have a history of severe rash with prior NNRTI use should not receive etravirine.
- *Less common:* Severe rash including Stevens-Johnson syndrome, hypersensitivity reactions (including constitutional findings and sometimes organ dysfunction including hepatic failure), and erythema multiforme have been reported. Discontinue etravirine immediately if signs or symptoms of severe skin reactions or hypersensitivity reactions develop (including severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial edema, hepatitis, eosinophilia). Clinical status including liver transaminases should be monitored and

appropriate therapy initiated. Delay in stopping etravirine treatment after the onset of severe rash may result in a life-threatening reaction. It is recommended that patients who have a prior history of severe rash with nevirapine or efavirenz not receive etravirine.

Resistance: The International AIDS Society-USA (IAS-USA) maintains a list of updated resistance mutations (see **http://www.iasusa.org/resistance_mutations/index.html**) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see **http://hivdb.stanford.edu/pages/GRIP/ETR.html**).

Pediatric Experience: The pharmacokinetics, safety, and efficacy of etravirine in pediatric patients have not been established. There is limited pediatric experience and pediatric trials are under way. Recently reported are the results of a Phase I dose finding study involving 21 children with virologic suppression on a stable lopinavir/ritonavir-containing regimen *[1]*. Etravirine therapy was added for 1 week and pharmacokinetic sampling and analysis were performed. The findings from this trial were used to determine the dose in the Phase II trial in pediatric patients that is currently under way. At this time data are insufficient to recommend a pediatric dose and further studies are warranted to determine the pharmacokinetics, safety, and efficacy of etravirine in children.

Recently reported was an analysis of genotypic and phenotypic HIV resistance profiles in 35 children from a Ugandan clinic with clinical failure of a first-line regimen containing an NNRTI other than etravirine *[2]*. Reduced etravirine susceptibility (fold-change >2.9) was found based on phenotypic analysis in 35% of samples.

References

1. Konigs C, Feiterna-Sperling C, Exposito S, et al. Pharmacokinetics and dose selection of etravirine in HIV-infected children between 6 and 17 years, inclusive. Paper presented at: 16th Conference on Retroviruses and Opportunistic Infections (CROI); February 8-11, 2009; Montreal, Canada. Abstract S-167.
2. Kekitiinwa A, Friedman D, Coakley E, et al. Profiling etravirine resistance in Ugandan children with extended failure of a NNRTI-inclusive regimen as first-line ART. Paper presented at: 16th Conference on Retroviruses and Opportunistic Infections (CROI); February 8-11, 2009; Montreal, Canada. Abstract 891.

Nevirapine (NVP, Viramune)

For more information see Drugs@FDA: **http://www.accessdata.fda.gov/scripts/cder/drugsatfda/**

Formulations

Tablets: 200 mg
Suspension: 10 mg/mL

Dosing Recommendations

Neonate/Infant dose (<14 days):
When used for prophylaxis of mother-to-child transmission of HIV see **Perinatal Guidelines**.[†]
Treatment dose not defined for infants ≤14 days of age.

Pediatric dose (≥15 days):
(See note below about initiation of therapy.)

<8 years:
200 mg/m^2 of body surface area/dose (maximum dose 200 mg) twice daily

≥8 years: 120–150 mg/m^2 of body surface area/dose (maximum dose 200 mg) twice daily

When adjusting the dose for a growing child, the mg dose need not be decreased as the child reaches 8 years; rather, the mg dose is left static to achieve the appropriate mg-per-m^2 dosage as the child grows, as long as there are no untoward effects.

NVP is initiated at a lower dose and increased in a stepwise fashion to allow induction of cytochrome P450 metabolizing enzymes, which results in increased clearance of the drug. The occurrence of rash is diminished by this stepwise increase in dose. Initiate therapy with the age-appropriate dose once daily for the first 14 days of therapy. If there is no rash or untoward effect, at 14 days of therapy increase to the age-appropriate dose administered twice daily. The total daily dose should not exceed 400 mg.

Adolescent/Adult dose:
200 mg twice daily

Initiate therapy with 200 mg given once daily for the first 14 days. Increase to 200 mg administered twice daily if there is no rash or other untoward effects.

Dosing Recommendations for Coadministration with Other Antiretroviral Drugs

NVP in combination with lopinavir/ritonavir (LPV/r)
A higher dose of LPV/r may be needed. See **LPV/r** section.

Selected Adverse Events

- Rash, including Stevens-Johnson syndrome
- Symptomatic hepatitis, including fatal hepatic necrosis
- Severe systemic hypersensitivity syndrome with potential for multisystem organ involvement and shock

Special Instructions

- Can be given without regard to food.
- May be administered concurrently with didanosine (ddI).
- NVP-associated skin rash usually occurs within the first 6 weeks of therapy. If rash occurs during the initial 14-day lead-in period, do not increase dose until rash resolves (see *Major Toxicities*).
- If NVP dosing is interrupted for >7 days, NVP dosing should be restarted with once-daily dosing for 14 days, followed by escalation to the full, twice-daily regimen.
- Most cases of NVP-associated hepatic toxicity occur during the first 12 weeks of therapy; frequent clinical and laboratory monitoring, including liver function tests, is important during this time period. However, about one-third of cases occurred after 12 weeks of treatment, so continued periodic monitoring of liver function tests is needed. In some cases, patients presented with nonspecific prodromal signs or symptoms of hepatitis and rapidly progressed to hepatic failure. Patients with symptoms or signs of hepatitis should have liver function tests performed. NVP should be permanently discontinued and not restarted in patients who develop clinical hepatitis or hypersensitivity reactions.
- Shake suspension well and store at room temperature.

Metabolism

- Metabolized by cytochrome P450 (3A inducer); 80% excreted in urine (glucuronidated metabolites).
- Dosing of NVP in patients with renal failure receiving hemodialysis: An additional dose of NVP should be given following dialysis.
- Dosing of NVP in patients with hepatic impairment: NVP should not be administered to patients with moderate or severe hepatic impairment.

[†] Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States

Drug Interactions (See also the ***Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents***.)***:***

- *Metabolism*: Induces hepatic cytochrome P450 including 3A (CYP3A) and 2B6; autoinduction of metabolism occurs in 2 to 4 weeks, with a 1.5–2-fold increase in clearance. There is potential for multiple drug interactions.
- Before administration, the patient's medication profile should be carefully reviewed for potential drug interactions. Nevirapine should not be coadministered to patients receiving atazanavir (with or without ritonavir).

Major Toxicities:

(*Note:* These are seen with continuous dosing regimens, not single-dose nevirapine prophylaxis.)

- *More common:* Skin rash (some severe and requiring hospitalization; some life-threatening, including Stevens-Johnson syndrome and toxic epidermal necrolysis), fever, nausea, headache, and abnormal hepatic transaminases. Nevirapine should be permanently discontinued and not restarted in children or adults who develop severe rash, rash with constitutional symptoms, or rash with elevated hepatic transaminases. Nevirapine-associated skin rash usually occurs within the first 6 weeks of therapy. If rash occurs during the initial 14-day lead-in period, do not increase dose until rash resolves. However, the risk of developing nevirapine resistance with extended lead-in dosing is unknown and is a concern that must be weighed against the patient's overall ability to tolerate the regimen and the current antiviral response. Nevirapine should be discontinued immediately and not restarted in patients who develop severe rash, a rash accompanied by constitutional symptoms (i.e., fever, oral lesions, conjunctivitis, or blistering), or rash accompanied by elevated hepatic transaminases.
- *Less common (more severe):* Severe, life-threatening, and in rare cases fatal hepatotoxicity, including fulminant and cholestatic hepatitis, hepatic necrosis, and hepatic failure (these are less common in children than adults). The majority of cases occur in the first 12 weeks of therapy; may be associated with rash or other signs or symptoms of hypersensitivity reaction. Risk factors for nevirapine-related hepatic toxicity in adults include baseline elevation in serum transaminase levels, hepatitis B or C infection, female gender, and higher CD4 count at time of therapy initiation (CD4 count >250 cells/mm^3 in adult females and >400 cells/mm^3 in adult males). Hypersensitivity reactions have been reported, including but not limited to severe rash or rash accompanied by fever, blisters, oral lesions, conjunctivitis, facial edema, muscle or joint aches, general malaise, and significant hepatic abnormalities. Nevirapine should be permanently discontinued and not restarted in children or adults who develop symptomatic hepatitis, severe transaminase elevations, or hypersensitivity reactions.

Resistance: The International AIDS Society-USA (IAS-USA) maintains a list of updated resistance mutations (see **http://www.iasusa.org/resistance_mutations/index.html**) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see **http://hivdb.stanford.edu/pages/GRIP/NVP.html**).

Pediatric Experience: Nevirapine has been studied in HIV-infected children in combination with NRTIs or with NRTIs and a PI *[1-9]*. Combination therapy with nevirapine, zidovudine, and didanosine in young infected infants was associated with sustained viral suppression in a small number of children *[6]*. A description of 15 infants initiating nevirapine-based antiretroviral treatment younger than 66 days of age in Belgium reported that complete viral suppression (<400 copies/mL) was achieved in 11 (73%) infants *[10]*. A larger study, PACTG 356, treated infants and young children with 3 different nevirapine-containing regimens: zidovudine/lamivudine/nevirapine, zidovudine/lamivudine/abacavir/nevirapine, or zidovudine/lamivudine/nevirapine/nelfinavir *[4]*. Twenty-four percent of 17 infants treated with the 3-drug regimen had viral suppression to <400 copies/mL HIV RNA, compared with 10 of 17 (41%) and 15 of 18 (83%), respectively, of infants treated with 4 drugs. Children who started therapy younger than 3 months of age had a better virologic outcome compared with children who started at an older age (3.5–24 months). PACTG 377 randomized 181 PI- and NNRTI-naïve mild to moderately immune suppressed children to 1 of 4 combination treatment regimens. All of the regimens contained stavudine and a PI (either ritonavir or nelfinavir); 3 of the 4 regimens also included nevirapine as part of combination therapy. Children in the nevirapine-containing arms experienced moderate or worse skin rash more frequently than did children not receiving nevirapine. Those children receiving a 4-drug regimen containing both nevirapine and a PI had a significantly greater increase in CD4 cell count from baseline to Week 24 than children receiving other regimens *[9]*. A study of 212 children in Cambodia treated with NNRTI-based combination therapy (82% nevirapine and 18% efavirenz) reported 156 of 212 children (73.6%) having undetectable viral load (<400 copies/mL) after 12 months of treatment. Only 2 children switched regimens due to intolerability of nevirapine *[1]*. In PACTG 403, 41 children with prior NRTI experience were randomized to receive stavudine/nelfinavir/nevirapine or didanosine/nelfinavir/ritonavir. After 48 weeks of therapy, only 28% (5/18) of those still on the nevirapine-inclusive regimen had viral suppression to <400 copies/mL compared with 65% (11/17) of children on the ritonavir-based treatment. The changes in CD4 percentage and the rates of toxicities were similar for both regimens. Three children developed nevirapine-related rashes leading to discontinuation of study treatment *[2]*.

In infants and children previously exposed to single-dose nevirapine for prevention of mother-to-child transmission (PMTCT), nevirapine-based antiretroviral therapy is less likely than lopinavir/ritonavir-based ART to control virus load. In a small, nonrandomized study in Botswana, 6-month virologic and immunologic responses were compared between 15 SD nevirapine-exposed and 15 -unexposed infants who initiated nevirapine-based antiretroviral treatment at a mean age of 8 months (range 2–33 months) in follow-up from a PMTCT study *[11]*. Only 34% of those with a history of exposure had an undetectable viral load (<400 copies/mL) compared with 91% of the unexposed cohort. CD4 percentage was also significantly lower in the exposed group compared with the unexposed group, 23% versus 31%, respectively. In contrast, in a study in Uganda, in which children with SD nevirapine exposure started nevirapine-based treatment at an older age of 1.6 years, there was no difference in response to therapy between children with and without prior SD nevirapine exposure *[12]*. In a large randomized clinical trial, P1060, 153 children (mean age 0.7 years) previously exposed to nevirapine for perinatal prophylaxis were treated with zidovudine plus lamivudine plus the randomized addition of nevirapine versus lopinavir/ritonavir. At 24 weeks post-randomization, 24% of children in the zidovudine/lamivudine/nevirapine arm reached a virologic endpoint (virologic failure [VF] defined as <1 log decrease in HIV RNA in Weeks 12–24 or HIV RNA >400 copies/mL at Week 24) compared with 7% in the zidovudine/lamivudine/lopinavir/ritonavir arm, p = 0.0009. When all primary endpoints were considered, including viral failure, death, and treatment discontinuation, the PI arm remained superior because 40% of children in the nevirapine arm met a primary endpoint versus 22% for the lopinavir/ritonavir arm, p = 0.027. Based on these findings the Data and Safety Monitoring Board (DSMB) recommended discontinuing enrollment in this cohort. Enrollment into the comparison study of nevirapine versus lopinavir/ritonavir in children 6–36 months of age not previously exposed to nevirapine is ongoing *[13]*.

Body surface area has traditionally been used to guide nevirapine dosing for infants and young children. It is important to avoid underdosing of nevirapine because a single point mutation may confer NNRTI resistance to both nevirapine and efavirenz. Younger children (≤8 years of age) have higher apparent oral clearance than older children and require a higher dosage to achieve equivalent drug exposure compared with children >8 years of age. *[6-7]*. Because of this, it is recommended that dosing for children younger than 8 years of age be 200 mg/m^2 of body surface area per dose (maximum dose 200 mg) administered twice daily. For children 8 years or older, the recommended dose is 120 mg/m^2 of body surface area per dose (maximum dose 200 mg) administered twice daily. When adjusting the dose in a growing child, the milligram dose need not be decreased (from 200 mg/m^2 to 120 mg/m^2) as the child reaches 8 years; rather, the milligram dose is left static as long as there are no untoward effects, and the dose is allowed to achieve the appropriate mg/m^2 dosage as the child grows. Some practitioners dose nevirapine at 150 mg/m^2 of body surface area every 12 hours (maximum of 200 mg per dose) regardless of age, as recommended in the FDA-approved product label.

References

1. Janssens B, Raleigh B, Soeung S, et al. Effectiveness of highly active antiretroviral therapy in HIV-positive children: evaluation at 12 months in a routine program in Cambodia. *Pediatrics.* 2007;120(5):e1134-1140.
2. King JR, Nachman S, Yogev R, et al. Efficacy, tolerability and pharmacokinetics of two nelfinavir-based regimens in human immunodeficiency virus-infected children and adolescents: pediatric AIDS clinical trials group protocol 403. *Pediatr Infect Dis J.* 2005;24(10):880-885.
3. Krogstad P, Lee S, Johnson G, et al; Pediatric AIDS Clinical Trials Group 377 Study Team. Nucleoside-analogue reverse-transcriptase inhibitors plus nevirapine, nelfinavir, or ritonavir for pretreated children infected with human immunodeficiency virus type 1. *Clin Infect Dis.* 2002;34(7):991-1001.
4. Luzuriaga K, McManus M, Mofenson L, et al. A trial of three antiretroviral regimens in HIV-1-infected children. *N Engl J Med.* 2004;350(24):2471-2480.
5. Luzuriaga K, Bryson Y, McSherry G, et al. Pharmacokinetics, safety, and activity of nevirapine in human immunodeficiency virus type 1-infected children. *J Infect Dis.* 1996;174(4):713-721.
6. Luzuriaga K, Bryson Y, Krogstad P, et al. Combination treatment with zidovudine, didanosine, and nevirapine in infants with human immunodeficiency virus type 1 infection. *N Engl J Med.* 1997;336(19):1343-1349.
7. Mirochnick M, Clarke DF, Dorenbaum A. Nevirapine: pharmacokinetic considerations in children and pregnant women. *Clin Pharmacokinet.* 2000;39(4):281-293.
8. Verweel G, Sharland M, Lyall H, et al. Nevirapine use in HIV-1-infected children. *AIDS.* 2003;17(11):1639-1647.
9. Wiznia A, Stanley K, Krogstad P, et al. Combination nucleoside analog reverse transcriptase inhibitor(s) plus nevirapine, nelfinavir, or ritonavir in stable antiretroviral therapy-experienced HIV-infected children: week 24 results of a randomized controlled trial--PACTG 377. Pediatric AIDS Clinical Trials Group 377 Study Team. *AIDS Res Hum Retroviruses.* 2000;16(12):1113-1121.

10. Van der Linden D, Hainaut M, Goetghebuer T, et al. Effectiveness of early initiation of protease inhibitor-sparing antiretroviral regimen in human immunodeficiency virus-1 vertically infected infants. *Pediatr Infect Dis J.* 2007;26(4):359-361.
11. Lockman S, Shapiro RL, Smeaton LM, et al. Response to antiretroviral therapy after a single, peripartum dose of nevirapine. *N Engl J Med.* 2007;356(2):135-147.
12. Barlow-Mosha L, Ajunua P, Mubiru M, et al. Early effectiveness of a NVP-based HAART regimen among HIV-infected children with and without prior single-dose NVP exposure. Paper presented at: 15th Conference on Retroviruses and Opportunistic Infections (CROI); February 3-6, 2008; Boston, MA. Abstract 583.
13. Palumbo P, Violari A, Lindsey J, et al. Nevirapine (NVP) vs lopinavir-ritonavir (LPV/r)-based antiretroviral therapy (ART) in single dose nevirapine (sdNVP)-exposed HIV-infected infants: preliminary results from the IMPAACT P1060 trial. Paper presented at: 5th International AIDS Society (IAS) Conference on HIV Pathogenesis, Treatment and Prevention; July 19-22, 2009; Capetown, South Africa. Abstract LBPEB12.

PROTEASE INHIBITORS

Atazanavir (ATV, Reyataz)

For additional information see Drugs@FDA: **http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm**

Formulations

Capsules: 100 mg, 150 mg, 200 mg, and 300 mg

Dosing Recommendations

Neonate/Infant dose:
Not approved for use in neonates/infants. ATV should not be administered to neonates due to the risks associated with hyperbilirubinemia (kernicterus).

Pediatric dose:
There are insufficient data to recommend dosing in all children younger than 6 years of age or for treatment-experienced children weighing less than 25 kg.

For children 6–18 years of age:

Weight (kg)	Once-Daily Dose*
Treatment-Naïve ** Children Only	
15 to <25 kg	ATV 150 mg + RTV 80 mg, both once daily with food
Both Treatment-Naïve and Treatment-Experienced Children	
25 to <32 kg	ATV 200 mg + RTV 100 mg, both once daily with food
32 to <39 kg	ATV 250 mg + RTV 100 mg, both once daily with food
≥39 kg	ATV 300 mg + RTV 100 mg, both once daily with food

*Higher doses than those currently recommended may be required for some patients. See discussion under pediatric experience.
**There are insufficient data to recommend this dose in treatment-experienced children weighing less than 25 kg.

For treatment-naive pediatric patients who do not tolerate ritonavir (RTV): **Atazanavir boosted with RTV is preferred for children and adolescents.** Current FDA-approved prescribing information does not recommend unboosted ATV in children younger than 13 years of age. If unboosted ATV is used in adolescents, higher doses than those used in adults may be required to achieve target drug levels (see pediatric experience section).

Adolescent (≥16–21 years)/Adult dose:
Antiretroviral-naïve patients:
ATV 300 mg + RTV 100 mg **or** ATV 400 mg once daily with food

Antiretroviral-experienced patients:
ATV 300 mg + RTV 100 mg, both once daily with food

Selected Adverse Events

- Indirect hyperbilirubinemia
- Prolonged PR interval, first degree symptomatic AV block in some patients
- Hyperglycemia
- Fat maldistribution
- Possible increased bleeding episodes in patients with hemophilia
- Nephrolithiasis

Special Instructions

- Administer ATV with food to enhance absorption.
- Unboosted ATV does not appear to increase cholesterol or triglyceride levels. However, ATV boosted with RTV may be associated with lipid abnormalities.
- Because ATV can prolong the electrocardiogram PR interval, use with caution in patients with pre-existing cardiac conduction system disease or with other drugs known to prolong the PR interval (e.g., calcium channel blockers, beta-blockers, digoxin, verapamil).
- ATV absorption is dependent on low gastric pH and when administered with medications that alter gastric pH, special dosing information is indicated. When administered with buffered didanosine (ddI) formulations or antacids, ATV should be taken at least 2 hours before or 1 hour after antacid or ddI administration.
- Individuals with HBV or HCV infections and individuals with marked elevations in transaminases prior to treatment may be at increased risk of further elevations in transaminases or hepatic decompensation.

Metabolism

- ATV is a substrate and inhibitor of CYP3A4 and an inhibitor of CYP1A2, CYP2C9, and UGT1A1.
- Dosing of ATV in patients with hepatic impairment: ATV should be used with caution in patients with mild-to-moderate hepatic impairment; consult manufacturer's prescribing information for adjustment of dosage in patients with moderate impairment. ATV should not be used in patients with severe hepatic impairment.
- Dosing of ATV in patients with renal impairment: No dose adjustment is required for patients with renal impairment. However, ATV should not be given to treatment-experienced patients with end-stage renal disease on hemodialysis.

Dosing Recommendations for Coadministration with Other Antiretroviral Drugs	
ATV in combination with efavirenz (EFV) in therapy-naïve patients only **Adult dose:** ATV 400 mg + RTV 100 mg + EFV 600 mg, all once daily but at separate times Although ATV/r should be taken with food, EFV should be taken on an empty stomach, preferably at bedtime. EFV should not be used with ATV (with or without RTV) in treatment-experienced patients because EFV decreases ATV exposure. ***ATV in combination with tenofovir (TDF)*** **Adult dose:** ATV 300 mg + RTV 100 mg + TDF 300 mg, all once daily with food Only RTV-boosted ATV should be used in combination with TDF because TDF decreases ATV exposure.	

Drug Interactions (See also the ***Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents****.)*:

- *Metabolism*: Atazanavir is both a substrate and an inhibitor of the CYP3A4 enzyme system and has significant interactions with drugs highly dependent on CYP3A4 for metabolism. Atazanavir also competitively inhibits CYP1A2 and CYP2C9. There is potential for multiple drug interactions. Atazanavir inhibits the glucuronidation enzyme uridine diphosphate glucoronosyltransferase (UGT1A1). Atazanavir is a weak inhibitor of CYP2C8.
- Before administration, the patient's medication profile should be carefully reviewed for potential drug interactions.
- *NRTIs*: Tenofovir decreases atazanavir plasma concentrations. Only ritonavir-boosted atazanavir should be used in combination with tenofovir.
- *NNRTIs*: Efavirenz, etravirine, and nevirapine decrease atazanavir plasma concentrations significantly. Nevirapine and etravirine should not be coadministered to patients receiving atazanavir (with or without ritonavir). Efavirenz should not be coadministered with atazanavir in treatment-experienced patients but may be used in treatment-naïve adults with atazanavir 400 mg plus ritonavir boosting.
- *Absorption*: Atazanavir absorption is dependent on low gastric pH and when administered with medications that alter gastric pH, special dosing information is indicated. No information is available in children when dosing atazanavir with medications that alter gastric pH.

Guidelines for dosing atazanavir with antacids, H2 receptor antagonists, and proton pump inhibitors in adults are as follows:

- *Antacids*: Antacids and buffered medications (including buffered didanosine formulations) decrease atazanavir concentrations if administered at the same time; atazanavir should be administered 2 hours before or 1 hour after these medications.
- *H2-Receptor Antagonists (unboosted atazanavir in treatment-naïve patients)*: H2-receptor antagonists are expected to decrease atazanavir concentrations by interfering with absorption. Atazanavir 400 mg should be administered at least 2 hours before or at least 10 hours after a dose of the H2-receptor antagonist (no single dose should exceed a dose comparable to famotidine 20 mg and total daily dose should not exceed a dose comparable to famotidine 40 mg).
- *H2-Receptor Antagonists (boosted atazanavir in treatment-naïve or -experienced patients)*: H2-receptor antagonists are expected to decrease atazanavir concentrations by interfering with absorption. Dose recommendations for H2-receptor antagonists are either a ≤40-mg dose equivalent of famotidine twice daily (treatment-naïve patients) or a ≤20-mg dose equivalent of famotidine twice daily (treatment-experienced patients). Dose (ATV 300 mg + RTV 100 mg) should be administered simultaneously with and/or ≥10 hours after the dose of H2-receptor antagonist.
- *H2-Receptor Antagonists (boosted atazanavir with tenofovir)*: In treatment-experienced patients, if tenofovir is used with H2-receptor antagonists, an increased dose of atazanavir should be given: 400 mg ATV + 100 mg RTV + 300 mg TDF.
- *Proton-pump Inhibitors:* Coadministration of atazanavir with proton-pump inhibitors is expected to substantially decrease atazanavir plasma concentrations and decrease therapeutic effect. Dose recommendations for therapy-naïve patients are

≤20-mg dose equivalent of omeprazole taken approximately 12 hours prior to boosted atazanavir (ATV 300 mg + RTV 100 mg). Coadministration of atazanavir with proton-pump inhibitors is not recommended in treatment-experienced patients.

Major Toxicities:

- *More common:* Indirect hyperbilirubinemia that can result in jaundice or icterus but is not a marker of hepatic toxicity. Headache, fever, arthralgia, depression, insomnia, dizziness, nausea, vomiting, diarrhea, and paresthesias.
- *Less common:* Prolongation of PR interval of electrocardiogram. Abnormalities in AV conduction generally limited to first-degree AV block, but with rare reports of second-degree AV block. Rash, generally mild to moderate, but in rare cases includes life-threatening Stevens-Johnson syndrome. Fat maldistribution and lipid abnormalities may be less common than with other PIs. However, the addition of ritonavir to atazanavir is associated with lipid abnormalities but to a lesser extent than with other boosted PIs.
- *Rare:* New onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of pre-existing diabetes mellitus, spontaneous bleeding in hemophiliacs, and elevation in serum transaminases. Nephrolithiasis. Hepatotoxicity (patients with hepatitis B or C are at increased risk).

Resistance: The International AIDS Society-USA (IAS-USA) maintains a list of updated resistance mutations (see **http://www.iasusa.org/resistance_mutations/index.html**) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see **http://hivdb.stanford.edu/pages/GRIP/ATV.html**).

Pediatric Experience: IMPAACT/PACTG 1020A is an ongoing Phase II international trial of atazanavir with and without ritonavir in children 3 months to 19 years of age. In addition to capsules, a powder formulation of atazanavir is also under study. In this trial, atazanavir plasma concentration monitoring is used to guide therapy and establish optimum starting doses. Both ritonavir-boosted and -unboosted atazanavir regimens are used for treatment-naïve and -experienced patients. In the trial, protocol-defined AUC, C_{min}, and C_{max} targets were deliberately set at levels higher than those achieved in the early adult atazanavir trials to compensate for the wide interpatient variability in pharmacokinetics values seen in adults in those trials; the pharmacokinetic targets were the same for atazanavir given with and without ritonavir boosting. In IMPAACT/PACTG 1020A, dosing for each age cohort was targeted to achieve AUC ≥30 μg*hour/mL and C24 ≥60 ng/mL.

To date, the results of the IMPAACT/PACTG 1020A trial in children and adolescents indicate that in the absence of ritonavir boosting, atazanavir can achieve protocol-defined pharmacokinetic targets, but only when used at higher doses of atazanavir (on a mg-per-kg body weight or mg-per-meter^2 body surface area basis) than doses currently recommended in adults. In IMPAACT/PACTG 1020A, children >6 and <13 years of age required atazanavir dosing of 520 mg per meter^2 of body surface area per day of atazanavir capsule formulation to achieve pharmacokinetic targets. For older adolescents, doses required were greater than the adult approved dose of 400 mg atazanavir given without ritonavir boosting once daily: adolescents age >13 years required ATV dosing of 620 mg per meter^2 of body surface area per day *[1-2]*. In this study, the AUCs for the unboosted arms were similar in the ritonavir-boosted atazanavir groups but the C_{max} was higher and C_{min} lower for the unboosted arms. Median doses of atazanavir in mg/m^2 both with and without ritonavir boosting from IMPAACT/PACTG 1020A are outlined in the following table. When dosing unboosted atazanavir in pediatric patients, therapeutic drug monitoring is recommended to ensure that adequate atazanavir plasma concentrations have been achieved. A minimum target trough concentration for atazanavir is 150ng/mL *[3]*. Higher target trough concentrations may be required in PI-experienced patients.

Summary of Dosing Information Obtained from IMPAACT/PACTG 1020A *[2]*

Age range (years)	Was ATV given with RTV boosting?	ATV median dose in mg/m^2*	ATV median dose in mg*
6–13 years	No	509	475
6–13 years	Yes	208	200
>13 years	No	620	900
>13 years	Yes	195	350

*Data satisfied protocol-defined AUC/pharmacokinetic parameters and met all acceptable safety targets. These doses differ from those recommended by the manufacturer. Therapeutic drug monitoring was used to determine patient-specific dosing in this trial.

A summary of the efficacy results from IMPAACT/PACTG 1020A is included in the prescribing information: In 99 patients (6 years to >18 years of age) treated with either boosted or unboosted atazanavir, the overall proportions of antiretroviral-naïve and -experienced patients with HIV RNA <50 copies/mL at Week 24 were 59% (24/41) and 24% (14/58), respectively. The median increase from baseline in absolute CD4 count at 20 weeks of therapy was 171 cells/mm^3 and 116 cells/mm^3 in antiretroviral-

naïve patients and antiretroviral-experienced patients, respectively *[4]*. Overall, 11 of 129 (8.5%) patients enrolled had a bilirubin >5 times the upper limit of normal. Asymptomatic electrocardiogram (EKG) abnormalities were observed in a small number of patients: 1 patient had a Grade 3 QTC prolongation, 9 had Grade 2 PR or HR changes, and 3 had Grade 3 PR prolongations. No significant changes in serum cholesterol or triglycerides were observed during 48 weeks of therapy in 63 children receiving unboosted atazanavir in combination with 2 NRTIs *[5]*.

In a small single site study, 23 pediatric patients (median age 16) on combination antiretroviral therapy were switched to a once-daily ritonavir-boosted atazanavir (ATV/r)-containing regimen for virologic failure (12) or for treatment simplification (11) *[6]*. Twenty of the patients had previously received protease inhibitor-based regimens with the median number of 2 atazanavir mutations. Patients received atazanavir doses lower than those currently recommended and many patients received concomitant therapy with tenofovir and/or didanosine; both drugs are known to have pharmacokinetic interactions with atazanavir. In this study, atazanavir plasma concentrations were measured at 12–15 hours after dosing: 6 patients had undetectable levels at multiple time points, and considerable interpatient variability in plasma atazanavir concentrations was noted. Four of the 13 patients with previously undetectable viral loads experienced virologic failure and 6 of the 12 patients who previously had virologic failure achieved undetectable viral loads. This study provides further evidence of the large interpatient variability in atazanavir pharmacokinetics in children, the need for higher doses, and the potential benefit of therapeutic drug monitoring to ensure that adequate atazanavir concentrations are achieved.

References

1. Kiser J, Rutstein R, Aldrovandi G, et al. Pharmacokinetics of atazanavir/ritonavir in HIV-infected infants, children, and adolescents: PACTG 1020. Paper presented at: 12th Conference on Retroviruses and Opportunistic Infections (CROI); February 22-25 2005; Boston, MA. Abstract 767.
2. Rutstein R, Samson P, Kiser J, et al. Atazanavir in HIV-infected children: The 1020a protocol. Paper presented at: 14th Conference on Retroviruses and Opportunistic Infections (CROI); February 27, 2007; Los Angeles, CA. Abstract 715.
3. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. December 1, 2009:1-161. http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf.
4. Bristol-Myers Squibb. Reyataz (atazanavir sulfate) package insert. Revised March 2008. www.reyataz.com.
5. Rutstein RM, Gebo KA, Flynn PM, et al. Immunologic function and virologic suppression among children with perinatally acquired HIV infection on highly active antiretroviral therapy. *Med Care.* 2005;43(9 Suppl):III15-22.
6. Macassa E, Delaugerre C, Teglas JP, et al. Change to a once-daily combination including boosted atazanavir in HIV-1-infected children. *Pediatr Infect Dis J.* 2006;25(9):809-814.

Darunavir (DRV, Prezista)

For additional information see Drugs@FDA: **http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm**

Formulations

Tablets: 75 mg, 150 mg, 400 mg, and 600 mg

Dosing Recommendations

Darunavir should not be used without ritonavir (RTV).

Neonate/Infant dose:
Not approved for use in neonates/infants.

Pediatric dose:
DRV should not be used in pediatric patients <3 years of age.

3 to <6 years:
Safety and efficacy have not been established.

6 to <18 years and ≥20 kg:

Weight	Dose (both twice daily* with food)
≥20 to <30 kg	DRV 375 mg + RTV 50 mg (0.6 ml of 80 mg/ml)
≥30 to <40 kg	DRV 450 mg + RTV 60 mg (0.8 ml of 80 mg/ml)
≥40 kg	DRV 600 mg + RTV 100 mg

* Do not use once-daily dosing in pediatric patients.

Adolescent (age ≥18 years)/Adult dose (treatment naïve):
DRV 800 mg + RTV 100 mg, both once daily with food

Adolescent (age ≥18 years)/Adult dose (treatment experienced):
DRV 600 mg + RTV 100 mg, both twice daily with food

Selected Adverse Events

- Skin rash (DRV has a sulfonamide moiety. Stevens-Johnson syndrome and erythema multiforme have been reported.)
- Hepatotoxicity
- Diarrhea
- Nausea
- Headaches
- Possible increased bleeding in patients with hemophilia
- Hyperlipidemia, transaminase elevation, hyperglycemia
- Fat maldistribution

Special Instructions

- Administer DRV with food, which increases AUC and Cmax by 30%. Drug exposure is not significantly altered by the number of calories and fat content of the meal.
- DRV contains a sulfa moiety. The potential for cross sensitivity between DRV and other drugs in the sulfonamide class is unknown. Use DRV with caution in patients with known sulfonamide allergy.
- Pediatric dosing requires administration of multiple 75-mg or 150-mg tablets to achieve the recommended doses of 375 mg or 450 mg depending on weight band. Pill burden may have a negative effect on adherence.
- Store at room temperature (25ºC or 77ºF).

Metabolism

- CYP 3A4 inhibitor and substrate.
- Dosing in patients with hepatic impairment: DRV is primarily metabolized by the liver. There are no data for dosing adult patients with varying degrees of hepatic impairment; caution should be used when administering DRV to such patients. DRV is not recommended in patients with severe hepatic impairment.
- Dosing in patients with renal impairment: No dose adjustment is required in patients with moderate renal impairment (CrCl 30–60 mL/min). There are no pharmacokinetic data in patients with severe renal impairment or end-stage renal disease.

Drug Interactions (See also the ***Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents***.)***:***

- *Metabolism:* Darunavir is primarily metabolized by cytochrome P450 3A4. Ritonavir inhibits CYP3A4, thereby increasing the plasma concentration of darunavir. There is the potential for multiple drug interactions.
- Before administration, the patient's medication profile should be carefully reviewed for potential drug interactions.

Major Toxicities:

- *More common:* Diarrhea, nausea, vomiting, abdominal pain, headache, and fatigue.
- *Less common:* Skin rash, including erythema multiforme and Stevens-Johnson syndrome, have been reported. Fever and elevated hepatic transaminases have been reported. Lipid abnormalities.

- *Rare:* New onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of pre-existing diabetes mellitus, spontaneous bleeding in hemophiliacs. Hepatic dysfunction, particularly in patients with underlying risk factors (e.g., hepatitis B or hepatitis C virus coinfection, baseline elevation in transaminases).

Resistance: The International AIDS Society-USA (IAS-USA) maintains a list of updated resistance mutations (see **http://www.iasusa.org/resistance_mutations/index.html**) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see **http://hivdb.stanford.edu/pages/GRIP/DRV.html**).

Pediatric Experience: FDA approval for use in children 6 years of age and older was based upon a randomized, open-label, multicenter study that enrolled 80 treatment-experienced pediatric subjects age 6–<18 years and weighing ≥20 kg. Patients were stratified according to their weight and received darunavir/ritonavir plus background therapy consisting of at least 2 non-PI antiretroviral drugs *[1]*. This was a 2-part Phase II trial to evaluate the pharmacokinetics and tolerance of darunavir/ritonavir in children. In Part I, a weight-adjusted dose of darunavir 9–15 mg/kg and ritonavir 1.5–2.5 mg/kg twice daily, equivalent to the standard adult dose of darunavir/ritonavir 600/100 mg twice daily, resulted in inadequate drug exposure in the pediatric population studied with AUC_{24h} of 81% and C_{0h} of 91% of the corresponding adult pharmacokinetic (PK) parameters. A pediatric dose 20%–33% higher than the scaled adult dose was needed to achieve drug exposure similar to that found in adults and was the dose selected for Part II of the study. The higher dose used for the safety and efficacy evaluation was darunavir 11–19 mg/kg and ritonavir 1.5–2.5 mg/kg twice daily. This resulted in AUC_{24h} of 123,276 ng*h/ml (range 71,850–201,520) and C_{0h} of 3,693 ng/mL (range 1,842–7,191), 102% and 114% of the respective PK values in adults. Patients were stratified by body weight: 20 to <30 kg and 30 to <40 kg. Doses were all given twice daily and were adjusted when patients changed weight categories. After the 2-week PK evaluation all patients were allowed to switch to ritonavir 100-mg capsules if desired to avoid the use of liquid oral ritonavir.

Based on the findings in the safety and efficacy portion of the study, weight band doses of darunavir/ritonavir were as follows: 375/50 mg twice daily for body weight 20 to <30kg, 450/60 mg twice daily for 30 to <40 kg, and 600/100 mg twice daily for ≥40 kg. Note that 27 of the 80 participants in this portion of the study switched from the ritonavir liquid formulation to ritonavir 100-mg capsules. The 80 subjects had a median age of 14 (range 6 to <18 years), 71% were male, 54% white, 30% black, 9% Hispanic, and 8% other. The mean baseline plasma HIV-1 RNA was 4.64 $\log_{10}$ copies/mL, and the median baseline CD4 cell count was 330 cells/mm^3 (range: 6–1,505 cells/mm^3). Overall, 38% of pediatric subjects had baseline plasma HIV RNA ≥100,000 copies/mL, 79% had previous use of at least 1 NNRTI, and 96% had previously used at least 1 PI. The subjects had a median of 11 PI mutations. Only 6% of subjects discontinued the study before Week 48 (only 1 for an adverse event). The proportion of pediatric subjects with HIV RNA <400 copies/mL and <50 copies/mL at Week 48 was 59% and 48%, respectively. The mean CD4 cell count increase from baseline was 110 cells/mm^3.

Although darunavir is approved for once-daily dosing in antiretroviral-naïve adults, it should not be used once daily in children because of more rapid clearance and absence of pediatric data.

References

1. Blanche S, Bologna R, Cahn P, et al. Pharmacokinetics, safety and efficacy of darunavir/ritonavir in treatment-experienced children and adolescents. *AIDS.* 2009;23(15):2005-2013.

Fosamprenavir (FPV, Lexiva)

For additional information see Drugs@FDA: **http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm**

Formulations

Oral suspension: 50 mg/mL
Tablets: 700 mg FPV calcium

Dosing Recommendations

Neonate/Infant dose: Not approved for use in neonates/infants.

Pediatric dose (2–18 years of age): Dosing regimen depends on whether patient is antiretroviral naïve or antiretroviral experienced. Once-daily dosing is not recommended for pediatric patients.

Antiretroviral-naïve patients (2–5 years):
Unboosted (without ritonavir [RTV])
FPV 30 mg/kg (maximum dose 1,400 mg) twice daily

Antiretroviral-naïve patients (≥6 years):
Unboosted (without RTV)
FPV 30 mg/kg (maximum dose 1,400 mg) twice daily
or
Boosted with RTV
FPV 18 mg/kg (maximum dose 700 mg) + RTV 3 mg/kg (maximum dose 100 mg), both twice daily

Antiretroviral-experienced patients (≥6 years):
Boosted with RTV
FPV 18 mg/kg (maximum dose 700 mg) + RTV 3 mg/kg (maximum dose 100 mg), both twice daily

When administered without RTV, the adult regimen of FPV tablets (FPV 1,400 mg twice daily) can be used for patients weighing ≥47 kg **or** when administered with RTV, the adult regimen of 700 mg FPV tablets + 100 mg RTV, both given twice daily, can be used in patients weighing ≥39 kg. RTV pills can be used in patients weighing ≥33 kg.

Adolescent (>18 years)/Adult dose:
Dosing regimen depends on whether the patient is antiretroviral naïve or experienced.

Antiretroviral-naïve patients:
Unboosted (without RTV), twice-daily regimen
FPV 1,400 mg twice daily
Boosted with RTV, twice-daily regimen
FPV 700 mg + RTV 100 mg, both twice daily
Boosted with RTV, once-daily regimen
FPV 1,400 mg + RTV 200 mg, both once daily **or**
FPV 1,400 mg + RTV 100 mg, both once daily

Protease inhibitor-experienced patients:
FPV 700 mg + RTV 100 mg, both twice daily

Once-daily administration of FPV + RTV is not recommended in PI-experienced patients.

Selected Adverse Events

- Diarrhea, nausea, vomiting
- Skin rash
- Headache
- Hyperlipidemia, hyperglycemia
- Nephrolithiasis
- Transaminase elevation
- Fat maldistribution
- Possible increased bleeding episodes in patients with hemophilia

Special Instructions

- Tablets can be taken with or without food. Adults should take the suspension without food. Pediatric patients can take the suspension with food.
- Patients taking antacids or buffered formulations of didanosine (ddI) should take FPV at least 1 hour before or after antacid or ddI use.
- FPV contains a sulfonamide. The potential for cross sensitivity between FPV and other drugs in the sulfonamide class is unknown. FPV should be used with caution in patients with sulfonamide allergy.
- Shake oral suspension well prior to use. Refrigeration is not required.

Metabolism

- The prodrug FPV is rapidly and almost completely hydrolyzed to amprenavir (APV) by cellular phosphatases in the gut as it is absorbed.
- APV is a cytochrome P450 3A4 inhibitor, inducer, and substrate.
- Dosage adjustment in patients with hepatic insufficiency is recommended.

Fosamprenavir (FPV, Lexiva)

Dosing Recommendations for Coadministration with Other Antiretroviral Drugs	
FPV in combination with efavirenz (EFV) Only FPV boosted with RTV should be used in combination with EFV. **Adult dose:** *Twice-daily regimen* FPV 700 mg + RTV 100 mg, both twice daily + EFV 600 mg once daily *PI-naïve patients only, once-daily regimen* FPV 1,400 mg + RTV 300 mg + EFV 600 mg, all once daily ***FPV in combination with maraviroc (MVC)*** **Adult dose:** See **MVC** section for dosing of FPV with MVC.	

Drug Interactions (See also the ***Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents***.)***:***

- Fosamprenavir has the potential for multiple drug interactions.
- Before administration, the patient's medication profile should be carefully reviewed for potential drug interactions.

Major Toxicities:

- *More common:* Vomiting, nausea, diarrhea, perioral paresthesias, headache, rash, and lipid abnormalities.
- *Less common (more severe):* Life-threatening rash, including Stevens-Johnson syndrome, in <1% of patients. Fat maldistribution, neutropenia, and elevated serum creatinine kinase levels.
- *Rare:* New onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of pre-existing diabetes mellitus, spontaneous bleeding in hemophiliacs, hemolytic anemia, elevation in serum transaminases, angioedema, and nephrolithiasis.

Resistance: The International AIDS Society-USA (IAS-USA) maintains a list of updated resistance mutations (see **http://www.iasusa.org/resistance_mutations/index.html**) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see **http://hivdb.stanford.edu/pages/GRIP/APV_FPV.html**).

Pediatric Experience: In June 2007, fosamprenavir suspension was approved for use in pediatric patients. The approval was based on two open label studies in pediatric patients 2–18 years of age *[1-2]*. Both studies enrolled treatment-experienced and treatment-naïve subjects. In one study, twice-daily dosing regimens (with or without ritonavir) were evaluated in combination with other antiretroviral agents. Overall, fosamprenavir was well tolerated and effective in suppressing viral load and increasing CD4 cell count. In one trial, after 24 weeks 67% of PI-naïve subjects in the fosamprenavir group (age 2–5 years only) and 70% of PI-naïve subjects in the fosamprenavir/ritonavir group (age 5–18 years) but only 57% of PI-experienced subjects in the fosamprenavir/ritonavir group (age 5–18 years) achieved HIV RNA <400 copies/mL. Median increases in CD4 percent at Week 24 occurred in all groups and ranged from 4% to 8% *[2]*. In a second trial, once-daily fosamprenavir/ritonavir was studied. Following information about suboptimal response to once-daily dosing in treatment-experienced adults, pediatric patients were allowed to switch to twice-daily therapy; however, few patients (10 of 69) opted to switch to twice-daily therapy (median time to switch: 45 weeks). At 24 and 48 weeks of therapy, HIV RNA was <400 copies/mL in 66% and 47% among PI-naïve subjects, respectively, and 57% and 43% among PI-experienced subjects, respectively. Median increase in CD4 percent at Week 48 was 10% for PI-naïve and 5% for PI-experienced subjects *[1]*. These data were insufficient to support a once-daily dosing regimen of ritonavir-boosted fosamprenavir in children and hence once-daily dosing is not recommended for pediatric patients. Toxicities from these trials included vomiting (3%–7%), diarrhea (3%–4%), and nausea (3%–4%).

A trial of pediatric patients taking the parent compound (amprenavir) demonstrated that the drug was relatively well tolerated with mild-to-moderate toxicity related mainly to the gastrointestinal system *[3]*.

References

1. Chadwick E, Borkowsky W, Fortuny C, et al. Safety and antiviral activity of fosamprenavir/ritonavir once daily regimens in HIV-infected pediatric subjects ages 2 to 18 years (48-week interim data, study apv20003). Paper presented at: 14th Conference on Retroviruses and Opportunistic Infections; February 25-28, 2007; Los Angeles, CA. Abstract 719.
2. Cunningham C, Freedman A, Read S, et al. Safety and antiviral activity of fosamprenavir-containing regmens in HIV-infected 2- to 18-year-old pediatric subjects (interim data, study apv29005). Paper presented at: 14th Conference on Retroviruses and Opportunistic Infections; February 25-28, 2007; Los Angeles, CA. Abstract 718.
3. Yogev R, Kovacs A, Chadwick EG, et al. Single-dose safety and pharmacokinetics of amprenavir (141W94), a human immunodeficiency virus type 1 (HIV-1) protease inhibitor, in HIV-infected children. *Antimicrob Agents Chemother*. 2005;49(1):336-341.

Indinavir (IDV, Crixivan)

For additional information see Drugs@FDA: **http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm**

Formulations

Capsules: 100 mg, 200 mg, and 400 mg

Dosing Recommendations

Neonate/Infant dose:
Not approved for use in neonates/infants.
Should not be administered to neonates due to the risks associated with hyperbilirubinemia (kernicterus).

Pediatric dose:
Not approved for use in children.

Investigational dose:
500 mg/m^2 of body surface area every 8 hours

Adolescent/Adult dose:
800 mg every 8 hours

IDV in combination with ritonavir (RTV)
Adolescent/Adult dose:
800 mg IDV + 100 or 200 mg RTV every 12 hours

Selected Adverse Events

- Nephrolithiasis
- GI intolerance, nausea
- Indirect hyperbilirubinemia
- Hyperlipidemia
- Headache, asthenia, blurred vision, dizziness, rash, metallic taste, thrombocytopenia, alopecia, and hemolytic anemia
- Hyperglycemia
- Fat maldistribution
- Possible increased bleeding episodes in patients with hemophilia

Special Instructions

- Administer on an empty stomach 1 hour before or 2 hours after a meal (or administer with a light meal). When given in combination with RTV, meal restrictions are no longer necessary.
- Adequate hydration is required to minimize risk of nephrolithiasis (≥48 oz of fluid daily in adult patients).
- If coadministered with didanosine (ddI), give ≥1 hour apart on an empty stomach.
- Capsules are sensitive to moisture; store at room temperature (59–86ºF) in original container with desiccant.

Metabolism

- Cytochrome P450 3A4 inhibitor and substrate.
- Decreased dosage should be used in patients with mild-to-moderate hepatic impairment (recommended dose for adults is 600 mg IDV every 8 hours). No dosing information is available for children with any degree of hepatic impairment or for adults with severe hepatic impairment.

Drug Interactions (See also the ***Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents***.)***:***

- *Metabolism*: Cytochrome P450 3A4 (CYP3A4) is the major enzyme responsible for metabolism. There is potential for multiple drug interactions.
- Before administration, the patient's medication profile should be carefully reviewed for potential drug interactions.

Major Toxicities:

- *More common:* Nausea, abdominal pain, headache, metallic taste, dizziness, asymptomatic hyperbilirubinemia (10%), lipid abnormalities, pruritis, and rash. Nephrolithiasis/urolithiasis with indinavir crystal deposits: cumulative frequency is higher in children (29%) than in adults (12.4%).
- *Less common (more severe):* Fat redistribution.
- *Rare:* New onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of pre-existing diabetes mellitus, spontaneous bleeding in hemophiliacs, acute hemolytic anemia, and hepatitis (life-threatening in rare cases).

Resistance: The International AIDS Society-USA (IAS-USA) maintains a list of updated resistance mutations (see **http://www.iasusa.org/resistance_mutations/index.html**) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see **http://hivdb.stanford.edu/pages/GRIP/IDV.html**).

Pediatric Experience: Indinavir has not been approved by the FDA for use in the pediatric population. It has been studied in HIV-infected children as monotherapy and in combination with other antiretroviral drugs in dosage ranges of 300–600 mg per

meter^2 of body surface area given every 8 hours *[1-16]*. Data in children indicate that a pediatric dose of 500–600 mg indinavir per meter^2 of body surface area given every 8 hours results in peak blood concentrations similar to those in adults; however, a significant proportion of children had trough indinavir concentrations less than the 0.1 mg/L value associated with virologic efficacy in adults *[3, 10]*.

Ritonavir-boosted indinavir has also been studied in children. One study evaluated 500 mg indinavir per meter^2 of body surface area plus 100 mg ritonavir per meter^2 of body surface area twice daily in 4 children 1–10 years of age; in 1 child, this resulted in high concentrations of both drugs and was accompanied by symptoms of renal toxicity *[11]*. Another study evaluated the pharmacokinetics of 400 mg indinavir per meter^2 of body surface area plus 125 mg ritonavir per meter^2 of body surface area twice daily in 14 children; this dosing resulted in AUC and trough concentrations similar to those observed with standard doses of indinavir /ritonavir in adults (800 mg indinavir/100 mg ritonavir twice daily), although the peak concentration was slightly decreased *[1]*. Clinical results from that trial demonstrated that virologic efficacy was good but that 4 of 21 patients developed nephrolithiasis and the overall rate of side effects and intolerance to the regimen was high *[5]*. In a study from Thailand a lower dose of indinavir (median 234 mg per meter^2) with low dose ritonavir resulted in low trough levels of indinavir in 2 of 12 children *[17]*.

In a study of 21 children receiving PI-containing antiretroviral therapy, all patients receiving indinavir experienced substantial increases in their triglyceride concentrations but no significant increases in total cholesterol occurred; blood glucose concentrations were not significantly different between baseline and follow-up evaluations *[18]*. In a study of 25 children toxicities observed with indinavir included flank pain and headache (16%), renal dysfunction (16%), hematuria (12%), and skin rash (12%) *[10]*. The cumulative frequency of nephrolithiasis is substantially higher in children (29%) than in adults (12.4%, range across clinical trials 4.7%–34.4%) *[19]*. This is likely due to the difficulty in maintaining adequate hydration in children. In a study of indinavir in 54 children, 13% developed hematuria *[9]* Children treated with indinavir also have a high cumulative incidence of sterile leukocyturia, which may be accompanied by elevations in serum creatinine in the absence of clinical symptoms of nephrolithiasis *[13]*. A large analysis of more than 2,000 HIV-infected children from PACTG 219 demonstrated a hazard ratio of 1.7 for the risk of renal dysfunction among children receiving combination antiretroviral therapy with indinavir *[20]*.

References

1. Bergshoeff AS, Fraaij PL, van Rossum AM, et al. Pharmacokinetics of indinavir combined with low-dose ritonavir in human immunodeficiency virus type 1-infected children. *Antimicrob Agents Chemother.* 2004;48(5):1904-1907.
2. Burger DM, van Rossum AM, Hugen PW, et al. Pharmacokinetics of the protease inhibitor indinavir in human immunodeficiency virus type 1-infected children. *Antimicrob Agents Chemother.* 2001;45(3):701-705.
3. Fletcher CV, Brundage RC, Remmel RP, et al. Pharmacologic characteristics of indinavir, didanosine, and stavudine in human immunodeficiency virus-infected children receiving combination therapy. *Antimicrob Agents Chemother.* 2000;44(4):1029-1034.
4. Fraaij PL, Bergshoeff AS, van Rossum AM, et al. Changes in indinavir exposure over time: a case study in six HIV-1-infected children. *J Antimicrob Chemother.* 2003;52(4):727-730.
5. Fraaij PL, Verweel G, van Rossum AM, et al. Indinavir/low-dose ritonavir containing HAART in HIV-1 infected children has potent antiretroviral activity, but is associated with side effects and frequent discontinuation of treatment. *Infection.* 2007;35(3):186-189.
6. Gatti G, Vigano A, Sala N, et al. Indinavir pharmacokinetics and parmacodynamics in children with human immunodeficiency virus infection. *Antimicrob Agents Chemother.* 2000;44(3):752-755.
7. Jankelevich S, Mueller BU, Mackall CL, et al. Long-term virologic and immunologic responses in human immunodeficiency virus type 1-infected children treated with indinavir, zidovudine, and lamivudine. *J Infect Dis.* 2001;183(7):1116-1120.
8. Kline MW, Fletcher CV, Harris AT, et al. A pilot study of combination therapy with indinavir, stavudine (d4T), and didanosine (ddI) in children infected with the human immunodeficiency virus. *J Pediatr.* 1998;132(3 Pt 1):543-546.
9. Mueller BU, Sleasman J, Nelson RP, et al. A phase I/II study of the protease inhibitor indinavir in children with HIV infection. *Pediatrics.* 1998;102(1 Pt 1):101-109.
10. Pelton SI, Stanley K, Yogev R, et al. Switch from ritonavir to indinavir in combination therapy for HIV-1-infected children. *Clin Infect Dis.* 2005;40(8):1181-1187.
11. van Rossum AM, de Groot R, Hartwig NG, et al. Pharmacokinetics of indinavir and low-dose ritonavir in children with HIV-1 infection. *AIDS.* 2000;14(14):2209-2210.

12. van Rossum AM, Niesters HG, Geelen SP, et al. Clinical and virologic response to combination treatment with indinavir, zidovudine, and lamivudine in children with human immunodeficiency virus-1 infection: a multicenter study in the Netherlands. On behalf of the Dutch Study Group for Children with HIV-1 infections. *J Pediatr.* 2000;136(6):780-788.
13. van Rossum AM, Dieleman JP, Fraaij PL, et al. Persistent sterile leukocyturia is associated with impaired renal function in human immunodeficiency virus type 1-infected children treated with indinavir. *Pediatrics.* 2002;110(2 Pt 1):e19.
14. Verweel G, van Rossum AM, Hartwig NG, et al. Treatment with highly active antiretroviral therapy in human immunodeficiency virus type 1-infected children is associated with a sustained effect on growth. *Pediatrics.* 2002;109(2):E25.
15. Vigano A, Dally L, Bricalli D, et al. Clinical and immuno-virologic characterization of the efficacy of stavudine, lamivudine, and indinavir in human immunodeficiency virus infection. *J Pediatr.* 1999;135(6):675-682.
16. Wintergerst U, Hoffmann F, Solder B, et al. Comparison of two antiretroviral triple combinations including the protease inhibitor indinavir in children infected with human immunodeficiency virus. *Pediatr Infect Dis J.* 1998;17(6):495-499.
17. Plipat N, Cressey TR, Vanprapar N, et al. Efficacy and plasma concentrations of indinavir when boosted with ritonavir in human immunodeficiency virus-infected Thai children. *Pediatr Infect Dis J.* 2007;26(1):86-88.
18. Temple ME, Koranyi KI, Nahata MC. Lipodystrophy in HIV-infected pediatric patients receiving protease inhibitors. *Ann Pharmacother.* 2003;37(9):1214-1218.
19. Food and Drug Administration (FDA). Indinavir product label. 2006; http://www.fda.gov/medwatch/safety/2006/Dec_PIs/Crixivan_PI.pdf.
20. Andiman WA, Chernoff MC, Mitchell C, et al. Incidence of persistent renal dysfunction in human immunodeficiency virus-infected children: associations with the use of antiretrovirals, and other nephrotoxic medications and risk factors. *Pediatr Infect Dis J.* 2009;28(7):619-625.

Lopinavir/Ritonavir (LPV/r, Kaletra)

For additional information see Drugs@FDA: **http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm**

Formulations

Pediatric oral solution: 80 mg/20 mg LPV/r/mL (contains 42.4% alcohol by volume)
Pediatric tablets: 100 mg/25 mg LPV/r
Tablets: 200 mg/50 mg LPV/r

Dosing Recommendations

Neonate/Infant dose:
Infants <14 days: No data on appropriate dose or safety. Should not be used in preterm infants in the immediate postnatal period.

Infants 14 days to 6 months: Once-daily dosing is **not** recommended.

The recommended dose of the oral solution is 300 mg/75 mg LPV/r per m^2 of body surface area or 16 mg/4 mg LPV/r per kg of body weight twice daily. Do not administer LPV/r with efavirenz (EFV), nevirapine (NVP), fosamprenavir (FPV), or nelfinavir (NFV) in infants <6 months of age.

Use of 300 mg/75 mg LPV/r per m2 of body surface area in infants <6 months of age is associated with lower LPV trough levels than those found in adults; infants should be evaluated and LPV dosing adjusted for growth at frequent intervals (see discussion).

Pediatric dose (>6 months to 18 years):
*For individuals **not** receiving concomitant EFV, NVP, FPV, or NFV:*

Once-daily dosing is **not** recommended.

Body surface area dosing:
230 mg/57.5 mg LPV/r/m^2 of body surface area per dose twice daily

Weight-based dosing:
<15 kg: 12 mg/3 mg LPV/r/kg body weight per dose twice daily

≥15 kg to 40 kg: 10 mg/2.5 mg LPV/r/kg body weight per dose twice daily

≥40 kg: 400 mg/100 mg LPV/r per dose twice daily

Dosing for 100 mg/25 mg LPV/r Pediatric Tablets for Children/Adolescents **Without** Concomitant EFV, NVP, FPV, or NFV.

Body Weight (kg)	Body Surface Area (m^2)*	Recommended Number of 100 mg/25 mg LPV/r Tablets Given Twice Daily
15 to 25 kg	≥0.6 to <0.9 m^2	2
>25 to 35 kg	≥0.9 to <1.4 m^2	3
>35 kg	≥1.4 m^2	4 (or two 200 mg/50 mg LPV/r adult tablets)

*Oral solution is available for children age 6 months to 18 years with a

Selected Adverse Events

- GI intolerance, nausea, vomiting, diarrhea
- Asthenia
- Hyperlipidemia, especially hypertriglyceridemia
- Elevated transaminases
- Hyperglycemia
- Fat maldistibution
- Possible increased bleeding in patients with hemophilia
- PR interval prolongation
- QT interval prolongation and torsade de pointes

Special Instructions

- LPV/r tablets can be administered without regard to food, but recognize that administration with or after meals may enhance GI tolerability.
- LPV/r tablets must be swallowed whole. Do not crush or split tablets.
- LPV/r oral solution should be administered with food. A high fat meal increases absorption, especially of the liquid preparation, which may enhance effectiveness by increasing drug exposure.
- If coadministered with didanosine (ddI), ddI should be given 1 hour before or 2 hours after LPV/r.
- LPV/r oral solution can be kept at room temperature up to 77ºF (25ºC) if used within 2 months. If kept refrigerated (2º to 8ºC or 36º to 46ºF) LPV/r oral solution remains stable until the expiration date printed on the label.
- LPV resistance-associated substitutions: LPV/r can be administered once daily (800 mg/200 mg) in adults with fewer than 3 LPV resistance-associated substitutions. Once-daily administration of LPV/r is not recommended for adult patients with 3 or more of the following LPV resistance-associated substitutions: L10F/I/R/V, K20M/N/R, L24I, L33F, M36I, I47V, G48V, I54L/T/V, V82A/C/F/S/T, and I84V.

Metabolism

- CYP 3A4 inhibitor and substrate.
- Dosing of LPV/r in patients with hepatic impairment: LPV/r is primarily metabolized by the liver. Caution should be used when administering LPV to patients with hepatic impairment. No dosing information is

body surface area <0.6 m^2 or those who are unable to reliably swallow a tablet; dosing should be calculated based on body surface area or weight as above.

Dosing Recommendations for Coadministration with Other Antiretroviral Drugs

Pediatric dose (>6 months to 18 years):
For individuals receiving concomitant NVP, EFV, FPV, or NFV. (These drugs induce LPV metabolism and reduce LPV plasma levels; increased LPV/r dosing is required with concomitant administration of these drugs and/or in treatment-experienced patients in whom reduced susceptibility to LPV is suspected [such as those with prior treatment with other PIs].)

Once-daily dosing is **not** recommended.

Body surface area dosing:
300 mg/75 mg LPV/r/m^2 of body surface area per dose twice daily

Weight-based dosing:
<15 kg: 13 mg /3.25 mg LPV/r per kg body weight per dose twice daily

≥15 kg to 45 kg: 11 mg/2.75 mg LPV/r per kg body weight per dose twice daily

≥45 kg: Use adult dose twice daily.

Dosing for 100 mg/25 mg LPV/r Pediatric Tablets for Children **With** Concomitant EFV, NVP, FPV , or NFV		
Body Weight (kg)	Body Surface Area (meter^2)*	Recommended Number of 100 mg/25 mg LPV/r Tablets Given Twice Daily
15 to 20 kg	≥0.6 to <0.8 m^2	2
>20 to 30 kg	≥0.8 to <1.2 m^2	3
>30 to 45 kg	≥1.2 to <1.7 m^2	4 (or two 200 mg/50 mg LPV/r tablets)
>45 kg	≥1.7 m^2	4 or 6 (or two or three 200 mg/50 mg LPV/r adult tablets)**

*Oral solution is available for children age 6 months to 18 years with a body surface area <0.6 m^2 or those who are unable to reliably swallow a tablet; dosing should be calculated based on body surface area or weight as above.
**The higher dose may be considered in treatment-experienced patients where decreased sensitivity to LPV is suspected due to clinical history or documented by resistance testing.

Use of 230 mg/57.5 mg LPV/r per m2 of body surface area (when not coadministered with NVP, EFV, FPV, or NFV) or use of 300 mg/75 mg LPV/r per m2 of body surface area in children (when coadministered with NVP, EFV, FPV, or NFV) is associated with AUC LPV levels similar to AUC achieved with standard doses in adults, but it is associated with lower trough levels in children than in adults. Therefore, some clinicians may choose to initiate therapy with higher doses of LPV/r when coadministered with these drugs or in PI-experienced pediatric patients who may have reduced PI currently available for children or adults with hepatic insufficiency.

- In the coformulation of LPV/r, the RTV acts as a pharmacokinetic enhancer, not as an antiretroviral agent. It does this by inhibiting the metabolism of LPV and increasing LPV plasma concentrations.

susceptibility (see discussion). **Adult (>18 years) dose**: *In patients with fewer than 3* LPV*-associated mutations (see Special Instructions for list):* 800 mg/200 mg LPV/r once daily; **or** 400 mg/100 mg LPV/r twice daily. Do **not** use once-daily dosing in children or adolescents. Once-daily dosing should not be used in patients receiving concomitant therapy with EFV, NVP, FPV, or NFV. *In patients with 3 or more LPV-associated mutations(see Special Instructions for list):* 400 mg/100 mg LPV/r twice daily *In patients receiving concomitant NVP, EFV, FPV, or NFV):* FDA-approved dose is 500 mg/125 mg LPV/r twice daily, given as a combination of 2 tablets of 200/50 mg LPV/r and 1 tablet of 100 mg/25 mg LPV/r. Most Panel members would use 600 mg/150 mg LPV/r for ease of dosing. Once-daily dosing should **not** be used. *LPV/r in combination with saquinavir (SQV) hard gel capsules (Invirase) or in combination with maraviroc (MVC):* SQV and MVC doses may need modification. See sections on **SQV** or **MVC**.	

Drug Interactions (See also the ***Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents.***)***:***

- *Metabolism*: Cytochrome P450 3A4 (CYP3A4) is the major enzyme responsible for metabolism. There is potential for multiple drug interactions.
- Before administration, the patient's medication profile should be carefully reviewed for potential drug interactions. Fluticasone, a commonly used inhaled steroid, should not be used in patients treated with lopinavir/ritonavir.

Major Toxicities:

- *More common:* Diarrhea, headache, asthenia, nausea and vomiting, and rash in patients receiving lopinavir/ritonavir with other antiretroviral drugs; hyperlipidemia, especially hypertriglyceridemia.
- *Less common (more severe):* Lipodystrophy.
- *Rare:* New onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of pre-existing diabetes mellitus, hemolytic anemia, spontaneous bleeding in hemophiliacs, pancreatitis, elevation in serum transaminases, and hepatitis (life threatening in rare cases). Possible increased bleeding episodes in patients with hemophilia. PR interval prolongation. QT interval prolongation and torsade de pointes may occur. Lopinavir/ritonavir should not be used in the immediate postnatal period in premature infants because life-threatening bradyarrhthymias and cardiac dysfunction have been described with its use in such infants *[1-2]*.

Resistance: The International AIDS Society-USA (IAS-USA) maintains a list of updated resistance mutations (see **http://www.iasusa.org/resistance_mutations/index.html**) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see **http://hivdb.stanford.edu/pages/GRIP/LPV.html**).

Pediatric Experience:

Lopinavir/ritonavir has been studied in HIV-infected children in combination with NRTIs and NNRTIs *[3-16]*. Ritonavir acts as a pharmacokinetic enhancer by inhibiting the metabolism of lopinavir and therefore increasing the plasma concentration of lopinavir.

Abbott Laboratories Study M98-940 was a Phase I/II open label study that evaluated the pharmacokinetics, tolerability, safety, and efficacy of lopinavir/ritonavir oral solution and either 2 NRTIs or nevirapine plus up to 2 NRTIs in 100 pediatric patients. Through 48 weeks of therapy, the proportion of patients with HIV RNA <400 copies/mL was 37 of 44 (84%) for antiretroviral-

naïve patients and 42 of 56 (75%) for antiretroviral-experienced patients. The mean increase from baseline in CD4 cell count was 404 cells/mm^3 for antiretroviral-naïve and 284 cells/mm^3 for antiretroviral-experienced patients. In patients with HIV RNA >400 copies/mL at 24 or 48 weeks, there were no detectable changes in susceptibility to lopinavir compared with baseline isolates, although there were resistance mutations to NRTIs and NNRTIs in the rebound isolates *[17]*.

There is some controversy about the dosing of lopinavir/ritonavir in children. Children have lower drug exposure than adults when treated with doses that are directly scaled for body surface area. The "directly scaled" dose approximation of the adult dose in children is calculated by dividing the adult dose by the usual adult body surface area of 1.73 m^2. For the adult dose of 400/100 mg lopinavir/ritonavir, the appropriate pediatric dose would be approximately 230/57.5 mg lopinavir/ritonavir per $meter^2$. However, younger children have enhanced lopinavir clearance and need higher drug doses to achieve drug exposures similar to those in adults treated with standard doses. To achieve similar C_{trough} to that observed in adults, the pediatric dose needs to be increased 30% over the directly body surface area-scaled dose.

For 12 children age 6 months to 12 years receiving 230 mg/57.5 mg lopinavir/ritonavir per m^2 of body surface area per dose twice daily (without nevirapine), the mean C_{trough} was 4.74 ± 2.93 mcg/mL (about 67% of the adult value of 7.1 ± 2.9 mcg/mL) *[4]*. For 15 children age 6 months to 12 years treated with 300 mg/75 mg lopinavir/ritonavir per m^2 of body surface area per dose twice daily (without nevirapine), the mean C_{trough} was 7.91 ± 4.52 mcg/mL, similar to that in adults treated with 400 mg/100 mg lopinavir/ritonavir twice daily *[4]*. Therefore, some clinicians may choose to initiate therapy in children age 6 months to 12 years using 300 mg/75 mg lopinavir/ritonavir per m^2 of body surface area per dose twice daily (when given without nevirapine, efavirenz, fosamprenavir, or nelfinavir) rather than the drug-label recommended 230 mg/57.5 mg lopinavir/ritonavir per m^2 of body surface area per dose twice daily *[12]*.

The pharmacokinetics of the oral solution at approximately 300 mg/75 mg lopinavir/ritonavir per m^2 of body surface area per dose twice daily was evaluated in infants younger than 6 weeks of age *[18]* and infants 6 weeks to 6 months of age *[14]*. Pharmacokinetic values found in these studies are compared to those in older children *[4]* and adults *[17]* in the table below. Values are means; all data shown performed in the absence of NNRTIs.

	Adults *[17]*	**Children** *[4]*	**Children** *[4]*	**Infants 6 wk–6 mo** *[14]*	**Infants <6 weeks** *[18]*
N	19	12	15	18	9
Dose LPV	400 mg	230 mg/m^2	300 mg/m^2	300 mg/m^2	300 mg/m^2
AUC mcg*hr/ml	92.6	72.6	116	74.5	43.4
C_{max} mcg/ml	9.8	8.2	12.5	9.4	5.2
C_{trough} mcg/ml	7.1	4.7	7.9	2.7	2.5
C_{min} mcg/ml	5.5	3.4	6.5	2.0	1.4

Even at this higher dose, predose (C_{trough}) levels were lower in infants than in children >6 months of age and were lower in the youngest infants at age <6 weeks compared with those between 6 weeks and 6 months. Predose (C_{trough}) levels were highly variable, and lower values (median 1.37 mcg/mL; range 0.13–5.98) were found in infants without viral suppression at 16 weeks compared with the higher predose (C_{trough}) values (median 2.28 mcg/mL; range 0.49–8.01) found in those infants with virologic suppression at 16 weeks (N = 17; p = 0.37) *[14]*. Because infants gain weight rapidly in the first months of life, one important way to optimize lopinavir dosing is to weigh the patient and adjust the dose for growth at frequent intervals. Some practitioners anticipate rapid infant growth and prescribe doses somewhat higher than the 300 mg/m^2 body surface area dose to let the infant "grow into" the 300 mg/m^2 body surface area amount.

For children, as in adults, the lopinavir C_{trough} is further reduced by concurrent treatment with NNRTIs or concomitant fosamprenavir or nelfinavir and, as in adults, higher doses of lopinavir are recommended if the drug is given in combination with nevirapine, efavirenz, fosamprenavir, or nelfinavir. In 14 children treated with 230 mg/57.5 mg lopinavir/ritonavir per m^2 of body surface area per dose twice daily plus nevirapine, the mean lopinavir C_{trough} was 3.77 ± 3.57 mcg/mL *[4]*. For 12 children treated with 300 mg/75 mg lopinavir/ritonavir per m^2 of body surface area per dose twice daily, the mean C_{trough} was 5.62 ± 3.32 mcg/mL. Not only are these trough plasma concentrations lower than those found in adults treated with standard doses of lopinavir/ritonavir, but the variability in concentration is much higher in children than adults *[4, 12]*. In a study of 15 children with HIV infection treated with the combination of lopinavir/ritonavir using an increased dose of 300 mg/75 mg lopinavir/ritonavir per m^2 of body surface area per dose twice daily plus efavirenz 14 mg/kg body weight per dose once daily, the median 12-hour lopinavir trough was 5.7 mcg/mL, but there was 34-fold interindividual variation in lopinavir trough concentrations, and 5 of 15 (33%) children had lopinavir 12-hour trough concentrations <1.0 mcg/mL, the plasma concentration needed to inhibit wild-type HIV *[5]*. A pharmacokinetic study in 20 children 10 to 16 years of age treated with the combination of lopinavir/ritonavir 300 mg/75

mg per m^2 of body surface area twice daily plus efavirenz 350 mg/m^2 of body surface area once daily showed adequacy of the lopinavir trough values *[19]*.

Lopinavir/ritonavir 800 mg/200 mg once daily is FDA approved for treatment of HIV infection in therapy-naïve adults >18 years of age. However, once-daily administration cannot be recommended for use in children in the absence of therapeutic drug monitoring because of high interindividual variability in drug exposure and trough plasma concentrations below the therapeutic range for wild-type virus in 21/59 (35.6%) of patients *[20-23]*.
Lopinavir/ritonavir has been shown to be effective as salvage therapy in children with HIV and severe immune suppression *[7, 24]*, although patients with greater prior exposure to antiretrovirals may have slower reductions in virus load to undetectable concentrations *[10, 24]* and less robust response in CD4 percentage *[25]*. Twice-daily doses of lopinavir used in this cohort were 230–300 mg/m^2 of body surface area in 39% of patients, 300–400 mg/m^2 of body surface area in 35%, and >400 mg/m^2 of body surface area per dose in 4% *[25]*.

More important than viral resistance to lopinavir is the relationship of the drug exposure (trough plasma concentration measured just prior to a dose, or C_{trough}) to the susceptibility of the HIV-1 isolate (EC_{50}). The ratio of C_{trough} to EC_{50} is called the inhibitory quotient, and in both adults and children treated with lopinavir/ritonavir, virus load reduction is more closely associated with inhibitory quotient than with either the C_{trough} or EC_{50} alone *[3, 26-28]*. A study of the practical application of the inhibitory quotient to guide therapy using higher doses of lopinavir/ritonavir in children and adolescents showed the safety and tolerability of doses of 400 mg/100 mg lopinavir/ritonavir per m^2 of body surface area per dose twice daily (without nevirapine or efavirenz) and 480 mg/120 mg lopinavir/ritonavir per m^2 of body surface area per dose twice daily (with nevirapine or efavirenz) *[16]*. A modeling study suggests the potential utility of therapeutic drug monitoring in children previously treated with protease inhibitors and now on salvage therapy with lopinavir/ritonavir *[29]*.

References

1. Lopriore E, Rozendaal L, Gelinck LB, et al. Twins with cardiomyopathy and complete heart block born to an HIV-infected mother treated with HAART. *AIDS.* 2007;21(18):2564-2565.
2. McArthur MA, Kalu SU, Foulks AR, et al. Twin preterm neonates with cardiac toxicity related to lopinavir/ritonavir therapy. *Pediatr Infect Dis J.* 2009;28(12):1127-1129.
3. Havens P, Frank M, Cuene B, et al. Pharmacokinetics and safety of lopinavir/ritonavir doses greater than 300 mg/m2/dose in children and adolescents with HIV infection. Paper presented at: 11th Conference on Retroviruses and Opportunistic Infections; February 8-11, 2004; San Francisco, CA. Abstract 937.
4. Saez-Llorens X, Violari A, Deetz CO, et al. Forty-eight-week evaluation of lopinavir/ritonavir, a new protease inhibitor, in human immunodeficiency virus-infected children. *Pediatr Infect Dis J.* 2003;22(3):216-224.
5. Bergshoeff AS, Fraaij PL, Ndagijimana J, et al. Increased dose of lopinavir/ritonavir compensates for efavirenz-induced drug-drug interaction in HIV-1-infected children. *J Acquir Immune Defic Syndr.* 2005;39(1):63-68.
6. Fraaij PL, Neubert J, Bergshoeff AS, et al. Safety and efficacy of a NRTI-sparing HAART regimen of efavirenz and lopinavir/ritonavir in HIV-1-infected children. *Antivir Ther.* 2004;9(2):297-299.
7. Resino S, Bellon JM, Ramos JT, et al. Salvage lopinavir-ritonavir therapy in human immunodeficiency virus-infected children. *Pediatr Infect Dis J.* 2004;23(10):923-930.
8. Ramos JT, De Jose MI, Duenas J, et al. Safety and antiviral response at 12 months of lopinavir/ritonavir therapy in human immunodeficiency virus-1-infected children experienced with three classes of antiretrovirals. *Pediatr Infect Dis J.* 2005;24(10):867-873.
9. Galan I, Jimenez JL, Gonzalez-Rivera M, et al. Virological phenotype switches under salvage therapy with lopinavir-ritonavir in heavily pretreated HIV-1 vertically infected children. *AIDS.* 2004;18(2):247-255.
10. Resino S, Galan I, Perez A, et al. Immunological changes after highly active antiretroviral therapy with lopinavir-ritonavir in heavily pretreated HIV-infected children. *AIDS Res Hum Retroviruses.* 2005;21(5):398-406.
11. Ananworanich J, Kosalaraksa P, Hill A, et al. Pharmacokinetics and 24-week efficacy/safety of dual boosted saquinavir/lopinavir/ritonavir in nucleoside-pretreated children. *Pediatr Infect Dis J.* 2005;24(10):874-879.
12. Verweel G, Burger DM, Sheehan NL, et al. Plasma concentrations of the HIV-protease inhibitor lopinavir are suboptimal in children aged 2 years and below. *Antivir Ther.* 2007;12(4):453-458.
13. Jullien V, Urien S, Hirt D, et al. Population analysis of weight-, age-, and sex-related differences in the pharmacokinetics of lopinavir in children from birth to 18 years. *Antimicrob Agents Chemother.* 2006;50(11):3548-3555.
14. Chadwick EG, Capparelli EV, Yogev R, et al. Pharmacokinetics, safety and efficacy of lopinavir/ritonavir in infants less than 6 months of age: 24 week results. *AIDS.* 2008;22(2):249-255.

15. Pinto J, Robbins B, Chen J, et al. Pharmacokinetics and 24-week efficacy and safety of lopinavir/ritonavir in HIV-1 infected infants <6 weeks of age. Paper presented at: 14th Conference on Retroviruses and Opportunistic Infections (CROI); Feb 25-28, 2007; Los Angeles, CA. Abstract 716.
16. Robbins BL, Capparelli EV, Chadwick EG, et al. Pharmacokinetics of high-dose lopinavir-ritonavir with and without saquinavir or nonnucleoside reverse transcriptase inhibitors in human immunodeficiency virus-infected pediatric and adolescent patients previously treated with protease inhibitors. *Antimicrob Agents Chemother.* 2008;52(9):3276-3283.
17. Food and Drug Administration (FDA). Lopinavir-ritonavir (Kaletra) product label. 2010; http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021226s030lbl.pdf.
18. Chadwick EG, Pinto J, Yogev R, et al. Early initiation of lopinavir/ritonavir in infants less than 6 weeks of age: pharmacokinetics and 24-week safety and efficacy. *Pediatr Infect Dis J.* 2009;28(3):215-219.
19. King JR, Acosta EP, Yogev R, et al. Steady-state pharmacokinetics of lopinavir/ritonavir in combination with efavirenz in human immunodeficiency virus-infected pediatric patients. *Pediatr Infect Dis J.* 2009;28(2):159-161.
20. Rosso R, Di Biagio A, Dentone C, et al. Lopinavir/ritonavir exposure in treatment-naive HIV-infected children following twice or once daily administration. *J Antimicrob Chemother.* 2006;57(6):1168-1171.
21. van der Lee M, Verweel G, de Groot R, et al. Pharmacokinetics of a once-daily regimen of lopinavir/ritonavir in HIV-1-infected children. *Antivir Ther.* 2006;11(4):439-445.
22. la Porte C, van Heeswijk R, Mitchell CD, et al. Pharmacokinetics and tolerability of once- versus twice-daily lopinavir/ritonavir treatment in HIV-1-infected children. *Antivir Ther.* 2009;14(4):603-606.
23. van der Flier M, Verweel G, van der Knaap LC, et al. Pharmacokinetics of lopinavir in HIV type-1-infected children taking the new tablet formulation once daily. *Antivir Ther.* 2008;13(8):1087-1090.
24. Resino S, Bellon JM, Munoz-Fernandez MA. Antiretroviral activity and safety of lopinavir/ritonavir in protease inhibitor-experienced HIV-infected children with severe-moderate immunodeficiency. *J Antimicrob Chemother.* 2006;57(3):579-582.
25. Larru B, Resino S, Bellon JM, et al. Long-term response to highly active antiretroviral therapy with lopinavir/ritonavir in pre-treated vertically HIV-infected children. *J Antimicrob Chemother.* 2008;61(1):183-190.
26. Casado JL, Moreno A, Sabido R, et al. Individualizing salvage regimens: the inhibitory quotient (Ctrough/IC50) as predictor of virological response. *AIDS.* 2003;17(2):262-264.
27. Delaugerre C, Teglas JP, Treluyer JM, et al. Predictive factors of virologic success in HIV-1-infected children treated with lopinavir/ritonavir. *J Acquir Immune Defic Syndr.* 2004;37(2):1269-1275.
28. Hsu A, Isaacson J, Brun S, et al. Pharmacokinetic-pharmacodynamic analysis of lopinavir-ritonavir in combination with efavirenz and two nucleoside reverse transcriptase inhibitors in extensively pretreated human immunodeficiency virus-infected patients. *Antimicrob Agents Chemother.* 2003;47(1):350-359.
29. Rakhmanina N, van den Anker J, Baghdassarian A, et al. Population pharmacokinetics of lopinavir predict suboptimal therapeutic concentrations in treatment-experienced human immunodeficiency virus-infected children. *Antimicrob Agents Chemother.* 2009;53(6):2532-2538.

Nelfinavir (NFV, Viracept)

For additional information see: **http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm**

Formulations

Powder for oral suspension: 50 mg/1 level gram scoopful (200 mg/1 level teaspoon)
(Oral powder contains 11.2 mg phenylalanine per gram of powder.)
Tablets: 250 mg and 625 mg

Dosing Recommendations

Neonatal/Infant dose:
Not approved for use in neonates/infants.

Pediatric dose (2–13 years):
45–55 mg/kg twice daily **or** 25–35 mg/kg three times daily

Adolescent/Adult dose:
1,250 mg (five 250-mg tablets or two 625-mg tablets) twice daily **or** 750 mg (three 250-mg tablets) three times daily

(Some adolescents require higher doses than adults to achieve equivalent drug exposures. Consider using therapeutic drug monitoring to guide appropriate dosing.)

Selected Adverse Events

- Diarrhea
- Hyperlipidemia
- Hyperglycemia
- Fat maldistribution
- Possible increase in bleeding episodes in patients with hemophilia
- Serum transaminase elevations

Special Instructions

- Administer with meal or light snack.
- If coadministered with didanosine (ddI), administer NFV 2 hours before or 1 hour after ddI.
- Powder for oral suspension may be mixed with water, milk, pudding, ice cream, or formula; mixture is stable for up to 6 hours.
- Do not mix with any acidic food or juice because of resulting poor taste.
- Do not add water to bottles of oral powder; a special scoop is provided with oral powder for measuring purposes.
- Patients unable to swallow the tablets can dissolve the tablets in a small amount of water. Once dissolved, patients should mix the cloudy mixture well and consume it immediately. The glass should be rinsed with water and the rinse swallowed to ensure that the entire dose is consumed. Tablets can also be crushed and administered with pudding.

Metabolism

- CYP2C19 and 3A4 substrate.
- Metabolized to active M8 metabolite.
- CYP3A inhibitor.

Drug Interactions (See also the ***Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents***.)***:***

- *Metabolism:* Nelfinavir is metabolized in part by CYP3A4 and is a substrate for CYP2C19 and 3A4. However, ritonavir boosting does not significantly increase nelfinavir concentrations and coadministration is not recommended.
- There is potential for multiple drug interactions.
- Before administration, the patient's medication profile should be carefully reviewed for potential drug interactions.

Major Toxicities:

- *More common:* Diarrhea (most common). Asthenia, abdominal pain, rash, and lipid abnormalities.
- *Less common (more severe):* Exacerbation of chronic liver disease, fat redistribution.
- *Rare:* New onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of pre-existing diabetes mellitus, spontaneous bleeding in hemophiliacs, and elevations in transaminases.

Resistance: The International AIDS Society-USA (IAS-USA) maintains a list of updated resistance mutations (see **http://www.iasusa.org/resistance_mutations/index.html**) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see **http://hivdb.stanford.edu/pages/GRIP/NFV.html**).

Pediatric Experience: Nelfinavir has been extensively studied in HIV-infected children in combination with other antiretroviral drugs *[1-23]*. In children 2–13 years of age receiving nelfinavir as part of triple antiretroviral therapy in randomized trials, the

proportion of patients with HIV RNA <400 copies/mL through 48 weeks of therapy has been quite variable, ranging from 26% to 69%. Virologic and immunologic response to nelfinavir-based therapy has varied by prior antiretroviral treatment, the number of drugs included in the combination regimen, patient age, and dose used in the study.

Highly variable drug exposure remains a significant problem with the use of nelfinavir in pediatric patients. Unpredictable drug exposure may be exacerbated in pediatric patients because of increased clearance compared with adults and difficulties with adherence to adequate food intake with dosing. In earlier studies, lower doses were used (20–30 mg/kg body weight per dose three times daily) than are currently recommended (45–55 mg/kg body weight per dose twice daily), accounting for some of the lower response rates. The relatively poor ability of nelfinavir to control plasma viremia in infants and children may be related in part to its reduced potency compared with other PIs or NNRTIs, as shown by studies in adults and adolescents *[23-24]*.

Poor outcome with nelfinavir in children may be related in part to lack of palatability of the powder formulation and pharmacokinetic differences in infants, children, and adolescents compared with adults *[6]*. The consistency of food or formula is altered by the addition of pediatric nelfinavir powder, making the drug/admixture unpalatable to some children. These children may prefer the bitterness of the crushed tablets to the sandy consistency of food or formula containing nelfinavir powder. In the PENTA-7 trial, 7 of 20 (35%) infants who started therapy with the nelfinavir powder were switched to crushed tablets because of the difficulty of administering the powder to infants *[1]*.

Analysis of data from PACTG 377 and PACTG 366 showed that CYP2C19 genotypes altered nelfinavir pharmacokinetics and the virologic responses to combination therapy in HIV-1-infected children. These findings suggest that CYP2C19 genotypes are important determinants of nelfinavir pharmacokinetics and virologic response in HIV-1-infected children *[25]*.

Better control of plasma viremia has been observed in antiretroviral-naïve than antiretroviral-experienced children receiving nelfinavir *[8, 11, 16]*. In treatment-experienced patients, better response rates have been seen with 4-drug regimens that have included 2 NRTIs plus an NNRTI *[11, 21]*. When lopinavir/ritonavir was compared with nelfinavir for salvage therapy in 35 treatment-experienced patients after 18 months, 50% of children receiving lopinavir/ritonavir had HIV RNA concentrations <400 copies/mL, compared with <20% of children receiving nelfinavir *[18]*.

Antiviral response in children <2 years of age is significantly less than in older children *[16, 19, 26]*. Improved virologic responses may be seen with nelfinavir-based therapy when it is used as part of a four-drug regimen in children <2 years of age *[14]*. Infants have even lower drug exposures and higher variability in plasma concentrations than children <25 kg; the presence of lower peak drug concentrations and higher apparent oral clearance suggests that both poor absorption and more rapid metabolism may be contributing factors *[3, 15]*. Even with doses of 150 mg/kg/day (given 2–3 times daily), 16.7% of children had peak concentrations and 27.8% of children had 24-hour AUC that were below the 10th percentile of adult values *[13]*. Although it is suggested that dosing in infants might improve if a mg/m^2 of body surface area dosing regimen were used *[2-3]*, such dosing is not recommended at this time. A population pharmacokinetic study predicts three-times daily dosing may be superior to twice-daily dosing in infants <2 months of age *[27]*. This model requires confirmation in infants.

Determining an appropriate and effective dose of nelfinavir in children is complicated by highly variable drug pharmacokinetics. In children 2–12 years of age, administration of a nelfinavir 30 mg/kg/dose three times daily achieves lower drug exposure than administration of a 55 mg/kg/dose twice daily, and this difference is most marked in children weighing <25 kg *[20]*. Children <25 kg may have less than half the drug exposure than children >25 kg when comparable body weight-adjusted doses are used *[7]*. The variability of drug exposure at any given dose is much higher for children than adults *[9]*, which has been attributed at least in part to differences in the diet between children and adults. Two population pharmacokinetic studies of nelfinavir and its active metabolite, M8, describe the large intersubject variability observed in children *[27-28]*.

Studies in adults and children have demonstrated an increased risk of virologic failure associated with low nelfinavir drug exposure, particularly with a nelfinavir C_{min} <1.0 mcg/mL *[29-31]*. In a study of 32 children treated with nelfinavir 90 mg/kg/day divided into 2 or 3 doses a day, 80% of those with morning trough nelfinavir plasma concentration >0.8 mcg/mL had Week 48 HIV RNA concentrations <50 copies/mL, compared with only 29% of those with morning trough <0.8 mcg/mL *[32]*. It is of note that the median age of the group with C_{trough} <0.8 mcg/mL was 3.8 years, while the median age of the group with C_{trough} >0.8 mcg/mL was 8.3 years *[32]*. Therapeutic drug monitoring of nelfinavir plasma concentrations, with appropriate adjustments for low drug exposure, results in improved outcome in adults treated with nelfinavir *[29, 33]*. Given the higher variability of nelfinavir plasma concentrations in infants and children, the benefits of therapeutic drug monitoring and appropriate dose adjustment might be even greater for children. A response rate of 78% was found in a recent pediatric study in which concentrations of nelfinavir and M8 were reported to treating physicians, suggesting a benefit of pharmacokinetic

monitoring in children *[28]*. In PACTG 382, among 50 children 3–16 years of age receiving both efavirenz and nelfinavir, better virologic outcomes (HIV RNA <400 copies/mL) occurred in those patients when nelfinavir AUC_{8h} was greater than the first quartile (>10 mg*h/L) when compared with those below the first quartile: 89% versus 42%, respectively *[5]*. Better virologic responses were obtained when doses were adjusted to achieve target AUC values, an approach that requires therapeutic drug monitoring.

References

1. Aboulker JP, Babiker A, Chaix ML, et al. Highly active antiretroviral therapy started in infants under 3 months of age: 72-week follow-up for CD4 cell count, viral load and drug resistance outcome. *AIDS.* 2004;18(2):237-245.
2. Bergshoeff AS, Fraaij PL, van Rossum AM, et al. Pharmacokinetics of nelfinavir in children: influencing factors and dose implications. *Antivir Ther.* 2003;8(3):215-222.
3. Capparelli EV, Sullivan JL, Mofenson L, et al. Pharmacokinetics of nelfinavir in human immunodeficiency virus-infected infants. *Pediatr Infect Dis J.* 2001;20(8):746-751.
4. Chaix ML, Rouet F, Kouakoussui KA, et al. Genotypic human immunodeficiency virus type 1 drug resistance in highly active antiretroviral therapy-treated children in Abidjan, Cote d'Ivoire. *Pediatr Infect Dis J.* 2005;24(12):1072-1076.
5. Fletcher CV, Brundage RC, Fenton T, et al. Pharmacokinetics and pharmacodynamics of efavirenz and nelfinavir in HIV-infected children participating in an area-under-the-curve controlled trial. *Clin Pharmacol Ther.* 2008;83(2):300-306.
6. Fletcher CV. Antiretroviral therapy for HIV-infected infants: progress and pitfalls. *AIDS.* 2004;18(2):325-326.
7. Floren LC, Wiznia A, Hayashi S, et al. Nelfinavir pharmacokinetics in stable human immunodeficiency virus-positive children: Pediatric AIDS Clinical Trials Group Protocol 377. *Pediatrics.* 2003;112(3 Pt 1):e220-227.
8. Funk MB, Linde R, Wintergerst U, et al. Preliminary experiences with triple therapy including nelfinavir and two reverse transcriptase inhibitors in previously untreated HIV-infected children. *AIDS.* 1999;13(13):1653-1658.
9. Gatti G, Castelli-Gattinara G, Cruciani M, et al. Pharmacokinetics and pharmacodynamics of nelfinavir administered twice or thrice daily to human immunodeficiency virus type 1-infected children. *Clin Infect Dis.* 2003;36(11):1476-1482.
10. King JR, Nachman S, Yogev R, et al. Efficacy, tolerability and pharmacokinetics of two nelfinavir-based regimens in human immunodeficiency virus-infected children and adolescents: pediatric AIDS clinical trials group protocol 403. *Pediatr Infect Dis J.* 2005;24(10):880-885.
11. Krogstad P, Lee S, Johnson G, et al. Nucleoside-analogue reverse-transcriptase inhibitors plus nevirapine, nelfinavir, or ritonavir for pretreated children infected with human immunodeficiency virus type 1. *Clin Infect Dis.* 2002;34(7):991-1001.
12. Krogstad P, Wiznia A, Luzuriaga K, et al. Treatment of human immunodeficiency virus 1-infected infants and children with the protease inhibitor nelfinavir mesylate. *Clin Infect Dis.* 1999;28(5):1109-1118.
13. Litalien C, Faye A, Compagnucci A, et al. Pharmacokinetics of nelfinavir and its active metabolite, hydroxy-tert-butylamide, in infants perinatally infected with human immunodeficiency virus type 1. *Pediatr Infect Dis J.* 2003;22(1):48-55.
14. Luzuriaga K, McManus M, Mofenson L, et al. A trial of three antiretroviral regimens in HIV-1-infected children. *N Engl J Med.* 2004;350(24):2471-2480.
15. Mirochnick M, Stek A, Acevedo M, et al. Safety and pharmacokinetics of nelfinavir coadministered with zidovudine and lamivudine in infants during the first 6 weeks of life. *J Acquir Immune Defic Syndr.* 2005;39(2):189-194.
16. Paediatric European Network for Treatment of AIDS (PENTA). Comparison of dual nucleoside-analogue reverse-transcriptase inhibitor regimens with and without nelfinavir in children with HIV-1 who have not previously been treated: the PENTA 5 randomised trial. *Lancet.* 2002;359(9308):733-740.
17. Resino S, Larru B, Maria Bellon J, et al. Effects of highly active antiretroviral therapy with nelfinavir in vertically HIV-1 infected children: 3 years of follow-up. Long-term response to nelfinavir in children. *BMC Infect Dis.* 2006;6:107.
18. Resino S, Bellon JM, Munoz-Fernandez MA. Antiretroviral activity and safety of lopinavir/ritonavir in protease inhibitor-experienced HIV-infected children with severe-moderate immunodeficiency. *J Antimicrob Chemother.* 2006;57(3):579-582.
19. Scherpbier HJ, Bekker V, van Leth F, et al. Long-term experience with combination antiretroviral therapy that contains nelfinavir for up to 7 years in a pediatric cohort. *Pediatrics.* 2006;117(3):e528-536.
20. Schuster T, Linde R, Wintergerst U, et al. Nelfinavir pharmacokinetics in HIV-infected children: a comparison of twice daily and three times daily dosing. *AIDS.* 2000;14(10):1466-1468.
21. Starr SE, Fletcher CV, Spector SA, et al. Combination therapy with efavirenz, nelfinavir, and nucleoside reverse-transcriptase inhibitors in children infected with human immunodeficiency virus type 1. Pediatric AIDS Clinical Trials Group 382 Team. *N Engl J Med.* 1999;341(25):1874-1881.
22. van Heeswijk RP, Scherpbier HJ, de Koning LA, et al. The pharmacokinetics of nelfinavir in HIV-1-infected children. *Ther Drug Monit.* 2002;24(4):487-491.
23. Wu H, Lathey J, Ruan P, et al. Relationship of plasma HIV-1 RNA dynamics to baseline factors and virological responses to highly active antiretroviral therapy in adolescents (aged 12-22 years) infected through high-risk behavior. *J Infect Dis.* 2004;189(4):593-601.

24. Walmsley S, Bernstein B, King M, et al. Lopinavir-ritonavir versus nelfinavir for the initial treatment of HIV infection. *N Engl J Med.* 2002;346(26):2039-2046.
25. Saitoh A, Capparelli E, Aweeka F, et al. CYP2C19 genetic variants affect nelfinavir pharmacokinetics and virologic response in HIV-1-infected children receiving highly active antiretroviral therapy. *J Acquir Immune Defic Syndr.* 2010;54(3):285-289.
26. Food and Drug Administration (FDA). Nelfinavir (Viracept®) product label. http://www.accessdata.fda.gov/drugsatfda_docs/label/2005/021503s006lbl.pdf.
27. Hirt D, Urien S, Jullien V, et al. Age-related effects on nelfinavir and M8 pharmacokinetics: a population study with 182 children. *Antimicrob Agents Chemother.* 2006;50(3):910-916.
28. Crommentuyn KM, Scherpbier HJ, Kuijpers TW, et al. Population pharmacokinetics and pharmacodynamics of nelfinavir and its active metabolite M8 in HIV-1-infected children. *Pediatr Infect Dis J.* 2006;25(6):538-543.
29. Burger DM, Hugen PW, Aarnoutse RE, et al. Treatment failure of nelfinavir-containing triple therapy can largely be explained by low nelfinavir plasma concentrations. *Ther Drug Monit.* 2003;25(1):73-80.
30. Gonzalez de Requena D, Nunez M, de Mendoza C, et al. Nelfinavir plasma concentrations in patients experiencing early failure with nelfinavir-containing triple combinations. *AIDS.* 2003;17(3):442-444.
31. Pellegrin I, Breilh D, Montestruc F, et al. Virologic response to nelfinavir-based regimens: pharmacokinetics and drug resistance mutations (VIRAPHAR study). *AIDS.* 2002;16(10):1331-1340.
32. Burger DM, Bergshoeff AS, De Groot R, et al. Maintaining the nelfinavir trough concentration above 0.8 mg/L improves virologic response in HIV-1-infected children. *J Pediatr.* 2004;145(3):403-405.
33. Burger D, Hugen P, Reiss P, et al. Therapeutic drug monitoring of nelfinavir and indinavir in treatment-naive HIV-1-infected individuals. *AIDS.* 2003;17(8):1157-1165.

Ritonavir (RTV, Norvir)

For additional information see Drugs@FDA: **http://www.accessdata.fda.gov/scripts/cder/drugsatfda/**

Formulations

Oral solution (contains 43% alcohol by volume): 80 mg/mL
Capsules: 100 mg
Tablets: 100 mg

Dosing Recommendations

RTV as a pharmacokinetic enhancer:
The major use of RTV is as a pharmacokinetic enhancer of other PIs. The dose of RTV recommended varies with the different PIs. See dosing information for specific PIs.

In the unusual situation when RTV is prescribed as sole PI:
See manufacturer guidelines.

Selected Adverse Events

- GI intolerance, nausea, vomiting, diarrhea
- Paresthesias—circumoral and extremities
- Hyperlipidemia, especially hypertriglyceridemia
- Hepatitis
- Asthenia
- Taste perversion
- Hyperglycemia
- Fat maldistribution
- Possible increased bleeding episodes in patients with hemophilia

Special Instructions

- Administer with food to increase absorption and help decrease gastrointestinal side effects.
- If RTV is prescribed with didanosine (ddI), administer drugs 2 hours apart.
- Refrigerate capsules only if the capsules will not be used within 30 days or cannot be stored below 77° F (25° C). Tablets are heat stable.
- Store oral solution at room temperature 68–77°F (20–25°C). Do not refrigerate. Shake well before use.
- Oral solution has limited shelf life; use within 6 months.

To increase tolerance of oral solution in children, try the following:

- Mix solution with milk, chocolate milk, or vanilla or chocolate pudding or ice cream.
- Before administration, give the child ice chips, popsicles, or spoonfuls of partially frozen orange or grape juice concentrate to dull the taste buds or peanut butter to coat the mouth.
- After administration, give the child strong-tasting foods such as maple syrup, cheese, or highly flavored chewing gum.

Metabolism

- CYP3A4 and CYP 2D6 inhibitor; CYP3A4 and CYP1A2 inducer.
- Dosing of RTV in patients with hepatic impairment: RTV is primarily metabolized by the liver. No dosage adjustment is necessary in patients with mild or moderate hepatic impairment. There are no data for dosing adult or pediatric patients with severe hepatic impairment. Use caution when administering RTV to patients with moderate-to-severe hepatic impairment.

Drug Interactions (See also the ***Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents***.)***:***

- *Metabolism*: Ritonavir is extensively metabolized by and is one of the most potent inhibitors of hepatic cytochrome P450 3A (CYP3A). There is potential for multiple drug interactions.
- Before administration, the patient's medication profile should be carefully reviewed for potential drug interactions and overlapping toxicities.
- Avoid concomitant use of intranasal/inhaled fluticasone.

Resistance: When ritonavir is used as a pharmacokinetic enhancer, resistance to ritonavir is not clinically relevant.

Major Toxicities:

- *More common:* Nausea, vomiting, diarrhea, headache, abdominal pain, anorexia, circumoral paresthesias, lipid abnormalities.
- *Less common (more severe):* Exacerbation of chronic liver disease, fat maldistribution.
- *Rare:* New onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of pre-existing diabetes mellitus, spontaneous bleeding in hemophiliacs, pancreatitis, and hepatitis (life-threatening in rare cases). Allergic reactions, including bronchospasm, urticaria, and angioedema.

Pediatric Experience: Ritonavir is typically used as a pharmacokinetic enhancer of other PIs in children. Ritonavir acts by inhibiting the metabolism of the other PI, therefore increasing the plasma concentration of the second PI. Lopinavir/ritonavir, a PI coformulation, has been well studied in children and is the preferred PI for initial therapy in children (see **Lopinavir/Ritonavir**). Pediatric dosing regimens including boosted fosamprenavir, tipranavir, darunavir, and atazanavir are now available (see individual PIs for more specific information).

Although ritonavir has been well studied, its use in children as a sole PI for initial therapy is recommended only under certain rare circumstances. Ritonavir is associated with a higher incidence of gastrointestinal toxicity and has a greater potential for drug-drug interactions than other PIs. Additionally, poor palatability of the liquid preparation and large pill burden with the capsules (adult dose is six capsules twice daily) limit its use as a sole PI. Concentrations are highly variable in children younger than 2 years of age, and doses of 350–450 mg/m^2 twice a day may not be sufficient for long-term suppression of viral replication in this age group *[1-12]*.

Full-dose ritonavir has been shown to prolong the PR interval in a study of healthy adults who were given ritonavir at 400 mg twice daily *[13]*. There have been reports of potentially life threatening arrhythmias in premature newborn infants treated with lopinavir/ritonavir and thus it should not be used in this group of patients *[14-15]*. The impact on the PR interval of coadministration of ritonavir with other drugs that prolong the PR interval (e.g., macrolides, quinolones, methadone) is not known, and coadministration should be undertaken with caution. In addition, patients with underlying structural heart disease, conduction system abnormalities, ischemic heart disease, or cardiomyopathy may be at increased risk of developing cardiac conduction abnormalities, and ritonavir should be used with caution in these patients.

References

1. Bergshoeff AS, Fraaij PL, van Rossum AM, et al. Pharmacokinetics of indinavir combined with low-dose ritonavir in human immunodeficiency virus type 1-infected children. *Antimicrob Agents Chemother.* 2004;48(5):1904-1907.
2. Fletcher CV, Yogev R, Nachman SA, et al. Pharmacokinetic characteristics of ritonavir, zidovudine, lamivudine, and stavudine in children with human immunodeficiency virus infection. *Pharmacotherapy.* 2004;24(4):453-459.
3. Chadwick EG, Rodman JH, Britto P, et al. Ritonavir-based highly active antiretroviral therapy in human immunodeficiency virus type 1-infected infants younger than 24 months of age. *Pediatr Infect Dis J.* 2005;24(9):793-800.
4. King JR, Nachman S, Yogev R, et al. Efficacy, tolerability and pharmacokinetics of two nelfinavir-based regimens in human immunodeficiency virus-infected children and adolescents: pediatric AIDS clinical trials group protocol 403. *Pediatr Infect Dis J.* 2005;24(10):880-885.
5. Krogstad P, Lee S, Johnson G, et al; Pediatric AIDS Clinical Trials Group 377 Study Team. Nucleoside-analogue reverse-transcriptase inhibitors plus nevirapine, nelfinavir, or ritonavir for pretreated children infected with human immunodeficiency virus type 1. *Clin Infect Dis.* 2002;34(7):991-1001.
6. Mueller BU, Nelson RPJr, Sleasman J, et al. A phase I/II study of the protease inhibitor ritonavir in children with human immunodeficiency virus infection. *Pediatrics.* 1998;101(3 Pt 1):335-343.

7. Nachman SA, Stanley K, Yogev R, et al. Nucleoside analogs plus ritonavir in stable antiretroviral therapy-experienced HIV-infected children: a randomized controlled trial. Pediatric AIDS Clinical Trials Group 338 Study Team. *JAMA.* 2000;283(4):492-498.
8. Palacios GC, Palafox VL, Alvarez-Munoz MT, et al. Response to two consecutive protease inhibitor combination therapy regimens in a cohort of HIV-1-infected children. *Scand J Infect Dis.* 2002;34(1):41-44.
9. Thuret I, Michel G, Chambost H, et al. Combination antiretroviral therapy including ritonavir in children infected with human immunodeficiency. *AIDS.* 1999;13(1):81-87.
10. van Rossum AM, de Groot R, Hartwig NG, et al. Pharmacokinetics of indinavir and low-dose ritonavir in children with HIV-1 infection. *AIDS.* 2000;14(14):2209-2210.
11. Wiznia A, Stanley K, Krogstad P, et al. Combination nucleoside analog reverse transcriptase inhibitor(s) plus nevirapine, nelfinavir, or ritonavir in stable antiretroviral therapy-experienced HIV-infected children: week 24 results of a randomized controlled trial--PACTG 377. Pediatric AIDS Clinical Trials Group 377 Study Team. *AIDS Res Hum Retroviruses.* 2000;16(12):1113-1121.
12. Yogev R, Lee S, Wiznia A, et al. for the Pediatric AIDS Clinical Trials Group 338 Study Team. Stavudine, nevirapine and ritonavir in stable antiretroviral therapy-experienced children with human immunodeficiency virus infection. *Pediatr Infect Dis J.* 2002;21(2):119-125.
13. Changes to Norvir labeling. *AIDS Patient Care STDS.* 2008;22(10):834-835.
14. Lopriore E, Rozendaal L, Gelinck LB, et al. Twins with cardiomyopathy and complete heart block born to an HIV-infected mother treated with HAART. *AIDS.* 2007;21(18):2564-2565.
15. McArthur MA, Kalu SU, Foulks AR, et al. Twin preterm neonates with cardiac toxicity related to lopinavir/ritonavir therapy. *Pediatr Infect Dis J.* 2009;28(12):1127-1129.

Saquinavir (SQV, Invirase)

For additional information see Drugs@FDA: **http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm**

Formulations

Hard gel capsules (HGC): 200 mg
Film-coated tablets: 500 mg

Dosing Recommendations

Neonate/Infant dose:
Not approved for use in neonates/infants.

Pediatric dose:
Not approved for use in children.

Investigational doses in treatment-experienced children:
SQV must be boosted with ritonavir (RTV):

<2 years of age:
Not recommended—no dose has been determined.

≥2 years of age (conditional recommendation based on limited data):

Weight (kg)	Dose SQV + RTV
5– <15 kg	SQV 50mg/kg + RTV 3 mg/kg, both twice daily
15–40 kg	SQV 50mg/kg + RTV 2.5 mg/kg, both twice daily
≥40 kg	SQV 50mg/kg + RTV 100 mg, both twice daily

Dosing Recommendations for Coadministration with Other Antiretroviral Drugs

SQV in combination with lopinavir/ritonavir (LPV/r)
Pediatric (≥7 years) dose:
SQV 750 mg/m^2 (max 1,600 mg) + LPV/r 400/100 mg/m^2, both twice daily

or

SQV 50 mg/kg + LPV/r 230/57.5 mg/m^2, both twice daily

There are limited or no data on SQV + LPV/r dosing for children <7 years of age. See pediatric experience section for details.

Adolescent (≥16 years)/Adult dose:
SQV 1,000 mg + RTV 100 mg, both twice daily
Should be taken within 2 hours after a full meal. SQV should **only** be used in combination with RTV or LPV/r (never unboosted).

Selected Adverse Events

- GI intolerance, nausea, and diarrhea
- Headache
- Elevated transaminases
- Hyperlipidemia
- Hyperglycemia
- Fat maldistribution
- Possible increased bleeding episodes in patients with hemophilia

Special Instructions

- Administer within 2 hours after a full meal to increase absorption.
- Sun exposure can cause photosensitivity reactions; advise patients to use sunscreen or protective clothing.

Metabolism

- Cytochrome P450 CYP3A4 substrate, 90% metabolized in the liver.
- Use with caution in patients with hepatic impairment.

Drug Interactions (See also the ***Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents***.)***:***

- *Metabolism:* Saquinavir is metabolized by the cytochrome P450 3A4 (CYP3A4) system in the liver, and there is potential for numerous drug interactions.
- Before administration, the patient's medication profile should be carefully reviewed for potential drug interactions.

Major Toxicities:

- *More common:* Diarrhea, abdominal discomfort, headache, nausea, paresthesias, skin rash, and lipid abnormalities.
- *Less common (more severe):* Exacerbation of chronic liver disease, fat maldistribution.

- *Rare:* New onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of pre-existing diabetes mellitus, spontaneous bleeding in hemophiliacs, pancreatitis, and elevation in serum transaminases. The combination of saquinavir and ritonavir could lead to prolonged PR and/or QT intervals with potential for heart block and torsades de pointes.

Resistance: The International AIDS Society-USA (IAS-USA) maintains a list of updated resistance mutations (see **http://www.iasusa.org/resistance_mutations/index.html**) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see **http://hivdb.stanford.edu/pages/GRIP/SQV.html**).

Pediatric Experience: Saquinavir has been studied with NRTIs and other PIs in HIV-infected children *[1-6]*. Initial studies suggested that saquinavir could not be used without boosting by ritonavir or lopinavir/ritonavir. A pharmacokinetic analysis of 5 children younger than 2 years of age and 13 children between the ages of 2 and 5 years using a dose of 50 mg/kg twice daily with boosting ritonavir revealed that drug exposure was lower in children <2 years whereas drug exposure was adequate in those 2 to 5 years of age *[7]*. For this reason, saquinavir should not be given to children younger than 2 years old until an appropriate dose is identified. In children ≥2 years of age, a dose of 50mg/kg twice daily (maximum dose = 1,000 mg) boosted with ritonavir 3 mg/kg twice daily (patients weighing 5 to <15 kg) or 2.5 mg/kg twice daily (patients weighing 15 to 40 kg) resulted in AUC and C_{trough} values similar to those in older children *[8-9]* and adults. Because there is no pediatric formulation, in one study saquinavir was formulated by breaking open the 200-mg hard gel capsules and mixing capsule contents with sugar syrup, jam, or baby formula. Sorbitol syrup was used for patients with diabetes or glucose intolerance *[7]*.

Both saquinavir/ritonavir and saquinavir/lopinavir/ritonavir regimens are promising in the salvage therapy setting *[1, 3-6, 8-10]*. In a study evaluating the addition of saquinavir (750 mg/m^2 of body surface area every 12 hours, maximum dose 1,600 mg) to a regimen containing lopinavir/ritonavir dosed at 400/100 mg/m^2 twice daily (for patients not concurrently taking an NNRTI) or lopinavir/ritonavir 480/120 mg/m^2 twice daily for patients concurrently administered an NNRTI, 18 subjects (median age 14.2 years, range 7.7–17.6) were enrolled. The addition of saquinavir at these doses was well tolerated and did not appear to alter lopinavir pharmacokinetics. Saquinavir dosing was adjusted in 4 subjects (decreased in 3, increased in 1) *[10]*.

In a study of 50 Thai children, saquinavir/lopinavir/ritonavir was initiated as second-line therapy based on extensive NRTI resistance. In this group, saquinavir was dosed at 50 mg/m^2 and lopinavir/ritonavir was dosed at 230/57.5 mg/m^2, all twice daily. After 96 weeks of treatment, 74% of the children achieved an undetectable plasma RNA load at <50 copies/ml. Therapeutic drug monitoring was used to establish adequate C_{min} values and to aid with alterations in drug dosage based upon toxicity. Most C_{min} values for saquinavir were above the desired trough value of 0.1 mg/l. The average C_{min} throughout 96 weeks for saquinavir was 1.37 mg/l, and when saquinavir doses were adjusted, most were decreased by an average of 21% (8mg/kg). Median total cholesterol and HDL values increased significantly through 96 weeks from 144 to 196 mg/dl and from 44 to 57 mg/dl, respectively *[8-9]*.

References

1. Ananworanich J, Kosalaraksa P, Hill A, et al. Pharmacokinetics and 24-week efficacy/safety of dual boosted saquinavir/lopinavir/ritonavir in nucleoside-pretreated children. *Pediatr Infect Dis J.* 2005;24(10):874-879.
2. De Luca M, Miccinesi G, Chiappini E, et al. Different kinetics of immunologic recovery using nelfinavir or lopinavir/ritonavir-based regimens in children with perinatal HIV-1 infection. *Int J Immunopathol Pharmacol.* 2005;18(4):729-735.
3. Grub S, DeLora P, Ludin E, et al. Pharmacokinetics and pharmacodynamics of saquinavir in pediatric patients with human immunodeficiency virus infection. *Clin Pharmacol Ther.* 2002;71(3):122-130.
4. Hoffmann F, Notheis G, Wintergerst U, et al. Comparison of ritonavir plus saquinavir- and nelfinavir plus saquinavir-containing regimens as salvage therapy in children with human immunodeficiency type 1 infection. *Pediatr Infect Dis J.* 2000;19(1):47-51.
5. Kline MW, Brundage RC, Fletcher CV, et al. Combination therapy with saquinavir soft gelatin capsules in children with human immunodeficiency virus infection. *Pediatr Infect Dis J.* 2001;20(7):666-671.
6. Palacios GC, Palafox VL, Alvarez-Munoz MT, et al. Response to two consecutive protease inhibitor combination therapy regimens in a cohort of HIV-1-infected children. *Scand J Infect Dis.* 2002;34(1):41-44.
7. Haznedar J, Zhang A, Labriola-Tompkins E, et al. A pharmacokinetic study of ritonavir-boosted saquinavir in HIV-infected children 4 months to <6 years old. Paper presented at: 17th Conference on Retroviruses and Opportunistic Infections (CROI); February 16-19, 2010; San Francisco, CA.

8. Kosalaraksa P, Bunupuradah T, Engchanil C, et al. Double boosted protease inhibitors, saquinavir, and lopinavir/ritonavir, in nucleoside pretreated children at 48 weeks. *Pediatr Infect Dis J.* 2008;27(7):623-628.
9. Bunupuradah T, van der Lugt J, Kosalaraksa P, et al. Safety and efficacy of a double-boosted protease inhibitor combination, saquinavir and lopinavir/ritonavir, in pretreated children at 96 weeks. *Antivir Ther.* 2009;14(2):241-248.
10. Robbins BL, Capparelli EV, Chadwick EG, et al. Pharmacokinetics of high-dose lopinavir-ritonavir with and without saquinavir or nonnucleoside reverse transcriptase inhibitors in human immunodeficiency virus-infected pediatric and adolescent patients previously treated with protease inhibitors. *Antimicrob Agents Chemother.* 2008;52(9):3276-3283.

Tipranavir (TPV, Aptivus)

For additional information see Drugs@FDA: **http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm**

Formulations

Oral solution: 100 mg TPV/ml with 116 IU vitamin E/ml
Capsules: 250 mg

Dosing Recommendations

TPV must be used with ritonavir (RTV) boosting. The RTV boosting dose is higher than that used for other PIs.

Pediatric dose (<2 years):
Not approved for use in children <2 years of age.

Pediatric dose (2–18 years):
Body surface area dosing:
TPV 375 mg/m2 + RTV 150 mg/m2, both twice daily
Maximum dose:
TPV 500 mg + RTV 200 mg, both twice daily

Weight-based dosing:
TPV 14 mg/kg + RTV 6 mg/kg, both twice daily
Maximum dose:
TPV 500 mg + RTV 200 mg, both twice daily

Adult dose:
TPV 500 mg (two 250-mg capsules) + RTV 200 mg, both twice daily

Selected Adverse Events

- Intracranial hemorrhage (rare)
- Skin rash
- Nausea, vomiting, diarrhea
- Hepatotoxicity
- Hyperlipidemia
- Hyperglycemia
- Fat maldistribution
- Possible increased bleeding episodes in patients with hemophilia

Special Instructions

- TPV can be taken with or without food; however, it is recommended that RTV be taken with food. Therefore, the combination may be better tolerated if taken with a meal or snack.
- The oral solution contains 116 IU of vitamin E per mL, which is significantly higher than the reference daily intake for vitamin E. Patients taking the oral solution should not take any supplemental vitamin E greater than a standard multivitamin.
- TPV contains a sulfonamide component. The potential for cross sensitivity between TPV and other drugs in the sulfonamide class is unknown. TPV should be used with caution in patients with sulfonamide allergy.
- Store oral solution at room temperature (77^{o} F); do not refrigerate or freeze. Oral solution must be used within 60 days after first opening bottle.
- Capsules can be kept at room temperature (up to 77^{o}F or 25^{o}C) if used within 2 months. Refrigerate capsules if longer storage or warmer room temperatures anticipated.
- Use TPV with caution in patients who may be at risk of increased bleeding from trauma, surgery, or other medical conditions or who are receiving medications known to increase the risk of bleeding such as antiplatelet agents, anticoagulants, or high doses of supplemental vitamin E.

Metabolism

- Cytochrome P450 CYP3A4 substrate.
- Renal impairment: No adjustment required.
- Liver impairment: No adjustment required for mild impairment; use contraindicated for moderate-to-severe impairment.

Drug Interactions (See also the ***Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents***.):

- Before administration, the patient's medication profile should be carefully reviewed for potential drug interactions.
- Tipranavir should be used with caution in patients who may be at risk of increased bleeding from trauma, surgery, or other medical conditions or who are receiving medications known to increase the risk of bleeding such as antiplatelet agents, anticoagulants, or high doses of supplemental vitamin E.

Major Toxicities:

- *More common:* Diarrhea, nausea, fatigue, headache, rash (more frequent in children than in adults), and vomiting. Laboratory abnormalities are elevated transaminases, cholesterol, and triglycerides.
- *Less common (more severe):* Lipodystrophy. Clinical hepatitis and hepatic decompensation, including some fatalities. Patients with chronic hepatitis B or C coinfection or elevations in transaminases are at increased risk of developing further transaminase elevations or hepatic decompensation (approximately 2.5-fold risk). Epistaxis.
- *Rare:* New onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of pre-existing diabetes mellitus, spontaneous bleeding in hemophiliacs. Possible association with increased risk of intracranial hemorrhage.

Resistance: The International AIDS Society-USA (IAS-USA) maintains a list of updated resistance mutations (see **http://www.iasusa.org/resistance_mutations/index.html**) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see **http://hivdb.stanford.edu/pages/GRIP/TPV.html**).

Pediatric Experience: Tipranavir is approved in children ≥2 years of age; approval was based on a multicenter, pediatric study of the safety, efficacy, and pharmacokinetics of tipranavir/ritonavir in HIV-infected children (PACTG 1051/BI-1182.14). This study enrolled treatment-experienced children (with the exception of 3 treatment-naïve patients) 2–18 years of age (median age 11.7 years) with baseline HIV RNA ≥1,500 copies/mL. Children were randomized to 1 of 2 doses of tipranavir coadministered with ritonavir in 3 age strata: tipranavir/ritonavir 290 mg/115 mg per m^2 body surface area (low dose, 58 patients) or 375 mg/150 mg per m^2 body surface area (high dose, 57 patients) twice daily plus optimized background therapy. All children initially received the oral solution; patients who were ≥12 years of age and received the maximum adult dose of 500 mg tipranavir/200 mg ritonavir twice daily could change to tipranavir capsules. At baseline, greater than 50% of patients were resistant to all commercially available protease inhibitors, and the number of protease resistance mutations increased with age *[1]*. Among the low-dose group (tipranavir/ritonavir 290/115 mg/m^2 body surface area), 40% achieved HIV RNA <400 copies/mL and 35% <50 copies/mL at 48 weeks. Among those receiving the higher dose (tipranavir/ritonavir 375/150 mg/m^2 body surface area), 46% achieved HIV RNA <400 copies/mL and 35% <50 copies/mL at 48 weeks. The proportion of patients with HIV RNA <400 copies/mL tended to be greater in the youngest group of patients (70%), who had less baseline resistance. Tipranavir treatment was associated with a mean increase in CD4 cell count of 100 cells/mm^3 and 59 cells/mm^3 in low- and high-dose groups, respectively. Overall, side effects were similar between treatment groups. Twenty-five percent of children experienced a drug-related serious adverse event, and 9% of patients discontinued study drugs due to adverse events. The most common adverse events were gastrointestinal disturbances. Moderate or severe laboratory toxicity was seen in 11% of children (primarily increase in GGT and CPK). Four patients (all in the low-dose group and three-fourths in the younger age group) developed AIDS-defining illnesses through 48 weeks. A Kaplan-Meier analysis comparing AIDS-defining events in the low-dose versus the high-dose group reached statistical significance ($p = 0.04$). In a multivariate model, 3 variables predicted virologic outcome: greater genotypic inhibitory quotient (GIQ), greater adherence, and baseline viral load <100K copies/mL, in that order. GIQ is a ratio of the median tipranavir trough concentration divided by the number of tipranavir mutations. The GIQ was consistently greater in the high-dose group. Based on these findings and the increased number of AIDS-defining events in the low-dose group, the high-dose regimen has been recommended.

Pharmacokinetics of the liquid formulation at steady state were assessed *[2]*. For children 2 to <12 years of age, tipranavir trough concentrations for pediatric patients receiving tipranavir/ritonavir 290/115 mg/m^2 body surface area were consistent with tipranavir trough concentrations achieved in adults receiving standard tipranavir/ritonavir 500 mg/200 mg dosing. However, children 12 to 18 years of age required a higher dose (375/150 mg/m^2 body surface area, 30% higher than the directly scaled adult dose) to achieve drug exposure similar to that in adults receiving the standard tipranavir/ritonavir dose. Population pharmacokinetic analysis demonstrated that tipranavir clearance can be affected by body weight and that volume of distribution can be affected by age *[2]*. Based on these studies the final dose of tipranavir/ritonavir was chosen as 375/150 mg/m^2 body surface area twice daily.

Vitamin E is an excipient in the oral solution, with a concentration of 116 IU of vitamin E and 100 mg tipranavir per ml of solution. Use of the recommended dose of tipranavir (14 mg per kg body weight) results in a vitamin E dose of 16 IU per kg

body weight per day, significantly higher than the reference daily intake for vitamin E (10 IU) and close to the upper limit of tolerability for children. The resultant high dose of vitamin E may lead to an increase in bleeding episodes, which were seen in 5.75% of children receiving the oral solution and 14.3% of children receiving capsules *[1]*.

References

1. Salazar JC, Cahn P, Yogev R, et al. Efficacy, safety and tolerability of tipranavir coadministered with ritonavir in HIV-1-infected children and adolescents. *AIDS.* 2008;22(14):1789-1798.
2. Sabo J, Cahn P, Della Negra M, et al. Population pharmacokinetic (PK) assessment of systemic steady-state tipranavir (TPV) concentrations for HIV+ pediatric patients administered tipranavir/ritonavir (TPV/r) 290/115 mg/m2 and 375/150 mg/m2 BID (BI 1192.14 and PACTG 1051 study team). Paper presented at: 13th Conference on Retroviruses and Opportunistic Infections (CROI); February 5-9, 2006; Denver, CO. Abstract R136, poster 687.

ENTRY AND FUSION INHIBITORS

Enfuvirtide (ENF, T-20, Fuzeon)

For additional information see Drugs@FDA: **http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm**

Formulations

Lyophilized powder for injection:
108-mg vial of ENF. Reconstitution with 1.1 mL sterile water will deliver 90 mg/mL.

Convenience kit*:*
60 single-use vials of ENF (90 mg strength), 60 vials of sterile water for injection, 60 reconstitution syringes (3 mL), 60 administration syringes (1 mL), alcohol wipes

Dosage Recommendations

Pediatric/Adolescent dose (6–16 years):
Children <6 years:
Not approved for use in children <6 years of age.

Children ≥6 years:
2 mg/kg (maximum dose, 90 mg [1 mL]) twice daily injected subcutaneously into the upper arm, anterior thigh, or abdomen

Adolescent (>16 years)/Adult dose:
90 mg (1 mL) twice daily injected subcutaneously into the upper arm, anterior thigh, or abdomen

Selected Adverse Events

- Local injection site reactions
- Increased bacterial pneumonia (unclear association)
- Hypersensitivity reaction—symptoms may include rash, fever, nausea, vomiting, chills, rigors, hypotension, or elevated serum transaminases. Rechallenge is not recommended.

Special Instructions

- Carefully instruct patient or caregiver in proper technique for drug reconstitution and administration of subcutaneous injections. ENF injection instructions are provided with convenience kits.
- Allow reconstituted vial to stand until the powder goes completely into solution, which could take up to 45 minutes. Do not shake.
- Once reconstituted, inject ENF immediately or keep refrigerated in the original vial until use. Reconstituted ENF must be used within 24 hours.
- Must be given subcutaneously; severity of reactions increased if given intramuscularly.
- Give each injection at a site different from the preceding injection site; do not inject into moles, scar tissue, bruises, or the navel. Both the patient/caregiver and health care provider should carefully monitor for signs and symptoms of local infection or cellulitis.
- To minimize local reactions apply ice or heat after injection or gently massage injection site to better disperse the dose. There are reports of injection-associated neuralgia and parasthesia if alternative delivery systems, such as needle-free injection devices, are used.
- Advise patient/caregiver of the possibility of a hypersensitivity reaction; instruct them to discontinue treatment and seek immediate medical attention if the patient develops signs and symptoms consistent with a hypersensitivity reaction.

Metabolism

- Catabolism to constituent amino acids.

Drug Interactions (See also the ***Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents****.)***:

- There are no known significant drug interactions.

Major Toxicities:

- *More common:* Almost all patients (87%–98%) experience local injection site reactions including pain and discomfort, induration, erythema, nodules and cysts, pruritis, and ecchymosis. Usually mild to moderate in severity but can be more severe. Average duration of local injection site reaction is 3 to 7 days, but was >7 days in 24% of patients.
- *Less common (more severe):* Increased rate of bacterial pneumonia (unclear association) and local site cellulitis (up to 11% in certain subgroups of patients in pediatric studies) *[1]*.
- *Rare:* Hypersensitivity reactions (<1%) including fever, nausea and vomiting, chills, rigors, hypotension, and elevated liver transaminases; immune-mediated reactions including primary immune complex reaction, respiratory distress, glomerulonephritis, and Guillain-Barre syndrome. Patients experiencing hypersensitivity reactions should seek immediate

medical attention. Therapy should not be restarted in patients with signs and symptoms consistent with hypersensitivity reactions.

Resistance: The International AIDS Society-USA (IAS-USA) maintains a list of updated resistance mutations (see **http://www.iasusa.org/resistance_mutations/index.html**) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see **http://hivdb.stanford.edu/pages/GRIP/ENF.html**).

Pediatric Experience: Enfuvirtide has been studied in HIV-infected children in combination with other antiretroviral drugs *[1-5]*. PACTG 1005 initially studied enfuvirtide in 14 HIV-infected children age 4–12 years with incomplete viral suppression (plasma RNA >10,000 copies/ml) while on a stable antiretroviral regimen consisting of 2 NRTIs plus an NNRTI or a PI for ≥16 weeks *[2]*. Part A included a single-dose pharmacokinetic evaluation of enfuvirtide given subcutaneously at 15, 30, or 60 mg/m^2 of body surface area. The dose of enfuvirtide that reliably resulted in the target trough concentration (1,000 ng/mL) was 60 mg/m^2 of body surface area per dose, the approximate "equivalent" of a 90-mg dose delivered subcutaneously to an adult with a body surface area of 1.7 m^2. This led to the recommended pediatric label dose in children age 6–16 years of 2 mg/kg (maximum 90 mg) administered subcutaneously twice daily. In a second pediatric study of 25 children age 5–16 years, the 2 mg/kg dose, with a maximum dose of 90 mg, was found to yield drug concentrations similar to 60 mg/m^2 of body surface area dose and drug exposure was found to be independent of age group, body weight, body surface area, and sexual maturation *[6]*. Further data are needed in children <6 years of age. No metabolic induction or inhibition of enfuvirtide has been observed in PACTG 1005 or subsequent studies, nor was there a statistical relationship, within the utilized dosing schedule, between drug exposure with this agent and virologic benefit *[5]*.

Part B of PACTG 1005 evaluated the safety and antiretroviral activity of chronic twice-daily subcutaneous enfuvirtide administration at 60 mg/m^2 per dose in 14 children. For 7 days, the drug was added to each child's background antiretroviral regimen; at Day 7, the background regimen was optimized and enfuvirtide was continued, and children were followed for up to 96 weeks. Two children elected to discontinue enfuvirtide within 24 weeks (1 due to injection aversion, 1 due to an unrelated surgical procedure), 4 discontinued due to virologic failure (defined as >1 log increase in viral load above baseline), and 2 discontinued due to Grade 3 toxicity (thrombocytopenia, edema). In this cohort, most children had local injection site reactions. Seventy-nine percent of children had >0.7 log reduction in HIV RNA by Day 7. At 24 weeks of treatment, 71% had a >1.0 log reduction, 43% were suppressed to <400 copies/mL, and 21% were suppressed to <50 copies/mL *[4]*. However, only 36% of children maintained virologic suppression (>1.0 log decrease in HIV RNA) at Week 96 *[3]*. Significant improvements in CD4 percentage and height *z* score were observed in children receiving enfuvirtide for 48 and 96 weeks.

T20-310, a Phase I/II study of enfuvirtide (2.0 mg/kg subcutaneously, maximum 90 mg, twice daily) plus an optimized background antiretroviral regimen enrolled 52 treatment-experienced children 3–16 years of age for 48 weeks. Of those completing 48 weeks of therapy (64%), the median decrease in HIV RNA was -1.17 $\log_{10}$ copies/mL (n = 32) and there was a median increase of 106 cells/mm^3 (n = 25). Local skin reactions were common in all age groups (87%). Treatment responses at Week 8 were superior in younger (<11 years of age) children when contrasted with adolescents as measured by plasma HIV RNA change from baseline (-2.85 vs. -0.12 $\log_{10}$ copies/mL) or those maintaining HIV RNA <400 (42% vs. 4%). Median increases in CD4 count were 257 cells/mm^3 in children and 84 cells/mm^3 in adolescents. The observed differential responses between children and adolescents probably reflect unique challenges to adherence with the prescribed regimen *[1]*.

An increased rate of bacterial pneumonia was observed in adults treated with enfuvirtide compared with the control arm in the Phase III clinical trials *[7]*. A recent French cohort study with 1,220 patients receiving enfuvirtide and 9,374 patients on optimized therapy without enfuvirtide failed to find an increased risk of pneumonia *[8]*. Pediatric studies have not been powered to answer this question.

References

1. Wiznia A, Church J, Emmanuel P, et al. Safety and efficacy of enfuvirtide for 48 weeks as part of an optimized antiretroviral regimen in pediatric human immunodeficiency virus 1-infected patients. *Pediatr Infect Dis J.* 2007;26(9):799-805.
2. Church JA, Cunningham C, Hughes M, et al. Safety and antiretroviral activity of chronic subcutaneous administration of T-20 in human immunodeficiency virus 1-infected children. *Pediatr Infect Dis J.* 2002;21(7):653-659.
3. Church JA, Hughes M, Chen J, et al. Long term tolerability and safety of enfuvirtide for human immunodeficiency virus 1-infected children. *Pediatr Infect Dis J.* 2004;23(8):713-718.

4. Cunningham C, Church J, Hughes M, et al. Chronic subcutaneous T-20 (enfuvirtide) in HIV-infected children: 48 week outcome. 40th Annual Meeting of the Infectious Disease Society of America. October 24-27, 2002; Chicago, IL. Abstract 441.
5. Soy D, Aweeka FT, Church JA, et al. Population pharmacokinetics of enfuvirtide in pediatric patients with human immunodeficiency virus: searching for exposure-response relationships. *Clin Pharmacol Thera.* 2003;74(6):569-580.
6. Bellibas SE, Siddique Z, Dorr A, et al. Pharmacokinetics of enfuvirtide in pediatric human immunodeficiency virus 1-infected patients receiving combination therapy. *Pediatr Infect Dis J.* 2004;23(12):1137-1141.
7. Food and Drug Administration (FDA). Fuzeon package insert, revised December 2009. http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/021481s017lbl.pdf.
8. Kousignian I, Launay O, Mayaud C, et al. Does enfuvirtide increase the risk of bacterial pneumonia in patients receiving combination antiretroviral therapy? *J Antimicrob Chemother.* 2010;65(1):138-144.

Maraviroc (MVC, Selzentry)

For additional information see Drugs@FDA: **http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm**

Formulations

Tablets: 150 mg and 300 mg

Dosing Recommendations

Neonate/Infant dose:
Not approved for use in neonates/infants.

Pediatric dose:
Not approved for use in children <16 years.
No data currently available on dosage for children <16 years.

Adolescent (>16 years)/Adult dose:

When given with potent CYP3A inhibitors (with or without CYP3A inducers) including PIs (except tipranavir/ritonavir [TPV/r])	150 mg twice daily
When given with NRTIs, enfuvirtide (ENF), TPV/r, nevirapine (NVP), raltegravir (RAL), and drugs that are not potent CYP3A inhibitors or inducers	300 mg twice daily
When given with potent CYP3A inducers including efavirenz (EFV) and etravirine (ETR) (without a strong CYP3A inhibitor)	600 mg twice daily

Selected Adverse Events

- Abdominal pain
- Cough
- Dizziness
- Musculoskeletal symptoms
- Fever
- Rash
- Upper respiratory tract infections
- Hepatotoxicity
- Orthostatic hypotension

Special Instructions

- Conduct testing with HIV tropism assay prior to use to exclude the presence of CXCR4-using or mixed/dual tropic HIV.
- Can be given without regard to food.
- Instruct patients on how to recognize symptoms of allergic reactions or hepatitis.
- Use caution when administering MVC to patients with underlying cardiac disease.

Metabolism

- Cytochrome P450 (CYP) 3A4 substrate.
- Use caution when administering MVC to patients with hepatic impairment. Because MVC is metabolized by the liver, concentrations may be increased.
- No dosage recommendation in those with renal impairment, but patients with CrCL <50 mL/min should receive MVC and CYP3A inhibitor only if the potential benefits outweigh the risk.

Drug Interactions (See also the ***Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents***.)***:***

- *Absorption:* Absorption of maraviroc is somewhat reduced with ingestion of a high fat meal; however, maraviroc can be given with or without food.
- *Metabolism:* Maraviroc is a cytochrome P450 (CYP) 3A4 and p-glycoprotein (Pgp) substrate and requires dosage adjustments when administered with CYP- or Pgp-modulating medications.
- Before administration, the patient's medication profile should be carefully reviewed for potential drug interactions.

Major Toxicities:

- *More common:* Cough, fever, upper respiratory tract infections, rash, musculoskeletal symptoms, abdominal pain, and dizziness.
- *Less common (more severe):* Serious adverse events occurred in less than 2% of maraviroc-treated adult patients and included cardiovascular abnormalities (e.g., angina, heart failure, myocardial infarction), hepatic cirrhosis or failure, cholestatic jaundice, viral meningitis, pneumonia, myositis, osteonecrosis, and rhabdomyolysis.

Resistance: The International AIDS Society-USA (IAS-USA) maintains a list of updated resistance mutations (see **http://www.iasusa.org/resistance_mutations/index.html**). Clinical failure may also represent the outgrowth of CXCR4-using (naturally resistant) HIV variants.

Pediatric Experience: The pharmacokinetics, safety, and efficacy of maraviroc in patients <16 years of age have not been established.

INTEGRASE INHIBITORS

Raltegravir (RAL, Isentress)

For additional information see Drugs@FDA: **http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm**

Formulations

Tablets: 400 mg (poloxamer tablet)

Dosing Recommendations	Selected Adverse Events
Neonate/Infant dose: Not approved for use in neonates/infants. **Pediatric dose:** Not approved for use in children <16 years of age. *Investigational dose in children ≥6 years of age (and >25 kg)*: 400 mg twice daily **Adolescent (≥16)/Adult dose:** 400 mg twice daily	• Nausea, diarrhea • Headache • Fever • CPK elevation **Special Instructions** • Can be given without regard to food. **Metabolism** • UGT1A1-mediated glucuronidation. • No dosage adjustment is necessary for patients with mild-to-moderate hepatic insufficiency. No dosing information is available for patients with severe hepatic impairment. • No dosage adjustment is necessary in patients with renal impairment.

Drug Interactions (See also the ***Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents***.):

- *Metabolism:* The major mechanism of clearance of raltegravir is mediated through glucuronidation by UGT1A1. Inducers of UGT1A1 such as rifampin and tipranavir may result in reduced plasma concentrations of raltegravir while inhibitors of UGT1A1 such as atazanavir may increase plasma concentrations of raltegravir.
- Before administration, the patient's medication profile should be carefully reviewed for potential drug interactions.

Major Toxicities:

- *More common:* Nausea, headache, dizziness, diarrhea, fatigue, and itching.
- *Less common:* Abdominal pain, vomiting. In patients with chronic active hepatitis B and/or C, worsening of laboratory abnormalities from baseline AST, ALT, or total bilirubin is more likely than in patients not coinfected.
- *Rare:* Creatine phosphokinase elevations (Grade 2–4) have been observed in some patients. Myopathy and rhabdomyolysis have been reported. Use raltegravir with caution in patients receiving medications associated with these toxicities. Anxiety, depression, especially in those with prior history. Rash and Stevens-Johnson syndrome have been reported. Thrombocytopenia.

Resistance: The International AIDS Society-USA (IAS-USA) maintains a list of updated resistance mutations (see **http://www.iasusa.org/resistance_mutations/index.html**) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see http://hivdb.stanford.edu/cgi-bin/INIResiNote.cgi).

Pediatric Experience: The pharmacokinetics, safety, and efficacy of raltegravir in patients <16 years of age have not been established. Raltegravir in combination with other antiretrovirals is currently being evaluated in IMPAACT 1066, a Phase I/II study in HIV-infected children. The study objectives include selecting an age-appropriate pediatric dose approximating the exposure (AUC and C_{min}) achieved in adults treated with 400 mg twice daily. The intensive pharmacokinetic evaluations are performed on Day 7–12 after raltegravir is added to a stable antiretroviral backbone. After the pharmacokinetic specimens are obtained the backbone regimen is changed.

Initially, intensive PK evaluations were performed in children 12 to <19 years of age, with raltegravir administered with food because there is no food or fasting requirement with its licensed use in adults *[1]*. However, because the effect of food made comparisons to data obtained in fasting adults difficult, the study was then amended to conduct PK evaluations in the fasted state. This led to selection of a dose of 400 mg twice daily of the approved formulation (poloxamer tablet) in children ≥12 to <19 years of age for longer term evaluation of safety and efficacy *[2]*. Preliminary data from 43 participants in this age group after 24 weeks of treatment with raltegravir plus an optimized background regimen demonstrated that 71% had either a viral

load <400 copies/ml or a 1.0 log decrease in viral load; 53% had a viral load <50 copies/ml; and the median CD4 count increase was 111 cells/mm^3. There were 4 Grade 3 adverse reactions judged possibly related to raltegravir (2 neutropenic episodes, 1 liver enzyme elevation, and 1 behavioral change); no participants discontinued therapy due to toxicity *[3]*.

Children ≥6 to <12 years of age were initially treated at a dose of 8 mg/kg twice daily. Evaluation of the pharmacokinetic data in 10 participants again led to choosing a uniform dose of 400 mg twice daily for those with a weight >25 kg. At 12 and 24 weeks of therapy, 78% and 67% of 14 children in this cohort had a viral load <400 copies/ml *[4]*. No unusual toxicity has been seen so far *[4-5]*.

In addition to the approved adult formulation (poloxamer tablet) two investigational raltegravir preparations are being evaluated in IMPAACT 1066: a chewable ethylcellulose formulation in children >2 to <12 years of age *[6]* and an oral suspension for children <2 years of age.

References

1. Acosta A, Wiznia A, Nachman S, et al. Raltegravir (RAL) pharmacokinetics (PK) in adolescents: Preliminary results from IMPAACT protocol 1066. Paper presented at: 9th International Workshop on Clinical Pharmacology of HIV Therapy; April 7-9, 2008; New Orleans, LA. Abstract P8.
2. Nachman S, Acosta E, Wiznia A, et al. Raltegravir phamacokinetics (PK) and safety in adolescents: Preliminary results from IMPAACT P1066. Paper presented at: 48th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC); October 25-28, 2008; Washington, DC. Abstract H-4059A.
3. Nachman S, Samson P, Frenkel L, et al. 24 week safety and efficacy from IMPAACT P1066: A phase I/II, multicenter, open-label, noncomparative study to evaluate raltegravir (RAL) in HIV-1 infected youth. Paper presented at: 49th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC); September 12-15, 2009; San Francisco, CA. Abstract H-924a.
4. Nachman S, Samson P, Acosta E, et al. Pharmacokinetic (PK), safety, and efficacy data on cohort IIA; youth aged 6 to 11 years from IMPAACT P1066: A phase I/II study to evaluate raltegravir (RAL) in HIV-1 infected youth. Paper presented at: 17th Conference on Retroviruses and Opportunistic Infections (CROI); February 16-19, 2010; San Francisco, CA. Abstract 873.
5. Wiznia A, Samson P, Acosta E, et al. Safety and efficacy of raltegravir (RAL) in pediatric HIV infection. Preliminary Analysis from IMPAACT P1066. Paper presented at: 16th Conference on Retroviruses and Opportunistic Infections (CROI); February 8-11, 2009; Montreal, Canada. Abstract 874.
6. Nachman S, Acosta E, Samson P, et al. Interim results from IMPAACT P1066: Raltegravir (RAL) oral chewable tablet (OCT) formulation in children 6 to 11 years. Paper presented at: 17th Conference on Retroviruses and Opportunistic Infections (CROI); February 16-19, 2010; San Francisco, CA. Abstract 161LB.

Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health *and* Interventions to Reduce Perinatal HIV Transmission in the United States

May 24, 2010

Revisions to the April 29, 2009 Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV-1-Transmission in the United States have been made by the Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission

How to Cite the Perinatal Guidelines:
Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission. Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States. May 24, 2010; pp 1-117. Available at **http://aidsinfo.nih.gov/ContentFiles/PerinatalGL.pdf**. Accessed (insert date) [include page numbers, table number, etc. if applicable]

It is emphasized that concepts relevant to HIV management evolve rapidly. The Panel has a mechanism to update recommendations on a regular basis, and the most recent information is available on the **AIDS*info* Web site** (**http://aidsinfo.nih.gov**).

Table of Contents

GUIDELINES PANEL MEMBERS iv

INTRODUCTION 1
- Guidelines Development Process 3

LESSONS FROM CLINICAL TRIALS OF ANTIRETROVIRAL INTERVENTIONS TO REDUCE PERINATAL TRANSMISSION OF HIV 6
- Mechanisms of Action of Antiretroviral Prophylaxis in Reducing Perinatal Transmission of HIV 7
- Lessons from International Clinical Trials of Short-Course Regimens for Prevention of Perinatal Transmission of HIV 8
- Perinatal Transmission of HIV and Maternal HIV RNA Copy Number 10

PRECONCEPTIONAL COUNSELING AND CARE FOR HIV-INFECTED WOMEN OF CHILDBEARING AGE 21
- Monitoring of Pregnant Women with a Partner Known to be HIV Infected 22

ANTEPARTUM CARE 24
- General Principles Regarding Use of Antiretroviral Drugs during Pregnancy 24
- Recommendations for Use of Antiretroviral Drugs during Pregnancy 26
- Monitoring of the Woman and Fetus during Pregnancy 58
- Special Considerations Regarding the Use of Antiretroviral Drugs by HIV-Infected Pregnant Women and their Infants 61
- Antiretroviral Drug Resistance and Resistance Testing in Pregnancy 73

INTRAPARTUM CARE 83
- Intrapartum Antiretroviral Therapy/Prophylaxis 83
- Transmission and Mode of Delivery 90
- Other Intrapartum Management Considerations 97

POSTPARTUM CARE 99
- Postpartum Follow-Up of HIV-Infected Women 99

NEONATAL POSTNATAL CARE 103
- Infants Born To Mothers with Unknown HIV Infection Status 103
- Infant Antiretroviral Prophylaxis 104

TABLES

Table 1. Outline of the Guidelines Development Process 3
Table 2. Rating Scheme for Recommendations 4
Table 3. Results of Major Studies on Antiretroviral Prophylaxis to Prevent Mother-to-Child HIV Transmission 12
Table 4. Preclinical and Clinical Data Relevant to the Use of Antiretrovirals in Pregnancy 36
Table 5. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy 39
Table 6. Clinical Scenario Summary Recommendations for Antiretroviral Drug Use by Pregnant HIV-Infected Women and Prevention of Perinatal Transmission of HIV-1 in the United States 46
Table 7. Intrapartum Maternal and Neonatal Zidovudine (ZDV) Dosing for Prevention of Mother-to-Child Transmission of HIV 88
Table 8. Intrapartum Maternal and Neonatal Dosing for Additional Antiretroviral Drugs to be Considered Only in Selected Circumstances 89
Table 9. Clinical Scenarios and Recommendations Regarding Mode of Delivery to Reduce Perinatal Transmission of HIV 94

APPENDIX: FINANCIAL DISCLOSURE FOR MEMBERS OF HHS PANEL ON TREATMENT OF HIV-INFECTED PREGNANT WOMEN AND PREVENTION OF PERINATAL TRANSMISSION – JANUARY 2010 ..... Appendix: 1

SUPPLEMENT: SAFETY AND TOXICITY OF INDIVIDUAL ANTIRETROVIRAL AGENTS IN PREGNANCY ..... Supplement: 1

Nucleoside and Nucleotide Analogue Reverse Transcriptase Inhibitors 1
Abacavir (Ziagen, ABC) 1
Didanosine (Videx, ddI) 2
Emtricitabine (Emtriva, FTC) 3
Lamivudine (Epivir, 3TC) 4
Stavudine (Zerit, d4T) 6
Tenofovir disoproxil fumarate (Viread, TDF) 7
Zalcitabine (HIVID, ddC) 9
Zidovudine (Retrovir, AZT, ZDV) 9
Non-Nucleoside Reverse Transcriptase Inhibitors 11
Delavirdine (Rescriptor, DLV) 11
Efavirenz (Sustiva, EFV) 11
Etravirine (Intelence, ETV) 13
Nevirapine (Viramune, NVP) 14
Protease Inhibitors 18
Amprenavir (Agenerase, APV) 18
Atazanavir (Reyataz, ATV) 18
Darunavir (Prezista, DRV) 20
Fosamprenavir (Lexiva, f-APV) 21

Indinavir (Crixivan, IDV) 22
Lopinavir + Ritonavir (Kaletra, LPV/r) 23
Nelfinavir (Viracept, NFV) 25
Ritonavir (Norvir, RTV) 26
Saquinavir (Invirase [Hard Gel Capsule], SQV) 27
Tipranavir (Aptivus, TPV) 29
Entry Inhibitors 30
Enfuvirtide (Fuzeon, T-20) 30
Maraviroc (Selzentry, MVC) 31
Integrase Inhibitors 31
Raltegravir (Isentress) 31
Antiretroviral Pregnancy Registry 32

Perinatal HIV-1 Guidelines Panel Members

Revisions to the April 29, 2009, Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health *and* Interventions to Reduce Perinatal Transmission in the United States have been made by the Department of Health and Human Services (HHS) Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission (a Working Group of the Office of AIDS Research Advisory Council).

Members of the Panel:

Erika Aaron, MSN, ANP, RNP	Drexel University College of Medicine, Philadelphia, PA
Elaine Abrams, MD	Harlem Hospital, New York City, NY
Jean Anderson, MD	Johns Hopkins University School of Medicine, Baltimore, MD
Dawn Averitt Bridge, BIS	The Well Project, Charlottesville, VA
Rana Chakraborty, MD, MSc, DPhil	Emory University School of Medicine, Atlanta, GA
Susan E. Cohn, MD, MPH	Northwestern University Feinberg School of Medicine, Chicago, IL
Amanda Cotter, MD	University of Miami Miller School of Medicine, Miami, FL
Susan Cu-Uvin, MD	The Miriam Hospital, Brown University, Providence, RI
Judith Feinberg, MD	University of Cincinnati College of Medicine, Cincinnati, OH
Patrician Flynn, MD	St. Jude Children's Research Hospital, Memphis, TN
Mary Glenn Fowler, MD, MPH	Johns Hopkins University School of Medicine, Baltimore, MD
Robert Maupin, MD	Louisiana State University Health Sciences Center, New Orleans, LA
Howard Minkoff, MD	Maimonides Medical Center, Brooklyn, NY
Mark Mirochnick, MD	Boston Medical Center/Boston University School of Medicine, Boston, MA
Fatima Y. Prioleau, MA	Brooklyn, NY
Stephen Spector, MD	University of California San Diego, La Jolla, CA
Ruth Tuomala, MD	Brigham and Women's Hospital, Harvard Medical School, Boston, MA
Geoffrey A. Weinberg, MD	University of Rochester School of Medicine and Dentistry, Rochester, NY

Ex Officio Member:

Jess Fogler Waldura, MD	Director, National Perinatal HIV Hotline, San Francisco, CA

Members from the Department of Health and Human Services:

Songhai Barclift, MD	Health Resources and Services Administration, Rockville, MD
Brian Feit, MPA	Health Resources and Services Administration, Rockville, MD
Edward Handelsman, MD	National Institutes of Health, Rockville, MD
Denise Jamieson, MD, MPH	Centers for Disease Control and Prevention, Atlanta, GA
Lynne Mofenson, MD	National Institutes of Health, Rockville, MD (Executive Secretary)
Alan Shapiro, MD, PhD	Food and Drug Administration, Rockville, MD
D. Heather Watts, MD	National Institutes of Health, Rockville, MD

Non-Voting Observers from Coordinating Center:

Carolyn Burr, EdD, RN	François-Xavier Bagnoud Center, UMDNJ, Newark, NJ
Supriya Modey, MPH	François-Xavier Bagnoud Center, UMDNJ, Newark, NJ
Andrea Norberg, MS, RN	National Resource Center at the François-Xavier Bagnoud Center, UMDNJ, Newark, NJ

Introduction (Updated May 24, 2010)

Recommendations regarding HIV screening and treatment of pregnant women and prophylaxis for perinatal HIV transmission have evolved considerably in the United States over the last 25 years, reflecting changes in the epidemic and the science of prevention *[1-2]*. Treatment of HIV disease in general and during pregnancy has progressed with an increasing proportion of women receiving combination antiretroviral therapy or triple antiretroviral drug prophylaxis throughout pregnancy. With the implementation of recommendations for universal prenatal HIV counseling and testing, antiretroviral prophylaxis, scheduled cesarean delivery, and avoidance of breastfeeding, the rate of perinatal HIV transmission has dramatically diminished to less than 2% in the United States and Europe *[3-4]*.

These guidelines update the April 29, 2009, Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1 Infected Women for Maternal Health *and* Interventions to Reduce Perinatal HIV Transmission in the United States. The Department of Health and Human Services (HHS) Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission, a working group of the Office of AIDS Research Advisory Council (OARAC), develops these guidelines. The guidelines provide health care providers with information for discussion with HIV-infected pregnant women to enable the patient/provider team to make informed decisions regarding the use of antiretroviral drugs during pregnancy and use of elective cesarean delivery to reduce perinatal HIV transmission. The recommendations in the guidelines are accompanied by discussion of various circumstances that commonly occur in clinical practice and the factors influencing treatment considerations. The Panel recognizes that strategies to prevent perinatal transmission and concepts related to management of HIV disease in pregnant women are rapidly evolving and will consider new evidence and adjust recommendations accordingly. The updated guidelines are available from the AIDS*info* Web site (**http://aidsinfo.nih.gov**).

Health care providers considering the use of antiretroviral agents for HIV-infected women during pregnancy must take into account two separate but related issues:

1. antiretroviral treatment of maternal HIV infection; and
2. antiretroviral chemoprophylaxis to reduce the risk of perinatal HIV transmission.

The benefits of antiretroviral therapy for a pregnant woman must be weighed against the risk of adverse events to the woman, fetus, and newborn. Combination drug regimens are considered the standard of care both for treatment of HIV infection and for prevention of perinatal HIV transmission *[2, 5]*. After counseling and discussion, a pregnant woman's informed choice on whether to take antiretroviral drugs either for her treatment or for prevention of mother-to-child transmission or to follow other medical recommendations intended to reduce perinatal HIV transmission should be respected. Coercive and punitive policies are potentially counterproductive in that they may undermine provider-patient trust and could discourage women from seeking prenatal care and adopting health care behaviors that optimize fetal and neonatal well-being.

The current guidelines have been structured to reflect the management of an individual mother-child pair and are organized into a brief discussion of preconception care followed by principles for management of the woman and her infant during the antepartum, intrapartum, and postpartum periods. Key issues and new information discussed in these guidelines include:

- **Rating Scheme for Guidelines (Table 2).** Recommendations are now rated based on strength of recommendation and quality of evidence.

- **Lessons Learned from Clinical Trials of Antiretroviral Interventions to Reduce Perinatal HIV Transmission and Table 3 (Results of Major Studies on Antiretroviral Prophylaxis to Prevent Mother-to-Child HIV Transmission).** Update on recent international clinical trials, including trials of prevention of postnatal transmission and drug resistance in infants infected despite infant or maternal antiretroviral prophylaxis of postnatal infection. The Panel reaffirms that in the United States, where safe, affordable, and feasible alternatives are available and culturally acceptable, breastfeeding is not recommended for HIV-infected women (including those receiving combination antiretroviral therapy or triple antiretroviral drug prophylaxis).
- **Recommendations for Use of Antiretroviral Drugs during Pregnancy.** New discussion of the categories and the criteria used for recommendations about use of specific drugs or drug regimens in pregnancy.
- **Special Situations.** Additional discussion of options for antiretroviral prophylaxis when an HIV/hepatitis B virus (HBV) coinfected pregnant woman does not require antiretroviral therapy for her own health or treatment for hepatitis B disease.
- **Stopping Antiretroviral Therapy during Pregnancy.** Discussion of stopping non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimens and strategies to reduce the risk of resistance, including short-term continuation of a dual nucleoside reverse transcriptase inhibitor (NRTI) component or switching to a protease inhibitor (PI) prior to discontinuing therapy.
- **Special Considerations for the Use of Antiretroviral Drugs by HIV-Infected Pregnant Women and their Infants.** Updated information on combination antiretroviral drug use and pregnancy outcome and nevirapine hepatic toxicity in pregnancy.
- **Antiretroviral Drug Resistance and Resistance Testing in Pregnancy.** New information regarding resistance following discontinuation of triple drug prophylaxis after delivery and new information from clinical trials on response to therapy following single-dose nevirapine exposure.
- **Intrapartum Antiretroviral Therapy/Prophylaxis.** New references on use of dual NRTI "tail" to reduce risk of nevirapine resistance.
- **Mode of Delivery.** Reorganization and update of section.
- **Neonatal Postnatal Care.**
  - **Short-Term Antiretroviral Drug Safety and Choice for Neonatal Prophylaxis.** Caution on use of lopinavir-ritonavir (and other boosted PIs) in newborns, particularly preterm infants, due to reports of cardiac toxicity (heart block).
  - **Infant Feeding Practices and the Risk of HIV Transmission.** Discussion of new data on feeding infants premasticated food and risk of HIV transmission.
  - **The National Perinatal HIV Hotline.** Contact information for the National Perinatal HIV Hotline, a free consultation service for clinicians.

These recommendations have been developed for use in the United States. Although perinatal HIV transmission occurs worldwide, alternative strategies may be appropriate in other countries. Policies and practices in other countries regarding the use of antiretroviral drugs for reduction of perinatal HIV transmission may differ from the recommendations in these guidelines and will depend on local considerations, including availability and cost of antiretroviral drugs, access by pregnant women to facilities for safe intravenous infusions during labor, and local recommendations regarding breastfeeding by HIV-infected women.

GUIDELINES DEVELOPMENT PROCESS

Table 1. Outline of the Guidelines Development Process

Page 1 of 2

Topic	Comment
Goal of the guidelines	Provide guidance to HIV care practitioners on the optimal use of antiretroviral agents in pregnant women for treatment of HIV infection and for prevention of mother-to-child transmission (MTCT) of HIV in the United States.
Panel members	The Panel is composed of approximately 30 voting members who have expertise in management of pregnant HIV-infected women (e.g., training in either obstetrics/gynecology or women's health) and interventions to prevent MTCT (e.g., pediatric specialists in HIV infection), as well as community representatives with knowledge of HIV infection in pregnant women and interventions to prevent MTCT. The U.S. government representatives, appointed by their agency, include at least one representative from each of the following HHS agencies: Centers for Disease Control and Prevention (CDC), Food and Drug Administration (FDA), Health Resources and Services Administration (HRSA), and the National Institutes of Health (NIH). Members who do not represent the U.S. government agencies are selected after an open announcement to call for nominations. Each member serves on the Panel for a 3-year period, with an option for reappointment. A list of current Panel members can be found on **Page iv** of this document.
Financial disclosure	All members of the Panel submit a written financial disclosure annually. A list of the latest disclosures can be found in the **Appendix** section of this document.
Users of the guidelines	Providers of care to HIV-infected pregnant women and to HIV-exposed infants
Funding source	Office of AIDS Research, NIH
Evidence collection	The recommendations are generally based on studies published in peer-reviewed journals. On some occasions, particularly when new information may affect patient safety, unpublished data presented at major conferences or prepared by the FDA and/or manufacturers as warnings to the public may be used as evidence to revise the guidelines.
Recommendation grading	See **Table 2**.
Method of synthesizing data	Each section of the guidelines is assigned to a small group of Panel members with expertise in the area of interest. The members synthesize the available data and propose a recommendation to the Panel. All proposals are discussed at monthly teleconferences and then are voted on by the Panel members before being endorsed as official recommendations.

Table 1. Outline of the Guidelines Development Process
Page 2 of 2

Topic	Comment
Other guidelines	These guidelines focus on HIV-infected pregnant women and their infants. Separate guidelines outline the use of antiretroviral therapy in nonpregnant HIV-infected adults and adolescents, HIV-infected children, and those who experience occupational or nonoccupational exposure to HIV. These guidelines are also available at the AIDS*info* Web site (**http://www.aidsinfo.nih.gov**). There is brief discussion of preconception management for nonpregnant women of reproductive age in this document. However, for more detailed discussion on issues of treatment of nonpregnant adults, the Working Group defers to the designated expertise offered by Panels that have developed those guidelines.
Update plan	The Panel meets monthly by teleconference to review data that may warrant modification of the guidelines. Updates may be prompted by new drug approvals (or new indications, dosing formulations, or frequency), new significant safety or efficacy data, or other information that may have a significant impact on the clinical care of patients. For cases in which significant new data become available that may affect patient safety, a warning announcement with the Panel's recommendations may be made on the AIDS*info* Web site until appropriate changes can be made in the guidelines document. Updated guidelines are available at the AIDS*info* Web site (**http://www.aidsinfo.nih.gov**).
Public comments	After release of an update on the AIDS*Info* Web site, the public is given a 2-week period to submit comments to the Panel. These comments are reviewed, and a determination is made as to whether revisions are indicated. The public is also able to submit comments to the Panel at any time at **contactus@aidsinfo.nih.gov**.

Basis for Recommendations

Recommendations in these guidelines are based on scientific evidence and expert opinion. Each recommended statement is rated with a letter of **A**, **B,** or **C** that represents the strength of the recommendation and with a numeral **I**, **II,** or **III**, according to the quality of evidence.

Table 2. Rating Scheme for Recommendations

Strength of Recommendation	Quality of Evidence for Recommendation
A: Strong recommendation for the statement **B:** Moderate recommendation for the statement **C:** Optional recommendation for the statement	**I:** One or more randomized trials with clinical outcomes and/or validated laboratory endpoints **II:** One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes **III:** Expert opinion

References

1. Centers for Disease Control and Prevention (CDC). Achievements in public health. Reduction in perinatal transmission of HIV infection--United States, 1985-2005. *MMWR Morb Mortal Wkly Rep.* 2006;55(21):592-597.
2. Jamieson DJ, Clark J, Kourtis AP, et al. Recommendations for human immunodeficiency virus screening, prophylaxis, and treatment for pregnant women in the United States. *Am J Obstet Gynecol.* 2007;197(3 Suppl):S26-32.
3. Cooper ER, Charurat M, Mofenson LM, et al. Combination antiretroviral strategies for the treatment of pregnant HIV-1 infected women and prevention of perinatal HIV-1 transmission. *J Acquir Immune Defic Syndr Hum Retrovirol.* 2002;29(5):484-494.
4. Townsend CL, Cortina-Borja M, Peckham CS, et al. Low rates of mother-to-child transmission of HIV following effective pregnancy interventions in the United Kingdom and Ireland, 2000-2006. *AIDS.* 2008;22(8):973-981.
5. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. December 1, 2009:1-161. http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf.

Lessons from Clinical Trials of Antiretroviral Interventions to Reduce Perinatal Transmission of HIV (Updated May 24, 2010)

One of the major achievements in HIV research was the demonstration by the Pediatric AIDS Clinical Trials Group 076 (PACTG 076) clinical trial that administration of zidovudine to the pregnant woman and her infant could reduce the risk of perinatal transmission by nearly 70% *[1]*. In PACTG 076, zidovudine was started orally at 14 to 34 weeks gestation, given intravenously to the mother during labor, and administered to the infant for 6 weeks.

Following the results of PACTG 076, in the United States and in other resource-abundant countries, implementation of the zidovudine regimen coupled with increased antenatal HIV counseling and testing rapidly resulted in significant declines in transmission *[2-5]*. Subsequent clinical trials and observational studies demonstrated that combination antiretroviral prophylaxis (initially dual and then triple combination therapy) given to the mother antenatally was associated with further declines in transmission to less than 2% *[2, 6-7]*. It is currently estimated that fewer than 200 HIV-infected infants are now born each year in the United States *[4, 8]*. However, although new perinatal HIV infections are becoming rare in resource-rich countries, infections continue to occur, and the birth of an infected infant is a sentinel event representing missed opportunities and barriers to prevention *[9-10]*. Important obstacles to eradication of perinatal transmission in the United States include the continued increase of HIV infection among women of childbearing age; absent or delayed prenatal care, particularly in women using illicit drugs; acute (primary) infection in late pregnancy and in women who are breastfeeding; poor adherence to prescribed antiretroviral regimens; and lack of full implementation of routine, universal prenatal HIV counseling and testing *[10]*.

Within resource-limited settings, the complexity and cost of the three-part PACTG 076 regimen significantly limit its applicability and implementation. Thus, researchers began to explore the development of shorter, less expensive prophylactic regimens more applicable to resource-constrained settings. Clinical trials initially focused on shortened zidovudine-alone prophylaxis regimens and moved to evaluating whether combination antiretroviral regimens, such as short-course zidovudine combined with lamivudine, might have improved efficacy over zidovudine alone. Studies also evaluated whether even simpler, less expensive, single-drug regimens, such as single-dose intrapartum/neonatal nevirapine, would be effective and whether combining such regimens with other short-course regimens might result in improved efficacy. These studies have provided important insights into the mechanisms of action of antiretroviral drugs in reducing perinatal transmission and in determining optimal regimens for use in the United States and other resource-rich countries, as discussed below.

MECHANISMS OF ACTION OF ANTIRETROVIRAL PROPHYLAXIS IN REDUCING PERINATAL TRANSMISSION OF HIV

Panel's Recommendation:

- ***Antiretroviral drugs reduce perinatal transmission by several mechanisms, including lowering maternal antepartum viral load and pre- and post-exposure prophylaxis of the infant. Therefore, for prevention of perinatal transmission of HIV, combined antepartum, intrapartum, and infant antiretroviral prophylaxis is recommended (AI).***

There are a number of mechanisms through which zidovudine or other antiretroviral drugs can reduce perinatal transmission. One important mechanism is by decreasing maternal viral load in the blood and genital secretions via antenatal drug administration, particularly in women with high viral loads. However, antiretroviral drugs have been shown to reduce the risk of transmission even among women with HIV RNA levels <1,000 copies/mL *[11]*. Additionally, the level of HIV RNA at delivery and receipt of antenatal antiretroviral therapy are each independently associated with the risk of transmission, suggesting that antiretroviral prophylaxis does not work solely through reduction in viral load *[2, 12]*.

An additional mechanism of protection is pre-exposure infant prophylaxis provided by administration of antiretroviral drugs that cross the placenta from the mother to the infant, resulting in adequate systemic drug levels in the infant. This mechanism of protection is likely particularly important during the infant's passage through the birth canal, a time of intensive exposure to maternal genital tract virus. Post-exposure infant prophylaxis is provided through administration of drug to the infant after birth. This mechanism protects the infant from cell-free or cell-associated virus that might have obtained access to the fetal/infant systemic circulation through maternal-fetal transfusion during uterine contractions occurring in labor or through systemic dissemination of virus swallowed by the infant during passage through the birth canal.

It is likely that efficacy of antiretroviral drugs in reducing perinatal transmission is multi-factorial, and each of these mechanisms is contributory. The efficacy of antiretroviral regimens administered only during labor and/or to the newborn in reducing perinatal transmission, as discussed below, demonstrates the importance of the pre- and post-exposure components of prophylaxis in reducing perinatal transmission *[13-19]*.

LESSONS FROM INTERNATIONAL CLINICAL TRIALS OF SHORT-COURSE REGIMENS FOR PREVENTION OF PERINATAL TRANSMISSION OF HIV

Panel's Recommendations:

- ***Combination antepartum antiretroviral drug regimens are more effective than single-drug regimens in reducing perinatal transmission and should be used for maternal prophylaxis (AI).***
- ***Longer duration of antepartum antiretroviral prophylaxis (e.g., starting at 28 weeks gestation) is more effective than shorter duration (e.g., starting at 36 weeks gestation). Therefore, for women who do not require immediate initiation of therapy for their own health, prophylaxis should be started after the first trimester and no later than 28 weeks gestation (see Recommendations for Use of Antiretroviral Drugs during Pregnancy) (AI).***
- ***In the absence of antepartum antiretroviral therapy, intrapartum antiretroviral drugs should be administered in combination with infant antiretroviral prophylaxis to reduce the risk of perinatal transmission (see Intrapartum Care) (AI), although this combination is not as effective as antepartum/intrapartum/infant prophylaxis.***
- ***If women do not receive antepartum or intrapartum antiretroviral drugs, postnatal infant antiretroviral prophylaxis is recommended with 6 weeks of zidovudine (see Neonatal Postnatal Care) (AII).***
- ***In the United States, the addition of single-dose intrapartum/newborn nevirapine to the standard antepartum combination antiretroviral regimens used for prophylaxis or treatment in pregnant women is not recommended because it does not appear to provide additional efficacy in reducing transmission and may be associated with the development of nevirapine resistance (AI).***
- ***Breastfeeding is not recommended for HIV-infected women (including those receiving combination antiretroviral therapy) in the United States, where safe, affordable and feasible alternatives are available and culturally acceptable (AII).***

A number of simple regimens have been identified that are effective in reducing perinatal transmission in resource-limited countries (see **Table 3**). Because the studies involved different patient populations residing in different geographic locations, infected with different viral subtypes and having different infant feeding practices, direct comparison of results between trials is difficult. However, some general conclusions can be drawn from the study results that are relevant to understanding use of antiretroviral drugs in both resource-limited and -rich countries.

Short-term efficacy has been demonstrated for a number of short-course antiretroviral regimens, including those with zidovudine alone; zidovudine plus lamivudine; single-dose nevirapine; and, more recently, combining single-dose nevirapine with either short-course zidovudine or zidovudine/lamivudine *[13-14, 16-23]*. In general, combination regimens are more effective than single-drug regimens in reducing perinatal transmission. Additionally, when it is feasible and affordable, a longer three-part regimen given antenatally, intrapartum, and postpartum is superior in preventing perinatal transmission than a shorter two-part antepartum/intrapartum or intrapartum/postpartum regimen *[14, 24-25]*.

Almost all trials in resource-limited countries have included an oral intrapartum prophylaxis component, with varying durations of maternal antenatal and/or infant (and sometimes maternal) postpartum prophylaxis. Perinatal transmission is reduced by regimens with antenatal components starting as late as 36 weeks gestation and lacking an infant prophylaxis component *[20-22]*. However, longer duration of antenatal therapy (starting at 28 weeks gestation) is more effective than shorter duration (starting at 36 weeks gestation), suggesting that a significant proportion of *in utero* transmission occurs between 28 and 36 weeks gestation *[23]*. More prolonged post-exposure prophylaxis of the infant does not appear to substitute for longer duration of maternal therapy *[23]*.

Because some women may lack antenatal care and first present for care during labor (possibly the majority of pregnant women in some resource-limited settings), regimens that do not include maternal therapy during pregnancy have been evaluated. Regimens that include only intrapartum and postpartum drug administration have also been shown to be effective in reducing perinatal transmission *[13-14, 16]*. However, intrapartum pre-exposure prophylaxis alone with nucleoside reverse transcriptase inhibitor (NRTI) drugs (zidovudine/lamivudine), without continued post-exposure prophylaxis of the infant, is not effective in reducing transmission*[14]*. The SAINT trial demonstrated that the two proven effective intrapartum/postpartum regimens (zidovudine/lamivudine or single-dose intrapartum/newborn nevirapine) are similar in efficacy and safety *[16]*.

In some situations, maternal antepartum and intrapartum therapy may not be possible, and only infant prophylaxis can be provided. Based on epidemiologic data *[15]*, in resource-rich countries, the standard prophylaxis regimen in the absence of maternal therapy is 6 weeks of infant zidovudine. To define the optimal infant prophylaxis regimen in the absence of maternal therapy, an ongoing multi-national study in infants born to women who have not received antenatal therapy is comparing the standard 6-week infant zidovudine regimen to 6 weeks of zidovudine combined with either one or two additional drugs.

In resource-limited settings, administration of even 6 weeks of infant zidovudine may be difficult to achieve, and single-dose nevirapine is widely used. In a study in South Africa of infants born to mothers who did not receive antenatal or intrapartum therapy, administration of single-dose infant nevirapine given within 24 hours of delivery was compared to 6 weeks of infant zidovudine therapy; overall perinatal transmission rates were not significantly different *[19]*. A trial in Malawi compared single-dose infant nevirapine to a combination of single-dose nevirapine with a week of zidovudine therapy when no antenatal maternal therapy was received. The addition of 1 week of zidovudine therapy to infant single-dose nevirapine reduced the risk of transmission by 36% compared to infant single-dose nevirapine alone *[17]*. However, when maternal intrapartum nevirapine was received, thereby providing pre-exposure prophylaxis in addition to post-exposure prophylaxis, single-dose infant nevirapine alone was as effective as the combined nevirapine/zidovudine infant post-exposure prophylaxis regimen *[18]*. One problem with the use of single-dose infant nevirapine alone or in combination with a week of zidovudine to prevent transmission is the risk of nevirapine resistance emerging in infants who become infected despite receiving antiretroviral prophylaxis *[26]*. Thus, in the United States, the standard recommendation for infant prophylaxis in the absence of maternal antenatal and intrapartum therapy remains 6 weeks of infant zidovudine.

In an attempt to improve the efficacy of short-course regimens but retain a regimen cost-appropriate for resource-limited countries, more recently researchers have evaluated whether the addition of a potent intrapartum intervention—the single-dose nevirapine regimen—to short-course regimens might increase efficacy. In the setting of short-course antenatal zidovudine alone or zidovudine/lamivudine, the Perinatal HIV Prevention Trial (PHPT)-2 study in nonbreastfeeding women in Thailand, the DITRAME studies in a partially breastfeeding population in the Cote d'Ivoire, and the Mashi study in Botswana (in the formula-fed, but not the breastfed, strata) demonstrated that the addition of single-dose nevirapine did significantly increase efficacy *[24, 27-28]*. The relative importance of the maternal and infant components of single-dose nevirapine in the context of short-course zidovudine regimens remains unclear. The Thailand PHPT-2 study suggests that the infant nevirapine dose at 48–72 hours of life may not add significant efficacy to the maternal nevirapine dose alone; however, the Botswana Mashi study suggests that maternal nevirapine may not be necessary when infant single-dose nevirapine is provided at birth *[27-28]*.

Whether single-dose nevirapine provides any additional efficacy when combined with the standard recommended antiretroviral prophylaxis regimens used in the United States (e.g., combination antiretroviral drugs in women with HIV RNA >1,000 copies/mL) was evaluated in PACTG 316, a clinical trial conducted in the United States, Europe, Brazil, and the Bahamas. This study

demonstrated that for nonbreastfeeding women in resource-rich countries, the addition of single-dose nevirapine did not offer significant benefit in the setting of combination antiretroviral therapy throughout pregnancy and very low viral load at the time of delivery *[7]*. Thus, the addition of single-dose intrapartum nevirapine is generally not recommended for women in the United States who are receiving the standard recommended antenatal antiretroviral prophylaxis regimens (see **Intrapartum Care** section).

In the United States and other parts of the world where replacement feeding is affordable, feasible, acceptable, sustainable, and safe, breastfeeding by HIV-infected women (including those receiving antiretroviral drugs) is not recommended. A number of studies have evaluated the use of maternal or infant antiretroviral prophylaxis during breastfeeding to reduce postnatal transmission (see **Table 3**). Observational data and randomized clinical trials have demonstrated that infant prophylaxis (primarily using daily infant nevirapine) during breastfeeding significantly decreases the risk of postnatal transmission in breast milk and that maternal triple drug prophylaxis during breastfeeding may likewise decrease postnatal infection *[29-36]*. However, neither infant nor maternal postpartum antiretroviral prophylaxis completely eliminates the risk of HIV transmission through breast milk, and the combination of maternal and infant postpartum regimens has not been evaluated. Therefore, breastfeeding is not recommended for HIV-infected women in the United States (including those receiving combination antiretroviral drug regimens), where safe, affordable and feasible alternatives are available and culturally acceptable. Both infant nevirapine prophylaxis and maternal triple drug prophylaxis during breastfeeding may be associated with the development of antiretroviral drug resistance in infants who become infected despite prophylaxis *[37-40]*. Three studies have found multi-class drug resistance in breastfeeding infants who became infected despite maternal triple drug prophylaxis *[38-40]*.

PERINATAL TRANSMISSION OF HIV AND MATERNAL HIV RNA COPY NUMBER

Panel's Recommendation:

- ***Use of antiretroviral drugs during pregnancy for prevention of perinatal transmission should be discussed with and provided to all infected pregnant women regardless of HIV RNA level (AI).***

Initial data regarding the correlation of viral load with risk of perinatal transmission were conflicting. Some studies suggested an absolute correlation between HIV RNA copy number and risk of transmission *[41]*. However, although higher HIV RNA levels have been observed in women who transmitted HIV to their infants, overlap in HIV RNA copy number has been observed in both women who did and women who did not transmit the virus. Transmission has been observed across the entire range of HIV RNA levels (including in women with undetectable viral load), and the predictive value of HIV RNA copy number for transmission in an individual woman is modest *[42-44]*. In PACTG 076, antenatal maternal HIV RNA copy number was associated with HIV transmission in women receiving placebo. In women receiving zidovudine, the relationship was markedly attenuated and no longer statistically significant *[12]*. An HIV RNA threshold below which there was no risk of transmission was not identified; zidovudine was effective in reducing transmission regardless of maternal HIV RNA copy number *[12, 45]*.

More recent data from larger numbers of zidovudine-treated, HIV-infected pregnant women indicate that HIV RNA levels correlate with risk of transmission even in women treated with antiretroviral agents *[46-49]*. Although the risk of perinatal transmission in women with undetectable HIV RNA levels appears to be extremely low, transmission from mother to infant has been reported among women with all levels of maternal HIV RNA. Additionally, although HIV RNA may be an important risk factor for transmission, other factors also appear to play a role *[46, 49-50]*.

Although there is a general correlation between viral load in plasma and in the genital tract, discordance has also been reported, particularly between HIV proviral load in blood and genital secretions, especially in the presence of other genital tract infections *[51-54]*. If exposure to HIV in the maternal genital tract during delivery is a risk factor for perinatal transmission, plasma HIV RNA levels might not always be an accurate indicator of risk. Long-term changes in one body compartment (such as can occur with antiretroviral treatment) may or may not be associated with comparable changes in other compartments. Further studies are needed to determine the effect of antiretroviral drugs on genital tract viral load and the association of such effects on the risk of perinatal HIV transmission. In the short-course zidovudine trial in Thailand, plasma and cervicovaginal HIV RNA levels were reduced by zidovudine treatment, and each independently correlated with perinatal transmission *[55]*. Use of antiretroviral drugs during pregnancy for prevention of perinatal transmission should be discussed with and offered to all infected pregnant women regardless of their HIV RNA level.

Results of epidemiologic and clinical trials suggest that women receiving potent combinations of antiretroviral drugs that effectively reduce HIV RNA to <1,000 copies/mL or undetectable levels have very low rates of perinatal transmission *[2, 6-7, 56]*. However, because transmission can occur even at low or undetectable HIV RNA copy numbers, HIV RNA levels should not be a determining factor when deciding whether to use antiretroviral drugs for prevention of perinatal transmission. Additionally, the efficacy of antiretroviral drugs is not solely related to lowering viral load *[2, 11-12, 57]*. Therefore, antiretroviral prophylaxis should be given even to women who have a very low or undetectable viral load on no therapy.

Table 3. Results of Major Studies on Antiretroviral Prophylaxis to Prevent Mother-to-Child HIV Transmission

Study Location(s) Mode of Infant Feeding	Antiretroviral Drugs	Antepartum and Intrapartum	Postpartum	Mother-to-Child Transmission Rate and Efficacy
PACTG 076 United States, France *[1]* Formula feeding	ZDV vs placebo	Long (from 14 weeks) Intravenous IP	Long (6 weeks), infant only	• MTCT at 18 months was 8.3% in ZDV arm vs 25.5% in placebo arm (68% efficacy).
CDC short-course ZDV trial Thailand *[22]* Formula feeding	ZDV vs placebo	Short (from 36 weeks) Oral IP	None	• MTCT at 6 months was 9.4% in ZDV arm vs 18.9% in placebo arm (50% efficacy).
DITRAME (ANRS 049a) trial Côte d'Ivoire, Burkina Faso *[21, 58]* Breastfeeding	ZDV vs placebo	Short (from 36 weeks) Oral IP	Short (1 week), mother only	• MTCT was 18.0% in ZDV arm vs 27.5% in placebo arm at 6 months (38% efficacy) and 21.5% vs 30.6% at 15 months (30% efficacy). • MTCT was 22.5% in ZDV arm vs 30.2% in placebo arm in pooled analysis at 24 months (26% efficacy).
CDC short-course ZDV trial Côte d'Ivoire *[20-21]* Breastfeeding	ZDV vs placebo	Short (from 36 weeks) Oral IP	None	• MTCT was 16.5% in ZDV arm vs 26.1% in placebo arm at 3 months (37% efficacy). • MTCT was 22.5% in ZDV arm vs 30.2% in placebo arm in pooled analysis at 24 months (26% efficacy).

PETRA trial South Africa, Tanzania, and Uganda *[14]* Breastfeeding and formula feeding	AP/IP/PP ZDV + 3TC vs IP/PP ZDV + 3TC vs IP-only ZDV + 3TC vs placebo	Short (from 36 weeks) Oral IP	Short (1 week), mother and infant	• MTCT was 5.7% at 6 weeks for AP/IP/PP ZDV + 3TC, 8.9% for IP/PP ZDV + 3TC, 14.2% for IP-only ZDV + 3TC, and 15.3% for placebo (efficacy compared to placebo: 63%, 42%, and 0%, respectively). • MTCT was 14.9% at 18 months for AP/IP/PP ZDV + 3TC, 18.1% for IP/PP ZDV + 3TC, 20.0% for IP-only ZDV + 3TC, and 22.2% for placebo (efficacy compared to placebo: 34%, 18%, and 0%, respectively).
HIVNET 012 trial Uganda *[13]* Breastfeeding	sdNVP vs ZDV	No AP ARV Oral IP: sdNVP vs oral ZDV	sdNVP within 72 hours of birth (infant only) vs ZDV (1 week), infant only	• MTCT was 11.8% in NVP arm vs 20.0% in ZDV arm at 6 to 8 weeks (42% efficacy); 15.7% in NVP arm vs 25.8% in ZDV arm at 18 months (41% efficacy).
SAINT trial South Africa *[16]* Breastfeeding and formula feeding	sdNVP vs ZDV + 3TC	No AP ARV Oral IP: sdNVP vs ZDV + 3TC	sdNVP within 48 hours of birth (mother and infant) vs ZDV + 3TC (1 week), mother and infant	• MTCT was 12.3% in sdNVP arm vs 9.3% in ZDV + 3TC arm at 8 weeks (difference not statistically significant, p=0.11).
Perinatal HIV Prevention Trial (PHPT-1) Thailand *[23]* Formula feeding	Four ZDV regimens with different durations of AP and infant PP administration, no placebo	Long (from 28 weeks), short (from 36 weeks) Oral IP	Long (6 weeks), short (3 days), infant only	• Short-short arm stopped at interim analysis (10.5%). MTCT was 6.5% in long-long arm vs 4.7% in long-short arm and 8.6% in short-long arm at 6 months (no statistical difference). *In utero* transmission was significantly higher with short vs long maternal therapy regimens (5.1% vs 1.6%).
PACTG 316 trial Bahamas, Belgium, Brazil, France, Germany, Italy, Spain, Sweden, Switzerland, United Kingdom, United States *[7]* Formula feeding	sdNVP vs placebo among women already receiving ZDV alone (23%) or ZDV + other ARV drugs (77% combination therapy)	Nonstudy ARV regimen Oral IP: placebo vs sdNVP + intravenous ZDV	Placebo vs sdNVP within 72 hours of birth + nonstudy ARV drugs (ZDV), infant only	• 77% of women received dual or triple combination ARV regimens during pregnancy. • Trial stopped early due to very low MTCT in both arms: 1.4% in sdNVP arm vs 1.6% in placebo arm (53% of MTCT was *in utero*).

Perinatal HIV Prevention Trial (PHPT-2) Thailand *[27]* Formula feeding	ZDV alone vs ZDV + maternal and infant sdNVP vs ZDV + maternal sdNVP	ZDV from 28 weeks Oral IP: ZDV alone or ZDV + sdNVP	ZDV for 1 week with or without sdNVP, infant only	• ZDV-alone arm was stopped due to higher MTCT than the NVP–NVP arm (6.3% vs 1.1%). In arms in which the mother received sdNVP, MTCT rate did not differ significantly between the infant receiving or not receiving sdNVP (2.0% vs 2.8%).
DITRAME Plus (ANRS 1201.0) trial Abidjan, Côte d'Ivoire *[24]* Breastfeeding and formula feeding	Open label, ZDV + sdNVP	ZDV from 36 weeks Oral IP: ZDV plus sdNVP	sdNVP + ZDV for 1 week, infant only	• MTCT was 6.5% (95% CI 3.9%–9.1%) at 6 weeks; MTCT for historical control group receiving short ZDV (98% breastfed) was 12.8%.
DITRAME Plus (ANRS 1201.1) trial Abidjan, Côte d'Ivoire *[24]* Breastfeeding and formula feeding	Open label, ZDV + 3TC + sdNVP	ZDV + 3TC from 32 weeks (stopped at 3 days PP) Oral IP: ZDV + 3TC + sdNVP	sdNVP + ZDV for 1 week, infant only	• MTCT was 4.7% (95% CI 2.4%–7.0%) at 6 weeks; MTCT for historical control group receiving short ZDV (98% breastfed) was 12.8%.
NVAZ trial Malawi *[17]* Breastfeeding	Neonatal sdNVP vs sdNVP + ZDV	No AP or IP ARV (latecomers)	sdNVP with or without ZDV for 1 week, infant only	• MTCT was 15.3% in sdNVP + ZDV arm and 20.9% in sdNVP-only arm at 6 to 8 weeks. MTCT rate at 6 to 8 weeks among infants who were HIV uninfected at birth was 7.7% and 12.1%, respectively (36% efficacy).
Postnatal NVP + ZDV trial Malawi *[18]* Breastfeeding	Neonatal sdNVP vs sdNVP + ZDV	No AP ARV Oral IP: sdNVP	sdNVP with or without ZDV for 1 week, infant only	• MTCT was 16.3% in NVP + ZDV arm and 14.1% in sdNVP-only arm at 6 to 8 weeks (difference not statistically significant). MTCT rate at 6 to 8 weeks among infants who were HIV uninfected at birth was 6.5% and 16.9%, respectively.
Post-exposure Infant Prophylaxis South Africa *[19]* Breastfeeding and formula feeding	Neonatal sdNVP vs ZDV for 6 weeks	No AP or IP ARV	sdNVP vs ZDV for 6 weeks	• For formula-fed infants only, MTCT was 14.3% in sdNVP arm vs14.1% in ZDV arm at 6 weeks (not significant, p=0.30). For breastfed infants only, MTCT was 12.2% in sdNVP arm and 19.6% in ZDV arm (p=0.03).

Mashi Botswana *[28, 59]* Breastfeeding and formula feeding	Initial: short-course ZDV with/without maternal and infant sdNVP and with/without breastfeeding Revised: short-course ZDV + infant sdNVP with/without maternal sdNVP and with/without breastfeeding; women with CD4 <200 receive combination therapy	1st randomization ZDV from 34 weeks Oral IP: ZDV + either sdNVP vs placebo	2nd randomization Breastfeeding + ZDV (infant) 6 months + sd NVP, infant only vs Formula feeding + ZDV (infant) 4 weeks + sdNVP, infant only	• Initial design: In formula-feeding arm, MTCT at 1 month was 2.4% in maternal and infant sdNVP arm and 8.3% in placebo arm (p=0.05). In breastfeeding + infant ZDV arm, MTCT at 1 month was 8.4% in sdNVP arm and 4.1% in placebo arm (difference not statistically significant). • Revised design: MTCT at 1 month was 4.3% in maternal + infant sdNVP arm and 3.7% in maternal placebo + infant sdNVP arm (no significant difference; no interaction with mode of infant feeding). • MTCT at 7 months was 9.1% in breastfeeding + ZDV arm and 5.6% in formula feeding arm; mortality at 7 months was 4.9% in breastfeeding + ZDV arm vs 9.3% in formula feeding arm; HIV-free survival at 18 months was 15.6% breastfeeding + ZDV arm vs 14.2% formula feeding arm.
SWEN Uganda, Ethiopia, India *[30]* Breastfeeding	sdNVP vs NVP for 6 weeks	No AP ARV Oral IP: sdNVP	Infant sdNVP vs NVP for 6 weeks	• Postnatal infection in infants uninfected at birth: - MTCT at 6 weeks was 5.3% in sdNVP arm vs 2.5% in extended NVP arm (risk ratio 0.54, p=0.009). - MTCT at 6 months was 9.0% in sdNVP arm vs 6.9% in extended NVP arm (risk ratio 0.80, p=0.16). • HIV-free survival significantly lower in extended NVP arm at both 6 weeks and 6 months

PEPI-Malawi Trial Malawi *[29]* Breastfeeding	sdNVP + ZDV for 1 week (control) vs two extended infant regimens (NVP or NVP/ZDV) for 14 weeks	No AP ARV Oral IP: sdNVP (if mother presents in time)	Infant sdNVP + ZDV for 1 week (control) vs control + NVP for 14 weeks vs control + NVP/ZDV for 14 weeks	• Postnatal infection in infants uninfected at birth: - MTCT at 6 weeks was 5.1% in control vs 1.7% in extended NVP (67% efficacy) and 1.6% in extended NVP/ZDV arms (69% efficacy). - MTCT at 9 months was 10.6% in control vs 5.2% in extended NVP (51% efficacy) and 6.4% in extended NVP/ZDV arms (40% efficacy). • No significant difference in MTCT between the extended prophylaxis arms; however, more hematologic toxicity with NVP/ZDV
MITRA Tanzania *[36]* Breastfeeding	Infant 3TC for 6 months (observational)	ZDV/3TC from 36 weeks through labor	Maternal ZDV/3TC for 1 week; infant 3TC for 6 months	• MTCT at 6 months was 4.9% (postnatal MTCT between 6 weeks and 6 months was 1.2%).
Kisumu Breastfeeding Study (KiBS) Kenya *[31]* Breastfeeding	Maternal triple drug prophylaxis (observational)	ZDV/3TC/NVP (NFV if CD4 >250) from 34 weeks through labor	Maternal ZDV/3TC/NVP (NFV if CD4 >250) for 6 months; infant sdNVP	• MTCT at 6 months was 5.0% (postnatal MTCT between 7 days and 6 months was 2.6%).
MITRA-PLUS Tanzania *[33]* Breastfeeding	Maternal triple drug prophylaxis (observational)	ZDV/3TC/NVP (NFV if CD4 >200) from 34 weeks through labor	Maternal ZDV/3TC/NVP (NFV if CD4 >200) for 6 months; infant ZDV/3TC for 1 week	• MTCT at 6 months was 5.0% (postnatal MTCT between 6 weeks and 6 months was 0.9%), not significantly different from 6 months infant prophylaxis in MITRA.

Kesho Bora Multi-African *[35]* Breastfeeding primarily	Antepartum ZDV/ sdNVP with no postnatal prophylaxis vs maternal triple drug prophylaxis in women with CD4 between 200 and 500	Arm 1: ZDV/3TC/LPV/r Arm 2: ZDV + sdNVP From 28 weeks through labor	Arm 1: Maternal ZDV/3TC/LPV/r for 6 months; infant sdNVP + ZDV for 1 week Arm 2: Maternal ZDV/3TC for 1 week (no further postnatal prophylaxis); infant sdNVP + ZDV for 1 week (no further postnatal prophylaxis)	• MTCT at birth was 1.8% with maternal triple drug prophylaxis Arm 1 and 2.2% with ZDV/sdNVP Arm 2, not significantly different. • MTCT at 12 months was 5.5% with maternal triple drug prophylaxis Arm 1 and 9.5% with ZDV/sdNVP (with no further postnatal prophylaxis after 1 week) Arm 2 (p=0.04).
Mma Bana Botswana *[34]* Breastfeeding	Maternal triple drug prophylaxis (compares 2 regimens) in women with CD4 >200	Arm 1: ZDV/3TC/ABC Arm 2: ZDV/3TC/LPV/r From 26 weeks through labor	Arm 1: Maternal ZDV/3TC/ABC for 6 months; infant sdNVP + ZDV for 4 weeks Arm 2: Maternal ZDV/3TC/LPV/r for 6 months; infant sdNVP + ZDV for 4 weeks	• MTCT at 6 months overall was 1.3%: 2.1% in ZDV/3TC/ABC Arm 1 and 0.4% in ZDV/3TC/LPV/r Arm 2 (p=0.53).
BAN Malawi *[32]* Breastfeeding	Postpartum maternal triple drug prophylaxis vs infant NVP in women with CD4 ≥250	No AP drugs IP regimens: Arm 1 (control): ZDV/3TC + sdNVP Arm 2: ZDV/3TC + sdNVP Arm 3: ZDV/3TC + sdNVP	Arm 1 (control): Maternal ZDV/3TC for 1 week; infant sdNVP + ZDV/3TC for 1 week Arm 2: Control as above, then maternal ZDV/3TC/LPV/r for 6 months Arm 3: Control as above, then infant NVP for 6 months	• Postnatal infection in infants uninfected at 2 weeks: - MTCT at 28 weeks was 5.7% in control Arm 1; 2.9% in maternal triple drug prophylaxis Arm 2 (p=0.009 vs control); 1.7% in infant NVP Arm 3 (<0.001 vs control). • No significant difference between maternal triple drug prophylaxis Arm 2 and infant NVP Arm 3 (p=0.12).

Key to Abbreviations: 3TC: lamivudine; ABC: abacavir; AP: antepartum; ARV: antiretroviral; CDC: Centers for Disease Control and Prevention; IP: intrapartum; LPV/r: lopinavir/ritonavir; MTCT: mother-to-child transmission; NFV: nelfinavir; NVP: nevirapine; PP: postpartum; sd: single-dose; ZDV: zidovudine

References

1. Connor EM, Sperling RS, Gelber R, et al. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. *N Engl J Med.* 1994;331(18):1173-1180.
2. Cooper ER, Charurat M, Mofenson LM, et al. Combination antiretroviral strategies for the treatment of pregnant HIV-1 infected women and prevention of perinatal HIV-1 transmission. *J Acquir Immune Defic Syndr Hum Retrovirol.* 2002;29(5):484-494.
3. Wortley PM, Lindegren ML, Fleming PL. Successful implementation of perinatal HIV prevention guidelines. A multistate surveillance evaluation. *MMWR Recomm Rep.* 2001;50(RR-6):17-28.
4. Centers for Disease Control and Prevention (CDC), Mofenson LM, Taylor AW, et al. Achievements in public health. Reduction in perinatal transmission of HIV infection--United States, 1985-2005. *MMWR Morb Mortal Wkly Rep.* 2006;55(21):592-597.
5. European Collaborative Study. HIV-infected pregnant women and vertical transmission in Europe since 1986. European collaborative study. *AIDS.* 2001;15(6):761-770.
6. Mandelbrot L, Landreau-Mascaro A, Rekacewicz C, et al. Lamivudine-zidovudine combination for prevention of maternal-infant transmission of HIV-1. *JAMA.* 2001;285(16):2083-2093.
7. Dorenbaum A, Cunningham CK, Gelber RD, et al. Two-dose intrapartum/newborn nevirapine and standard antiretroviral therapy to reduce perinatal HIV-1 transmission: a randomized trial. *JAMA.* 2002;288(2):189-198.
8. McKenna MT, Hu X. Recent trends in the incidence and morbidity that are associated with perinatal human immunodeficiency virus infection in the United States. *Am J Obstet Gynecol.* 2007;197(3 Suppl):S10-16.
9. Peters V, Liu KL, Dominguez K, et al. Missed opportunities for perinatal HIV prevention among HIV-exposed infants born 1996-2000, pediatric spectrum of HIV disease cohort. *Pediatrics.* 2003;111(5 Part 2):1186-1191.
10. Mofenson LM. Successes and challenges in the perinatal HIV-1 epidemic in the United States as illustrated by the HIV-1 Serosurvey of childbearing women. *Arch Pediatr Adolesc Med.* 2004;158(5):422-425.
11. Ioannidis JP, Abrams EJ, Ammann A, et al. Perinatal transmission of human immunodeficiency virus type 1 by pregnant women with RNA virus loads <1000 copies/mL. *J Infect Dis.* 2001;183(4):539-545.
12. Sperling RS, Shapiro DE, Coombs RW, et al. Maternal viral load, zidovudine treatment, and the risk of transmission of human immunodeficiency virus type 1 from mother to infant. Pediatric AIDS Clinical Trials Group Protocol 076 Study Group. *N Engl J Med.* 1996;335(22):1621-1629.
13. Jackson JB, Musoke P, Fleming T, et al. Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: 18-month follow-up of the HIVNET 012 randomised trial. *Lancet.* 2003;362(9387):859-868.
14. Petra Study Team. Efficacy of three short-course regimens of zidovudine and lamivudine in preventing early and late transmission of HIV-1 from mother to child in Tanzania, South Africa, and Uganda (Petra study): a randomised, double-blind, placebo-controlled trial. *Lancet.* 2002;359(9313):1178-1186.
15. Wade NA, Birkhead GS, Warren BL, et al. Abbreviated regimens of zidovudine prophylaxis and perinatal transmission of the human immunodeficiency virus. *N Engl J Med.* 1998;339(20):1409-1414.
16. Moodley D, Moodley J, Coovadia H, et al. A multicenter randomized controlled trial of nevirapine versus a combination of zidovudine and lamivudine to reduce intrapartum and early postpartum mother-to-child transmission of human immunodeficiency virus type 1. *J Infect Dis.* 2003;187(5):725-735.
17. Taha TE, Kumwenda NI, Gibbons A, et al. Short postexposure prophylaxis in newborn babies to reduce mother-to-child transmission of HIV-1: NVAZ randomised clinical trial. *Lancet.* 2003;362(9391):1171-1177.
18. Taha TE, Kumwenda NI, Hoover DR, et al. Nevirapine and zidovudine at birth to reduce perinatal transmission of HIV in an African setting: a randomized controlled trial. *JAMA.* 2004;292(2):202-209.
19. Gray GE, Urban M, Chersich MF, et al. A randomized trial of two postexposure prophylaxis regimens to reduce mother-to-child HIV-1 transmission in infants of untreated mothers. *AIDS.* 2005;19(12):1289-1297.
20. Wiktor SZ, Ekpini E, Karon JM, et al. Short-course oral zidovudine for prevention of mother-to-child transmission of HIV-1 in Abidjan, Côte d'Ivoire: a randomised trial. *Lancet.* 1999;353(9155):781-785.
21. Leroy V, Karon JM, Alioum A, et al. Twenty-four month efficacy of a maternal short-course zidovudine regimen to prevent mother-to-child transmission of HIV-1 in West Africa. *AIDS.* 2002;16(4):631-641.
22. Shaffer N, Chuachoowong R, Mock PA, et al. Short-course zidovudine for perinatal HIV-1 transmission in Bangkok, Thailand: a randomised controlled trial. Bangkok Collaborative Perinatal HIV Transmission Study Group. *Lancet.* 1999;353(9155):773-780.

23. Lallemant M, Jourdain G, Le Coeur S, et al. A trial of shortened zidovudine regimens to prevent mother-to-child transmission of human immunodeficiency virus type 1. Perinatal HIV Prevention Trial (Thailand) Investigators. *N Engl J Med.* 2000;343(14):982-991.
24. Dabis F, Bequet L, Ekouevi DK, et al. Field efficacy of zidovudine, lamivudine and single-dose nevirapine to prevent peripartum HIV transmission. *AIDS.* 2005;19(3):309-318.
25. Leroy V, Sakarovitch C, Cortina-Borja M, et al. Is there a difference in the efficacy of peripartum antiretroviral regimens in reducing mother-to-child transmission of HIV in Africa? *AIDS.* 2005;19(16):1865-1875.
26. Eshleman SH, Hoover DR, Chen S, et al. Resistance after single-dose nevirapine prophylaxis emerges in a high proportion of Malawian newborns. *AIDS.* 2005;19(18):2167-2169.
27. Lallemant M, Jourdain G, Le Coeur S, et al. Single-dose perinatal nevirapine plus standard zidovudine to prevent mother-to-child transmission of HIV-1 in Thailand. *N Engl J Med.* 2004;351(3):217-228.
28. Shapiro RL, Thior I, Gilbert PB, et al. Maternal single-dose nevirapine versus placebo as part of an antiretroviral strategy to prevent mother-to-child HIV transmission in Botswana. *AIDS.* 2006;20(9):1281-1288.
29. Kumwenda NI, Hoover DR, Mofenson LM, et al. Extended antiretroviral prophylaxis to reduce breast-milk HIV-1 transmission. *N Engl J Med.* 2008;359(2):119-129.
30. Six Week Extended-Dose Nevirapine (SWEN) Study Team, Bedri A, Gudetta B, et al. Extended-dose nevirapine to 6 weeks of age for infants to prevent HIV transmission via breastfeeding in Ethiopia, India, and Uganda: an analysis of three randomised controlled trials. *Lancet.* 2008;372(9635):300-313.
31. Thomas T, Masaba R, Ndivo R, et al. PMTCT of HIV-1 among mothers using HAART: the Kisumu Breastfeeding Study, Kisumu, Kenya 2003-2007. Paper presented at: 15th Conference on Retroviruses and Opportunistic Infections; February 3-6, 2008; Boston, MA. Abstract 45aLB, page 87.
32. Chasela C, Hudgens M, Jaimeson D, et al. Maternal antiretrovirals or infant nevirapine to reduce HIV-1 transmission. *N Eng J Med.* 2010 (in press).
33. Kilewo C, Karlsson K, Ngarina M, et al. Prevention of mother-to-child transmission of HIV-1 through breastfeeding by treating mothers with triple antiretroviral therapy in Dar es Salaam, Tanzania: the Mitra Plus study. *J Acquir Immune Defic Syndr.* 2009;52(3):406-416.
34. Shapiro R, Hughes M, Ogwu A, et al. A randomized comparison of antiretroviral regimens used to prevent mother-to-child HIV transmission among breastfeeding women in Botswana. *N Engl J Med.* 2010 (in press).
35. de Vincenzi I, Kesho Bora Study Group. Triple-antiretroviral prophylaxis during pregnancy and breastfeeding compared to short-ARV prophylaxis to prevent mother-to-child transmission of HIV-1: the Kesho Bora randomized controlled clinical trial in five sites in Burkina Faso, Kenya and South Africa. Paper presented at: 5th International AIDS Society Conference on HIV Pathogenesis, Treatment, and Prevention; July 19-22, 2009; Capetown, South Africa. Abstract LBPE C01.
36. Kilewo C, Karlsson K, Massawe A, et al. Prevention of mother-to-child transmission of HIV-1 through breast-feeding by treating infants prophylactically with lamivudine in Dar es Salaam, Tanzania: the Mitra Study. *J Acquir Immune Defic Syndr.* 2008;48(3):315-323.
37. Moorthy A, Gupta A, Bhosale R, et al. Nevirapine resistance and breast-milk HIV transmission: effects of single and extended-dose nevirapine prophylaxis in subtype C HIV-infected infants. *PLoS One.* 2009;4(1):e4096.
38. Zeh C, Weidle P, Nafisa L, et al. Emergence of HIV-1 Drug Resistance among Breastfeeding Infants Born to HIV-infected Mothers Taking Antiretrovirals for Prevention of Mother-to-Child Transmission of HIV: The Kisumu Breastfeeding Study, Kenya. Paper presented at: 15th Conference on Retroviruses and Opportunistic Infections; February 3-6, 2008; Boston, MA. Abstract 84LB.
39. Lidstrom J, Guay L, Musoke P, et al. Multi-class drug resistance arises frequently in HIV-infected breastfeeding infants whose mothers initiate HAART postpartum. Paper presented at: 17th Conference on Retroviruses and Opportunistic Infections; February 16-19, 2010; San Francisco, CA. Abstract 920.
40. Lidstrom J, Kumwenda N, Kafulafula G, et al. Antiretroviral treatment of HIV-infected women can induce multi-class drug resistance in their breastfeeding infants. *Antiviral Ther.* 2009;14 Suppl 1:A158.
41. Dickover RE, Garratty EM, Herman SA, et al. Identification of levels of maternal HIV-1 RNA associated with risk of perinatal transmission: effect of maternal zidovudine treatment on viral load. *JAMA.* 1996;275(8):599-605.
42. Cao Y, Krogstad P, Korber BT, et al. Maternal HIV-1 viral load and vertical transmission of infection: The Ariel Project for the prevention of HIV transmission from mother to infant. *Nat Med.* 1997;3(5):549-552.

43. Mayaux MJ, Dussaix E, Isopet J, et al. Maternal virus load during pregnancy and the mother-to-child transmission of human immunodeficiency virus type 1: the French Perinatal Cohort Studies. *J Infect Dis.* 1997;175(1):172-175.
44. Thea DM, Steketee RW, Pliner V, et al. The effect of maternal viral load on the risk of perinatal transmission of HIV-1. *AIDS.* 1997;11(4):437-444.
45. Shapiro DE, Sperling RS, Coombs RW. Effect of zidovudine on perinatal HIV-1 transmission and maternal viral load. *Lancet.* 1999;354(9173):156; author reply 157-158.
46. Shaffer N, Roongpisuthipong A, Siriwasin W, et al. Maternal virus load and perinatal human immunodeficiency virus subtype E transmission, Thailand. *J Infect Dis.* 1999;179(3):590-599.
47. Mofenson LM, Lambert JS, Stiehm ER, et al. Risk factors for perinatal transmission of human immunodeficiency virus type 1 in women treated with zidovudine. Pediatric AIDS Clinical Trials Group Study 185 Team. *N Engl J Med.* 1999;341(6):385-393.
48. Garcia PM, Kalish LA, Pitt J, et al. Maternal levels of plasma human immunodeficiency virus type 1 RNA and the risk of perinatal transmission. *N Engl J Med.* 1999;341(6):394-402.
49. Maternal viral load and vertical transmission of HIV-1: an important factor but not the only one. The European Collaborative Study. *AIDS.* 1999;13(11):1377-1385.
50. Mock PA, Shaffer N, Bhadrakom C, et al. Maternal viral load and timing of mother-to-child HIV transmission, Bangkok, Thailand. Bangkok Collaborative Perinatal HIV Transmission Study Group. *AIDS.* 1999;13(3):407-414.
51. Hart CE, Lennox JL, Pratt-Palmore M, et al. Correlation of human immunodeficiency virus type 1 RNA levels in blood and the female genital tract. *J Infect Dis.* 1999;179(4):871-882.
52. Iversen AK, Larsen AR, Jensen T, et al. Distinct determinants of human immunodeficiency virus type 1 RNA and DNA loads in vaginal and cervical secretions. *J Infect Dis.* 1998;177(5):1214-1220.
53. Shaheen F, Sison AV, McIntosh L, et al. Analysis of HIV-1 in cervicovaginal secretions and blood of pregnant and non-pregnant women. *J Hum Virol.* 1999;2(3):154-166.
54. Rasheed S, Li Z, Xu D, et al. Presence of cell-free human immunodeficiency virus in cervicovaginal secretions is independent of viral load in the blood of human immunodeficiency virus-infected women. *Am J Obstet Gynecol.* 1996;175(1):122-129.
55. Chuachoowong R, Shaffer N, Siriwasin W, et al. Short-course antenatal zidovudine reduces both cervicovaginal human immunodeficiency virus type 1 RNA levels and risk of perinatal transmission. *J Infect Dis.* 2000;181(1):99-106.
56. McGowan JP, Crane M, Wiznia AA, et al. Combination antiretroviral therapy in human immunodeficiency virus-infected pregnant women. *Obstet Gynecol.* 1999;94(5 Pt 1):641-646.
57. Melvin AJ, Burchett SK, Watts DH, et al. Effect of pregnancy and zidovudine therapy on viral load in HIV-1-infected women. *J Acquir Immune Defic Syndr Hum Retrovirol.* 1997;14(3):232-236.
58. Dabis F, Msellati P, Meda N, et al. 6-month efficacy, tolerance, and acceptability of a short regimen of oral zidovudine to reduce vertical transmission of HIV in breastfed children in Côte d'Ivoire and Burkina Faso: a double-blind placebo-controlled multicentre trial. DITRAME Study Group. DIminution de la Transmission Mère-Enfant. *Lancet.* 1999;353(9155):786-792.
59. Thior I, Lockman S, Smeaton LM, et al. Breastfeeding plus infant zidovudine prophylaxis for 6 months vs formula feeding plus infant zidovudine for 1 month to reduce mother-to-child HIV transmission in Botswana: a randomized trial: the Mashi Study. *JAMA.* 2006;296(7):794-805.

Preconceptional Counseling and Care for HIV-Infected Women of Childbearing Age

(Updated May 24, 2010)

Panel's Recommendations:

- ***Contraceptive counseling is an essential component of care for HIV-infected women of reproductive age and should include counseling on effective and appropriate contraceptive methods to reduce the likelihood of unintended pregnancy (AI).***
- ***Preconception counseling should include counseling on safe sexual practices and eliminating alcohol, illicit drug use, and smoking, which are important for the health of the woman as well as for fetal/infant health should pregnancy occur (AII).***
- ***Evaluation of the HIV-infected woman should include assessment of her HIV disease status and need for antiretroviral therapy for her own health (AII).***
- ***If already on therapy, her regimen should be reviewed in terms of potential pregnancy (e.g., teratogenic potential of the drugs in the regimen) (AII).***
- ***Choice of an antiretroviral treatment regimen for HIV-infected women of childbearing potential needs to include consideration of effectiveness for treatment of maternal disease, teratogenic potential of the drugs in the regimen should pregnancy occur, and possible adverse outcomes for mother and fetus (AII).***
- ***HIV-infected women who are on therapy and wish to become pregnant should attain a stable maximally suppressed viral load prior to conception (AIII).***

The Centers for Disease Control and Prevention (CDC), the American College of Obstetrics and Gynecology (ACOG), and other national organizations recommend offering all women of childbearing age the opportunity to receive preconception counseling and care as a component of routine primary medical care. The purpose of preconception care is to improve the health of each woman prior to conception by identifying risk factors for adverse maternal or fetal outcome, providing education and counseling targeted to the patient's individual needs, and treating or stabilizing medical conditions to optimize maternal and fetal outcomes *[1]*. Preconception care is not a single clinical visit but rather a process of ongoing care and interventions integrated into primary care to address the needs of women during the different stages of reproductive life. Because more than half of all pregnancies in the United States are unintended *[2-3]* it is important that preconception care be integrated into routine health visits. Therefore, HIV care providers who routinely care for women of reproductive age play an important role in promoting preconception health.

The fundamental principles of preconception counseling and care are outlined in the CDC Preconception Care Work Group's **Recommendations to Improve Preconception Health and Health Care**. In addition to the general components of preconception counseling and care that are appropriate for all women of reproductive age, HIV-infected women have specific needs that should be addressed *[4]*. Because many women infected with HIV are aware of their HIV status prior to pregnancy, issues that impact pregnancy may be addressed prior to conception during their routine medical care for HIV disease. In addition to those outlined by the CDC Preconception Care Work Group *[5]*, the following components of preconception counseling and care are specifically recommended for HIV-infected women. Health care providers should:

a. Offer all women effective and appropriate contraceptive methods to reduce the likelihood of unintended pregnancy. Providers should be aware of potential interactions of antiretroviral drugs with hormonal contraceptives that could lower contraceptive efficacy (see the ***Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents***, Tables 13, 14a, 14b) *[6]*.

b. Counsel on safe sexual practices that prevent HIV transmission to sexual partners, protect women from acquiring sexually transmitted infections (STIs), and reduce the potential to acquire more virulent or resistant HIV strains.

c. Counsel on eliminating alcohol, illicit drug use, and cigarette smoking.

d. Educate and counsel women about risk factors for perinatal transmission of HIV, strategies to reduce those risks, potential effects of HIV or treatment on pregnancy course and outcomes, and that breastfeeding by HIV-infected women is not recommended in the United States due to risk of HIV transmission and the availability of safe and sustainable infant feeding alternatives.

e. When prescribing antiretroviral treatment to women of childbearing potential, consider the regimen's effectiveness for treatment of HIV, hepatitis B disease status, the drugs' potential for teratogenicity should pregnancy occur, and possible adverse outcomes for mother and fetus *[7-8]*.

f. For women who are contemplating pregnancy, strongly consider the use of antiretroviral regimens that do not contain efavirenz or other drugs with teratogenic potential.

g. For women who are on antiretroviral therapy and want to get pregnant, set attaining a stable, maximally suppressed maternal viral load prior to conception as a primary treatment goal to decrease the risk of mother-to-child transmission of HIV.

h. Evaluate and appropriately manage therapy-associated side effects that may adversely impact maternal-fetal health outcomes (e.g., hyperglycemia, anemia, hepatic toxicity).

i. Evaluate the need for appropriate prophylaxis or treatment for opportunistic infections including safety, tolerability, and potential toxicity of specific agents when used in pregnancy.

j. Administer medical immunizations (e.g., influenza, pneumococcal, or hepatitis A and B vaccines) as indicated.

k. Encourage sexual partners to receive HIV testing and counseling and appropriate HIV care if infected.

l. Counsel regarding available reproductive options, such as intrauterine or intravaginal insemination, that prevent HIV exposure to an uninfected partner. Expert consultation is recommended *[9]*.

m. Counsel regarding available reproductive options to reduce risk of transmission to an uninfected female partner with an HIV-infected male partner; expert consultation is recommended *[10]*.

MONITORING OF PREGNANT WOMEN WITH A PARTNER KNOWN TO BE HIV INFECTED

Increasingly clinicians may be faced with the situation in which an HIV-uninfected woman presents during pregnancy and relates that she has an HIV-infected partner. As is recommended for all pregnant women, the woman should be notified that HIV screening is recommended and that she will receive an HIV test as part of the routine panel of prenatal tests unless she declines. In addition, she should receive a second HIV test during the third trimester, preferably before 36 weeks of gestation, as is recommended for high-risk women. Furthermore, if the pregnant woman presents in labor without third-trimester testing and result, then she should be screened with a rapid HIV test on the labor and delivery unit. If at any time during pregnancy the clinician suspects that a pregnant woman may be in the "window" period of seroconversion (i.e., has signs or symptoms consistent with acute HIV infection), then a plasma HIV RNA test can be used in conjunction with an HIV antibody test, and HIV testing may be repeated in 4–6 weeks. Women should be counseled regarding the symptoms of acute retroviral syndrome (i.e., fever, pharyngitis, rash, myalgia, arthralgia, diarrhea, headache) and the importance of seeking medical care and testing if they experience such symptoms.

If results from either conventional or rapid HIV testing are positive, then the woman should receive appropriate evaluation and interventions to reduce perinatal transmission of HIV, including immediate initiation of appropriate antiretroviral prophylaxis and consideration of elective cesarean delivery according to

established guidelines (see **Transmission and Mode of Delivery**). In cases where confirmatory testing results are not readily available (e.g., rapid testing during labor), it is appropriate to initiate interventions to reduce perinatal transmission even in the absence of confirmatory results (see **Infant Antiretroviral Prophylaxis**). If HIV testing results are negative, then pregnant women with HIV-infected partners should be regularly counseled regarding the ongoing risk of HIV transmission. If the partner's HIV status is at all uncertain, he should be encouraged to seek testing and appropriate care. All women and their partners should be counseled about the importance of correct and consistent condom use.

References

1. American College of Obstetricians and Gynecologists. ACOG Committee Opinion number 313, September 2005. The importance of preconception care in the continuum of women's health care. *Obstet Gynecol.* 2005;106(3):665-666.
2. Henshaw SK. Unintended pregnancy in the United States. *Fam Plann Perspect.* 1998;30(1):24-29, 46.
3. Johnson K, Posner SF, Biermann J, et al. Recommendations to improve preconception health and health care--United States. A report of the CDC/ATSDR Preconception Care Work Group and the Select Panel on Preconception Care. *MMWR Recomm Rep.* 2006;55(RR-6):1-23.
4. Lampe MA. Human immunodeficiency virus-1 and preconception care. *Matern Child Health J.* 2006;10(5 Suppl):S193-195.
5. Centers for Disease Control and Prevention (CDC). Incorporating HIV prevention into the medical care of persons living with HIV. Recommendations of CDC, the Health Resources and Services Administration, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. *MMWR Recomm Rep.* 2003;52(RR-12):1-24.
6. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. December 1, 2009:1-161. http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf.
7. Cotter AM, Garcia AG, Duthely ML, et al. Is antiretroviral therapy during pregnancy associated with an increased risk of preterm delivery, low birth weight, or stillbirth? *J Infect Dis.* 2006;193(9):1195-1201.
8. Tuomala RE, Shapiro DE, Mofenson LM, et al. Antiretroviral therapy during pregnancy and the risk of an adverse outcome. *N Engl J Med.* 2002;346(24):1863-1870.
9. Daar ES, Daar JF. Human immunodeficiency virus and fertility care: embarking on a path of knowledge and access. *Fertil Steril.* 2006;85(2):298-300; discussion 301.
10. Aberg JA, Kaplan JE, Libman H, et al. Primary care guidelines for the management of persons infected with human immunodeficiency virus: 2009 update by the HIV medicine Association of the Infectious Diseases Society of America. *Clin Infect Dis.* 2009;49(5):651-681.

Antepartum Care (Updated May 24, 2010)

GENERAL PRINCIPLES REGARDING USE OF ANTIRETROVIRAL DRUGS DURING PREGNANCY

Panel's Recommendations:

- ***Initial evaluation of an infected pregnant woman should include an assessment of HIV disease status and recommendations regarding initiating antiretroviral therapy or altering her current antiretroviral regimen (AIII). The National Perinatal HIV Hotline (1-888-448-8765) provides free clinical consultation on all aspects of perinatal HIV care.***
- ***Antiretroviral prophylaxis for prevention of perinatal transmission of HIV during the antepartum period should be recommended to all pregnant, HIV-infected women regardless of plasma HIV RNA copy number or CD4 cell count (AI).***
- ***The known benefits and potential risks of antiretroviral use during pregnancy should be discussed with all women (AIII).***
- ***Zidovudine should be included in the antenatal antiretroviral regimen unless there is severe toxicity or documented resistance or the woman is already on a fully suppressive regimen (AIII).***
- ***If HIV RNA is detectable (e.g., >500–1,000 copies/mL), antiretroviral drug resistance studies should be performed before starting or modifying therapy (see Antiretroviral Drug Resistance and Resistance Testing in Pregnancy) (AI).***
- ***The importance of adherence to the antiretroviral treatment or prophylaxis regimen should be emphasized (AII).***
- ***Coordination of services among prenatal care providers, primary care and HIV specialty care providers, mental health and drug abuse treatment services, and public assistance programs, if necessary, should be assured as part of recommending antiretroviral drugs during pregnancy (AIII).***

In addition to the standard antenatal assessments for all pregnant women, the initial evaluation of an HIV-infected pregnant woman should include an assessment of HIV disease status and recommendations for HIV-related medical care. This initial assessment should include the following:

a. review of prior HIV-related illnesses, past CD4+ cell counts, and past plasma HIV viral loads;

b. current CD4+ cell count;

c. current plasma HIV RNA copy number;

d. assessment of the need for prophylaxis against opportunistic infections such as *Pneumocystis jirovecii* pneumonia (PCP) or *Mycobacterium avium* complex (MAC) *[1];*

e. baseline complete blood cell count and renal and liver function testing;

f. history of prior and current antiretroviral therapy;

g. history of prior antiretroviral drug use for prevention of perinatal HIV transmission;

h. results of prior and current HIV antiretroviral drug resistance studies; and

i. assessment of supportive care needs.

In general, guidelines for the use of antiretroviral drug treatment for the benefit of maternal health during pregnancy are the same as guidelines for women who are not pregnant. Antiretroviral prophylaxis is recommended for all pregnant women with HIV infection, regardless of viral load (see **HIV-Infected Pregnant Women Not on Antiretroviral Therapy Who Require Antiretroviral Prophylaxis Solely to Prevent Perinatal HIV Transmission**).

Decisions regarding initiating or altering antiretroviral drug regimens during pregnancy include considerations regarding the benefits and risks of antiretroviral drug use that are common to all HIV-infected adults in addition to considerations unique to pregnancy. Maternal toxicities and risks of therapy must be considered, along with the additional considerations of the potential impact of such therapy on the outcome of pregnancy and on the fetus and infant. These decisions are further complicated because there are only limited data on the long-term maternal consequences of antiretroviral drug use during pregnancy solely for prophylaxis of transmission. Similarly, there are only limited data on the long-term consequences of *in utero* antiretroviral exposure for the infant. The potential for drug-associated teratogenicity, toxicity, or the lack of data on specific drugs in pregnancy are important considerations in terms of drug regimen choice in a pregnant woman (**Table 3**).

Discussion of antiretroviral use with a pregnant woman should be noncoercive, and the final decision regarding use of antiretroviral drugs is the responsibility of the woman. The known benefits and known and unknown risks of antiretroviral drug use during pregnancy should be considered and discussed (see **Special Considerations Regarding the Use of Antiretroviral Drugs by HIV-infected Pregnant Women and their Infants**). Results from preclinical and animal studies and available clinical information about use of the various agents during pregnancy should be discussed with the woman (**Table 4** and **Table 5**). Potential risks of these drugs should be placed into perspective by also discussing substantial benefits of antiretroviral drugs for the health of the infected woman and for reducing the risk of HIV transmission to her infant.

Discussion with the woman about initiation of antiretroviral therapy should include the following:

a. maternal risk of disease progression and the benefits and risks of initiation of therapy for her own health;

b. benefit of combination antiretroviral regimens for preventing perinatal HIV transmission *[2]*;

c. Potential adverse effects of antiretroviral drugs for mother, fetus, and infant;

d. the limited long-term outcome data for both infants with *in utero* antiretroviral exposure and for women who temporarily use antiretroviral drugs during pregnancy for prophylaxis of transmission; and

e. the possibility of development of antiretroviral resistance, including the need for strict adherence to the prescribed drug regimen to avoid its development.

Although zidovudine should be a component of the antenatal antiretroviral regimen, there may be circumstances, such as the occurrence of severe zidovudine-related toxicity (e.g., severe anemia) or documented zidovudine resistance, when this is not possible. Additionally, women receiving an antiretroviral regimen that does not contain zidovudine but who have HIV RNA levels that are undetectable have a very low risk of perinatal transmission *[3]*, and there may be concerns that substitution of zidovudine for another component of the regimen or the addition of zidovudine to the current regimen could compromise adherence to treatment. In such cases, continuing a non-zidovudine-containing regimen that is fully suppressive is reasonable.

If plasma HIV RNA is detectable (greater than 500 to 1,000 copies/mL), antiretroviral drug resistance studies should be performed before starting antiretroviral therapy for maternal health or prophylaxis. However, if HIV is diagnosed late in pregnancy, therapy or prophylaxis should be initiated while

awaiting results of resistance testing (see **Antiretroviral Drug Resistance and Resistance Testing in Pregnancy**).

The importance of adherence to the antiretroviral treatment or prophylaxis regimen should be emphasized. Depending on individual circumstances, provision of support services, mental health services, and drug abuse treatment may be required. Coordination of services among prenatal care providers, primary care and HIV specialty care providers, mental health and drug abuse treatment services, and public assistance programs is essential to ensure adherence of the infected woman to the antiretroviral treatment regimen. Long-range plans should be developed with the woman regarding continuity of medical care and decisions about antiretroviral therapy for her own health after the birth of her infant.

Medical care of the HIV-infected pregnant woman requires coordination and communication between HIV specialists and obstetrical providers. General counseling should include current knowledge regarding risk factors for perinatal transmission. Potentially modifiable factors including cigarette smoking, illicit drug use, genital tract infections, and unprotected sexual intercourse with multiple partners during pregnancy have been associated with risk of perinatal HIV transmission *[4-8]*. In addition to improving maternal health, cessation of cigarette smoking and drug use, treatment of genital tract infections, and use of condoms with sexual intercourse during pregnancy may reduce risk of perinatal transmission. In addition, the CDC recommends that HIV-infected women in the United States (including those receiving antiretroviral therapy) refrain from breastfeeding to avoid postnatal transmission of HIV to their infants through breast milk *[9]*.

The National Perinatal HIV Hotline (1-888-448-8765)

The National Perinatal HIV Hotline is a federally funded service providing free clinical consultation to providers caring for HIV-infected women and their infants.

RECOMMENDATIONS FOR USE OF ANTIRETROVIRAL DRUGS DURING PREGNANCY

The Panel recommends that choice of antiretroviral drug regimens for HIV-infected pregnant women be based on the same principles used to choose regimens for non-pregnant individuals, unless there are compelling pregnancy-specific maternal or fetal safety issues regarding specific drug choices. The Panel reviews clinical trial data published in peer-reviewed journals and data prepared by manufacturers for FDA review related to treatment of HIV-infected adult women, both pregnant and nonpregnant. The durability, tolerability, and simplicity of the medication regimen is of particular importance in order to preserve options in the future for those women who will be stopping medications following delivery and for those women who meet standard criteria for initiation of antiretroviral therapy per adult guidelines and will continue the regimen after pregnancy. Regimen selection should be individualized and should consider a number of factors including:

- comorbidities,
- patient adherence potential,
- convenience,
- potential adverse drug effects on the mother,
- potential drug interactions with other medications,
- results of genotypic resistance testing,
- pharmacokinetic (PK) changes in pregnancy, and
- potential teratogenic effects on the fetus and other adverse effects on the fetus or newborn.

Criteria used by the Panel for recommending specific drugs or regimens for pregnant women include:

- Data from randomized prospective clinical trials that demonstrate durable viral suppression as well as immunologic and clinical improvement;
- Incidence rates and descriptions of short- and long-term drug toxicity of antiretroviral regimens with special attention to maternal toxicity and safety and teratogenic effects on the fetus;
- Specific knowledge about drug tolerability and simplified dosing regimens;
- Drug regimens that are known to be effective in reducing transmission to the fetus;
- Pharmacokinetic data during the prenatal period: The physiologic changes of pregnancy have the potential to alter the pharmacokinetics of drugs. Antiretroviral dosing during pregnancy should be based on pharmacokinetic data from studies in pregnant women. Physiologic changes are not fixed throughout pregnancy but rather reflect a continuum of change as pregnancy progresses, with return to baseline at various rates in the postpartum period.

Categories of antiretroviral regimens include:

- ***Preferred:*** Drugs or drug combinations are designated as preferred for use in pregnant women when clinical trial data in adults have demonstrated optimal efficacy and durability with acceptable toxicity and ease of use; pregnancy-specific pharmacokinetic data are available to guide dosing; and no evidence of teratogenic effects on the fetus or established association with teratogenic or clinically significant adverse outcomes for the mother, fetus, or newborn are present.

- ***Alternative:*** Drugs or drug combinations are designated as alternatives for initial therapy in pregnant women when clinical trial data in adults show efficacy but any one or more of the following conditions apply: there is limited experience in pregnancy; there is lack of data on teratogenic effects on the fetus; or there are dosing, formulation, administration, or interaction issues for that drug or regimen.

- ***Use in Special Circumstances:*** Drug or drug combinations in this category can be considered for use when intolerance or resistance prohibits use of other drugs with fewer toxicity concerns or the woman has comorbidities or requires concomitant medications that may limit drug choice (e.g., chronic hepatitis B infection, active tuberculosis requiring rifampin therapy).

- ***Not Recommended:*** Drugs and drug combinations listed in this category are not recommended for therapy in pregnant women because of inferior virologic response, potential serious safety concerns for the mother or fetus, or pharmacologic antagonism.

- ***Insufficient Data to Recommend:*** Although approved for use in adults, the drugs and drug combinations in this category do not have pregnancy-specific pharmacokinetic or safety data available or such data are too limited to make a recommendation for use for pregnancy.

All women who receive antiretroviral drugs during pregnancy either for treatment or prophylaxis should receive combination regimens containing at least three agents. A combination regimen including two nucleoside reverse transcriptase inhibitors (NRTIs) and either a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a protease inhibitor (PI) (with or without low-dose ritonavir) should be used. The preferred NRTI regimen in pregnancy, based on efficacy studies in preventing perinatal transmission (see **Lessons from Clinical Trials of Antiretroviral Interventions to Reduce Perinatal HIV Transmission**) and large experience with use in pregnancy, is zidovudine/lamivudine. Alternate regimens may be used for women who have intolerance of zidovudine because of toxicity such as severe anemia or with known resistance to zidovudine. Tenofovir, a preferred NRTI in nonpregnant women, should be used only in special circumstances (such as intolerance or resistance to zidovudine or chronic hepatitis B infection) because of concerns regarding the potential for fetal toxicity. Animal studies have shown decreased fetal growth and reduction in fetal bone porosity, and studies in infected children on chronic tenofovir-based therapy have shown bone demineralization in some children. The combination of stavudine/didanosine should not be used in pregnant women because of fatal cases of lactic acidosis and hepatic failure reported in pregnant women who received this combination throughout pregnancy.

In addition to the two NRTIs, either an NNRTI or a PI should be included in antiretroviral regimens prescribed for maternal health. Efavirenz, the preferred NNRTI for nonpregnant adults, is not recommended for use in the first trimester of pregnancy because of animal data showing risk of anencephaly, micro-ophthalmia, and facial clefts as well as concerning case reports of several neural tube defects and a single case of anophthalmia with severe facial cleft in humans. Use of efavirenz after the first trimester of pregnancy may be considered if alternate agents are not tolerated. Nevirapine may be used in women with CD4+ lymphocyte counts less than 250 cells/mm^3 or continued for women already receiving a nevirapine-based regimen. Nevirapine should generally not be initiated for treatment-naïve women with CD4+ cell counts greater than 250 cells/mm^3 because of an increased risk of symptomatic and potentially fatal rash and hepatic toxicity. Etravirine has insufficient safety or pharmacokinetic data in pregnancy to recommend its use. Lopinavir/ritonavir is the preferred protease inhibitor regimen for pregnant women because of efficacy studies in adults and experience with use in pregnancy (see **Table 5** for dosing considerations). Alternative protease inhibitors include ritonavir-boosted atazanavir, saquinavir, or indinavir, although experience with these regimens in pregnancy is more limited and the latter two may be less well tolerated. Data on use in pregnancy for darunavir, fosamprenavir, and tipranavir are too limited to recommend routine use in pregnancy, although they may be considered if other agents are not tolerated.

Safety and pharmacokinetics data in pregnancy are insufficient to recommend use of the entry inhibitors enfuvirtide and maraviroc and the integrase inhibitor raltegravir during pregnancy. Use of these agents for women who have failed therapy with several other classes of antiretroviral drugs could be considered in consultation with HIV and obstetric specialists.

In addition, recommendations for the use of antiretroviral drugs for prophylaxis to prevent perinatal HIV transmission in women for whom therapy would not otherwise be indicated include the agents/combinations discussed above and some that are not considered preferred regimens in nonpregnant adults, such as triple NRTI regimens with abacavir and the use of nelfinavir with two NRTIs. These options are discussed in more detail below.

Although data are insufficient to support or refute the teratogenic risk of antiretroviral drugs when administered during the first 10 weeks of gestation, information to date does not support major teratogenic effects of the majority of antiretroviral drugs. (For further data, see **www.APRegistry.com**.) However, certain drugs are of more concern than others (**Table 4** and see **Teratogenicity** and **Supplement: Safety and Toxicity of Individual Antiretroviral Drugs in Pregnancy**). For example, efavirenz should be avoided during the first trimester of pregnancy.

Recommendations for antiretroviral therapy during pregnancy must be individualized according to the specific antiretroviral history of the HIV-infected pregnant woman. Some women may be receiving antiretroviral therapy for their own health at the time they become pregnant and present for obstetrical care on such therapy. Other HIV-infected women may not be receiving antiretroviral therapy at the time they present for obstetrical care. Some of these women have never received antiretroviral drugs before, while other women may have previously received antiretroviral drugs, either for treatment that was stopped or for prophylaxis to prevent perinatal HIV transmission in prior pregnancies. Considerations for initiating therapy will differ for such women according to whether antiretroviral drugs are currently indicated for maternal health or solely for fetal protection. The antiretroviral recommendations below are divided into sections according to antiretroviral treatment status at the time the woman presents for care and whether there are maternal indications for therapy.

Table 5 provides recommendations about the use of specific antiretroviral drugs in pregnancy as well as data on pharmacokinetics and toxicity in pregnancy. **Table 6** provides a summary of management recommendations for the mother and infant in a variety of clinical scenarios.

HIV-Infected Pregnant Women Who Are Currently Receiving Antiretroviral Treatment

Panel's Recommendations:

- ***Pregnant women receiving and tolerating an antiretroviral treatment regimen that is currently effective in suppressing viral replication should continue on the regimen; however, the use of efavirenz should be avoided in the first trimester of pregnancy (AIII).***
- ***HIV antiretroviral drug resistance testing is recommended if the pregnant woman has detectable viremia (e.g., >500–1,000 copies/mL) on therapy (see Failure of Viral Suppression) (AI).***
- ***Pregnant women receiving nevirapine-containing regimens who are virologically suppressed and tolerating the regimen should continue the regimen, regardless of CD4 count (AIII).***

In general, women who have been receiving antiretroviral treatment for their HIV infection should continue treatment during pregnancy. Discontinuation of therapy could lead to an increase in viral load with possible decline in immune status and disease progression as well as adverse consequences for the fetus, including increased risk of HIV transmission. Therefore, when pregnancy is identified after the first trimester in HIV-infected women receiving antiretroviral therapy at the time of conception, therapy should always be continued.

HIV-infected women receiving antiretroviral treatment who present for care during the first trimester of pregnancy should be counseled regarding the benefits and potential risks of antiretroviral administration during this period, and continuation of therapy should be recommended. However, the use of efavirenz should be avoided during the first trimester of pregnancy. If a woman is receiving efavirenz and her pregnancy is recognized during the first trimester, an alternative antiretroviral drug should be substituted when possible (see **Monitoring of the Woman and Fetus during Pregnancy**).

Resistance testing should be performed in women who are on therapy but not fully suppressed. Results of this testing can be used to select a regimen that may have greater chance to suppress viral loads to undetectable. It should be noted that resistance assays vary depending on the HIV RNA level required to detect resistance mutations. Some assays require HIV RNA levels of ≥1,000 copies/mL; other assays can be performed with lower viral loads.

Pregnant women who are receiving nevirapine-containing regimens with viral suppression and are tolerating the regimen well should continue therapy, regardless of CD4 count. Although hepatic toxicity is a concern in women who have a CD4 count >250 cells/mm^3 when they first start a nevirapine-containing regimen, an increased risk of hepatic toxicity has not been seen in women who are receiving nevirapine-based therapy and have immune reconstitution with therapy.

HIV-Infected Pregnant Women Who Have Never Received Antiretroviral Drugs (Antiretroviral Naïve)

Panel's Recommendations:

- ***HIV-infected pregnant women who meet standard criteria for initiation of antiretroviral therapy per adult antiretroviral treatment guidelines should receive standard potent combination antiretroviral therapy as recommended for nonpregnant adults, taking into account what is known about the use of specific drugs in pregnancy and risk of teratogenicity (Table 5) (AI).***
  - ***For women who require immediate initiation of therapy for their own health, treatment should be started as soon as possible, including in the first trimester of pregnancy (AII). (Note that the use of efavirenz should be avoided during the first trimester.)***
- ***HIV-infected pregnant women who do not require treatment for their own health should also receive three-drug combination antiretroviral regimens for prophylaxis of perinatal transmission (AII). The use of zidovudine alone as prophylaxis is controversial but may be considered for those women initiating prophylaxis with plasma HIV RNA levels <1,000 copies/mL on no therapy (CII).***
  - ***For women who are receiving antiretroviral drugs solely for prevention of perinatal transmission, delaying initiation of prophylaxis until after the first trimester of pregnancy can be considered (BIII).***
- ***Zidovudine should be used as a component of the antiretroviral regimen when feasible (AIII).***
- ***HIV antiretroviral drug resistance testing should be performed prior to initiating antiretroviral prophylaxis or therapy (AI)*.***
- ***Nevirapine may be used as a component of initial therapy for pregnant women with CD4 cell counts <250 cells/mm^3. However, due to an increased risk of hepatic toxicity, nevirapine should only be used as a component of antiretroviral therapy in pregnant women with CD4 cell counts >250 cells/mm^3 if the benefit clearly outweighs the risk (AII).***

**Dependent on the resistance assay being used; some assays require HIV RNA levels of ≥1,000 copies/mL for performance of the resistance assay, while other assays can be used with lower levels of viral replication.*

Pregnant women with HIV infection should receive standard clinical, immunologic, and virologic evaluation. Decisions about the need for initiation of therapy should be based on the standard guidelines for nonpregnant adults *[10]*.

HIV-Infected Pregnant Women Not on Antiretroviral Therapy and Who Need Antiretroviral Treatment for Their Own Health

Any HIV-infected pregnant woman who meets standard criteria for initiation of antiretroviral therapy as per adult antiretroviral guidelines should receive potent combination antiretroviral therapy, generally consisting of NRTIs plus an NNRTI or PIs, with continuation of therapy postpartum. For women who require immediate initiation of therapy for their own health, treatment should be started as soon as possible, including in the first trimester, because the potential benefit of treatment for the mother outweighs potential fetal risks. The regimen should generally be chosen from those recommended for nonpregnant adults (e.g., a preferred or alternative regimen), taking into account what is known about use of the drugs during pregnancy and risk of teratogenicity (see **Table 5** and **Teratogenicity**) *[10]*.

Women with CD4 counts >250 cells/mm^3 have an increased risk of developing symptomatic, often rash-associated, nevirapine-related hepatotoxicity that can be severe, life-threatening, and in some cases fatal *[11-12]*. Therefore, nevirapine should only be used as a component of a combination regimen when antiretroviral therapy is being initiated in women with CD4 counts >250 cells/mm^3 if the benefit clearly outweighs the risk. If nevirapine is used, frequent and careful monitoring of

transaminase levels, particularly during the first 18 weeks of treatment, is required (see **Nevirapine and Hepatic/Rash Toxicity**). Transaminase levels should be checked in all women who develop a rash while receiving nevirapine. Nevirapine should be stopped immediately in all women who develop signs or symptoms of hepatitis.

HIV-Infected Pregnant Women Not on Antiretroviral Therapy Who Require Antiretroviral Prophylaxis Solely to Prevent Perinatal HIV Transmission

HIV-infected pregnant women should be counseled regarding the benefits of antiretroviral drugs for prevention of perinatal transmission even when initiation of antiretroviral therapy for maternal health is not recommended or is considered optional on the basis of current guidelines for treatment of nonpregnant persons *[10]*. Although such women are at low risk of clinical disease progression if antiretroviral treatment is delayed, use of an antiretroviral regimen that successfully reduces plasma HIV RNA to undetectable levels substantially lowers the risk of perinatal HIV transmission and lessens the need for consideration of elective cesarean delivery as an intervention to reduce transmission risk.

Because the fetus is most susceptible to the potential teratogenic effects of drugs during the first 10 weeks of gestation and the risks of antiretroviral therapy during that period are not fully known, women in the first trimester of pregnancy who do not require immediate initiation of therapy for their own health may consider delaying initiation until after 10 to 12 weeks gestation. This decision should be carefully considered by the health care provider and the woman; a discussion should include an assessment of the woman's health status, the benefits and risks to her of delaying initiation of therapy for several weeks, and the fact that most perinatal HIV transmission likely occurs late in pregnancy or during delivery.

Antiretroviral prophylaxis is recommended for all pregnant women with HIV infection, regardless of viral load. Although rates of perinatal transmission are low in women with undetectable or low HIV RNA levels (e.g., <1,000 copies/mL), there is no threshold below which lack of transmission can be assured *[2, 13-14]*. The mechanism by which antiretroviral drugs reduce perinatal HIV transmission is multifactorial. Although lowering maternal antenatal viral load is an important component of prevention in women with higher viral load, antiretroviral prophylaxis is effective even in women with low viral load *[15-19]*. Additional mechanisms of protection include pre-exposure prophylaxis of the infant, provided by passage of the antiretroviral drug across the placenta so that inhibitory levels of drug are present in the fetus particularly during the birth process, and post-exposure prophylaxis through continued administration to the infant. Although placental passage of zidovudine is excellent, that of many other antiretroviral drugs may be variable (**Table 4**). Therefore, when combination antiretroviral therapy is initiated during pregnancy, zidovudine should be included as a component of antenatal therapy whenever possible. If antenatal zidovudine use is not possible, at least one agent with known transplacental passage should be part of the antiretroviral regimen (see **Table 4**).

Combination antiretroviral regimens containing at least three drugs for prevention of perinatal HIV transmission should be discussed and offered to all pregnant women with HIV infection. A number of studies suggest that antenatal use of combination antiretroviral regimens further reduces transmission compared to use of zidovudine alone. In a longitudinal epidemiologic study conducted in the United States since 1990, transmission was observed in 20% of women with HIV infection who received no antiretroviral treatment during pregnancy, 10.4% who received zidovudine alone, 3.8% who received combination therapy without protease inhibitors (primarily dual NRTIs), and 1.2% who received combination therapy with protease inhibitors *[2]*. However, in these older studies, zidovudine alone was often used in women with higher viral load and lower CD4, in whom treatment would now be recommended. In more recent data from the United Kingdom and Ireland, perinatal transmission occurred among 9.1% of women who received no antiretroviral drugs, 0.5% of women who received single drug prophylaxis (primarily zidovudine, as recommended by U.K. guidelines for women with HIV RNA levels less than 10,000 copies/mL), 0.8% of women who received dual drug prophylaxis,

and 1.0% of women who received triple drug regimens for treatment or prophylaxis. There were no significant differences in transmission rate between the drug regimen groups; the majority of women in all groups were delivered by scheduled cesarean delivery. Among 2,117 infants born to women on triple drug combination antiretroviral therapy or prophylaxis with HIV RNA less than 50 copies/mL at delivery, only 0.1% were infected *[20]*.

A three-drug combination antiretroviral regimen not regarded as one of the standard first-line regimens recommended for adults who require therapy may be considered for the pregnant woman if the regimen is given solely to reduce perinatal transmission, is only needed because the woman is pregnant, and will be discontinued postpartum. The triple NRTI combination zidovudine/lamivudine/abacavir regimen may be considered because of known pharmacokinetic profiles and published data suggesting acceptable toxicities during pregnancy. Testing for HLA-B*5701 identifies patients at risk of hypersensitivity reactions *[21-22]* and should be done and documented as negative before starting abacavir. Triple drug regimens containing the PI nelfinavir, which is not part of standard first-line therapy, may also be considered because there is a large experience with its safe use during pregnancy. However, these regimens have inferior long-term virologic efficacy, and for women with high CD4 counts but high viral load (i.e., CD4 count >350/mm^3 and HIV RNA >100,000 copies/mL), the use of first-line, more potent regimens should be considered. Dual NRTI therapy without the addition of a third drug (i.e., a PI, NNRTI, or a third NRTI) is not recommended because of the potential for inadequate viral suppression and rapid development of resistance *[10, 23]*.

The time-limited use of zidovudine alone during pregnancy for chemoprophylaxis against perinatal transmission is controversial. However, some women who may wish to restrict exposure of their fetus to antiretroviral drugs during pregnancy while still reducing the risk of transmitting HIV to their infants may opt for use of zidovudine alone. Additionally, for women with low viral load, time-limited use of zidovudine during the second and third trimesters of pregnancy is less likely to induce the development of resistance than in women with higher viral loads because of the low level of viral replication in the virologically suppressed women and the short duration of exposure to the antiretroviral drug *[24-25]*. For example, the development of zidovudine resistance was unusual among the healthy population of women who participated in PACTG 076 *[26]*. Thus, although controversial, the use of zidovudine chemoprophylaxis alone during pregnancy might be an appropriate option for this subset of women (i.e., women with HIV RNA levels <1,000 on no treatment).

In general, if antiretroviral drugs are given solely for prevention of perinatal HIV transmission, the antiretroviral drugs are discontinued postnatally, with the option to reinitiate standard potent treatment regimens in the future according to the usual criteria for nonpregnant individuals. Discussion regarding the decision to continue or stop antiretrovirals postpartum should occur before beginning antiretrovirals during pregnancy. Generally, when drugs are discontinued postnatally, all drugs should be stopped simultaneously. However, as discussed later (see **Stopping Antiretroviral Therapy during Pregnancy**), in women receiving NNRTI-based regimens, continuing the dual NRTI backbone for a period of time after stopping the NNRTI should be considered to reduce the development of NNRTI resistance. An alternative strategy is to replace the NNRTI with a PI drug while continuing the NRTIs, then to discontinue all the drugs at the same time *[27]*. The optimal interval between stopping an NNRTI and the other antiretroviral drugs is not known; at least 7 days is recommended. In patients receiving an efavirenz-based NNRTI regimen after the first trimester, detectable drug concentrations may be observed for more than 3 weeks after stopping efavirenz. Therefore, some experts recommend continuing the other antiretroviral agents or substituting a PI plus two other agents for up to 30 days in such patients.

HIV-Infected Pregnant Women Who Have Previously Received Antiretroviral Treatment or Prophylaxis but Are Not Currently Receiving Any Antiretroviral Medications

Panel's Recommendations:

- ***Obtain an accurate history of all prior antiretroviral regimens used for treatment of HIV disease or prevention of transmission and results of prior resistance testing (AIII).***
- ***Perform HIV antiretroviral drug resistance testing prior to initiating repeat antiretroviral prophylaxis or therapy (AI).***
- ***Initiate a combination antiretroviral drug regimen, with regimen chosen based on resistance testing and prior antiretroviral therapy history, and avoid drugs with teratogenic potential (efavirenz in the first trimester of pregnancy) or with known adverse potential for the pregnant mother (e.g., combination stavudine/didanosine) (AII).***
- ***Women who do not show an appropriate virologic response to their antiretroviral regimens (see Monitoring of the Woman and Fetus During Pregnancy) require repeat antiretroviral drug resistance testing (AI), as well as consultation with a clinician experienced in HIV treatment, to guide changes in antiretroviral therapy.***

There are no data to guide the choice of antiretroviral regimens to be used in a subsequent pregnancy for women who previously received antiretroviral prophylaxis for prevention of perinatal HIV transmission. Although there is concern that time-limited use of antiretroviral drugs during pregnancy may lead to genotypic resistance, reduced efficacy of standard regimens, particularly those containing the dual NRTI backbone of zidovudine and lamivudine, in successive pregnancies has not been demonstrated. Given the lack of substantive data, it is reasonable to make preliminary decisions about antiretroviral regimens based on results of initial resistance testing. However, interpretation of resistance testing following discontinuation of antiretroviral drugs can be complex because the assay may not detect low-level drug-resistant viral variants. Thus, careful monitoring of virologic response to the chosen antiretroviral regimen is important. Decisions to alter therapy based on lack of virologic response should be guided by repeat resistance testing.

Some women may have received antiretroviral treatment for their own health in the past, having discontinued the drugs for a variety of reasons and for variable lengths of time prior to pregnancy. Appropriate choice of antiretroviral drugs will vary according to the history of antiretroviral use, the indication for stopping therapy, and the results of past and current resistance testing. For example, women with a history of prior antiretroviral therapy associated with successful suppression of viral load who then stopped all drugs simultaneously (or staggered discontinuation if NNRTI based) and who have no evidence of resistance may be able to restart the same regimen. Alternatively, selection of an appropriate antiretroviral regimen for women with advanced HIV disease, a history of extensive prior antiretroviral therapy, or history of significant toxicity to antiretroviral drugs in the past may be challenging even for health care providers experienced in HIV care. In addition to obtaining genotypic resistance testing as described above, it is recommended that specialists in the treatment of HIV infection be consulted about the choice of antiretroviral therapy in such cases.

References

1. Centers for Disease Control and Prevention (CDC). Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. *MMWR Recomm Rep.* 2009;58(RR-4):1-207; quiz CE201-204.
2. Cooper ER, Charurat M, Mofenson LM, et al. Combination antiretroviral strategies for the treatment of pregnant HIV-1 infected women and prevention of perinatal HIV-1 transmission. *J Acquir Immune Defic Syndr Hum Retrovirol.* 2002;29(5):484-494.

3. Shapiro D, Tuomala R, Pollack H, et al. Mother-to child HIV transmission risk according to antiretroviral therapy, mode of delivery, and viral load in 2895 U.S. women (PACTG 367). 11th Conference on Retroviruses and Opportunistic Infections; February 8-11, 2004; San Francisco, CA. Abstract 99.
4. Burns DN, Landesman S, Muenz LR, et al. Cigarette smoking, premature rupture of membranes and vertical transmission of HIV-1 among women with low $CD4^+$ levels. *J Acquir Immune Defic Syndr Hum Retrovirol.* 1994;7(7):718-726.
5. Turner BJ, Hauck WW, Fanning R, Markson LE. Cigarette smoking and maternal-child HIV transmission. *J Acquir Immune Defic Syndr Human Retrovirol.* 1997;14(4):327-337.
6. Rodriguez EM, Mofenson LM, Chang BH, et al. Association of maternal drug use during pregnancy with maternal HIV culture positivity and perinatal HIV transmission. *AIDS.* 1996;10(3):273-282.
7. Bulterys M, Landesman S, Burns DN, et al. Sexual behavior and injection drug use during pregnancy and vertical transmission of HIV-1. *J Acquir Immune Defic Syndr Human Retrovirol.* 1997;15(1):76-82.
8. Matheson PB, Thomas PA, Abrams EJ, et al. Heterosexual behavior during pregnancy and perinatal transmission of HIV-1. *AIDS.* 1996;10(11):1249-1256.
9. CDC. Revised recommendations for HIV testing of adults, adolescents and pregnant women in health care settings. *MMWR.* 2006;55(RR-14):1-17.
10. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. December 1, 2009:1-161. http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf.
11. Stern JO, Robinson PA, Love J, et al. A comprehensive hepatic safety analysis of nevirapine in different populations of HIV infected patients. *J Acquir Immune Defic Syndr.* 2003;34 Suppl 1:S21-33.
12. Boehringer-Ingelheim Pharmaceuticals Inc. Viramune drug label. Revised June 24, 2008.
13. Mofenson LM, Lambert JS, Stiehm ER, et al. Risk factors for perinatal transmission of human immunodeficiency virus type 1 in women treated with zidovudine. Pediatric AIDS Clinical Trials Group Study 185 Team. *N Engl J Med.* 1999;341(6):385-393.
14. Garcia PM, Kalish LA, Pitt J, et al. Maternal levels of plasma human immunodeficiency virus type 1 RNA and the risk of perinatal transmission. *N Engl J Med.* 1999;341(6):394-402.
15. Ioannidis JP, Abrams EJ, Ammann A, et al. Perinatal transmission of human immunodeficiency virus type 1 by pregnant women with RNA virus loads <1000 copies/mL. *J Infect Dis.* 2001;183(4):539-545.
16. Wade NA, Birkhead GS, Warren BL, et al. Abbreviated regimens of zidovudine prophylaxis and perinatal transmission of the human immunodeficiency virus. *N Engl J Med.* 1998;339(20):1409-1414.
17. Jackson JB, Musoke P, Fleming T, et al. Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: 18-month follow-up of the HIVNET 012 randomised trial. *Lancet.* 2003;362(9387):859-868.
18. Petra Study Team. Efficacy of three short-course regimens of zidovudine and lamivudine in preventing early and late transmission of HIV-1 from mother to child in Tanzania, South Africa, and Uganda (Petra study): a randomised, double-blind, placebo-controlled trial. *Lancet.* 2002;359(9313):1178-1186.
19. Moodley D, Moodley J, Coovadia H, et al. A multicenter randomized controlled trial of nevirapine versus a combination of zidovudine and lamivudine to reduce intrapartum and early postpartum mother-to-child transmission of human immunodeficiency virus type 1. *J Infect Dis.* 2003;187(5):725-735.
20. Townsend CL, Cortina-Borja M, Peckham CS, et al. Low rates of mother-to-child transmission of HIV following effective pregnancy interventions in the United Kingdom and Ireland, 2000-2006. *AIDS.* 2008;22(8):973-981.
21. Mallal S, Phillips E, Carosi G, et al. HLA-B*5701 screening for hypersensitivity to abacavir. *N Engl J Med.* 2008;358(6):568-579.
22. Saag M, Balu R, Phillips E, et al. High sensitivity of human leukocyte antigen-b*5701 as a marker for immunologically confirmed abacavir hypersensitivity in white and black patients. *Clin Infect Dis.* 2008;46(7):1111-1118.
23. Clarke JR, Braganza R, Mirza A, et al. Rapid development of genotypic resistance to lamivudine when combined with zidovudine in pregnancy. *J Med Virol.* 1999;59(3):364-368.
24. Read P, Costelloe S, Mullen J, et al. New mutations associated with resistance not detected following zidovudine monotherapy in pregnancy when used in accordance with British HIV Association guidelines. *HIV Med.* 2008;9(7):448-451.
25. Larbalestier N, Mullen J, O'Shea S, et al. Drug resistance is uncommon in pregnant women with low viral loads taking zidovudine monotherapy to prevent perinatal HIV transmission. *AIDS.* 2003;17(18):2665-2667.

26. Eastman PS, Shapiro DE, Coombs RW, et al. Maternal viral genotypic zidovudine resistance and infrequent failure of zidovudine therapy to prevent perinatal transmission of human immunodeficiency virus type 1 in Pediatric AIDS Clinical Trial Group Protocol 076. *J Infect Dis.* 1998;177(3):557-564.
27. Fox Z, Phillips A, Cohen C, et al. Viral resuppression and detection of drug resistance following interruption of a suppressive non-nucleoside reverse transcriptase inhibitor-based regimen. *AIDS.* 2008;22(17):2279-2289.

Table 4. Preclinical and Clinical Data Relevant to the Use of Antiretrovirals in Pregnancy (See *Supplement: Safety and Toxicity of Individual Antiretroviral Agents in Pregnancy* for more detail on drugs.)

Antiretroviral Generic name (Abbreviation)/ Trade name	FDA Pregnancy Category *	Placental Passage Newborn: Mother Drug Ratio	Long-term Animal Carcinogenicity Studies	Animal Teratogenicity Studies
Nucleoside and nucleotide analogue reverse transcriptase inhibitors				
Abacavir (ABC)/ Ziagen	C	Yes (rats)	Positive (malignant and non-malignant tumors of liver and thyroid in female rats and preputial and clitoral glands in mice and rats at 6–32x human exposure)	Positive (rodent anasarca and skeletal malformations at 1,000 mg/kg [35x human exposure] during organogenesis; not seen at 8.5x human exposure in rabbits)
Didanosine (ddI)/ Videx	B	Yes (humans) 0.5	Negative (no tumors in lifetime rodent study at 0.7–3x maximum human exposure)	Negative (at 12x and 14.2x human exposure in rabbits and rats, respectively)
Emtricitabine (FTC)/ Emtriva	B	Yes (mice and rabbits) 0.4–0.5	Negative (no tumors in lifetime rodent study at 26–31x human exposure)	Negative (at 60x, 60x, and 120x human exposure in rats, mice, and rabbits, respectively)
Lamivudine (3TC)/ Epivir	C	Yes (humans) ~1.0	Negative (no tumors in lifetime rodent study at 10–58x human exposure)	Negative (at 35x human exposure in rats and rabbits; however, embryolethality seen in rabbits at 1x human exposure)
Stavudine (d4T)/ Zerit	C	Yes (rhesus monkeys) 0.76	Positive (in mice and rats at very high dose exposure; liver and bladder tumors [rats only] at 250x and 732x human exposure in mice and rats, respectively)	Negative (at 399x [rats] and 183x [rabbits] human exposure, although sternal bone ossification decreased and rat neonatal mortality increased at 399x human exposure in rats)
Tenofovir DF (TDF)/ Viread	B	Yes (humans) 0.95–0.99	Positive (hepatic adenomas in female mice only at 16x human exposure)	Negative (at 14x and 19x human exposure in rats and rabbits, respectively)
Zidovudine (AZT, ZDV)/ Retrovir	C	Yes (humans) 0.85	Positive (nonmetastasizing vaginal epithelial tumors at 3x and 24x human exposure in mice and rats, respectively)	Positive (increased fetal malformations associated with maternal toxicity at 300x human exposure in rats. Increased fetal resorptions at 66–226x and 12–87x human exposure in rats and rabbits, respectively, with no developmental abnormalities)
Non-nucleoside reverse transcriptase inhibitors				
Efavirenz (EFV)/ Sustiva	D	Yes (cynomolgus monkeys, rats, rabbits) ~1.0	Positive (hepatocellular adenomas and carcinomas and pulmonary alveolar/bronchiolar adenomas in female mice at 1.7x human exposure; no increases in tumors in rats at 0.2x human exposure)	Positive (anencephaly, anophthalmia, microophthalmia, and cleft palate in cynomolgus monkey at exposures comparable to human exposure; no reproductive toxicities in pregnant rabbits at 0.5–1x human exposure)

Antiretroviral Generic name (Abbreviation)/ Trade name	FDA Pregnancy Category *	Placental Passage Newborn: Mother Drug Ratio	Long-term Animal Carcinogenicity Studies	Animal Teratogenicity Studies
Non-nucleoside reverse transcriptase inhibitors (cont)				
Etravirine (ETR)/ Intelence	B	Unknown	Positive (hepatocellular adenomas and carcinomas in female mice at 0.6x human exposure; no findings in rats at 0.2–0.7x human exposure)	Negative (in rats and rabbits at exposures comparable to human exposures)
Nevirapine (NVP)/ Viramune	B	Yes (humans) ~1.0	Positive (hepatocellular adenomas and carcinomas in mice and rats at less than human exposure)	Negative (in rats and rabbits at 1–1.5x human exposure; however, decreased fetal body weight in rats at 1.5x human exposure)
Protease inhibitors				
Atazanavir (ATV)/ Reyataz	B	Minimal/variable (humans)	Positive (benign hepatocellular adenomas in female mice at 7.2x human exposure)	Negative (at 2x and 1x human exposure in rats and rabbits, respectively)
Darunavir (DRV)/ Prezista	C	Unknown	Positive (hepatic adenomas, carcinomas [male mice], thyroid neoplasms [rats only] at 0.1–0.3x and 0.7–1x human exposure in mice and rats, respectively)	Negative (at 0.5x and 0.05x human exposure in rats/mice and rabbits, respectively)
Fosamprenavir (f-APV)/ Lexiva)	C	Unknown	Positive (hepatic adenomas and carcinomas [mice and rats]; thyroid adenomas, interstitial cell hyperplasia, and uterine endometrial adenocarcinoma [rats only] at 0.1–0.7x and 0.3–1.4x human exposure in mice and rats, respectively	Negative (at 0.8x and 2x human exposure in rabbits and rats respectively; increased incidence of abortions in rabbits at 0.8x human exposure)
Indinavir (IDV)/ Crixivan	C	Minimal (humans)	Positive (thyroid adenomas in male rats at 1.3x human exposure)	Negative (however supernumerary ribs in rats at exposures less than or slightly greater than human exposure)
Lopinavir + Ritonavir (LPV/r)/ Kaletra)	C	Yes (humans) 0.20±0.13	Positive (hepatic adenomas and carcinomas at 1.6–2.2x and 0.5x human exposure in mice and rats, respectively)	Positive (no effects in rabbits and dogs at ~1x human exposure; decreased fetal viability and body weight, delayed skeletal ossification and increase in skeletal variations in rats at maternally toxic doses [at 0.7x and 1.8x human exposure for lopinavir and ritonavir, respectively])
Nelfinavir (NFV)/ Viracept	B	Minimal/variable (humans)	Positive (thyroid follicular adenomas and carcinomas at 1–3x human exposure in rats)	Negative (in rats at human exposure and in rabbits at significantly lower than human exposure)

Antiretroviral Generic name (Abbreviation)/ Trade name	FDA Pregnancy Category *	Placental passage Newborn: Mother Drug Ratio	Long-term Animal Carcinogenicity Studies	Animal Teratogenicity Studies
Protease inhibitors (cont)				
Ritonavir (RTV)/ Norvir	B	Minimal (humans)	Positive (hepatic adenomas and carcinomas in male mice at 0.3x human exposure)	Positive (early resorptions, decreased fetal body weight, ossification delays, and developmental variations in rats at maternally toxic dose [~0.3x human exposure]; cryptorchidism in rats at 0.22x human exposure)
Saquinavir (SQV) Invirase	B	Minimal (humans)	Negative (at 0.29x and 0.65x human exposure [coadministration with ritonavir] in rats and mice, respectively)	Negative (at 0.29x and 0.21x human exposure [coadministration with ritonavir] in rats and rabbits, respectively)
Tipranavir (TPV)/ Aptivus	C	Unknown	Positive (hepatic adenomas and carcinomas in mice at less than human exposure; thyroid follicular cell adenoma in female rats at exposures comparable to human exposure)	Negative (decreased ossification and pup weights in rats at 0.8x human exposure)
Entry inhibitors				
Enfuvirtide (T-20)/ Fuzeon	B	None (based on very limited human data)	Not conducted	Negative
Maraviroc (MVC)/ Selzentry	B	Unknown	Negative (in transgenic mice and rats at 11x human exposure)	Negative (at 20x and 5x human exposure in rats and rabbits, respectively)
Integrase inhibitors				
Raltegravir (RAL)/ Isentress	C	Yes (rats, rabbits) † Rats: 1.5–2.5 Rabbits: 0.02	In progress	Negative (however, supernumerary ribs in rats at 3x human exposure)

* Food and Drug Administration Pregnancy Categories:
A - Adequate and well-controlled studies of pregnant women fail to demonstrate a risk to the fetus during the first trimester of pregnancy (and no evidence exists of risk during later trimesters).
B - Animal reproduction studies fail to demonstrate a risk to the fetus, and adequate but well-controlled studies of pregnant women have not been conducted.
C - Safety in human pregnancy has not been determined; animal studies are either positive for fetal risk or have not been conducted, and the drug should not be used unless the potential benefit outweighs the potential risk to the fetus.
D - Positive evidence of human fetal risk that is based on adverse reaction data from investigational or marketing experiences, but the potential benefits from the use of the drug among pregnant women might be acceptable despite its potential risks.
X - Studies among animals or reports of adverse reactions have indicated that the risk associated with the use of the drug for pregnant women clearly outweighs any possible benefit.

† Values obtained from fetal (not newborn) blood samples. See text under "Placental and breast milk passage" in section on Raltegravir (Isentress) in ***Supplement: Safety and Toxicity of Individual Antiretroviral Agents in Pregnancy***.

Table 5. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy

(See also "Supplement: Safety and Toxicity of Individual Antiretroviral Drugs in Pregnancy" for additional toxicity data and "Guidelines for the Use of Antiretroviral Agents in HIV-1-infected Adults and Adolescents" for detailed guidelines regarding treatment options.)

Antiretroviral Drug	Pharmacokinetics in Pregnancy	Concerns in Pregnancy	Recommendations for Use in Pregnancy
NRTIs/ NtRTIs		See text for discussion of potential maternal and infant mitochondrial toxicity.	NRTIs are recommended for use as part of combination regimens, usually including two NRTIs with either an NNRTI or one or more PIs. Use of single or dual NRTIs alone is not recommended for treatment of HIV infection. (Zidovudine alone may be considered for prophylaxis of perinatal transmission in pregnant women with HIV RNA <1,000 copies/mL.)
Recommended Agents			
Lamivudine*	Pharmacokinetics not significantly altered in pregnancy; no change in dose indicated *[1]*.	No evidence of human teratogenicity (can rule out 1.5-fold increase in overall birth defects) *[2]*. Well-tolerated, short-term safety demonstrated for mother and infant. If hepatitis B coinfected, possible hepatitis B flare if drug stopped postpartum (see **Special Considerations: Hepatitis B Virus Coinfection**).	Because of extensive experience with lamivudine in pregnancy in combination with zidovudine, lamivudine plus zidovudine is the recommended dual NRTI backbone for pregnant women.
Zidovudine*	Pharmacokinetics not significantly altered in pregnancy; no change in dose indicated *[3]*.	No evidence of human teratogenicity (can rule out 1.5-fold increase in overall birth defects) *[2]*. Well-tolerated, short-term safety demonstrated for mother and infant.	Preferred NRTI for use in combination antiretroviral regimens in pregnancy based on efficacy studies and extensive experience. Zidovudine should be included in the antenatal antiretroviral regimen unless there is severe toxicity, stavudine use, documented resistance, or the woman is already on a fully suppressive regimen.
Alternate Agents			
Abacavir*	Pharmacokinetics not significantly altered in pregnancy; no change in dose indicated.	No evidence of human teratogenicity (can rule out 2-fold increase in overall birth defects) *[2]*. Hypersensitivity reactions occur in ~5%–8% of nonpregnant persons; fatal reactions occur in a much smaller percentage of persons and are usually associated with rechallenge. Rate of hypersensitivity reactions in pregnancy is unknown. Testing for HLA-B*5701 identifies patients at risk of reactions *[4-5]* and should be done and documented as negative before starting abacavir. Patient should be educated regarding symptoms of hypersensitivity reaction.	Alternate NRTI for dual nucleoside backbone of combination regimens. See footnote regarding use in triple NRTI regimen. #
Didanosine	Pharmacokinetics not significantly altered in pregnancy; no change in dose indicated *[6]*.	Cases of lactic acidosis, some fatal, have been reported in pregnant women receiving didanosine and stavudine together *[7-8]*.	Alternate NRTI for dual nucleoside backbone of combination regimens. Didanosine should be used with stavudine only if no other alternatives are available.

Antiretroviral Drug	Pharmacokinetics in Pregnancy	Concerns in Pregnancy	Recommendations for Use in Pregnancy
Alternate Agents (continued)			
Emtricitabine†	Pharmacokinetic study shows slightly lower levels in third trimester compared to postpartum *[9]*. No clear need to increase dose.	No evidence of human teratogenicity (can rule out 2-fold increase in overall birth defects) *[2]*.	Alternate NRTI for dual nucleoside backbone of combination regimens.
Stavudine	Pharmacokinetics not significantly altered in pregnancy; no change in dose indicated *[10]*.	No evidence of human teratogenicity (can rule out 2-fold increase in overall birth defects) *[2]*. Cases of lactic acidosis, some fatal, have been reported in pregnant women receiving didanosine and stavudine together *[7-8]*.	Alternate NRTI for dual nucleoside backbone of combination regimens. Stavudine should be used with didanosine only if no other alternatives are available. Do not use with zidovudine due to potential for antagonism.
Use in Special Circumstances			
Tenofovir†	Limited studies in human pregnancy; data indicate AUC lower in third trimester than postpartum but trough levels similar.	No evidence of human teratogenicity (can rule out 2-fold increase in overall birth defects) *[2]*. Studies in monkeys at doses approximately 2-fold higher than dosage for human therapeutic use show decreased fetal growth and reduction in fetal bone porosity within 2 months of starting maternal therapy *[11]*. Clinical studies in humans (particularly children) show bone demineralization with chronic use; clinical significance unknown *[12-13]*. Significant placental passage in humans (cord:maternal blood ratio 0.6–0.99). If hepatitis B coinfected, possible hepatitis B flare if drug stopped postpartum (see **Special Considerations: Hepatitis B Virus Coinfection)**.	Because of limited data on use in human pregnancy and concern regarding potential fetal bone effects, tenofovir should be used as a component of a maternal combination regimen only after careful consideration of other alternatives. Because of potential for renal toxicity, renal function should be monitored.
NNRTIs		Hypersensitivity reactions, including hepatic toxicity, and rash more common in women; unclear if increased in pregnancy.	NNRTIs are recommended for use in combination regimens with 2 NRTI drugs.
Recommended Agents			
Nevirapine	Pharmacokinetics not significantly altered in pregnancy; no change in dose indicated *[14-15]*.	No evidence of human teratogenicity (can rule out 2-fold increase in overall birth defects) *[2]*. Increased risk of symptomatic, often rash-associated, and potentially fatal liver toxicity among women with CD4 counts >250/mm^3 when first initiating therapy *[16-17]*; unclear if pregnancy increases risk.	Nevirapine should be initiated in pregnant women with CD4 counts >250 cells/mm^3 only if benefit clearly outweighs risk, due to the increased risk of potentially life-threatening hepatotoxicity in women with high CD4 counts. Women who enter pregnancy on nevirapine regimens and are tolerating them well may continue therapy, regardless of CD4 count.

Antiretroviral Drug	Pharmacokinetics in Pregnancy	Concerns in Pregnancy	Recommendations for Use in Pregnancy
Use in Special Circumstances			
Efavirenz†	Small study in 13 breastfeeding women in Rwanda of 600 mg once daily; postpartum peak levels during lactation were 61% higher than previously reported in HIV-infected nonpregnant individuals at that dose *[18]*.	FDA Pregnancy Class D; significant malformations (anencephaly, anophthalmia, cleft palate) were observed in 3 (15%) of 20 infants born to cynomolgus monkeys receiving efavirenz during the first trimester at a dose giving plasma levels comparable to systemic human therapeutic exposure. There are 6 retrospective case reports and 1 prospective case report of neural tube defects in humans with first-trimester exposure *[2, 19-20]*; relative risk unclear.	Use of efavirenz should be avoided in the first trimester. Use after the first trimester can be considered if, after consideration of other alternatives, this is the best choice for a specific woman. If efavirenz is to be continued postpartum, adequate contraception must be assured. Women of childbearing potential must be counseled regarding the teratogenic potential of efavirenz and avoidance of pregnancy while on the drug. Because of the known failure rates even with contraception, alternate antiretroviral regimens should be strongly considered in women of childbearing potential.
Insufficient Data to Recommend Use			
Etravirine	No pharmacokinetic studies in human pregnancy.	No experience in human pregnancy.	Safety and pharmacokinetics in pregnancy data are insufficient to recommend use during pregnancy.
Protease Inhibitors (PIs)		Hyperglycemia, new onset or exacerbation of diabetes mellitus, and diabetic ketoacidosis reported with PI use; unclear if pregnancy increases risk. Conflicting data regarding preterm delivery in women receiving PIs (see text).	PIs are recommended for use in combination regimens with 2 NRTI drugs.
Recommended Agents			
Lopinavir/ ritonavir	Pharmacokinetic studies of the new lopinavir/ ritonavir tablet formulation are under way, but data are not yet available.	No evidence of human teratogenicity (can rule out 2-fold increase in overall birth defects) *[2]*. Well-tolerated, short-term safety demonstrated in Phase I/II studies.	Pharmacokinetic studies of the new tablet formulation are under way but are not yet conclusive as to the optimal dose in pregnancy. Some experts would administer standard dosing (2 tablets twice daily) throughout pregnancy and monitor virologic response and lopinavir drug levels, if available. Other experts, extrapolating from the capsule formulation pharmacokinetic data, would increase the dose of the tablet formulation during the third trimester (from 2 tablets to 3 tablets twice daily), returning to standard dosing postpartum. Once-daily lopinavir/ritonavir dosing is not recommended during pregnancy because there are no data to address whether drug levels are adequate with such administration.

Antiretroviral Drug	Pharmacokinetics in Pregnancy	Concerns in Pregnancy	Recommendations for Use in Pregnancy
Alternate Agents			
Atazanavir (recommended to be combined with low-dose ritonavir boosting)	Two of three intensive pharmacokinetic studies of atazanavir with ritonavir boosting during pregnancy suggest that standard dosing results in decreased plasma concentrations compared to nonpregnant adults *[21-23]*. Atazanavir concentrations further reduced ~25% with concomitant tenofovir use *[23]*.	No evidence of human teratogenicity (can rule out 2-fold increase in overall birth defects) *[2]*. Transplacental passage is low, with cord blood concentration averaging 10%–16% of the maternal delivery atazanavir concentration *[21, 23]*. Theoretical concern re: increased indirect bilirubin levels exacerbating physiologic hyperbilirubinemia in the neonate not observed in clinical trials to date *[21-24]*.	Alternative PI for use in combination regimens in pregnancy. Should give as low-dose ritonavir-boosted regimen, may use once-daily dosing. In treatment-naïve patients unable to tolerate ritonavir, 400 mg once-daily dosing without ritonavir boosting may be considered, although there are no data describing atazanavir concentrations or efficacy under these circumstances. If coadministered with tenofovir, atazanavir must be given with low-dose ritonavir boosting.
Indinavir (combined with low-dose ritonavir boosting)	Two studies including 18 women receiving indinavir 800 mg three times daily showed markedly lower levels during pregnancy compared to postpartum, although suppression of HIV RNA was seen *[25-26]*. In a study of ritonavir-boosted indinavir (400 mg indinavir/100 mg ritonavir twice daily), 82% of women met the target trough level *[27]*.	No evidence of human teratogenicity (can rule out 2-fold increase in overall birth defects) *[2]*. Theoretical concern re: increased indirect bilirubin levels, which may exacerbate physiologic hyperbilirubinemia in the neonate, but minimal placental passage. Use of unboosted indinavir during pregnancy is not recommended.	Alternate PI for use in combination regimens in pregnancy. Must give as low-dose ritonavir-boosted regimen.
Nelfinavir	Adequate drug levels are achieved in pregnant women with nelfinavir 1,250 mg given twice daily, although levels are variable in late pregnancy *[28-30]*. In a study of pregnant women in their second and third trimester dosed at 1,250 mg given twice daily, women in the third trimester had lower concentration of nelfinavir than women in the second trimester *[30]*. In a study of the new 625-mg tablet formulation dosed at 1,250 mg twice daily, lower AUC and peak levels were observed during the third trimester of pregnancy than postpartum *[31]*.	No evidence of human teratogenicity (can rule out 2-fold increase in overall birth defects) *[2]*. Well-tolerated, short-term safety demonstrated for mother and infant.	Given pharmacokinetic data and extensive experience with use in pregnancy, nelfinavir is an alternative PI for combination regimens in pregnant women receiving combination antiretroviral drugs only for perinatal prophylaxis. In clinical trials of initial therapy in nonpregnant adults, nelfinavir-based regimens had a lower rate of viral response compared to lopinavir-ritonavir or efavirenz-based regimens but similar viral response to atazanavir- or nevirapine-based regimens.

Antiretroviral Drug	Pharmacokinetics in Pregnancy	Concerns in Pregnancy	Recommendations for Use in Pregnancy
Alternate Agents (continued)			
Ritonavir	Phase I/II study in pregnancy showed lower levels during pregnancy compared to postpartum *[2, 32]*.	Limited experience at full dose in human pregnancy; has been used as low-dose ritonavir boosting with other PIs.	Given low levels in pregnant women when used alone, recommended for use in combination with second PI as low-dose ritonavir "boost" to increase levels of second PI.
Saquinavir HGC (combined with low-dose ritonavir boosting)	Limited pharmacokinetic data on saquinavir HGC and the new 500-mg tablet formulation suggest that 1,000 mg saquinavir HGC/100 mg ritonavir given twice daily achieves adequate saquinavir drug levels in pregnant women *[33]*.	Well-tolerated, short-term safety demonstrated for mother and infant for saquinavir in combination with low-dose ritonavir.	There are only limited pharmacokinetic data on saquinavir HGC and the new tablet formulation in pregnancy. Ritonavir-boosted saquinavir HGC or saquinavir tablets are alternative PIs for combination regimens in pregnancy and are alternative initial antiretroviral recommendations for nonpregnant adults. Must give as low-dose ritonavir-boosted regimen.
Insufficient Data to Recommend Use			
Darunavir (combined with low-dose ritonavir boosting)	No pharmacokinetic studies in human pregnancy.	No experience in human pregnancy.	Safety and pharmacokinetics in pregnancy data are insufficient to recommend use during pregnancy. Must give as low-dose ritonavir-boosted regimen.
Fosamprenavir (recommended to be combined with low-dose ritonavir boosting)	No pharmacokinetic studies in human pregnancy.	Limited experience in human pregnancy.	Safety and pharmacokinetics in pregnancy data are insufficient to recommend use during pregnancy. Recommended to be given as low-dose ritonavir-boosted regimen.
Tipranavir (combined with low-dose ritonavir boosting)	No pharmacokinetic studies in human pregnancy.	No experience in human pregnancy.	Safety and pharmacokinetics in pregnancy data are insufficient to recommend use during pregnancy. Must give as low-dose ritonavir-boosted regimen.
Entry Inhibitors			
Insufficient Data to Recommend Use			
Enfuvirtide	No pharmacokinetic studies in human pregnancy.	Minimal data in human pregnancy *[34]*.	Safety and pharmacokinetics in pregnancy data are insufficient to recommend use during pregnancy.
Maraviroc	No pharmacokinetic studies in human pregnancy.	No experience in human pregnancy.	Safety and pharmacokinetics in pregnancy data are insufficient to recommend use during pregnancy.

Antiretroviral Drug	Pharmacokinetics in Pregnancy	Concerns in Pregnancy	Recommendations for Use in Pregnancy
Integrase Inhibitors			
Insufficient Data to Recommend Use			
Raltegravir	No pharmacokinetic studies in human pregnancy.	No experience in human pregnancy.	Safety and pharmacokinetics in pregnancy data are insufficient to recommend use during pregnancy.

Abbreviations: AUC: area under the curve; HGC: hard gel capsule; NRTI: nucleoside reverse transcriptase inhibitor; NtRTI: nucleotide reverse transcriptase inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor; PI: protease inhibitor.

* Zidovudine and lamivudine are included as a fixed-dose combination in Combivir; zidovudine, lamivudine, and abacavir are included as a fixed-dose combination in Trizivir; lamivudine and abacavir are included as a fixed-dose combination in Epzicom.

† Emtricitabine and tenofovir are included as a fixed-dose combination in Truvada; emtricitabine, tenofovir, and efavirenz are included as a fixed-dose combination in Atripla.

\# Triple NRTI regimens including abacavir have been less potent virologically compared to PI-based combination antiretroviral drug regimens. Triple NRTI regimens should be used only when an NNRTI- or PI-based combination regimen cannot be used (e.g., due to significant drug interactions).

References

1. Moodley J, Moodley D, Pillay K, et al. Pharmacokinetics and antiretroviral activity of lamivudine alone or when coadministered with zidovudine in human immunodeficiency virus type 1-infected pregnant women and their offspring. *J Infect Dis.* 1998;178(5):1327-1333.
2. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral pregnancy registry international interim report for 1 Jan 1989 – 31 July 2009. Wilmington, NC: Registry coordinating center; 2009.
3. O'Sullivan MJ, Boyer PJ, Scott GB, et al. The pharmacokinetics and safety of zidovudine in the third trimester of pregnancy for women infected with human immunodeficiency virus and their infants: phase I acquired immunodeficiency syndrome clinical trials group study (protocol 082). Zidovudine Collaborative Working Group. *Am J Obstet Gynecol.* 1993;168(5):1510-1516.
4. Mallal S, Phillips E, Carosi G, et al. HLA-B*5701 screening for hypersensitivity to abacavir. *N Engl J Med.* 2008;358(6):568-579.
5. Saag M, Balu R, Phillips E, et al. High sensitivity of human leukocyte antigen-b*5701 as a marker for immunologically confirmed abacavir hypersensitivity in white and black patients. *Clin Infect Dis.* 2008;46(7):1111-1118.
6. Wang Y, Livingston E, Patil S, et al. Pharmacokinetics of didanosine in antepartum and postpartum human immunodeficiency virus--infected pregnant women and their neonates: an AIDS clinical trials group study. *J Infect Dis.* 1999;180(5):1536-1541.
7. Bristol-Myers Squibb Company. Healthcare Provider Important Drug Warning Letter. January 5, 2001.
8. Sarner L, Fakoya A. Acute onset lactic acidosis and pancreatitis in the third trimester of pregnancy in HIV-1 positive women taking antiretroviral medication. *Sex Transm Infect.* 2002;78(1):58-59.
9. Best B, Stek A, Hu C, et al. for the PACTG/IMPAACT P1026S team. High-dose lopinavir and standard-dose emtricitabine pharmacokinetics during pregnancy and postpartum. 15th Conference on Retroviruses and Opportunistic Infections, February 3-8, 2008; Boston, MA. Abstract 629.
10. Wade NA, Unadkat JD, Huang S, et al. Pharmacokinetics and safety of stavudine in HIV-infected pregnant women and their infants: Pediatric AIDS Clinical Trials Group protocol 332. *J Infect Dis.* 2004;190(12):2167-2174.
11. Tarantal AF, Castillo A, Ekert JE, et al. Fetal and maternal outcome after administration of tenofovir to gravid rhesus monkeys (Macaca mulatta). *J Acquir Immune Defic Syndr.* 2002;29(3):207-220.
12. Gafni RI, Hazra R, Reynolds JC, et al. Tenofovir disoproxil fumarate and an optimized background regimen of antiretroviral agents as salvage therapy: impact on bone mineral density in HIV-infected children. *Pediatrics.* 2006;118(3):e711-718.

13. Schooley RT, Ruane P, Myers RA, et al. Tenofovir DF in antiretroviral-experienced patients: results from a 48-week, randomized, double-blind study. *AIDS.* 2002;16(9):1257-1263.
14. Aweeka F, Lizak P, Frenkel L, et al. Steady state nevirapine pharmacokinetics during 2nd and 3rd trimester pregnancy and postpartum: PACTG 1022. 11th Conference on Retroviruses and Opportunistic Infections; February 8-11, 2004; San Francisco, CA. Abstract 932.
15. Mirochnick M, Siminski S, Fenton T, et al. Nevirapine pharmacokinetics in pregnant women and in their infants after in utero exposure. *Pediatr Infect Dis J.* 2001;20(8):803-805.
16. Baylor MS, Johann-Liang R. Hepatotoxicity associated with nevirapine use. *J Acquir Immune Defic Syndr.* 2004;35(5):538-539.
17. Dieterich DT, Robinson PA, Love J, Stern JO. Drug-induced liver injury associated with the use of nonnucleoside reverse-transcriptase inhibitors. *Clin Infect Dis.* 2004;38 Suppl 2:S80-89.
18. Schneider S, Peltier A, Gras A, et al. Efavirenz in human breast milk, mothers', and newborns' plasma. *J Acquir Immune Defic Syndr.* 2008;48(4):450-454.
19. De Santis M, Carducci B, De Santis L, et al. Periconceptional exposure to efavirenz and neural tube defects. *Arch Intern Med.* 2002;162(3):355.
20. Fundaro C, Genovese O, Rendeli C, et al. Myelomeningocele in a child with intrauterine exposure to efavirenz. *AIDS.* 2002;16(2):299-300.
21. Ripamonti D, Cattaneo D, Maggiolo F, et al. Atazanavir plus low-dose ritonavir in pregnancy: pharmacokinetics and placental transfer. *AIDS.* 2007;21(18):2409-2415.
22. Eley T, Vandeloise E, Child M, et al. Steady State Pharmacokinetics and Safety of Atazanavir after Treatment with ATV 300 mg Once Daily/Ritonavir 100 mg Once Daily + ZDV/3TC during the Third Trimester in HIV+ Women. 15th Conference on Retoviruses and Opportunistic Infections; February 3-6, 2008; Boston, MA. Abstract 624.
23. Mirochnick M, Kafulafula G, Kreitchmann R, et al. The pharmacokinetics (PK) of tenofovir disoproxil fumarate (TDF) after administration to HIV-1 infected pregnant women and their newborns. 16th Conference on Retroviruses and Opportunistic Infections; February, 2009; Montreal, Canada Abstract 939.
24. Natha, M. Hay, P. Taylor, G. et al. . Atazanavir use in pregnancy: a report of 33 cases. 14th Conference on Retroviruses and Opportunistic Infections; February 25-28, 2007; Los Angeles, CA. Abstract 750.
25. Unadkat JD, Wara DW, Hughes MD, et al. Pharmacokinetics and safety of indinavir in human immunodeficiency virus-infected pregnant women. *Antimicrob Agents Chemother.* 2007;51(2):783-786.
26. Hayashi S, Beckerman K, Homma M, et al. Pharmacokinetics of indinavir in HIV-positive pregnant women. *AIDS.* 2000;14(8):1061-1062.
27. Ghosn J, De Montgolfier I, Cornélie C, et al. Antiretroviral therapy with a twice-daily regimen containing 400 milligrams of indinavir and 100 milligrams of ritonavir in human immunodeficiency virus type 1-infected women during pregnancy. *Antimicrob Agents Chemother.* 2008;52(4):1542-1544.
28. Bryson Y, Stek A, Mirochnick M, et al. for the PACTG 353 Team. Pharmacokinetics, antiviral activity and safety of nelfinavir (NFV) in combination with ZDV/3TC in pregnant HIV-infected women and their infants: PACTG 353 Cohort 2. 9th Conference on Retroviruses and Opportunistic Infections; February 24-28, 2002; Seattle, WA. Abstract 795-W.
29. Aweeka F, Tierney C, Stek A, et al. ACTG 5153s: pharmacokinetic exposure and virological response in HIV-1-infected pregnant women treated with PI. 14th Conference on Retroviruses and Opportunistic Infections; February 25-28, 2007; Los Angeles, CA. Abstract 739.
30. Villani P, Floridia M, Pirillo MF, et al. Pharmacokinetics of nelfinavir in HIV-1-infected pregnant and nonpregnant women. *Br J Clin Pharmacol.* 2006;62(3):309-315.
31. Read, J. Best, B. Stek, A. et al. . Nelfinavir pharamacokinetics (625 mg tablets) during the third trimester of pregnancy and postpartum. 14th Conference on Retroviruses and Opportunistic Infections; February 25-28, 2007; Los Angeles, CA. Abstract 740.
32. Scott GB, Rodman JH, Scott WA, et al. for the PACTG 354 Protocol Team. Pharmacokinetic and virologic response to ritonavir (RTV) in combination with zidovudine (XDV) and lamivudine (3TC) in HIV-1 infected pregnant women and their infants. 9th conference on Retroviruses and opportunistic Infections; February 24-28, 2002; Seattle, WA. Abstract 794-W.
33. Burger DM, Eggink A, van der Ende ME, et al. The pharmacokinetics of saquinavir new tablet formulation + ritonavir (1000/100 mg BID) in HIV-1-infected pregnant women. 14th Conference on Retroviruses and Opportunistic Infections; February 25-28, 2007; Los Angeles, CA. Abstract 741.
34. Meyohas MC, Lacombe K, Carbonne B, et al. Enfuvirtide prescription at the end of pregnancy to a multi-treated HIV-infected woman with virological breakthrough. *AIDS.* 2004;18(14):1966-1968.

Table 6. Clinical Scenario Summary Recommendations for Antiretroviral Drug Use by Pregnant HIV-Infected Women and Prevention of Perinatal Transmission of HIV-1 in the United States

Clinical Scenario	Recommendations
Nonpregnant HIV-infected woman of childbearing potential who has indications for initiating antiretroviral therapy	• Initiate combination antiretroviral drug therapy as per adult treatment guidelines. • Avoid drugs with teratogenic potential (e.g., efavirenz) if the woman is trying to conceive or is not using adequate contraception. Exclude pregnancy before starting treatment with efavirenz.
HIV-infected woman on combination antiretroviral drug therapy who becomes pregnant	**Woman:** • In general, if woman requires treatment, antiretroviral drugs should not be stopped during the first trimester or during pregnancy. • Continue current combination antiretroviral therapy regimen if successfully suppressing viremia; however, avoid use of efavirenz or other potentially teratogenic drugs in the first trimester and drugs with known adverse potential for mother (e.g., combination stavudine/didanosine) throughout the pregnancy. • Perform HIV antiretroviral drug resistance testing if the woman has detectable viremia on therapy. • Continue combination antiretroviral therapy regimen during intrapartum period (zidovudine given as continuous infusion[1] during labor while other antiretroviral agents are continued orally) and postpartum. • Schedule cesarean delivery at 38 weeks gestation if plasma HIV RNA remains >1,000 copies/mL near the time of delivery. **Infant:** • Start zidovudine as soon as possible after birth and administer for 6 weeks.[2]
HIV-infected pregnant woman who is antiretroviral naïve and has indications for antiretroviral therapy	**Woman:** • Perform HIV antiretroviral drug resistance testing prior to initiating combination antiretroviral drug therapy and repeat after initiating therapy if viral suppression is suboptimal. • Initiate combination antiretroviral regimen. - Avoid use of efavirenz or other potentially teratogenic drugs in the first trimester and drugs with known adverse potential for mother (e.g., combination stavudine/didanosine). - Use zidovudine as a component of the antiretroviral regimen when feasible. - Use nevirapine as a component of the antiretroviral regimen only if the woman has CD4 count ≤250 cells/mm^3. If the woman has CD4 count >250 cells/mm^3, use nevirapine as a component of therapy only if the benefit clearly outweighs the risk due to an increased risk of severe hepatic toxicity. • If woman requires immediate initiation of therapy for her own health, initiate treatment as soon as possible, including in the first trimester. • Continue combination antiretroviral therapy regimen during intrapartum period (zidovudine given as continuous infusion[1] during labor while other antiretroviral agents are continued orally) and postpartum. • Schedule cesarean delivery at 38 weeks gestation if plasma HIV RNA remains >1,000 copies/mL near the time of delivery. **Infant:** • Start zidovudine as soon as possible after birth and administer for 6 weeks.[2]

Clinical Scenario	Recommendations
HIV-infected pregnant woman who is antiretroviral naïve and does not require treatment for her own health	**Woman:** • Perform HIV antiretroviral drug resistance testing prior to initiating combination antiretroviral drug therapy and repeat after initiation of therapy if viral suppression is suboptimal. • Prescribe a combination antiretroviral drug prophylaxis regimen (i.e., at least 3 drugs) for prophylaxis of perinatal transmission. - Consider delaying initiation of antiretroviral prophylaxis until after first trimester is completed. - Avoid use of efavirenz or other potentially teratogenic drugs in the first trimester and drugs with known adverse potential for mother (e.g., combination stavudine/didanosine). - Use zidovudine as a component of the antiretroviral regimen when feasible. - If the woman has CD4 count >250 cells/mm^3 use nevirapine as a component of therapy only if the benefit clearly outweighs the risk due to an increased risk of severe hepatic toxicity. • Although use of zidovudine prophylaxis alone is controversial, consider if woman has plasma HIV RNA level <1,000 copies/mL on no therapy. • Continue antiretroviral prophylaxis regimen during intrapartum period (zidovudine given as continuous infusion[1] during labor while other antiretroviral agents are continued orally). • Evaluate need for continuing the combination regimen postpartum; discontinue the combination regimen unless the woman has indications for continued therapy. If regimen includes drug with long half-life like NNRTI, consider stopping NRTIs at least 7 days after stopping NNRTI. (Only limited data exist on this; see **Stopping Antiretroviral Therapy** and **Prevention of Antiretroviral Drug Resistance**.) • Schedule cesarean delivery at 38 weeks gestation if plasma HIV RNA remains >1,000 copies/mL near the time of delivery. **Infant**: • Start zidovudine as soon as possible after birth and administer for 6 weeks.[2]
HIV-infected pregnant woman who is antiretroviral experienced but not currently receiving antiretroviral drugs	**Woman:** • Obtain full antiretroviral treatment history, including prior resistance testing, and evaluate need for antiretroviral treatment for maternal health. • Perform HIV antiretroviral drug resistance testing prior to initiating repeat antiretroviral prophylaxis or therapy and repeat after initiating combination antiretroviral regimen if suboptimal viral suppression. • Initiate a combination antiretroviral regimen (e.g., at least 3 drugs), with regimen chosen based on resistance testing and prior therapy history. - Avoid use of efavirenz or other potentially teratogenic drugs in the first trimester and drugs with known adverse potential for the mother (e.g., combination stavudine/didanosine). - Use zidovudine as a component of the antiretroviral regimen when feasible. - If woman has CD4 count >250 cells/mm^3, use nevirapine as a component of therapy only if the benefit clearly outweighs the risk due to an increased risk of severe hepatic toxicity. • Continue the combination regimen during intrapartum period (zidovudine given as continuous infusion[1] during labor while other antiretroviral agents are continued orally). • Evaluate need for continuing the combination regimen postpartum; discontinue the combination regimen unless the woman has indications for continued therapy. If regimen includes drug with long half-life like NNRTI, consider stopping NRTIs at least 7 days after stopping NNRTI. (Limited data exist on this; see **Stopping Antiretroviral Therapy** and **Prevention of Antiretroviral Drug Resistance**.)

Clinical Scenario	Recommendations
	• Schedule cesarean delivery at 38 weeks gestation if plasma HIV RNA remains >1,000 copies/mL near the time of delivery. **Infant**: • Start zidovudine as soon as possible after birth and administer for 6 weeks.[2]
HIV-infected woman who has received no antiretroviral therapy prior to labor	Zidovudine **Woman:** Give zidovudine as continuous infusion[1] during labor. **Infant:** Start zidovudine as soon as possible after birth and administer for 6 weeks.[2] ***OR*** Combination Zidovudine + Single-dose Nevirapine **Woman:** Give zidovudine as continuous infusion[1] during labor, plus single-dose nevirapine [3] at onset of labor. Consider adding lamivudine during labor and maternal zidovudine/lamivudine for at least 7 days postpartum, which may reduce development of nevirapine resistance. **Infant:** Give single-dose nevirapine[3] plus zidovudine for 6 weeks. ***OR*** **Woman:** Give zidovudine as continuous infusion[1] during labor. **Infant:** Although some clinicians may choose to use zidovudine in combination with additional drugs in the infant, appropriate dosing for neonates is incompletely defined and the additional efficacy of this approach in reducing transmission is not known. Consider consultation with a pediatric HIV specialist. • Evaluate need for initiation of maternal therapy postpartum.
Infant born to HIV-infected woman who has received no antiretroviral therapy prior to or during labor	• Start zidovudine as soon as possible after birth and administer for 6 weeks.[2] ***OR*** • Although some clinicians may choose to use zidovudine in combination with additional drugs, appropriate dosing for neonates is incompletely defined and the additional efficacy of this approach in reducing transmission is not known. Consider consultation with a pediatric HIV specialist. • Evaluate need for initiation of maternal therapy postpartum.

[1] Zidovudine continuous infusion: 2 mg/kg zidovudine intravenously over 1 hour, followed by continuous infusion of 1 mg/kg/hour until delivery.

[2] Zidovudine dosing for infants <35 weeks gestation at birth is 1.5 mg/kg/dose intravenously or 2.0 mg/kg/dose orally, every 12 hours, advancing to every 8 hours at 2 weeks of age if ≥30 weeks gestation at birth or at 4 weeks of age if <30 weeks gestation at birth.

[3] Single-dose nevirapine: Mother: 200 mg given once orally at onset of labor; Infant: 2 mg/kg body weight given once orally at 2–3 days of age if mother received intrapartum single-dose nevirapine or given at birth if mother did not receive intrapartum single-dose nevirapine.

Hepatitis B Virus Coinfection

Panel's Recommendations:

- ***Screening for hepatitis B virus (HBV) infection is recommended for all HIV-infected pregnant women who have not been screened during the current pregnancy (AII).***
- ***Pregnant women who screen negative for hepatitis B should receive the HBV vaccine series (AII).***
- ***Pregnant women with HBV infection should be screened for hepatitis A virus (HAV) and those who screen negative should receive the HAV vaccine series (AII).***
- ***Interferon-alpha and pegylated interferon-alpha are not recommended during pregnancy (AIII).***
- ***Because the optimal management for pregnant and postpartum women with HIV/HBV coinfection is not well defined, consultation with an expert in HIV and HBV is strongly recommended (AIII).***
- ***Decisions about the choice of antiretroviral regimen during pregnancy for HIV/HBV-coinfected women should take into account indications for HIV therapy as determined by maternal CD4 cell count and HIV disease status, HBV levels and indications for HBV therapy, gestational age when starting the antiretroviral regimen, and patient preference (AIII).***
- ***The determination of optimal antepartum antiretroviral regimen for an HIV/HBV-coinfected woman depends on whether she requires anti-HIV treatment for her own health, anti-HBV treatment, both, or neither.***
    - ***For coinfected women with indications for antiretroviral therapy for their own health and who are expected to continue drugs postpartum and/or who require treatment for HBV infection:***
        - ***A three-drug combination antepartum antiretroviral regimen including two agents with anti-HBV activity (e.g., tenofovir plus either lamivudine or emtricitabine) should be used and continued postpartum (BII).***
    - ***For coinfected women who receive antiretroviral drugs during pregnancy solely as prophylaxis for prevention of mother-to-child transmission of HIV, who are expected to discontinue antiretroviral prophylaxis after delivery, and who do not require treatment for HBV infection, the choice is more complex and can include:***
        - ***A three-drug combination antepartum antiretroviral regimen including two NRTI agents with anti-HBV activity (e.g., tenofovir plus either lamivudine or emtricitabine) and stopping prophylaxis after delivery (with monitoring for HBV flare) (BIII); or***
        - ***A three-drug combination antepartum antiretroviral regimen that includes only NRTI agents without anti-HBV activity (e.g., abacavir, didanosine, stavudine, or zidovudine) and stopping prophylaxis after delivery (BIII); or***
        - ***A three-drug combination antepartum antiretroviral regimen including lamivudine as the sole anti-HBV agent could be considered for women presenting late in pregnancy (e.g., after 28 weeks gestation) and stopping prophylaxis after delivery (with monitoring for HBV flare) (CIII).***
- ***Pregnant women with HBV/HIV coinfection receiving antiretroviral drugs should be counseled about signs and symptoms of liver toxicity, and liver transaminases should be assessed 2 weeks following initiation of antiretroviral therapy or prophylaxis and then at least monthly (BIII).***
- ***Infants born to women with hepatitis B infection should receive hepatitis B immune globulin (HBIG) and the first dose of the hepatitis B vaccine series within 12 hours of birth; the second and third doses of vaccine should be administered at 1 and 6 months of age, respectively (AI).***

For additional information on hepatitis B and HIV, see *Hepatitis B Virus Infection* (pages 75–84) in the "Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents, Recommendations from CDC, NIH, and the HIV Medicine Association (HIVMA) of the Infectious Diseases Society of America (IDSA)" at **http://www.cdc.gov/mmwr/pdf/rr/rr5804.pdf** *[1]*.

All HIV-infected pregnant women should be screened for hepatitis A, B, and C. The management of HBV/HIV coinfection in pregnancy is complex and consultation with an expert in HIV and HBV infection is strongly recommended. HIV-infected women who are found to have chronic hepatitis B on the basis of hepatitis B surface antigen for at least 6 months and who are hepatitis A IgG negative should receive the hepatitis A virus (HAV) vaccine series because of the added risk of acute hepatitis A in persons with chronic viral hepatitis.

HIV-infected women who are found to be hepatitis B surface antibody and hepatitis B surface antigen negative should receive the HBV vaccine series. Some patients test positive for anti-HBc alone, which might signify a false-positive result; exposure in the past with subsequent loss of anti-HBs; or "occult" HBV infection, which can be confirmed by detection of HBV DNA *[2-3]*. The clinical significance of isolated anti-HBc is unknown *[4-5]*. Some specialists recommend that HIV-infected persons with anti-HBc alone should be tested for HBV DNA before vaccination for HBV or before initiating antiretroviral drug treatment or prophylaxis because of the risk of reactivation of HBV and the occurrence of immune reconstitution inflammatory syndrome (IRIS) *[1]*. There are limited data regarding the optimal treatment of HIV-infected pregnant women with chronic HBV coinfection (i.e., hepatitis B surface antigen positive for >6 months). There are no definitive studies on the safety of antiviral therapy for hepatitis B infection during pregnancy and breastfeeding; interferon and peg-interferon are not recommended during pregnancy.

Current treatment guidelines for HBV/HIV-coinfected nonpregnant adults who require treatment of their HIV infection recommend the NRTI combination of tenofovir plus emtricitabine or tenofovir plus lamivudine as the dual NRTI backbone of an antiretroviral regimen, regardless of the need for concomitant HBV treatment *[6]*.Tenofovir, lamivudine, and emtricitabine all show activity against HBV. Because of the risk of development of HBV-resistant mutants, use of two agents active against HBV (tenofovir plus lamivudine or emtricitabine) is recommended as the dual NRTI backbone when antiretroviral treatment is required.

Lamivudine is a recommended NRTI and emtricitabine is an alternative NRTI for use in pregnancy. There are only limited data on the use of tenofovir during pregnancy. Tenofovir is not teratogenic in animals but reversible bone changes at high doses were seen in multiple animal species. Although tenofovir is not generally recommended in pregnancy as a first-line agent for antiretroviral regimens being used solely for prophylaxis of mother-to-child transmission of HIV, HBV/HIV coinfection in pregnancy may be a special circumstance where tenofovir may be more strongly considered (see **Table 5**). For pregnant women with HBV/HIV coinfection who require treatment of HIV disease for their own health or who require treatment of chronic HBV disease, the benefit of tenofovir outweighs potential risks, and tenofovir plus lamivudine or emtricitabine is recommended as the dual NRTI backbone of a three-drug therapeutic regimen. Although zidovudine should generally be a component of antiretroviral regimens in pregnancy, in HBV/HIV-coinfected women this may not be feasible.

A three-drug regimen including tenofovir plus lamivudine or emtricitabine is also recommended for HBV/HIV-coinfected pregnant women who do not require treatment of HIV but who do require treatment of their HBV disease. In nonpregnant coinfected patients who require treatment of HBV disease but not of HIV, pegylated interferon-alpha treatment is recommended. However, this drug is not recommended in pregnancy. Additionally, the use of tenofovir plus lamivudine or emtricitabine without a third antiretroviral drug should be avoided because of the rapid development of drug-resistant HIV mutations. Entecavir should not be used for treatment of HBV infection without concomitant combination treatment for HIV infection because recent data suggest that the M184V resistance mutation may emerge in HIV-infected patients receiving entecavir alone *[7]*. Entecavir is associated with skeletal anomalies in rats and rabbits but only at high, maternally toxic doses. Data on use of entecavir in human pregnancy are not available. Postpartum, the patient could stop the antiretroviral regimen and initiate HBV-specific therapy (e.g., pegylated interferon-alpha) to continue HBV treatment or continue the three-drug antiretroviral regimen.

There is controversy regarding the appropriate approach to therapy for pregnant women with HBV/HIV coinfection who do not require treatment of HIV or HBV disease, and therefore are receiving antiretroviral drugs solely for prevention of perinatal transmission of HIV and will discontinue therapy postpartum. Although there are only limited data about the safety of tenofovir in pregnancy, some experts recommend use of a three-drug regimen that includes the anti-HBV drug tenofovir plus lamivudine or emtricitabine as the dual NRTI backbone due to concern about HBV immune reconstitution inflammatory syndrome (IRIS) with initiation of therapy. Although concern about antiretroviral treatment-induced HBV IRIS should be less in this group of pregnant women because they do not require therapy for their own health and therefore do not have severe immunodeficiency (the greatest risk factor for development of IRIS following initiation of antiretroviral therapy), treating a potential HBV flare in the postpartum period after discontinuing HBV-active therapy may be associated with less risk than treating an immune-mediated flare during pregnancy. In addition, using drugs with anti-HBV activity during pregnancy will lower HBV levels and potentially decrease the risk of failure of hepatitis B immune globulin (HBIG) and hepatitis B vaccine to prevent perinatal transmission of HBV, which is increased among women with very high HBV DNA levels. If such an approach is followed, liver function should be carefully monitored postpartum following discontinuation of drugs; if severe flare-up of HBV disease occurs postpartum, initiation of anti-HBV-specific therapy such as pegylated interferon-alpha can be considered.

Alternatively, for women who require prophylaxis of perinatal HIV infection but do not require treatment for HBV infection, some experts choose to use an antiretroviral regimen without anti-HBV activity (e.g., use of a dual NRTI backbone that contains drugs other than tenofovir, lamivudine, or emtricitabine, such as zidovudine and didanosine, could be considered) to avoid the possibility of an HBV flare when treatment is discontinued postpartum. Another alternative used by some specialists for women who require prophylaxis of perinatal HIV infection but do not require treatment of HBV infection is a highly active antiretroviral regimen that includes lamivudine as the only antiretroviral agent with activity against HBV, especially if the regimen is started later in pregnancy because of late care or delayed HIV diagnosis. This option avoids the use of tenofovir during pregnancy because there are only limited data on safety, while still treating HBV; the risk of HBV development of resistance to lamivudine with short-term temporary exposure of less than 6 months is extremely low *[8]*.

An elevation in hepatic enzymes following initiation of antiretroviral therapy may occur in HBV/HIV-coinfected women due to an immune-mediated flare in HBV disease secondary to immune reconstitution with therapy, particularly in women with low CD4+ cell count at the time of initiation of therapy. HBV infection may also increase hepatotoxic risk of certain antiretroviral agents, specifically protease inhibitors and nevirapine. Pregnant women with HBV/HIV coinfection should be counseled about signs and symptoms of liver toxicity, and transaminases should be assessed 2 weeks following initiation of antiretroviral therapy or prophylaxis in women not already receiving drugs and then at least monthly. If hepatic toxicity occurs, substitution of a less hepatotoxic drug regimen may need to be considered or, if clinical symptoms or significant elevations of transaminases occur, drugs may need to be temporarily discontinued. It can be difficult to differentiate a flare in HBV disease due to immune reconstitution from drug toxicity, and consultation with an expert in HIV infection is recommended.

All infants born to HBV surface antigen positive mothers should receive hepatitis B immune globulin (HBIG) and the first dose of the hepatitis B vaccination series within 12 hours of birth. The second and third doses of vaccine should be administered at 1 and 6 months of age, respectively. This regimen is >95% effective in preventing HBV infection in these infants.

References

1. Centers for Disease Control and Prevention (CDC). Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. *MMWR Recomm Rep*. 2009;58(RR-4):1-207; quiz CE201-204.

2. Grob P, Jilg W, Bornhak H, et al. Serological pattern "anti-HBc alone": report on a workshop. *J Med Virol.* 2000;62(4):450-455.
3. Hofer M, Joller-Jemelka HI, Grob PJ, et al. Frequent chronic hepatitis B virus infection in HIV-infected patients positive for antibody to hepatitis B core antigen only. Swiss HIV Cohort Study. *Eur J Clin Microbiol Infect Dis.* 1998;17(1):6-13.
4. Silva AE, McMahon BJ, Parkinson AJ, et al. Hepatitis B virus DNA in persons with isolated antibody to hepatitis B core antigen who subsequently received hepatitis B vaccine. *Clin Infect Dis.* 1998;26(4):895-897.
5. Lok AS, Lai CL, Wu PC. Prevalence of isolated antibody to hepatitis B core antigen in an area endemic for hepatitis B virus infection: implications in hepatitis B vaccination programs. *Hepatology.* 1988;8(4):766-770.
6. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. December 1, 2009:1-161. http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf.
7. McMahon MA, Jilek BL, Brennan TP, et al. The HBV drug entecavir - effects on HIV-1 replication and resistance. *N Engl J Med.* 2007;356(25):2614-2621.
8. Benhamou Y, Bochet M, Thibault V, et al. Long-term incidence of hepatitis B virus resistance to lamivudine in human immunodeficiency virus-infected patients. *Hepatology.* 1999;30(5):1302-1306.

Hepatitis C Virus Coinfection

Panel's Recommendations:

- ***Screening for hepatitis C virus (HCV) infection is recommended for all HIV-infected pregnant women who have not been screened during the current pregnancy (AIII).***
- ***Pegylated interferon-alpha is not recommended and ribavirin is contraindicated during pregnancy (AII).***
- ***Recommendations for antiretroviral drug use during pregnancy are the same for women who are coinfected with HCV as for those without HCV coinfection (BIII).***
- ***Pregnant women with HCV/HIV coinfection receiving antiretroviral drugs should be counseled about signs and symptoms of liver toxicity, and transaminases should be assessed 2 weeks following initiation of antiretroviral therapy or prophylaxis in women not already receiving drugs and then at least monthly (BIII).***
- ***Decisions concerning mode of delivery in HCV/HIV-coinfected pregnant women should be based on considerations related to HIV infection alone (see Intrapartum Care) (BIII).***
- ***Infants born to women with HCV/HIV coinfection should be evaluated for HCV infection (AIII) by HCV RNA testing between 2 and 6 months of age and/or HCV antibody testing after 15 months of age (CIII).***
- ***Because of the added risk of acute hepatitis A and B in persons with chronic viral hepatitis C, women who are found to have chronic HCV infection should be screened for hepatitis A and hepatitis B infections. If women with chronic hepatitis C are hepatitis A IgG negative, they should receive the hepatitis A virus (HAV) vaccine series, and if they are hepatitis B uninfected (e.g., hepatitis B surface Ag negative, hepatitis B core antibody negative, and hepatitis B surface antibody negative), they should receive the HBV vaccine series (AIII).***

For additional information on hepatitis C and HIV, see *Hepatitis C Virus Infection* (pages 84–91) of the "Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-infected Adults and Adolescents, Recommendations from CDC, NIH, and the HIV Medicine Association (HIVMA) of the Infectious Diseases Society of America (IDSA)" at **http://www.cdc.gov/mmwr/pdf/rr/rr5804.pdf** *[1]*.

HCV/HIV coinfection is not uncommon in HIV-infected women, particularly among women infected via parenteral drug use; among HIV-infected pregnant women, the HCV seroprevalence rate ranges from 17%–54% *[2]*. Screening for HCV infection using a sensitive immunoassay for HCV antibody is recommended for all HIV-infected individuals, including pregnant women. False-negative anti-HCV immunoassay results may occur among HIV-infected persons, particularly those with very low CD4 counts, but this is uncommon with the most sensitive immunoassays. If serologic test results are indeterminate or HCV infection is suspected due to elevated aminotransaminases or risk factors such as a history of intravenous drug use, testing for HCV RNA should be performed.

There are few data on the optimal management of HIV-infected pregnant women with HCV coinfection. There are no definitive studies on the safety of HCV antiviral therapy during pregnancy. Interferon and peg-interferon are not recommended for use in pregnancy, and ribavirin is contraindicated in pregnancy. Although interferons are not teratogenic, they are abortifacient at high doses in monkeys and should not be used in pregnant women because of the direct antigrowth and antiproliferative effects of these agents *[3]*. Ribavirin is labeled as FDA pregnancy category X because of its teratogenicity at low doses in multiple animal species; defects noted in animals include limb abnormalities, craniofacial defects, anencephaly, and anophthalmia. Pregnancy does not appear to influence the course of HCV infection and women with chronic viral hepatitis generally do quite well during pregnancy, providing that they have not progressed to decompensated cirrhosis *[4]*.

Because of the added risk of acute hepatitis A and B in persons with chronic viral hepatitis C, women who are found to have chronic HCV infection should be screened for hepatitis A and hepatitis B infections. If women with chronic HCV infection are hepatitis A IgG negative, they should receive the HAV vaccine series, and if they are hepatitis B uninfected (e.g., hepatitis B surface Ag negative, hepatitis B core antibody negative, and hepatitis B surface antibody negative), they should receive the HBV vaccine series.

Coinfection with HIV has been shown to increase significantly the risk of perinatal transmission of HCV, likely related to increase in HCV viremia and/or other HIV-related impact on HCV disease activity *[5]*. A European study of perinatal transmission of HCV found that use of effective combination antiretroviral therapy was associated with a strong trend for reduction in HCV transmission (OR 0.26, 95% CI, 0.07–1.01) *[6]*. However, although the median HCV viral load was lower among women treated with combination antiretroviral regimens compared to women on a single drug or receiving no treatment (656,101 copies/mL vs. 850,000 copies/mL, respectively), this difference was neither statistically nor clinically significant. Maternal HCV/HIV coinfection may also increase the risk of perinatal transmission of HIV *[7]*. Therefore, potent combination antiretroviral therapy with three drugs should be considered for all HCV/HIV-coinfected pregnant women, regardless of CD4 count or HIV viral load, with discontinuation of therapy postpartum in women who do not require therapy for their own health.

Similar to HBV infection, an elevation in hepatic enzymes following initiation of antiretroviral therapy may occur in HCV/HIV-coinfected women. This elevation in hepatic enzymes may be due to an immune-mediated flare in HCV disease secondary to immune reconstitution with therapy, particularly in women with low CD4 cell count at the time of initiation of therapy. Like HBV, HCV infection may increase hepatotoxic risk of certain antiretroviral agents, specifically protease inhibitors and nevirapine. Pregnant women with HCV/HIV coinfection should be counseled about signs and symptoms of liver toxicity, and transaminases should be assessed 2 weeks following initiation of antiretroviral therapy or prophylaxis in women not already receiving drugs and then at least monthly. If hepatic toxicity occurs, substitution of a less hepatotoxic drug regimen may need to be considered or, if clinical symptoms or significant elevations of transaminases occur, drugs may need to be temporarily discontinued. It can be difficult to differentiate a flare in HCV disease due to immune reconstitution from drug toxicity, and consultation with an expert in HIV infection is recommended.

Similar to HIV transmission, internal fetal monitoring and duration of membrane rupture greater than 6 hours may increase risk of HCV transmission; general recommendations for intrapartum management are unchanged from those for women with HIV infection alone (see **Intrapartum Care**). Data are inconclusive regarding the role of scheduled cesarean delivery in reducing the risk of HCV transmission in the setting of HIV infection. Currently, there is no evidence from randomized controlled trials upon which to base any practice recommendations regarding scheduled cesarean delivery versus vaginal delivery for preventing mother-to-infant transmission of HCV *[8]*. In two observational studies from the European Hepatitis C Virus Network, the first study reported that scheduled cesarean delivery was protective against HCV transmission in HIV-coinfected women, but the second study found no benefit to scheduled cesarean delivery, possibly related to the increased use of combination antiretroviral drug regimens in the second report *[9]*. At the current time, decisions concerning mode of delivery in HCV/HIV-coinfected pregnant women should be based on HIV considerations alone (see **Intrapartum Care**).

Infants born to women with HCV/HIV coinfection should be assessed for HCV infection by HCV RNA virologic testing between 2 and 6 months of age (at least two negative tests are needed to exclude HCV infection because HCV viremia can be intermittent) and/or testing for anti-HCV antibody after age 15 months *[10]*.

References

1. Centers for Disease Control and Prevention (CDC). Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. *MMWR Recomm Rep.* 2009;58(RR-4):1-207; quiz CE201-204.
2. Thomas SL, Newell ML, Peckham CS, et al. A review of hepatitis C virus (HCV) vertical transmission: risks of transmission to infants born to mothers with and without HCV viraemia or human immunodeficiency virus infection. *Int J Epidemiol.* 1998;27(1):108-117.
3. Boskovic R, Wide R, Wolpin J, et al. The reproductive effects of beta interferon therapy in pregnancy: a longitudinal cohort. *Neurology.* 2005;65(6):807-811.
4. Sookoian S. Effect of pregnancy on pre-existing liver disease: chronic viral hepatitis. *Ann Hepatol.* 2006;5(3):190-197.
5. Polis CB, Shah SN, Johnson KE, et al. Impact of maternal HIV coinfection on the vertical transmission of hepatitis C virus: a meta-analysis. *Clin Infect Dis.* 2007;44(8):1123-1131.
6. European Paediatric Hepatitis C Virus Network. A significant sex--but not elective cesarean section--effect on mother-to-child transmission of hepatitis C virus infection. *J Infect Dis.* 2005;192(11):1872-1879.
7. Hershow RC, Riester KA, Lew J, et al. Increased vertical transmission of human immunodeficiency virus from hepatitis C virus-coinfected mothers. Women and Infants Transmission Study. *J Infect Dis.* 1997;176(2):414-420.
8. McIntyre PG, Tosh K, McGuire W. Caesarean section versus vaginal delivery for preventing mother to infant hepatitis C virus transmission. *Cochrane Database Syst Rev.* 2006(4):CD005546.
9. European Paediatric Hepatitis C Virus Network. Effects of mode of delivery and infant feeding on the risk of mother-to-child transmission of hepatitis C virus. European Paediatric Hepatitis C Virus Network. *BJOG.* 2001;108(4):371-377.
10. National Institutes of Health Consensus Development Conference statement Management of Hepatitis C: 2002 June 10-12, 2002. *HIV Clin Trials.* 2003;4(1):55-75.

Stopping Antiretroviral Therapy during Pregnancy

Panel's Recommendations:

- ***If an antiretroviral drug regimen is stopped acutely for severe or life-threatening toxicity or severe pregnancy-induced hyperemesis unresponsive to anti-emetics, all drugs should be stopped at the same time and reinitiated at the same time (AIII).***
- ***If an antiretroviral drug regimen is stopped electively and the patient is receiving an NNRTI drug, consideration should be given to either (1) stopping the NNRTI first and continuing the other antiretroviral drugs for a period of time or (2) switching from an NNRTI to a PI prior to interruption and continuing the PI with the other antiretroviral drugs for a period of time before electively stopping. The optimal interval between stopping an NNRTI and the other antiretroviral drugs is not known; at least 7 days is recommended. Given the potential for prolonged detectable NNRTI concentrations for more than 3 weeks in patients receiving efavirenz-based therapy, some experts recommend continuing the other antiretroviral agents or substituting a PI plus two other agents for up to 30 days (CIII).***
- ***If nevirapine is stopped and more than 2 weeks have passed prior to restarting therapy, nevirapine should be restarted with the 2-week dose escalation period (AII).***

Discontinuation of antiretroviral drug regimens during pregnancy may be indicated in some situations including serious drug-related toxicity, pregnancy-induced hyperemesis, acute illnesses or planned surgeries that preclude oral intake, lack of available medication, or patient request.

Continuation of all drugs during the intrapartum period is generally recommended. Women who are having an elective cesarean section can take oral medications prior to the scheduled surgery and restart drugs following

surgery. Given that most drugs are given once or twice daily, the woman would either not miss any doses or at most receive the postpartum dose a few hours late.

When short-term drug interruption is indicated, in most cases, all antiretroviral drugs should be stopped and reintroduced at the same time. This can be problematic with drugs that have a long half-life. However, in conditions such as severe or life-threatening toxicity or severe pregnancy-induced hyperemesis unresponsive to anti-emetics, the clinician has no choice but to stop all therapy at the same time.

NNRTI drugs like nevirapine and efavirenz have very long half-lives and can be detected for 21 days or longer after discontinuation; efavirenz has a longer half-life than nevirapine *[1-5]*. As the other drugs with shorter half-lives are cleared, only the NNRTI drug may persist, resulting in persistent subtherapeutic drug levels that can increase the risk of selection of NNRTI-resistant mutations. In addition, it is known that certain genetic polymorphisms may result in slower rate of clearance. These polymorphisms may be more common among some ethnic groups, such as in African Americans and in Hispanics *[3, 5]*. To prevent prolonged exposure to a single drug, some experts recommend stopping the NNRTI first and continuing the other antiretroviral drugs for a period of time *[2]*. However, the optimal interval between stopping an NNRTI and the other antiretroviral drugs is not known; detectable levels of NNRTIs may be present from less than 1 week to greater than 3 weeks after discontinuation (the longer duration is primarily observed with efavirenz) *[5]*. An alternative strategy is to substitute a PI for the NNRTI and to continue the PI with dual NRTIs for a period of time. In a post-study analysis of the patients who interrupted therapy in the SMART trial, patients who were switched from an NNRTI to a PI-based regimen prior to interruption had a lower rate of NNRTI-resistant mutation after interruption and a greater chance of resuppression of HIV-RNA after restarting therapy than those who stopped all the drugs simultaneously or stopped the NNRTI before the dual-NRTIs *[6]*. The optimal duration needed to continue either dual nucleosides or the substituted PI-based regimen after stopping the NNRTI is not known; at least 7 days is recommended based on studies to reduce resistance following single-dose nevirapine *[7]*. With efavirenz use, there is the potential of prolonged detectable NNRTI concentrations for more than 3 weeks; therefore some suggest if stopping efavirenz-based therapy, the dual nucleosides or PI may need to be continued for up to 30 days. Further research is needed to assess appropriate strategies for stopping NNRTI-containing combination regimens.

An additional consideration is reintroduction of nevirapine if it is temporarily stopped for some reason and subsequently restarted. Currently, a 2-week, half-dose escalation is recommended in patients who are started on nevirapine. Dose escalation is necessary because nevirapine induces its own metabolism by inducing CYP3A4 liver metabolic enzymes; thus, initial administration of the full therapeutic dose will result in elevated drug levels until metabolic enzyme induction has occurred. In cases where nevirapine has been discontinued for more than 2 weeks, it is recommended that another 2-week dose escalation be used when it is reintroduced.

Failure of Viral Suppression

Panel's Recommendations:

- ***If there is failure of viral suppression after an adequate period of treatment:***
  - ***Assess resistance and adherence (AII).***
  - ***Consult an expert in the care of HIV-infected adults (AIII).***
- ***Scheduled cesarean delivery is recommended for HIV-infected pregnant women who have HIV RNA levels >1,000 copies/mL near the time of delivery (AII).***

The management of women on chronic antiretroviral therapy who have suboptimal suppression of HIV RNA (i.e., detectable virus at any time during pregnancy) should include evaluation for resistant virus, assessment of adherence, incorrect dosing or potential problems with absorption (e.g., with nausea/vomiting or lack of attention to food requirements), and consideration of modification of antiretroviral therapy. Experts in the care

of antiretroviral-experienced adults should be consulted, in particular when a change in drug regimen is necessary.

HIV RNA levels should be assessed 2 to 6 weeks following initiation or change of antiretroviral drug regimen to provide an initial assessment of efficacy *[8]*. Baseline HIV RNA levels have been shown to affect the time course of response in pregnant as well as nonpregnant individuals *[9]*. Most patients with an adequate viral response at 24 weeks have had at least a 1 $\log_{10}$ copies/mL HIV RNA decrease by 1 to 4 weeks after starting therapy *[8]*. Treatment-naïve individuals should have HIV RNA <400 copies/mL after 24 weeks of treatment and <50 copies/mL after 48 weeks of treatment.

Because maternal antenatal viral load correlates with risk of perinatal HIV transmission, suppression of HIV RNA to undetectable levels should be achieved as rapidly as possible. Scheduled cesarean delivery is recommended for HIV-infected pregnant women who have HIV RNA levels >1,000 copies/mL near the time of delivery (see **Transmission and Mode of Delivery**).

References

1. Cressey TR, Jourdain G, Lallemant MJ, et al. Persistence of nevirapine exposure during the postpartum period after intrapartum single-dose nevirapine in addition to zidovudine prophylaxis for the prevention of mother-to-child transmission of HIV-1. *J Acquir Immune Defic Syndr.* 2005;38(3):283-288.
2. Mackie NE, Fidler S, Tamm N, et al. Clinical implications of stopping nevirapine-based antiretroviral therapy: relative pharmacokinetics and avoidance of drug resistance. *HIV Med.* 2004;5(3):180-184.
3. Nolan M, Fowler MG, Mofenson LM. Antiretroviral prophylaxis of perinatal HIV-1 transmission and the potential impact of antiretroviral resistance. *J Acquir Immune Defic Syndr.* 2002;30(2):216-229.
4. Sadiq ST, Fredericks S, Khoo SH, et al. Efavirenz detectable in plasma 8 weeks after stopping therapy and subsequent development of non-nucleoside reverse transcriptase inhibitor-associated resistance. *AIDS.* 2005;19(15):1716-1717.
5. Ribaudo HJ, Haas DW, Tierney C, et al. Pharmacogenetics of plasma efavirenz exposure after treatment discontinuation: an Adult AIDS Clinical Trials Group Study. *Clin Infect Dis.* 2006;42(3):401-407.
6. Fox Z, Phillips A, Cohen C, et al. Viral resuppression and detection of drug resistance following interruption of a suppressive non-nucleoside reverse transcriptase inhibitor-based regimen. *AIDS.* 2008;22(17):2279-2289.
7. McIntyre JA, Hopley M, Moodley D, et al. Efficacy of short-course AZT plus 3TC to reduce nevirapine resistance in the prevention of mother-to-child HIV transmission: a randomized clinical trial. *PLoS Med.* 2009;6(10):e1000172.
8. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. December 1, 2009:1-161. http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf.
9. European Collaborative Study, Patel D, Cortina-Borja M, et al. Time to undetectable viral load after highly active antiretroviral therapy initiation among HIV-infected pregnant women. *Clin Infect Dis.* 2007;44(12):1647-1656.

MONITORING OF THE WOMAN AND FETUS DURING PREGNANCY

Panel's Recommendations:

- ***CD4 cell count should be monitored at the initial antenatal visit (AI) and at least every 3 months during pregnancy (BIII).***
- ***Plasma HIV RNA levels should be monitored at the initial visit (AI); 2 to 4 weeks after initiating (or changing) antiretroviral therapy (BI); monthly until RNA levels are undetectable (BII); and then at least every 3 months during pregnancy (BIII). HIV RNA levels should also be assessed at approximately 34 to 36 weeks gestation to inform decisions on mode of delivery (see Transmission and Mode of Delivery) (AIII).***
- ***Antiretroviral drug resistance testing should be performed in all pregnant women prior to initiating antiretroviral treatment or prophylaxis, in pregnant women who have suboptimal viral suppression after initiation of antiretroviral drugs (failure to achieve a 1 log_{10} copies/mL drop in HIV RNA at 30 days or lack of progressive decline to undetectable HIV RNA levels by 16 to 24 weeks of therapy), and in pregnant women who have persistently detectable plasma HIV RNA levels after treatment previously suppressed the virus to lower than the assay level of detection (AII).***
- ***Monitoring for complications of antiretroviral drugs during pregnancy should be based on what is known about side effects of the drugs the woman is receiving (AIII).***
- ***First-trimester ultrasound is recommended for confirmation of gestational age and potential timing for scheduled cesarean delivery, if needed (see Transmission and Mode of Delivery) (AII).***
- ***Given the limited data on the effect of combination therapy on the fetus, most experts would recommend second-trimester ultrasound to assess fetal anatomy for women who have received combination antiretroviral therapy (particularly if the regimen included efavirenz) during the first trimester (BIII).***
- ***Among women on combination antiretroviral drug regimens, no perinatal transmissions have been reported after amniocentesis, but a small risk of transmission cannot be ruled out. If amniocentesis is indicated in HIV-infected women, it should be done only after initiation of combination antiretroviral drug therapy or prophylaxis and ideally when HIV RNA levels are undetectable (BIII).***

CD4 cell count should be monitored in HIV-infected pregnant women at the initial visit and at least every 3 months during pregnancy, similar to recommendations in nonpregnant adults. Viral load should be monitored in HIV-infected pregnant women at the initial visit, 2 to 4 weeks after initiating or changing antiretroviral therapy, monthly until undetectable, and then at least every 3 months. If there is concern regarding adherence, more frequent monitoring is recommended because of the potential increased risk of perinatal HIV infection if there is detectable HIV viremia during pregnancy. More frequent monitoring of viral load is recommended in pregnant versus nonpregnant individuals because of the urgency to lower viral load as rapidly as possible to reduce perinatal transmission risk. Therefore, there is a need to identify pregnant women whose decline in viral load is slower than expected. Adult antiretroviral guidelines note that patients should have a decrease in plasma HIV RNA level by at least one log_{10} copies/mL by 1 month after initiation of potent therapy (Adult guidelines). Generally, most treatment-adherent individuals not harboring resistance mutations to the drugs they are receiving achieve viral suppression in 16 to 24 weeks, although rarely it may take longer for some patients. Viral load should also be assessed at approximately 34 to 36 weeks gestation to inform decisions on mode of delivery (see **Transmission and Mode of Delivery**).

Due to physiologic changes such as hemodilution during pregnancy, CD4 percentage may be more stable than absolute CD4 count during pregnancy *[1-2]*. However, because parameters for initiating therapy are based primarily on absolute CD4 count, most clinicians still rely on CD4 count to evaluate immune status during pregnancy.

Antiretroviral drug resistance testing should be performed in pregnant women prior to initiating antiretroviral treatment or prophylaxis and in those women who have suboptimal viral suppression after initiation of antiretroviral drugs or who have persistently detectable plasma HIV RNA levels after treatment previously suppressed the virus to lower than the assay level of detection (see **Antiretroviral Drug Resistance and Resistance Testing in Pregnancy**). Drug resistance testing in the setting of viral failure should be performed while the patient is receiving antiretroviral drugs or immediately (i.e., up to 4 weeks) after discontinuing therapy.

Monitoring for potential complications of antiretroviral drugs during pregnancy should be based on what is known about the side effects of the drugs the woman is receiving. For example, routine hematologic monitoring is recommended for women receiving zidovudine-containing regimens. Liver function should be monitored in all women receiving antiretroviral drugs. Hepatic dysfunction has been observed in pregnant women on protease inhibitors, and hepatic steatosis and lactic acidosis in pregnancy has been related to NRTI use. Women, particularly those with CD4 counts >250 cells/mm^3, have an increased risk of developing symptomatic, rash-associated, nevirapine-associated hepatotoxicity within the first 18 weeks after initiation of therapy. Pregnant women initiating therapy with nevirapine should have more frequent and careful monitoring of transaminase levels (see **Nevirapine and Hepatic/Rash Toxicity**).

First-trimester ultrasound is recommended for confirmation of gestational age and, if needed, to guide potential timing of scheduled cesarean delivery because scheduled cesarean deliveries for prevention of perinatal HIV transmission should be performed at 38 weeks gestation (see **Transmission and Mode of Delivery**). Research studies show that first-trimester ultrasound, which is currently recommended by the American Congress of Obstetricians and Gynecologists is the most accurate procedure for dating of pregnancy *[3-4]*. If the patient is not seen until later in gestation, then second-trimester ultrasound can be used for both anatomy scanning and determining gestational age.

Because less is known about the effect of combination antiretroviral therapy on the fetus during pregnancy, some experts consider more intensive fetal assessment for mothers receiving such therapy. Most experts would recommend second-trimester assessment of fetal anatomy with ultrasound in women who have received combination antiretroviral therapy during the first trimester, particularly if the regimen included efavirenz. Furthermore, in addition to standard clinical monitoring, some experts would also recommend ultrasound assessment of fetal growth and well-being during the third trimester if the woman was receiving a combination drug regimen for which there is limited experience with use in pregnancy. The need for additional assessments such as non-stress testing should be determined based on ultrasound findings and any maternal comorbidities.

In the pre-HAART era, invasive procedures such as amniocentesis and chorionic villus sampling were associated with a two- to four-fold increased risk of vertical transmission of HIV *[5-7]*. Data from the HAART era are still limited but do not suggest an increased risk of transmission for women receiving combination antiretroviral drug regimens before amniocentesis or other invasive diagnostic procedure. In an evaluation of transmission rates over time among women with or without amniocentesis, the transmission rate among women undergoing the procedure from 1984 to 1996 (pre-HAART) was 3 (30%) of 10 compared to 40 (16.2%) of 247 among women without amniocentesis (NS) *[8]*. No transmissions were noted among 18 women undergoing amniocentesis between 1997 and 2000 and receiving antiretroviral drug regimens *[8]*. In a multi-center study from Italy including deliveries between 1997 and 2003, 2 (3.3%) of 60 infants were HIV infected after early invasive diagnostic procedures (chorionic villus sampling, amniocentesis, or cordocentesis) during pregnancy compared to 1.7% of 712 infants born to women without invasive procedures (p = 0.30) *[9]*. No transmissions occurred among 45 women on combination antiretroviral drug regimens during the

procedure. One mother of an infected infant had not been diagnosed as HIV infected at the time of amniocentesis so was not receiving antiretroviral prophylaxis; the newborn's virologic test at birth was negative. The mother of a second infected infant had been receiving zidovudine prophylaxis for 3 weeks and had an HIV RNA level of 10,000 copies/mL at the time of the procedure; the preterm infant had a positive virologic test at birth. In 2 other single-center series, no transmissions occurred in the 6 and 9 liveborns after amniocentesis among HIV-infected pregnant women on combination antiretroviral drug regimens *[10-11]*. In the largest series to date, no transmissions were seen among 81 women receiving combination antiretroviral drug regimens at the time of amniocentesis *[12]*. Thus among 159 cases reported to date of amniocentesis or other invasive diagnostic procedures among women on combination antiretroviral drug regimens, no transmissions have occurred but a small increase in risk cannot be ruled out. HIV-infected women who have indications for invasive testing in pregnancy, such as abnormal ultrasound or serum marker screening, should be counseled about the potential risk of HIV transmission along with other risks of the procedure and allowed to make an informed decision about testing. Some experts consider chorionic villus sampling and cordocentesis too risky to offer to HIV-infected women and recommend limiting procedures to amniocentesis *[10]*. Women should be on a combination antiretroviral drug regimen (e.g., at least 3 drugs), ideally with an undetectable HIV RNA level, before any procedure. Any procedure should be done under continuous ultrasound guidance, and the placenta should not be traversed during amniocentesis.

References

1. Miotti PG, Liomba G, Dallabetta GA, et al. T lymphocyte subsets during and after pregnancy: analysis in human immunodeficiency virus type 1-infected and -uninfected Malawian mothers. *J Infect Dis.* 1992;165(6):1116-1119.
2. Tuomala RE, Kalish LA, Zorilla C, et al. Changes in total, CD4+, and CD8+ lymphocytes during pregnancy and 1 year postpartum in human immunodeficiency virus-infected women. The Women and Infants Transmission Study. *Obstet Gynecol.* 1997;89(6):967-974.
3. ACOG Committee on Practice Bulletins. ACOG Practice Bulletin No. 58. Ultrasonography in pregnancy. *Obstet Gynecol.* 2004;104(6):1449-1458.
4. Bennett KA, Crane JM, O'Shea P, et al. First trimester ultrasound screening is effective in reducing postterm labor induction rates: a randomized controlled trial. *Am J Obstet Gynecol.* 2004;190(4):1077-1081.
5. Mandelbrot L, Mayaux MJ, Bongain A, et al. Obstetric factors and mother-to-child transmission of human immunodeficiency virus type 1: the French perinatal cohorts. SEROGEST French Pediatric HIV Infection Study Group. *Am J Obstet Gynecol.* 1996;175(3 Pt 1):661-667.
6. Shapiro DE, Sperling RS, Mandelbrot L, et al. Risk factors for perinatal human immunodeficiency virus transmission in patients receiving zidovudine prophylaxis. Pediatric AIDS Clinical Trials Group protocol 076 Study Group. *Obstet Gynecol.* 1999;94(6):897-908.
7. Tess BH, Rodrigues LC, Newell ML, et al. Breastfeeding, genetic, obstetric and other risk factors associated with mother-to-child transmission of HIV-1 in Sao Paulo State, Brazil. Sao Paulo Collaborative Study for Vertical Transmission of HIV-1. *AIDS.* 1998;12(5):513-520.
8. Maiques V, Garcia-Tejedor A, Perales A, et al. HIV detection in amniotic fluid samples. Amniocentesis can be performed in HIV pregnant women? *Eur J Obstet Gynecol Reprod Biol.* 2003;108(2):137-141.
9. Somigliana E, Bucceri AM, Tibaldi C, et al. Early invasive diagnostic techniques in pregnant women who are infected with the HIV: a multicenter case series. *Am J Obstet Gynecol.* 2005;193(2):437-442.
10. Coll O, Suy A, Hernandez S, et al. Prenatal diagnosis in human immunodeficiency virus-infected women: a new screening program for chromosomal anomalies. *Am J Obstet Gynecol.* 2006;194(1):192-198.
11. Ekoukou D, Khuong-Josses MA, Ghibaudo N, et al. Amniocentesis in pregnant HIV-infected patients. Absence of mother-to-child viral transmission in a series of selected patients. *Eur J Obstet Gynecol Reprod Biol.* 2008;140(2):212-217.
12. Mandelbrot L, Jasseron C, Ekoukou D, et al. Amniocentesis and mother-to-child human immunodeficiency virus transmission in the Agence Nationale de Recherches sur le SIDA et les Hepatites Virales French Perinatal Cohort. *Am J Obstet Gynecol.* 2009;200(2):160 e161-169.

SPECIAL CONSIDERATIONS REGARDING THE USE OF ANTIRETROVIRAL DRUGS BY HIV-INFECTED PREGNANT WOMEN AND THEIR INFANTS

Panel's Recommendations:

- ***All cases of antiretroviral drug exposure during pregnancy should be reported to the Antiretroviral Pregnancy Registry (see details at http://www.APRegistry.com) (AIII).***
- ***Some protease inhibitors (e.g., lopinavir/ritonavir) may require altered dosing during pregnancy (see Table 5) (AIII).***
- ***Efavirenz is an FDA Pregnancy Category D drug because of animal data showing an increased risk of central nervous system (CNS) defects and a small number of concerning case reports in humans. Efavirenz should not be used in the first trimester of pregnancy and women on efavirenz should be counseled to avoid pregnancy (AIII).***
- ***Although currently published data are conflicting, clinicians should be aware of a possible small increased risk of preterm birth in pregnant women receiving protease inhibitor-based combination antiretroviral therapy or prophylaxis; however, given the clear benefits of such therapy for both the woman's health and the prevention of mother-to-child transmission, protease inhibitors should not be withheld for fear of altering pregnancy outcome (AIII).***
- ***Women with CD4 counts >250 cells/mm^3 initiating nevirapine-containing regimens have an increased risk of developing symptomatic, often rash-associated, nevirapine-related hepatotoxicity that can be severe, life-threatening, and in some cases fatal. Pregnancy does not seem to modify this risk. Therefore, nevirapine should only be used in this setting if the benefits clearly outweigh the risks (AII). However, nevirapine-related toxicity has not been observed with use of single-dose nevirapine for prevention of mother-to-child transmission of HIV.***
- ***HIV-infected women receiving antiretroviral therapy during pregnancy should receive glucose screening with a standard, 1-hour, 50-gram glucose loading test at 24 to 28 weeks gestation (AIII). Some experts would perform earlier glucose screening in women with ongoing chronic protease inhibitor-based therapy initiated prior to pregnancy, similar to recommendations for women with high-risk factors for glucose intolerance (BIII).***

Recommendations regarding the choice of antiretroviral drugs for treatment of HIV-infected pregnant women are subject to unique considerations. These include:

a. possible changes in dosing requirements resulting from physiologic changes associated with pregnancy;

b. potential toxicities of antiretroviral drugs that may be magnified in the pregnant woman;

c. the potential short- and long-term effects of the antiretroviral drug on the fetus and newborn, including the potential for preterm birth, teratogenicity, mutagenicity, or carcinogenicity, which may not be known for certain antiretroviral drugs; and

d. the pharmacokinetics and toxicity of transplacentally transferred drugs.

Treatment recommendations for pregnant women infected with HIV have been based on the concept that therapies of known benefit to women should not be withheld during pregnancy unless there are known adverse effects on the mother, fetus, or infant and unless these adverse effects outweigh the benefit to the woman *[1]*. Pregnancy should not preclude the use of optimal therapeutic regimens. The decision to use any antiretroviral drug during pregnancy should be made by the woman after

discussing with her health care provider the known and potential benefits and risks to her and her fetus.

Although clinical data on antiretroviral drugs in pregnant women are more limited than in nonpregnant individuals, there are sufficient data on some of the available antiretroviral drugs to be able to provide recommendations related to drug choice. **Table 5** provides information on pharmacokinetics in pregnancy and pregnancy-related concerns for each of the available antiretroviral drugs; drugs are classified for use in pregnancy as recommended, alternative, insufficient information, or not recommended. This table should be used in conjunction with the ***Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*** when developing treatment regimens for pregnant women.

Pharmacokinetic Changes

Physiologic changes that occur during pregnancy may affect the kinetics of drug absorption, distribution, biotransformation, and elimination, thereby also affecting requirements for drug dosing and potentially altering the susceptibility of the pregnant woman to drug toxicity *[2-3]*. During pregnancy, gastrointestinal transit time becomes prolonged; body water and fat increase throughout gestation and are accompanied by increases in cardiac output, ventilation, and liver and renal blood flow; plasma protein concentrations decrease; renal sodium reabsorption increases; and changes occur in metabolic enzyme pathways in the liver. Placental transport of drugs, compartmentalization of drugs in the embryo/fetus and placenta, biotransformation of drugs by the fetus and placenta, and elimination of drugs by the fetus also can affect drug pharmacokinetics in the pregnant woman.

Currently available data on the pharmacokinetics of antiretrovirals in pregnancy are summarized in **Table 5**. In general, the pharmacokinetics of NRTI and NNRTI drugs are similar in pregnant and nonpregnant women, although protease inhibitor (e.g., lopinavir/ritonavir) pharmacokinetics are more variable, particularly in later pregnancy.

Teratogenicity

The potential harm to the fetus from maternal ingestion of a specific drug depends not only on the drug itself but also on the dose ingested; the gestational age of the fetus at exposure; the duration of exposure; the interaction with other agents to which the fetus is exposed; and, to an unknown extent, the genetic makeup of the mother and fetus.

Information regarding the safety of drugs in pregnancy is derived from animal toxicity data, anecdotal experience, registry data, and clinical trials. Data are limited for antiretroviral drugs, particularly when used in combination therapy. Drug choice should be individualized and must be based on discussion with the woman and available data from preclinical and clinical testing of the individual drugs. Preclinical data include results of *in vitro* and animal *in vivo* screening tests for carcinogenicity, clastogenicity/mutagenicity, and reproductive and teratogenic effects. However, the predictive value of such tests for adverse effects in humans is unknown. For example, of approximately 1,200 known animal teratogens, only about 30 are known to be teratogenic in humans *[4]*. Limited data exist regarding placental passage, long-term animal carcinogenicity, and animal teratogenicity for the FDA-approved antiretroviral drugs (**Table 4**).

Human data on teratogenicity of FDA-approved antiretrovirals are summarized in **Table 5**. Concerns have been raised about the risk of several of the antiretroviral agents. In cynomolgus monkeys treated with efavirenz from gestational days 20 to 150 at a dose resulting in plasma concentrations comparable to systemic human therapeutic exposure, significant malformations were observed in 3 of 20 infant monkeys *[5]*. The malformations included anencephaly and unilateral anophthalmia in 1;

microphthalmia in another; and cleft palate in the third. In prospectively reported pregnancies with exposure to efavirenz-based regimens in the Antiretroviral Pregnancy Registry through July 2009, birth defects were observed in 14 (2.8%) of 501 live births with first-trimester exposure; this proportion is not significantly different from that observed among U.S. births in the general population (2.7%) as reported by the Registry *[6]*. Defects reported prospectively included 1 report of myelomeningocele and a separate report of anophthalmia. The case of anophthalmia included severe oblique facial clefts and amniotic banding that is known to be associated with anophthalmia *[6]*. In addition, there have been 5 retrospectively detected cases of central nervous system defects, including myelomeningocele, in infants born to mothers receiving efavirenz during the first trimester *[5]*.

Although a causal relationship of these events to the use of efavirenz has not been established, in light of similar findings in primates, efavirenz is classified as FDA Pregnancy Category D and may cause fetal harm when administered to a pregnant woman during the first trimester. Because of the potential for teratogenicity, pregnancy should be avoided in women receiving efavirenz, and treatment with efavirenz should be avoided during the first trimester, which is the primary period of fetal organogenesis. Women of childbearing potential should undergo pregnancy testing prior to initiation of efavirenz and should be counseled about the potential risk to the fetus and need to avoid pregnancy. Alternate antiretroviral regimens that do not include efavirenz should be strongly considered in women who are planning to become pregnant or who are sexually active and not using effective contraception. Use after the first trimester can be considered if, after consideration of other alternatives, this is the best choice for an individual woman. If efavirenz is to be continued postpartum, adequate contraception must be assured (**Table 5**).

Zalcitabine has been associated with an increased risk of hydrocephalus at very high doses in rodents and delavirdine has been associated with an increased risk of ventricular septal defects in rodents. Neither drug is currently available for use in the United States.

Tenofovir has not demonstrated teratogenicity in rodents or monkeys. At doses resulting in levels approximately 25 times those used in humans, low birth weights and reductions in fetal bone porosity were seen. Chronic administration of tenofovir to immature animals of multiple species has resulted in reversible bone abnormalities; these effects were dose, exposure, age, and species specific. Data from the Antiretroviral Pregnancy Registry show a birth defect incidence of 2.4% in 756 women with first-trimester tenofovir exposure, similar to that in the general population *[6]*. However, because of the limited data on use in human pregnancy and concern regarding potential fetal bone effects and potential nephrotoxicity, tenofovir should be used as a component of maternal combination regimen only after careful consideration of alternatives (**Table 5**).

Among cases of first-trimester didanosine exposure reported to the Antiretroviral Pregnancy Registry, defects have been noted in 4.6% (17/370), compared to a rate of 1.9% (5/257) among those with exposures later in pregnancy *[6]*. All defects were reviewed in detail by the Registry, and no pattern of defects was discovered. However, these data do suggest a possible higher risk of birth defects with exposure to didanosine in the first trimester compared to the frequency of birth defects observed in the general population and with the use of other antiretroviral agents, and the Registry continues to follow this.

See **Supplement: Safety and Toxicity of Individual Antiretroviral Drugs in Pregnancy** to obtain detailed information on individual drugs.

Referrals should be directed to:
Antiretroviral Pregnancy Registry
Research Park
1011 Ashes Drive
Wilmington, NC 28405

Telephone: 1–800–258–4263
Fax: 1–800–800–1052
http://www.APRegistry.com

Health care providers who are treating HIV-infected pregnant women and their newborns are strongly advised to report instances of prenatal exposure to antiretroviral drugs (either alone or in combination) to the Antiretroviral Pregnancy Registry. This registry is an epidemiologic project to collect observational, nonexperimental data regarding antiretroviral exposure during pregnancy for the purpose of assessing the potential teratogenicity of these drugs. Registry data will be used to supplement animal toxicology studies and assist clinicians in weighing the potential risks and benefits of treatment for individual patients. The Antiretroviral Pregnancy Registry is a collaborative project of pharmaceutical manufacturers with an advisory committee of obstetric and pediatric practitioners. The registry does not use patient names, and registry staff obtain birth outcome follow-up information from the reporting physician.

Combination Antiretroviral Therapy and Pregnancy Outcome

Early data were conflicting as to whether receipt of combination antiretroviral therapy during pregnancy is associated with adverse pregnancy outcomes, in particular preterm delivery. The European Collaborative Study and the Swiss Mother + Child HIV Cohort Study investigated the effects of combination antiretroviral therapy in a population of 3,920 mother-child pairs. Adjusting for CD4 count and intravenous drug use, they found a roughly 2-fold increased odds of preterm delivery for infants exposed to combination therapy with or without protease inhibitors, compared to no treatment; women receiving combination therapy that had been initiated before their pregnancy were twice as likely to deliver prematurely as those starting therapy during the third trimester *[7]*. However, protease inhibitor-based combination therapy was received by only 108 (3%) of the women studied; confounding by severity or indication may have biased the results (i.e., sicker women may have received protease inhibitors more often, but their advanced HIV infection may have actually caused the preterm births). Exposure to NRTI single-drug prophylaxis (primarily zidovudine) was not associated with prematurity. An updated report from the European Collaborative Study including 2,279 mother-child pairs found, in an adjusted analysis, a 1.9-fold increased risk of delivery at less than 37 weeks with combination antiretroviral therapy started during pregnancy and 2.1-fold for combination antiretroviral therapy started prepregnancy compared to mono- or dual-NRTI prophylaxis *[8]*. In this report, 767 women received combination antiretroviral therapy during pregnancy, although the proportion receiving protease inhibitors was not specified. The risk of delivery before 34 weeks of gestation was increased by 2.5-fold for those starting combination antiretroviral therapy during pregnancy and 4.4-fold for those entering pregnancy on combination antiretroviral therapy.

In contrast, in an analysis of 7 prospective clinical studies that included 2,123 HIV-infected pregnant women who delivered infants during 1990–1998 and had received antenatal antiretroviral therapy and 1,143 women who did not receive antenatal antiretroviral therapy, the use of multiple antiretroviral drugs compared to no treatment or treatment with 1 drug was not associated with increased rates of preterm labor, low birth weight, low Apgar scores, or stillbirth *[9]*. Nor were any significant associations between use of antiretrovirals by class or by category, including combination antiretroviral therapy, and adverse pregnancy outcome found in an analysis from the Women and Infants Transmission Study, including 2,543 HIV-infected women (some of whom were included in the previous meta-analysis) *[10]*.

More recent data have continued to be conflicting as to whether preterm delivery is increased with combination antiretroviral therapy. A prospective cohort study including 681 women from Brazil, Argentina, Mexico, and the Bahamas did not find significant associations between use of combination antiretroviral therapy and preterm birth or low birth weight *[11]*. A single-center study from Miami including 1,337 women did find a 1.8-fold increased chance of preterm birth among the 134 women in the cohort who received

protease inhibitor-containing combination antiretroviral therapy compared to other combination therapy, after adjustment for possible confounding variables *[12]*. However, women receiving protease inhibitor-containing combination antiretroviral therapy uniformly were women with advanced disease or those who had failed other combination therapy. The risk of low birth weight and stillbirth were not increased in any therapy groups. A recent meta-analysis of 14 European and American clinical studies found no increase in risk of preterm birth with either antiretroviral therapy compared to no therapy, or combination antiretroviral therapy regimens including protease inhibitors compared to no therapy *[13]*. A slightly increased risk of preterm birth in women who received protease inhibitor combination therapy compared to combination regimens without protease inhibitors was found (OR 1.35; 95% CI, 1.08–1.70).

Other studies have detected small but significant increases (OR of 1.2–1.5 in the largest studies) in preterm birth with protease inhibitor or non-protease inhibitor-based combination antiretroviral therapy as well *[14-17]*. Another variable that may confound these observational studies is the increased rate of preterm birth if combination antiretroviral therapy is begun before conception compared to later during pregnancy, which itself may again reflect confounding by severity or indication *[18]*. When data from the IMPAACT P1025 observational cohort were examined by multivariable analysis to correct for HIV disease stage, protease inhibitor-based combination antiretroviral therapy was no more likely than non-protease inhibitor-based combination antiretroviral therapy to be associated with spontaneous preterm birth (OR 1.22; 95% CI, 0.70–2.12) *[19]*. Clinicians should be aware of a possible increased risk of preterm birth with combination antiretroviral therapy use, but given the clear benefits for maternal health and reduction in perinatal transmission, these agents should not be withheld because of the possibility of increased risk of preterm delivery. Until more information is known, HIV-infected pregnant women who are receiving combination therapy for their HIV infection should continue their provider-recommended regimens. They should receive careful, regular monitoring for pregnancy complications and for potential toxicities.

Nevirapine and Hepatic/Rash Toxicity

Increases in hepatic transaminase levels (ALT and AST) associated with rash or systemic symptoms may be observed during the first 18 weeks of treatment with nevirapine. Signs and symptoms of systemic toxicity may be nonspecific and can include fatigue, malaise, anorexia, nausea, jaundice, liver tenderness, or hepatomegaly, with or without initially abnormal hepatic transaminases *[20]*. The development of severe nevirapine-associated skin rash has been reported to be 5.5 to 7.3 times more common in women than men and has been reported in pregnant women *[21-22]*. Other studies have found that hepatic adverse events with systemic symptoms (predominantly rash) were 3.2-fold more common in women than men *[23-24]*. The degree of risk of hepatic toxicity also appears to vary with CD4 count. In a summary analysis of data from 17 clinical trials of nevirapine therapy, women with CD4 counts >250 cells/mm^3 were 9.8 times more likely than women with lower CD4 counts to experience symptomatic, rash-associated, nevirapine-related hepatotoxicity *[23]*; a single-center study also found higher CD4 counts to be associated with increased risk of severe nevirapine-associated skin rash *[21]*. In controlled clinical trials, clinical hepatic events, regardless of severity, occurred in 4.0% (range 0%–11.0%) of patients who received nevirapine; severe or life-threatening rash occurred in approximately 2% of patients receiving nevirapine *[25]*.

Several early reports of death due to hepatic failure in HIV-infected pregnant women receiving nevirapine as part of a combination antiretroviral regimen raised concerns that pregnant women might be at increased risk of hepatotoxicity from nevirapine compared to other antiretroviral drugs *[26-27]*. Recent data challenge the notion that nevirapine is uniquely associated with increased hepatotoxicity during pregnancy *[28]*. In an analysis of two multi-center prospective cohorts, pregnancy itself was a risk factor for liver enzyme elevations (RR 4.7; 5% CI; 3.4–6.5), but nevirapine use was not, regardless of pregnancy status *[28]*. Further data from the same cohorts did not show any increased risk of hepatotoxicity in HIV-infected pregnant women receiving nevirapine-based combination antiretroviral therapy versus non-nevirapine-based combination antiretroviral therapy *[29]*. These data suggest that nevirapine is no more toxic in pregnant women than in nonpregnant women.

Nevertheless, if nevirapine is used in pregnancy, health care providers should be aware of potential hepatotoxicity with or without rash and should conduct frequent and careful monitoring of clinical symptoms and hepatic transaminases (i.e., ALT and AST), particularly during the first 18 weeks of therapy. Some clinicians measure serum transaminases at baseline, every 2 weeks for the first month, monthly through month 4, and every 1 to 3 months thereafter (see the *Hepatotoxicity* section of Table 12 in the ***Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents***). In patients with pre-existing liver disease, monitoring should be performed more frequently when initiating therapy and then monthly *[20]*. Transaminase levels should be checked in all women who develop a rash while receiving nevirapine. Patients who develop suggestive clinical symptoms accompanied by elevation in serum transaminase levels (ALT and/or AST) or who have asymptomatic but severe transaminase elevations (i.e., >5 times the upper limit of normal) should stop nevirapine and not receive nevirapine therapy in the future.

Hepatic toxicity has not been seen in women receiving single-dose nevirapine during labor for prevention of perinatal transmission of HIV *[30]*. Women who enter pregnancy on nevirapine-containing regimens and are tolerating them well may continue therapy, regardless of CD4 count.

NRTI Drugs and Mitochondrial Toxicity

NRTI drugs are known to induce mitochondrial dysfunction because the drugs have varying affinity for mitochondrial gamma DNA polymerase. This affinity can interfere with mitochondrial replication, resulting in mitochondrial DNA depletion and dysfunction *[31]*. The relative potency of the NRTI drugs in inhibiting mitochondrial gamma DNA polymerase *in vitro* is highest for zalcitabine, followed by didanosine, stavudine, zidovudine, lamivudine, abacavir, and tenofovir *[32]*. In a recent study, didanosine and didanosine-containing regimens were associated with the greatest degree of mitochondrial suppression *[33]*. Toxicity related to mitochondrial dysfunction has been reported to occur in infected patients receiving long-term treatment with NRTI drugs and generally has resolved with discontinuation of the drug or drugs; a possible genetic susceptibility to these toxicities has been suggested *[31]*. These toxicities may be of particular concern for pregnant women and infants with *in utero* exposure to NRTI drugs.

During Pregnancy

Clinical disorders linked to mitochondrial toxicity include neuropathy, myopathy, cardiomyopathy, pancreatitis, hepatic steatosis, and lactic acidosis. Among these disorders, symptomatic lactic acidosis and hepatic steatosis may have a female preponderance *[34-35]*. These syndromes have similarities to rare but life-threatening syndromes that occur during pregnancy, most often during the third trimester: acute fatty liver and the syndrome of hemolysis, elevated liver enzymes, and low platelets (the HELLP syndrome). Data suggest that a disorder of mitochondrial fatty acid oxidation in the mother or her fetus during late pregnancy may play a role in the development of acute fatty liver of pregnancy and HELLP syndrome *[36-39]* and possibly contribute to susceptibility to antiretroviral-associated mitochondrial toxicity. HELLP may also occur postpartum among women with severe pre-eclampsia *[40]*. In addition to low platelets and elevated liver enzymes, other laboratory findings reported among HIV-infected pregnant women on antiretroviral therapy include mitochondrial placental depletion but without evidence of ultrastructual damage to placental cells. The clinical significance of reduced mitochondrial DNA in placentas exposed to antiretroviral drugs remains unknown *[41]*.

Lactic acidosis with microvacuolar hepatic steatosis is a toxicity related to NRTI drugs that is thought to be related to mitochondrial toxicity; it has been reported to occur in infected persons treated with NRTI drugs for long periods (>6 months). In a report from the FDA Spontaneous Adverse Event Program, typical initial symptoms included 1 to 6 weeks of nausea, vomiting, abdominal pain, dyspnea, and weakness *[42]*. Metabolic acidosis with elevated serum lactate and elevated hepatic enzymes was common. Patients described in that report were predominantly female and overweight.

The incidence of this syndrome may be increasing, possibly as a result of increased use of combination NRTI therapy or increased recognition of the syndrome.

The frequency of this syndrome in pregnant HIV-infected women receiving NRTI drugs is unknown. In 1999, Italian researchers reported a case of severe lactic acidosis in an infected pregnant woman who was receiving stavudine-lamivudine at the time of conception and throughout pregnancy and who experienced symptoms and fetal death at 38 weeks gestation *[43]*. Bristol-Myers Squibb has reported three maternal deaths due to lactic acidosis, two with and one without accompanying pancreatitis, among women who were either pregnant or postpartum and whose antepartum therapy during pregnancy included stavudine and didanosine in combination with other antiretroviral agents (either a protease inhibitor or nevirapine) *[44-45]*. All women were receiving treatment with these agents at the time of conception and continued for the duration of pregnancy; all presented late in gestation with symptomatic disease that progressed to death in the immediate postpartum period. Two cases were also associated with fetal death. Nonfatal cases of lactic acidosis in pregnant women receiving combination stavudine-didanosine also have been reported *[46]*.

It is unclear if pregnancy augments the incidence of the lactic acidosis/hepatic steatosis syndrome that has been reported for nonpregnant persons receiving NRTI drugs. However, because pregnancy itself can mimic some of the early symptoms of the lactic acidosis/hepatic steatosis syndrome or be associated with other disorders of liver metabolism, these cases emphasize the need for physicians caring for HIV-infected pregnant women receiving NRTI drugs to be alert for early signs of this syndrome.

Additionally, because of the reports of several cases of maternal mortality secondary to lactic acidosis with prolonged use of the combination of stavudine and didanosine by HIV-infected pregnant women, clinicians should not prescribe this antiretroviral combination during pregnancy. The combination stavudine-didanosine is also not recommended for nonpregnant adults.

In Utero Exposure

It has been suggested that mitochondrial dysfunction might develop in infants with *in utero* exposure to NRTI drugs. Data from a French cohort of 1,754 uninfected infants born to HIV-infected women who received antiretroviral drugs during pregnancy identified 8 infants with *in utero* or neonatal exposure to either zidovudine/lamivudine (4 infants) or zidovudine alone (4 infants) who developed indications of mitochondrial dysfunction after the first few months of life *[47]*. Two of these infants (both exposed to zidovudine/lamivudine) contracted severe neurologic disease and died; 3 had mild to moderate symptoms; and 3 had no symptoms but had transient laboratory abnormalities. In a larger cohort of 4,392 uninfected children (including the children in the previous study) followed within the French Pediatric Cohort or identified within a French National Register, the 18-month incidence of clinical symptoms of mitochondrial dysfunction was 0.26% and 0.07% for mortality *[48]*. All children had perinatal antiretroviral exposure; risk was higher among infants exposed to combination antiretroviral drugs (primarily zidovudine/lamivudine) than to zidovudine alone. The children presented with neurologic symptoms, often with abnormal magnetic resonance imaging and/or episode of significant hyperlactatemia, and deficits in mitochondrial respiratory chain complex enzyme function on biopsy of muscle. The same group also has reported an increased risk of simple febrile seizures in the first 18 months of life and persistently lower (but clinically insignificant) neutrophil, lymphocyte, and platelet counts in infants with *in utero* NRTI exposure *[49-50]*. More recently, in continued follow-up of the French Perinatal Cohort, researchers reported severe neurologic symptoms in the first 2 years of life as a rare event (0.30.5%) *[51]*.

Clinical studies in the United States and Europe generally have not duplicated the French reports *[52-58]*. The Perinatal Safety Review Working Group performed a retrospective review of deaths occurring

among children born to HIV-infected women and followed during 1986–1999 in 5 large prospective U.S. perinatal cohorts. No deaths similar to those reported from France or with clinical findings attributable to mitochondrial dysfunction were identified in a database of >16,000 uninfected children born to HIV-infected women with and without antiretroviral drug exposure *[53]*. However, most of the infants with antiretroviral exposure had been exposed to zidovudine alone and only a relatively small proportion (approximately 6%) had been exposed to zidovudine/lamivudine. The European Collaborative Study reviewed clinical symptoms in 2,414 uninfected children in their cohort with median follow-up of 2.2 years (maximum, 16 years); 1,008 had perinatal antiretroviral exposure *[55]*. No association of clinical manifestations suggestive of mitochondrial abnormalities was found with perinatal antiretroviral exposure. Of the 4 children with seizures in this cohort, none had perinatal antiretroviral exposure. In a report from a long-term follow-up study in the United States (PACTG 219/219C), 20 children with possible symptoms of mitochondrial dysfunction were identified in a cohort of 1,037 uninfected infants born to HIV-infected mothers *[57]*. Definitive diagnosis was not available because none of the children had biopsies for mitochondrial function. Three of the 20 children had no exposure to antiretroviral drugs. In the 17 remaining children, although overall exposure to NRTI drugs was not associated with symptoms, there was an association of symptoms with first exposure to zidovudine/lamivudine limited to the third trimester.

Laboratory abnormalities without clinical symptoms have been reported among infants with perinatal antiretroviral exposure compared to unexposed infants in a number of studies, most of which are limited by small numbers of subjects. In 1 study, mitochondrial DNA quantity was lower in cord and peripheral blood white cells at age 1 and 2 years among 20 infants born to HIV-infected women compared to 30 infants born to uninfected women and was lowest among 10 HIV-exposed infants with zidovudine exposure compared to 10 without zidovudine exposure *[59]*. In a subsequent study, mitochondrial changes were evaluated in umbilical cord endothelial cells and cord blood from human infants and monkeys with *in utero* exposure to various NRTI-containing regimens *[60]*. Similar morphologic changes and mitochondrial DNA depletion were seen in the human and monkey infants. In the monkeys, mitochondrial damage demonstrated a gradient with greatest damage with stavudine/lamivudine > zidovudine/didanosine > zidovudine/lamivudine > lamivudine. In a Canadian study of 73 antiretroviral-exposed infants and 81 controls with blood samples during the first 8 months of life, investigators found that in the first weeks of life, blood mitochondrial DNA levels were higher and blood mitochondrial RNA levels were lower in the HIV- and antiretroviral-exposed infants compared to infants without HIV and antiretroviral exposure *[61]*. In another study, transient hyperlactatemia during the first few weeks of life was reported among 17 HIV-exposed infants with perinatal antiretroviral exposure; lactate levels returned to normal in all children and none developed symptoms of mitochondrial dysfunction during follow-up *[62]*. Similarly, the French Perinatal cohort study has reported asymptomatic hyperlactatemia in one-third of zidovudine-exposed newborns, which resolved following perinatal drug exposure *[51]*. Clinically asymptomatic hematologic findings have been reported by several investigators among uninfected infants with *in utero* exposure to antiretroviral therapy in the United States and Europe *[63-65]*, and infants with triple combination antiretroviral therapy exposure were found to be at increased risk of lowered hemoglobin compared to those with perinatal exposure to zidovudine or zidovudine/lamivudine *[66]*. The clinical significance of these laboratory findings is unclear, and further long-term studies are needed to validate the findings and assess the degree to which they affect growth and development of infants exposed to antiretroviral therapy.

Thus, there are conflicting data regarding whether mitochondrial dysfunction is associated with perinatal antiretroviral exposure, and further studies are needed. Even if an association is more clearly demonstrated, the development of severe or fatal mitochondrial disease appears to be extremely rare and should be compared to the clear benefit of antiretroviral prophylaxis in reducing transmission of a fatal infection by 70% or more *[55, 67-68]*. Mitochondrial dysfunction should be considered in uninfected children with perinatal antiretroviral exposure who present with severe clinical findings of unknown etiology, particularly neurologic findings. These results emphasize the importance of the

existing HHS recommendation for long-term follow-up for any child with *in utero* exposure to antiretroviral drugs.

Protease Inhibitor Therapy and Hyperglycemia

Hyperglycemia, new-onset diabetes mellitus, exacerbation of existing diabetes mellitus, and diabetic ketoacidosis have been reported with receipt of protease inhibitor antiretroviral drugs by HIV-infected patients *[69-72]*. In addition, pregnancy is itself a risk factor for hyperglycemia. However, the majority of data to date have not shown an increased risk of glucose intolerance with protease inhibitor therapy during pregnancy. One small retrospective study that included 41 women receiving protease inhibitor-based combination antiretroviral therapy found an increased risk of glucose intolerance, but not gestational diabetes, among women on combination antiretroviral therapy compared to zidovudine alone *[73]*, while two other retrospective studies did not find an increased risk of glucose intolerance with protease inhibitors *[74-75]*. Secondary analyses of two large cohorts did not find an association with type of antiretroviral therapy and gestational diabetes, except for an association of protease inhibitor initiation before pregnancy or during the first trimester and gestational diabetes in the PACTG 316 cohort *[10, 76]*. Finally, a prospective study including detailed evaluations for glucose intolerance and insulin resistance among HIV-infected pregnant women did not find differences between women on protease inhibitor-containing and non-protease inhibitor-containing regimens *[77]*. The rate of impaired glucose tolerance was high (38%) in both groups, likely related to high body mass index and race/ethnicity among trial subjects.

HIV-infected women receiving antiretroviral therapy during pregnancy should receive standard glucose screening with a standard, 1-hour, 50-gram glucose loading test at 24 to 28 weeks of gestation. Some experts would perform earlier glucose screening in women with ongoing protease inhibitor-based therapy initiated prior to pregnancy (particularly in women of minority race/ethnicity), similar to recommendations for women with high-risk factors for glucose intolerance, such as maternal obesity, advanced maternal age, and family history of type II diabetes mellitus.

References

1. Minkoff H, Augenbraun M. Antiretroviral therapy for pregnant women. *Am J Obstet Gynecol.* 1997;176(2):478-489.
2. Mirochnick M, Capparelli E. Pharmacokinetics of antiretrovirals in pregnant women. *Clin Pharmacokinet.* 2004;43(15):1071-1087.
3. Roustit M, Jlaiel M, Leclercq P, et al. Pharmacokinetics and therapeutic drug monitoring of antiretrovirals in pregnant women. *Br J Clin Pharmacol.* 2008;66(2):179-195.
4. Mills JL. Protecting the embryo from X-rated drugs. *N Engl J Med.* 1995;333(2):124-125.
5. Bristol-Myers Squibb. Sustiva drug label, 9/23/2009. http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020972s033,021360s021lbl.pdf.
6. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral pregnancy registry international interim report for 1 Jan 1989 – 31 July 2009. Wilmington, NC: Registry coordinating center; 2009.
7. European Collaborative Study, Swiss Mother and Child HIV Cohort Study. Combination antiretroviral therapy and duration of pregnancy. *AIDS.* 2000;14(18):2913-2920.
8. Thorne C, Patel D, Newell ML. Increased risk of adverse pregnancy outcomes in HIV-infected women treated with highly active antiretroviral therapy in Europe. *AIDS.* 2004;18(17):2337-2339.
9. Tuomala RE, Shapiro DE, Mofenson LM, et al. Antiretroviral therapy during pregnancy and the risk of an adverse outcome. *N Engl J Med.* 2002;346(24):1863-1870.
10. Tuomala RE, Watts DH, Li D, et al. Improved obstetric outcomes and few maternal toxicities are associated with antiretroviral therapy, including highly active antiretroviral therapy during pregnancy. *J Acquir Immune Defic Syndr.* 2005;38(4):449-473.
11. Szyld EG, Warley EM, Freimanis L, et al. Maternal antiretroviral drugs during pregnancy and infant low birth weight and preterm birth. *AIDS.* 2006;20(18):2345-2353.

12. Cotter AM, Garcia AG, Duthely ML, et al. Is antiretroviral therapy during pregnancy associated with an increased risk of preterm delivery, low birth weight, or stillbirth? *J Infect Dis.* 2006;193(9):1195-1201.
13. Kourtis AP, Schmid CH, Jamieson DJ, et al. Use of antiretroviral therapy in pregnant HIV-infected women and the risk of premature delivery: a meta-analysis. *AIDS.* 2007;21(5):607-615.
14. Townsend CL, Cortina-Borja M, Peckham CS, et al. Antiretroviral therapy and premature delivery in diagnosed HIV-infected women in the United Kingdom and Ireland. *AIDS.* 2007;21(8):1019-1026.
15. Schulte J, Dominguez K, Sukalac T, et al. Declines in low birth weight and preterm birth among infants who were born to HIV-infected women during an era of increased use of maternal antiretroviral drugs: Pediatric Spectrum of HIV Disease, 1989-2004. *Pediatrics.* 2007;119(4):e900-906.
16. Ravizza M, Martinelli P, Bucceri A, et al. Treatment with protease inhibitors and coinfection with hepatitis C virus are independent predictors of preterm delivery in HIV-infected pregnant women. *J Infect Dis.* 2007;195(6):913-914; author reply 916-917.
17. Grosch-Woerner I, Puch K, Maier RF, et al. Increased rate of prematurity associated with antenatal antiretroviral therapy in a German/Austrian cohort of HIV-1-infected women. *HIV Med.* 2008;9(1):6-13.
18. Machado ES, Hofer CB, Costa TT, et al. Pregnancy outcome in women infected with HIV-1 receiving combination antiretroviral therapy before versus after conception. *Sex Transm Infect.* 2009;85(2):82-87.
19. Patel K, Shapiro DE, Brogly SB, et al. Prenatal protease inhibitor use and risk of preterm birth among HIV-infected women initiating antiretroviral drugs during pregnancy. *J Infect Dis.* 2010;201(7):1035-1044.
20. Kontorinis N, Dieterich DT. Toxicity of non-nucleoside analogue reverse transcriptase inhibitors. *Semin Liver Dis.* 2003;23(2):173-182.
21. Bersoff-Matcha SJ, Miller WC, Aberg JA, et al. Sex differences in nevirapine rash. *Clin Infect Dis.* 2001;32(1):124-129.
22. Mazhude C, Jones S, Murad S, et al. Female sex but not ethnicity is a strong predictor of non-nucleoside reverse transcriptase inhibitor-induced rash. *AIDS.* 2002;16(11):1566-1568.
23. Baylor MS, Johann-Liang R. Hepatotoxicity associated with nevirapine use. *J Acquir Immune Defic Syndr.* 2004;35(5):538-539.
24. Stern JO, Robinson PA, Love J, et al. A comprehensive hepatic safety analysis of nevirapine in different populations of HIV infected patients. *J Acquir Immune Defic Syndr.* 2003;34 Suppl 1:S21-33.
25. Boehringer-Ingelheim Pharmaceuticals Inc. Viramune drug label. Revised June 24, 2008.
26. Lyons F, Hopkins S, Kelleher B, et al. Maternal hepatotoxicity with nevirapine as part of combination antiretroviral therapy in pregnancy. *HIV Med.* 2006;7(4):255-260.
27. Hitti J, Frenkel LM, Stek AM, et al. Maternal toxicity with continuous nevirapine in pregnancy: results from PACTG 1022. *J Acquir Immune Defic Syndr.* 2004;36(3):772-776.
28. Ouyang DW, Shapiro DE, Lu M, et al. Increased risk of hepatotoxicity in HIV-infected pregnant women receiving antiretroviral therapy independent of nevirapine exposure. *AIDS.* 2009;23(18):2425-2430.
29. Ouyang DW, Brogly SB, Lu M, et al. Lack of increased hepatotoxicity in HIV-infected pregnant women receiving nevirapine compared with other antiretrovirals. *AIDS.* 2010;24(1):109-114.
30. McKoy JM, Bennett CL, Scheetz MH, et al. Hepatotoxicity associated with long- versus short-course HIV-prophylactic nevirapine use: a systematic review and meta-analysis from the Research on Adverse Drug events And Reports (RADAR) project. *Drug Saf.* 2009;32(2):147-158.
31. Brinkman K, Ter Hofstede HJM, Burger DM, et al. Adverse effects of reverse transcriptase inhibitors: mitochondrial toxicity as common pathway. *AIDS.* 1998;12(14):1735-1744.
32. Birkus G, Hitchcock MJ, Cihlar T. Assessment of mitochondrial toxicity in human cells treated with tenofovir: comparison with other nucleoside reverse transcriptase inhibitors. *Antimicrob Agents Chemother.* 2002;46(3):716-723.
33. Saitoh A, Haas RH, Naviaux RK, et al. Impact of nucleoside reverse transcriptase inhibitors on mitochondrial DNA and RNA in human skeletal muscle cells. *Antimicrob Agents Chemother.* 2008;52(8):2825-2830.
34. Currier JS. Sex differences in antiretroviral therapy toxicity: lactic acidosis, stavudine, and women. *Clin Infect Dis.* 2007;45(2):261-262.
35. Bolhaar MG, Karstaedt AS. A high incidence of lactic acidosis and symptomatic hyperlactatemia in women receiving highly active antiretroviral therapy in Soweto, South Africa. *Clin Infect Dis.* 2007;45(2):254-260.
36. Ibdah JA, Bennett MJ, Rinaldo P, et al. A fetal fatty-acid oxidation disorder as a cause of liver disease in pregnant women. *N Engl J Med.* 1999;340(22):1723-1731.

37. Strauss AW, Bennett MJ, Rinaldo P, et al. Inherited long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency and a fetal-maternal interaction cause maternal liver disease and other pregnancy complications. *Semin Perinatol.* 1999;23(2):100-112.
38. Sims HF, Brackett JC, Powell CK, et al. The molecular basis of pediatric long-chain 3-hydroxyacyl Co-A dehydrogenase deficiency associated with maternal acute fatty liver of pregnancy. *Proc Natl Acad Sci USA.* 1995;92(3):841-845.
39. Ibdah JA, Yang Z, Bennett MJ. Liver disease in pregnancy and fetal fatty acid oxidation defects. *Mol Genet Metab.* 2000;71(1-2):182-189.
40. Gasem T, Al Jama FE, Burshaid S, et al. Maternal and fetal outcome of pregnancy complicated by HELLP syndrome. *J Matern Fetal Neonatal Med.* 2009;22(12):1140-1143.
41. Gingelmaier A, Grubert TA, Kost BP, et al. Mitochondrial toxicity in HIV type-1-exposed pregnancies in the era of highly active antiretroviral therapy. *Antivir Ther.* 2009;14(3):331-338.
42. Fleischer R, Boxwell D, Sherman KE. Nucleoside analogues and mitochondrial toxicity. *Clin Infect Dis.* 2004;38(8):e79-80.
43. Luzzati, R. Del Bravo, P. Di Perri, G. Luzzani, A. Concia, E. Riboflavine and severe lactic acidosis. *Lancet.* 1999;353(9156):901-902.
44. Bristol-Myers Squibb Company. Healthcare Provider Important Drug Warning Letter. January 5, 2001.
45. Sarner L, Fakoya A. Acute onset lactic acidosis and pancreatitis in the third trimester of pregnancy in HIV-1 positive women taking antiretroviral medication. *Sex Transm Infect.* 2002;78(1):58-59.
46. Mandelbrot L, Kermarrec N, Marcollet A, et al. Case report: nucleoside analogue-induced lactic acidosis in the third trimester of pregnancy. *AIDS.* 2003;17(2):272-273.
47. Blanche S, Tardieu M, Rustin P, et al. Persistent mitochondrial dysfunction and perinatal exposure to antiretroviral nucleoside analogues. *Lancet.* 1999;354(9184):1084-1089.
48. Barret B, Tardieu M, Rustin P, et al. Persistent mitochondrial dysfunction in HIV-1-exposed but uninfected infants: clinical screening in a large prospective cohort. *AIDS.* 2003;17(12):1769-1785.
49. Landreau-Mascaro A, Barret B, Mayaux MJ, et al. Risk of early febrile seizure with perinatal exposure to nucleoside analogues. *Lancet.* 2002;359(9306):583-584.
50. Le Chenadec J, Mayaux MJ, Guihenneuc-Jouyaux C, et al. Perinatal antiretroviral treatment and hematopoiesis in HIV-uninfected infants. *AIDS.* 2003;17(14):2053-2061.
51. Benhammou V, Tardieu M, Warszawski J, et al. Clinical mitochondrial dysfunction in uninfected children born to HIV-infected mothers following perinatal exposure to nucleoside analogues. *Environ Mol Mutagen.* 2007;48(3-4):173-178.
52. Sperling RS, Shapiro DE, McSherry GD, et al. Safety of the maternal-infant zidovudine regimen utilized in the Pediatric AIDS Clinical Trials Group 076 Study. *AIDS.* 1998;12(14):1805-1813.
53. The Perinatal Safety Review Working Group. Nucleoside exposure in the children of HIV-infected women receiving antiretroviral drugs: absence of clear evidence for mitochondrial disease in children who died before 5 years of age in five United States cohorts. *J Acquir Immune Defic Syndr.* 2000;25(3):261-268.
54. Lipshultz SE, Easley KA, Orav EJ, et al. Absence of cardiac toxicity of zidovudine in infants. *N Engl J Med.* 2000;343(11):759-766.
55. European Collaborative Study. Exposure to antiretroviral therapy in utero or early life: the health of uninfected children born to HIV-infected women. *J Acquir Immune Defic Syndr.* 2003;32(4):380-387.
56. Alimenti A, Forbes JC, Oberlander TF, et al. A prospective controlled study of neurodevelopment in HIV-uninfected children exposed to combination antiretroviral drugs in pregnancy. *Pediatrics.* 2006;118(4):e1139-1145.
57. Brogly SB, Ylitalo N, Mofenson LM, et al. In utero nucleoside reverse transcriptase inhibitor exposure and signs of possible mitochondrial dysfunction in HIV-uninfected children. *AIDS.* 2007;21(8):929-938.
58. Hankin C, Lyall H, Peckham C, et al. Monitoring death and cancer in children born to HIV-infected women in England and Wales: use of HIV surveillance and national routine data. *AIDS.* 2007;21(7):867-869.
59. Poirier MC, Divi RL, Al-Harthi L, et al. Long-term mitochondrial toxicity in HIV-uninfected infants born to HIV-infected mothers. *J Acquir Immune Defic Syndr.* 2003;33(2):175-183.
60. Divi RL, Leonard SL, Kuo MM, et al. Transplacentally exposed human and monkey newborn infants show similar evidence of nucleoside reverse transcriptase inhibitor-induced mitochondrial toxicity. *Environ Mol Mutagen.* 2007;48(3-4):201-209.
61. Cote HC, Raboud J, Bitnun A, et al. Perinatal exposure to antiretroviral therapy is associated with increased blood mitochondrial DNA levels and decreased mitochondrial gene expression in infants. *J Infect Dis.* 2008;198(6):851-859.

62. Giaquinto C, De Romeo A, Giacomet V, et al. Lactic acid levels in children perinatally treated with antiretroviral agents to prevent HIV transmission. *AIDS.* 2001;15(8):1074-1075.
63. Pacheco SE, McIntosh K, Lu M, et al. Effect of perinatal antiretroviral drug exposure on hematologic values in HIV-uninfected children: An analysis of the women and infants transmission study. *J Infect Dis.* 2006;194(8):1089-1097.
64. European Collaborative Study. Levels and patterns of neutrophil cell counts over the first 8 years of life in children of HIV-1-infected mothers. *AIDS.* 2004;18(15):2009-2017.
65. Bunders M, Thorne C, Newell ML, et al. Maternal and infant factors and lymphocyte, CD4 and CD8 cell counts in uninfected children of HIV-1-infected mothers. *AIDS.* 2005;19(10):1071-1079.
66. Feiterna-Sperling C, Weizsaecker K, Buhrer C, et al. Hematologic effects of maternal antiretroviral therapy and transmission prophylaxis in HIV-1-exposed uninfected newborn infants. *J Acquir Immune Defic Syndr.* 2007;45(1):43-51.
67. Morris AA, Carr A. HIV nucleoside analogues: new adverse effects on mitochondria? *Lancet.* 1999;354(9184):1046-1047.
68. Cooper ER, Charurat M, Mofenson LM, et al. Combination antiretroviral strategies for the treatment of pregnant HIV-1 infected women and prevention of perinatal HIV-1 transmission. *J Acquir Immune Defic Syndr Hum Retrovirol.* 2002;29(5):484-494.
69. Food and Drug Administration. FDA Public Health Advisory: reports of diabetes and hyperglycemia in patients receiving protease inhibitors for treatment of human immunodeficiency virus (HIV). Food and Drug Administration, Public Health Service, Department of Health and Human Services. Rockville, MD: June 11, 1997.
70. Visnegarwala F, Krause KL, Musher DM. Severe diabetes associated with protease inhibitor therapy. *Ann Intern Med.* 1997;127(10):947.
71. Eastone JA, Decker CF. New-onset diabetes mellitus associated with use of protease inhibitor [letter]. *Ann Intern Med.* 1997;127(10):948.
72. Dube MP, Sattler FR. Metabolic complications of antiretroviral therapies. *AIDS Clin Care.* 1998;10(6):41-44.
73. Chmait R, Franklin P, Spector SA, et al. Protease inhibitors and decreased birth weight in HIV-infected pregnant women with impaired glucose tolerance. *J Perinatol.* 2002;22(5):370-373.
74. Dinsmoor MJ, Forrest ST. Lack of an effect of protease inhibitor use on glucose tolerance during pregnancy. *Infect Dis Obstet Gynecol.* 2002;10(4):187-191.
75. Tang JH, Sheffield JS, Grimes J, et al. Effect of protease inhibitor therapy on glucose intolerance in pregnancy. *Obstet Gynecol.* 2006;107(5):1115-1119.
76. Watts DH, Balasubramanian R, Maupin RT, Jr., et al. Maternal toxicity and pregnancy complications in human immunodeficiency virus-infected women receiving antiretroviral therapy: PACTG 316. *Am J Obstet Gynecol.* 2004;190(2):506-516.
77. Hitti J, Andersen J, McComsey G, et al. Protease inhibitor-based antiretroviral therapy and glucose tolerance in pregnancy: AIDS Clinical Trials Group A5084. *Am J Obstet Gynecol.* 2007;196(4):331.e331-337.

ANTIRETROVIRAL DRUG RESISTANCE AND RESISTANCE TESTING IN PREGNANCY

Indications for Antiretroviral Drug Resistance Testing in HIV-Infected Pregnant Women

Panel's Recommendations:

- ***HIV drug resistance testing is recommended for:***
  - ***All pregnant women not currently receiving antiretroviral drugs, before starting treatment or prophylaxis (AIII).***
  - ***All pregnant women receiving antenatal antiretroviral therapy who have persistently detectable HIV RNA levels (AI) or who have suboptimal viral suppression after initiation of antiretroviral therapy (AII).***
- ***For optimal prevention of perinatal transmission, empiric initiation of antiretroviral therapy before results of resistance testing are available may be warranted, with adjustment as needed after the test results are available (BIII).***

Resistance testing is recommended for all antiretroviral-naïve pregnant women before initiating treatment or prophylaxis if prior resistance testing has not been done. For details regarding genotypic and phenotypic resistance testing see ***Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents***. Ideally, resistance testing would be done at a preconception visit to allow receipt of results and selection of an antiretroviral drug regimen to be used during pregnancy or started before pregnancy if maternal therapy is indicated. There is accumulating evidence that:

- transmitted resistant mutants may persist for indefinite periods after initial infection;
- these viral variants may be detectable by standard assays used in clinical practice;
- the prevalence of resistance in antiretroviral-naïve patients is increasing; and
- previous resistance may be associated with adverse virologic outcomes *[1-8]*.

For these reasons, resistance testing is now recommended for all pregnant women prior to initiating antiretroviral drugs for treatment or prophylaxis of mother-to-child transmission of HIV *[9-10]*.

Resistance testing should also be performed before initiation of therapy or prophylaxis in pregnant women who received prophylaxis in previous pregnancies and are now restarting antiretroviral drugs for prevention of perinatal transmission. There are no data currently addressing the utility of resistance testing in the setting of pregnancy, when short-term prophylactic therapy is often initiated in women who do not yet need treatment for their own disease, and women who have multiple pregnancies may undergo several periods of antiretroviral prophylaxis to prevent mother-to-child transmission. The identification of baseline resistance mutations may allow selection of more effective and more durable antiretroviral regimens in women needing treatment and greater preservation of future treatment options in women receiving antiretroviral therapy only for perinatal prophylaxis. However, there is no evidence that baseline resistance testing in pregnancy is associated with a reduction in perinatal transmission rates.

For pregnant women already receiving antiretroviral therapy at the time they present for obstetrical care or are seen for follow-up after initiation of therapy, resistance testing is indicated if there is suboptimal initial viral suppression following initiation of antiretroviral therapy or virologic failure on the current regimen as signified by persistently detectable HIV RNA levels.

In most settings, the results of resistance testing guide selection of the initial antiretroviral regimen. However, in some clinical situations, the clinician may choose to initiate empiric antiretroviral therapy or prophylaxis before resistance testing results are available in order to maximize prevention of perinatal transmission. Once resistance test results are obtained, the antiretroviral drug regimen may be modified as needed. Such situations

include when women have initial resistance testing in the third trimester and test results may not be back in time to allow effective reduction of viral load before delivery. If results of resistance testing performed in the latter half of a woman's pregnancy cannot be obtained within 7 days, most experts believe that the benefits of immediate initiation of antiretroviral drugs—taking into account a woman's previous antiretroviral history—outweigh the possible risk of initiating a regimen that could be suboptimal due to pre-existing resistance.

Significance of Antiretroviral Drug Resistance in Pregnancy

The development of antiretroviral drug resistance is one of the major factors leading to therapy failure in HIV-infected persons. Resistant viral variants emerge under selective pressure, especially with incompletely suppressive regimens, because of the mutation-prone process of reverse transcription in viral replication. Although specific resistance mutations may become undetectable when selective drug pressure is removed, resistant viral variants are believed to be archived permanently in latent HIV reservoirs and can re-emerge with re-exposure to drugs to which decreased susceptibility had been established *[11]*. The administration of combination antiretroviral regimens with maximal suppression of viral replication to undetectable levels limits the development of antiretroviral resistance in both pregnant and nonpregnant persons.

In addition to the concerns about development of drug resistance in the general population, pregnancy presents some special concerns related to the development of drug resistance. Pre-existing resistance to a drug in an antiretroviral prophylaxis regimen may diminish efficacy of that regimen in preventing perinatal transmission. Development of resistance to drugs used during pregnancy for prophylaxis of perinatal transmission may limit future maternal treatment options or decrease the effectiveness of prophylactic regimens in the current pregnancy or future pregnancies. Additionally, if maternal resistance is present or develops and resistant virus is transmitted, infant treatment options may be limited.

Several factors unique to pregnancy may increase the chance of development of resistance. Antiretroviral drugs may be used during pregnancy solely for prophylaxis of perinatal transmission and discontinued after delivery in women who do not require therapy for their own health. If regimens used for prophylaxis include drugs with significant differences in half-life, such as nevirapine or efavirenz combined with two nucleoside analogue drugs, discontinuation of all regimen components simultaneously postpartum may result in persistent subtherapeutic drug levels and increase the risk of development of NNRTI resistance (see **Stopping Antiretroviral Therapy during Pregnancy**). Problems such as nausea and vomiting in early pregnancy may compromise adherence and increase the risk of resistance in women receiving antiretroviral treatment.

Prevalence of Antiretroviral Drug Resistance

General Population

The reported prevalence of antiretroviral drug resistance varies depending on several factors, including characteristics of the population studied (e.g., newly infected versus chronically infected), prior and current exposure to antiretroviral drugs and type of regimen (HAART versus non-HAART), geographic area, and type of resistance assay used (genotypic versus phenotypic). In genotypic resistance surveys of newly infected, therapy-naïve persons conducted in the United States and Europe, rates of primary resistance mutations appear to be increasing over time and have been reported as high as 23% *[5, 12-13]*. The presence of high-level phenotypic resistance (>10-fold increase in 50% inhibitory concentration [IC50]) increased from 3.4% in 1995–1998 to 12.4% in 1999–2000 in a retrospective analysis from 10 U.S. cities and was associated with longer time to viral suppression and shorter time to virologic failure *[12]*.

Other studies have examined antiretroviral drug resistance in treatment-naïve persons with newly diagnosed HIV infection of unknown duration. In this population more typical of patients presenting for initial evaluation and care, 8.3% to 10.8% of patients had HIV with genotypic mutations associated with reduced antiretroviral

susceptibility, with prevalence increasing over time *[4-5]*. The highest rates of antiretroviral drug resistance have been reported in antiretroviral treatment-experienced individuals, with resistance rates as high as 88% reported in viremic individuals currently receiving therapy and 30% in individuals with a past history of treatment *[14]*.

Pregnancy

Data about the prevalence of antiretroviral drug resistance in pregnant women are limited. The available data suggest that rates of resistance are similar in pregnant women and in nonpregnant individuals, with antiretroviral drug resistance more frequent among antiretroviral-experienced women. A study from a university hospital in St. Louis found that 3 (17%) of 18 antiretroviral-naïve pregnant women followed at the hospital had primary genotypic resistance to NNRTI drugs, which was equal to the overall prevalence of such resistance in the antiretroviral-naïve population in the same city *[15]*. In a retrospective review of 45 consecutive HIV-infected pregnant women with amplifiable virus presenting for care in New York, 0 of 22 antiretroviral-naïve pregnant women and 11 (48%) of 23 antiretroviral-experienced women had major drug resistance mutations *[16]*. Among 220 pregnant antiretroviral-experienced women in the Perinatal AIDS Collaborative Transmission Study (PACTS), all of whom had prior zidovudine exposure in pregnancy from 1991 to 1997, 17.3% had zidovudine-associated mutations *[17]*. In a substudy of the Pediatric AIDS Clinical Trials Group (PACTG) Protocol 316, an international, multi-center clinical trial comparing single-dose nevirapine with placebo in HIV-infected pregnant women receiving standard antiretroviral therapy, 7 (3.2%) of 217 women with detectable HIV RNA had mutations associated with nevirapine resistance at 6 weeks postpartum, despite no history of prior exposure to non-nucleoside drugs or receipt of nevirapine at delivery *[18]*. Additionally, more than 60% of women receiving combination therapy (either dual nucleosides or combinations containing a PI) had the M184V mutation conferring resistance to lamivudine, and 25 (11%) of 217 women had primary or secondary protease mutations.

Despite the increasing prevalence of drug resistance in treatment-naïve and -experienced individuals, there is currently no evidence to indicate on a population basis that antiretroviral drug resistance in HIV-infected pregnant women is compromising the efficacy of perinatal HIV prevention efforts in North America or Europe, where mother-to-child transmission rates remain less than 2% *[19-20]*.

Incidence of Antiretroviral Resistance with Perinatal Prophylactic Regimens

The presence of mutations conferring resistance to nucleoside analogue drugs appears to be correlated with more advanced maternal disease and duration of prior or current exposure to these drugs *[17, 21-23]*. Development of zidovudine drug resistance when zidovudine is used alone appears uncommon in women with higher CD4 count and low viral load *[24-25]* but is more of a concern in women who have more advanced disease and lower CD4 count *[21]*.

Nevirapine also has a low genetic barrier to resistance, with 1 point mutation conferring resistance to nevirapine and to other NNRTI drugs. Furthermore, its long half-life, with blood levels detectable up to 21 days after a single dose in labor, increases selection pressure and risk of resistance *[26]*. Factors associated with increased risk of resistance following single-dose nevirapine exposure include high baseline viral load, low baseline CD4 cell count, viral subtype, and number of maternal doses. The rate of genotypic resistance after exposure to single-dose nevirapine has varied in studies, ranging from 15% to 75% *[18, 27-36]*. Studies using more sensitive real-time polymerase chain reaction (PCR) techniques suggest that up to one-half of resistance that develops is not detected by conventional sequence analysis *[35-38]*. However, these studies demonstrate that although resistance occurs in the first few weeks post-exposure in the majority of women exposed to single-dose nevirapine, the prevalence of resistance declines rapidly over time and the proportion of resistant virus in those with detectable virus 12 months after exposure is low; additionally, archiving of resistance in cellular provirus may be infrequent. In a study of virus from 67 South African women, using a sensitive allele-specific resistance assay, the K103N mutation was seen in 87% of women at 6 weeks but in

only 11% at 12 months after single-dose nevirapine exposure, with a median frequency of the mutation of 0.7% (range 0.5%–5.4%) in women with detectable resistance at 12 months. The K103N mutation was found in cellular DNA in only 4.2% of women at 12 months post-exposure *[38]*. A recent study has examined the presence of resistant mutations in HIV-1-infected women receiving antiretrovirals limited to pregnancy. All women evaluated received zidovudine and lamivudine with 76% receiving nelfinavir and 8% nevirapine. In women receiving dual or triple prophylaxis, postpartum rates of the M184V/I mutations were 65% and 29%, respectively. NNRTI resistance was identified postpartum among 38% of nevirapine recipients, whereas only 1% of PI recipients developed resistance *[39]*.

Addition of single-dose nevirapine to other background regimens (77% of women received antenatal combination antiretroviral therapy) still resulted in nevirapine resistance in 14 of 95 (15%; 95% CI, 8%–23%) women in the PACTG 316 study *[18]*. Because PACTG 316 demonstrated that the addition of single-dose nevirapine in situations where combination antiretroviral therapy is being received did not provide any additional efficacy in prevention of mother-to-child transmision, and because there is a risk of nevirapine resistance, this approach is not recommended.

Impact of Resistance in Pregnancy

Perinatal Transmission

Although perinatal transmission of resistant virus has been reported, it appears to be unusual, and there is little evidence that the presence of resistant mutations increases the risk of transmission when current recommendations for antiretroviral management in pregnancy are followed. A substudy of the Women and Infants Transmission Study followed pregnant women receiving zidovudine alone for treatment of HIV disease in the early 1990s. In this study, detection of zidovudine resistance conferred an increased risk of transmission when analysis was adjusted for duration of membrane rupture and total lymphocyte count *[21]*; however, women in this cohort had characteristics that would indicate treatment with combination antiretroviral therapy under the current HHS recommendations for maternal health and for prevention of perinatal transmission. When transmitting mothers had mixed viral populations of wild-type and virus with low-level zidovudine resistance, only wild-type virus was found in the infant *[40]*, and other studies have suggested that drug resistance mutations may diminish the fitness of the virus *[41]*, possibly leading to a decrease in transmissibility. The prevalence of antiretroviral drug resistance was examined among HIV-infected newborns in New York State. Eleven (12.1%) of 91 infants born in 1989–1999 and 8 (19%) of 42 infants born in 2001–2002 had mutations associated with decreased drug susceptibility. However, perinatal antiretroviral exposure was not found to be a significant risk factor for the presence of resistance in either time period *[42-43]*. Neither resistance to nevirapine that develops as a result of exposure to single-dose nevirapine nor exposure to single-dose nevirapine in a prior pregnancy has been shown to affect perinatal transmission rates *[44-45]*.

Maternal Response to Subsequent Treatment Regimens

Because nevirapine resistance mutations can be detected in the postpartum period in a significant proportion of women receiving single-dose intrapartum/infant nevirapine prophylaxis, the response to non-nucleoside-based combination therapy when later required for maternal health reasons has been a concern *[30, 38, 44-47]*. The Optimal Combination Therapy After Nevirapine Exposure (OCTANE)/A5208 trial conducted in Africa compared nevirapine versus lopinavir/ritonavir-based therapy in women requiring therapy who had prior exposure to single-dose nevirapine prophylaxis. The results suggest that prior exposure to single-dose nevirapine within 24 months of initiating therapy may be associated with higher risk of viral failure with nevirapine-based therapy compared to lopinavir/ritonavir-based therapy. In this study, significantly more women in the nevirapine arm (29, 24%) failed to achieve undetectable viral load (25) or died (4) compared to women in the lopinavir/ritonavir arm (8, 7%; 7 virologic failures and 1 death; $p < 0.0005$). Of those women with documented nevirapine resistance at the start of therapy, 38% (5 of 13) either had detectable virus or died. One caveat to the OCTANE study, however, is that the women who received lopinavir/ritonavir had a 93%

rate of viral suppression, a percentage substantially greater than that found in comparable studies. However, this study further supports that women with documented nevirapine resistance are most likely to benefit from combination therapy that does not contain nevirapine (and because of cross-resistance, efavirenz) *[48]*.

There are few data evaluating response to subsequent therapy in women who receive current combination drug regimens for prophylaxis and discontinue the drugs postpartum. However, if the regimen that was discontinued had fully suppressed viral replication, theoretically, resistance should not occur. Issues relating to discontinuation of nevirapine-based combination therapy are discussed in the section **Prevention of Antiretroviral Drug Resistance**.

Management of Antiretroviral Drug Resistance during Pregnancy

Panel's Recommendations:

- ***Women who have documented zidovudine resistance and are on regimens that do not include zidovudine for their own health should still receive intravenous zidovudine during labor whenever possible, along with their established antiretroviral regimens and postnatal oral zidovudine for their infants (AII). For women who are receiving a stavudine-containing regimen, stavudine should be discontinued during labor while intravenous zidovudine is being administered (see Intrapartum Care).***
- ***The optimal prophylactic regimen for newborns of women with antiretroviral resistance is unknown (see Infant Antiretroviral Prophylaxis). Therefore, antiretroviral prophylaxis for an infant born to a woman with known or suspected drug resistance should be determined in consultation with a pediatric HIV specialist, preferably before delivery (AIII).***

Ideally, antiretroviral regimens used during pregnancy for treatment or prophylaxis should be chosen based on the results of antiretroviral resistance testing. However, antiretroviral drugs are also used during pregnancy for prevention of mother-to-child transmission. Although most transmission occurs during the intrapartum period, 30% to 35% of transmission may occur *in utero [49-51]*; the majority of *in utero* infection is thought to occur later in pregnancy *[49]* and may be more likely in women with advanced HIV disease and/or high viral load *[50-51]*. Therefore, delay in initiation of an antiretroviral drug regimen to await results of resistance testing could result in *in utero* infection of the infant, particularly in women at high risk of transmission or who are late in pregnancy at the time the drugs are initiated. In such circumstances, as noted earlier, empiric initiation of antiretroviral prophylaxis may be warranted to maximize prevention of perinatal transmission, with the regimen modified if needed once resistance testing results become available.

For women who have documented zidovudine resistance and whose antepartum regimen does not include zidovudine, intravenous zidovudine during labor should still be administered whenever possible (see **Intrapartum Care**). If the woman's antepartum regimen includes stavudine, which may be antagonistic to zidovudine, stavudine should be stopped during the intrapartum period and restarted after delivery (see **Intrapartum Care**). Other antiretrovirals should be continued orally during labor to the extent possible. Zidovudine should also be administered orally to the infant for 6 weeks. For an infant born to a woman with known zidovudine-resistant virus, many clinicians would choose to provide additional antiretroviral agents to the infant in combination with zidovudine (see **Infant Antiretroviral Prophylaxis**). Such a decision must be accompanied by a discussion with the woman of the potential benefits and risks of this approach and the lack of data to address its efficacy and safety. The optimal prophylactic regimen for newborns of women with antiretroviral drug-resistant virus is unknown. Therefore, antiretroviral prophylaxis for the infant born to a woman with known or suspected drug-resistant virus should be determined with a pediatric HIV specialist, preferably before delivery.

The rationale for including zidovudine intrapartum and to the infant when a woman is known to harbor virus with zidovudine resistance is based on several factors. Data thus far have suggested that when mothers have mixed populations of wild-type virus and virus with low-level zidovudine resistance, only wild-type virus is

found in the infant *[40]*. Other studies have suggested that drug resistance mutations may diminish viral fitness and possibly decrease transmissibility *[41]*. Efficacy of the zidovudine prophylaxis appears to be based not only on reduction of HIV levels in the mother but also on pre- and post-exposure prophylaxis in the infant *[52-54]*. Zidovudine crosses the placenta readily and has one of the highest maternal-to-cord blood ratios among the nucleoside analogue agents. Additionally, zidovudine is metabolized to the active triphosphate within the placenta *[55-56]*, which may provide additional protection against transmission. Metabolism to the active triphoshate, which is required for activity of all nucleoside analogue agents, has not been observed within the placenta with other nucleoside analogues that have been evaluated (didanosine and zalcitabine) *[57-58]*. In addition, zidovudine has been shown to reduce genital HIV RNA levels, and genital viral levels have been shown to correlate with perinatal transmission *[59]*. Data on levels of other nucleoside analogues in the genital tract are more limited, and it is unknown if other nucleoside analogue agents will provide a similar reduction in genital tract HIV RNA levels *[60-62]*. Zidovudine has better penetration into the central nervous system (CNS) compared to other nucleoside analogues with the exception of stavudine, whose CNS penetration is similar; this may help to eliminate a potential reservoir for transmitted HIV in the infant *[63-64]*. Thus, intravenous intrapartum and oral zidovudine for the infant should be included even in the presence of known zidovudine resistance because of the unique characteristics of zidovudine and its proven record in reducing perinatal transmission.

Prevention of Antiretroviral Drug Resistance

Panel's Recommendations:

- ***HIV-infected pregnant women should use combination antiretroviral drug regimens to maximally suppress viral replication; this is the most effective strategy to prevent the development of resistance and to minimize the risk of perinatal transmission (AII).***
- ***All pregnant women should be counseled about the importance of adherence to prescribed antiretroviral medications to reduce the potential for development of resistance (AII).***
- ***For pregnant women receiving an NNRTI-based combination antiretroviral therapy regimen for prophylaxis only, with plans to discontinue therapy after delivery, the nucleoside analogue agents should be given for at least 7 days after stopping the NNRTI to minimize the risk of resistance (AI). An alternative strategy is to substitute a PI for the NNRTI prior to the interruption and to continue the PI with dual NRTIs. The optimal interval between stopping an NNRTI and the other antiretroviral drugs is not known. Given the potential of prolonged detectable NNRTI concentrations for more than 3 weeks in patients receiving efavirenz-based therapy, some experts recommend continuing the other antiretroviral agents or substituting a PI plus two other agents for up to 30 days. (CIII) (See Stopping Antiretroviral Therapy during Pregnancy and Postpartum Follow-Up of HIV-Infected Women.)***
- ***The addition of single-dose maternal/infant nevirapine to an ongoing combination antiretroviral treatment or prophylaxis regimen does not provide additional efficacy in reducing perinatal transmission and may result in nevirapine drug resistance in the mother and/or infant; therefore single-dose maternal/infant nevirapine is not recommended in this situation (AI).***

The most effective way to prevent the development of antiretroviral drug resistance in pregnancy is to use and adhere to an effective combination of antiretroviral drugs to achieve maximal viral suppression. Selection of a regimen should take into account prior antiretroviral treatment history, including documented clinical, immunologic, or virologic failure with or without genotypic or phenotypic resistance testing; history of nonadherence; and problems with intolerance.

When nevirapine or other NNRTI drugs are used as part of a prophylactic combination antiretroviral regimen that is stopped after delivery, there is a risk of development of NNRTI resistance because of the drug's prolonged half-life, leading to a period of persistent subtherapeutic levels of a single drug if all drugs are discontinued at once. Studies in South Africa and Cote d'Ivoire have shown that the development of

nevirapine resistance following exposure to single-dose intrapartum nevirapine (given alone or in combination with antenatal antiretroviral therapy) was significantly decreased (but not eliminated) if zidovudine/lamivudine was given intrapartum and administered for 3 to 7 days postpartum after intrapartum nevirapine *[65-66]*. In a cohort of 39 women who initiated combination antiretroviral therapy in pregnancy and had genotypic testing performed at 6 weeks postpartum, 5 (13%) had primary mutations detected *[31]*. All 5 were on combination regimens that included nevirapine, were treatment naïve prior to pregnancy, and had staggered drug discontinuation after delivery (the dual nucleoside component of the regimen was continued for 5 days after stopping nevirapine). It is not known whether the incidence of resistance would have been significantly higher if drug discontinuation had not been staggered. An alternative strategy is to substitute a PI for the NNRTI and to continue the PI with dual NRTIs for a period of time *[67]*. The optimal duration needed to continue either dual nucleosides or the substituted PI-based regimen after stopping the NNRTI is not known. NNRTI drugs have long half-lives, and drug levels can persist for up to 1 to 3 weeks after stopping the drug; efavirenz levels persist longer than nevirapine levels *[26, 68]*. Further research is needed on the optimal duration of time and regimen to "cover" this period of prolonged NNRTI exposure to prevent the emergence of resistance following discontinuation of NNRTI-based therapy. Many experts will stop the NNRTI drug and continue the other antiretroviral drugs for at least 7 days, although other experts would recommend up to 30 days, particularly if an efavirenz-based regimen is being stopped.

References

1. Pao D, Andrady U, Clarke J, et al. Long-term persistence of primary genotypic resistance after HIV-1 seroconversion. *J Acquir Immune Defic Syndr.* 2004;37(5):1570-1573.
2. Barbour JD, Hecht FM, Wrin T, et al. Persistence of primary drug resistance among recently HIV-1-infected adults. *AIDS.* 2004;18(12):1683-1689.
3. Ghosn J, Pellegrin I, Goujard C, et al. HIV-1 resistant strains acquired at the time of primary infection massively fuel the cellular reservoir and persist for lengthy periods of time. *AIDS.* 2006;20(2):159-170.
4. Novak RM, Chen L, MacArthur RD, et al. Prevalence of antiretroviral drug resistance mutations in chronically HIV-infected, treatment-naive patients: implications for routine resistance screening before initiation of antiretroviral therapy. *Clin Infect Dis.* 2005;40(3):468-474.
5. Weinstock HS, Zaidi I, Heneine W, et al. The epidemiology of antiretroviral drug resistence among drug-naïve HIV-1 infected persons in 10 US cities. *J Infect Dis.* 2004;189(12):2174-2180.
6. Wensing AM, van de Vijver D, Angarano G, et al. Prevalence of drug-resistant HIV-1 variants in untreated individuals in Europe: implications for clinical management. *J Infect Dis.* 2005;192(6):958-966.
7. Metzner KJ, Rauch P, Walter H, et al. Detection of minor populations of drug-resistant HIV-1 in acute seroconverters. *AIDS.* 2005;19(16):1819-1825.
8. Derdelinckx I, Van Laethem K, Maes B, et al. Current levels of drug resistance among therapy-naïve patients have significant impact on treatment response. *J Acquir Immune Defic Syndr.* 2004;37(5):1664-1666.
9. Hecht FM, Grant RM. Resistance testing in drug-naïve HIV-infected patients: is it time? *Clin Infect Dis.* 2005;41(9):1324-1325.
10. Sax PE, Islam R, Walensky RP, et al. Should resistance testing be performed for treatment-naïve HIV-infected patients? A cost-effectiveness analysis. *Clin Infect Dis.* 2005;41(9):1316-1323.
11. Siliciano JD, Siliciano RF. A long-term latent reservoir for HIV-1: discovery and clinical implications. *J Antimicrob Chemother.* 2004;54(1):6-9.
12. Little SJ, Holte S, Routy JP, et al. Antiretroviral drug resistance among patients recently infected with HIV. *N Engl J Med.* 2002;347(6):385-394.
13. Boden D, Hurley A, Zhang L, et al. HIV-1 drug resistance in newly infected individuals. *JAMA.* 1999;282(12):1135-1141.
14. Richman DD, Morton SC, Wrin T, et al. The prevalence of antiretroviral drug resistance in the United States. *AIDS.* 2004;18(10):1393-1401.
15. Juethner SN, Williamson C, Ristig MB, et al. Nonnucleoside reverse transcriptase inhibitor resistance among antiretroviral-naive HIV-positive pregnant women. *J Acquir Immune Defic Syndr.* 2003;32(2):153-156.

16. Shah SS, Crane M, Monaghan K, et al. Genotypic resistance testing in HIV-infected pregnant women in an urban setting. *Int J STD AIDS.* 2004;15(6):384-387.
17. Palumbo P, Holland B, Dobbs T, et al. Antiretroviral resistance mutations among pregnant human immunodeficiency virus type 1-infected women and their newborns in the United States: vertical transmission and clades. *J Infect Dis.* 2001;184(9):1120-1126.
18. Cunningham CK, Chaix ML, Rekacewica C, et al. Development of resistance mutations in women on standard antiretroviral therapy who received intrapartum nevirapine to prevent perinatal HIV-1 transmission: a substudy of pediatric AIDS clinical trials group protocol 316. *J Infect Dis.* 2002;186(2):181-188.
19. Cooper ER, Charurat M, Mofenson LM, et al. Combination antiretroviral strategies for the treatment of pregnant HIV-1 infected women and prevention of perinatal HIV-1 transmission. *J Acquir Immune Defic Syndr Hum Retrovirol.* 2002;29(5):484-494.
20. European Collaborative Study. Mother-to-child transmission of HIV infection in the era of highly active antiretroviral therapy. *Clin Infect Dis.* 2005;40(3):458-465.
21. Welles SL, Pitt J, Colgrove R, et al. HIV-1 genotypic zidovudine drug resistance and the risk of maternal-infant transmission in the Women and Infants Transmission Study Group. *AIDS.* 2000;14(3):263-271.
22. Kully C, Yerly S, Erb P, et al. Codon 215 mutations in human immunodeficiency virus-infected pregnant women. *J Infect Dis.* 1999;179(3):705-708.
23. Sitnitskaya Y, Rochford G, Rigaud M, et al. Prevalence of the T215Y mutation in human immunodeficiency virus type 1-infected pregnant women in a New York cohort, 1995-1999. *Clin Infect Dis.* 2001;33(1):e3-7.
24. Eastman PS, Shapiro DE, Coombs RW, et al. Maternal viral genotypic zidovudine resistance and infrequent failure of zidovudine therapy to prevent perinatal transmission of human immunodeficiency virus type 1 in Pediatric AIDS Clinical Trial Group Protocol 076. *J Infect Dis.* 1998;177(3):557-564.
25. Larbalestier N, Mullen J, O'Shea S, et al. Drug resistance is uncommon in pregnant women with low viral loads taking zidovudine monotherapy to prevent perinatal HIV transmission. *AIDS.* 2003;17(18):2665-2671.
26. Cressey TR, Jourdain G, Lallemant MJ, et al. Persistence of nevirapine exposure during the postpartum period after intrapartum single-dose nevirapine in addition to zidovudine prophylaxis for the prevention of mother-to-child transmission of HIV-1. *J Acquir Immune Defic Syndr.* 2005;38(3):283-288.
27. Eshleman SH, Mracna M, Guay LA, et al. Selection and fading of resistance mutations in women and infants receiving nevirapine to prevent HIV-1 vertical transmission (HIVNET 012). *AIDS.* 2001;15(15):1951-1957.
28. Eshleman SH, Guay LA, Mwatha A, et al. Characterization of nevirapine resistance mutations in women with subtype A vs. D HIV-1 6-8 weeks after single-dose nevirapine (HIVNET 012). *J Acquir Immune Defic Syndr.* 2004;35(2):126-130.
29. Sullivan J. South African Intrapartum Nevirapine Trial: selection of resistance mutations. Paper presented at: XIV International Conference on AIDS; July 7-12, 2002; Barcelona, Spain.
30. Jourdain G, Ngo-Giang-Huong N, Le Coeur S, et al. Intrapartum exposure to nevirapine and subsequent maternal responses to nevirapine-based antiretroviral therapy. *N Engl J Med.* 2004;351(3):229-240.
31. Lyons FE, Coughlan S, Byrne CM, et al. Emergence of antiretroviral resistance in HIV-positive women receiving combination antiretroviral therapy in pregnancy. *AIDS.* 2005;19(1):63-67.
32. Eshleman SH, Becker-Pergola G, Deseyve M, et al. Impact of human immunodeficiency virus type 1 (HIV-1) subtype on women receiving single-dose nevirapine prophylaxis to prevent HIV-1 vertical transmission (HIV network for prevention trials 012 study). *J Infect Dis.* 2001;184(7):914-917.
33. Servais J, Lambert C, Karita E, et al. HIV type 1 pol gene diversity and archived nevirapine resistance mutation in pregnant women in Rwanda. *AIDS Res Hum Retroviruses.* 2004;20(3):279-283.
34. Eshleman SH, Guay LA, Mwatha A, et al. Comparison of nevirapine (NVP) resistance in Ugandan women 7 days vs. 6-8 weeks after single-dose nvp prophylaxis: HIVNET 012. *AIDS Res Hum Retroviruses.* 2004;20(6):595-599.
35. Eshleman SH, Hoover DR, Chen S, et al. Nevirapine (NVP) resistance in women with HIV-1 subtype C, compared with subtypes A and D, after the administration of single-dose NVP. *J Infect Dis.* 2005;192(1):30-36.
36. Johnson JA, Li JF, Morris L, et al. Emergence of drug-resistant HIV-1 after intrapartum administration of single-dose nevirapine is substantially underestimated. *J Infect Dis.* 2005;192(1):16-23.

37. Flys T, Nissley DV, Claasen CW, et al. Sensitive drug-resistance assays reveal long-term persistence of HIV-1 variants with the K103N nevirapine (NVP) resistance mutation in some women and infants after the administration of single-dose NVP: HIVNET 012. *J Infect Dis.* 2005;192(1):24-29.
38. Loubser S, Balfe P, Sherman G, et al. Decay of K103N mutants in cellular DNA and plasma RNA after single-dose nevirapine to reduce mother to child HIV transmission. *AIDS.* 2006;20(7):995-1002.
39. Paredes R, Cheng I, Kuritzkes DR, et al. Postpartum antiretroviral drug resistance in HIV-1-infected women receiving pregnancy-limited antiretroviral therapy. *AIDS.* 2010;24(1):45-53.
40. Colgrove RC, Pitt J, Chung PH, et al. Selective vertical transmission of HIV-1 antiretroviral resistance mutations. *AIDS.* 1998;12(17):2281-2288.
41. Nijhuis M, Deeks S, Boucher C. Implications of antiretroviral resistance on viral fitness. *Curr Opin Infect Dis.* 2001;14(1):23-28.
42. Parker M, Wade N, Lloyd RM, Jr., et al. Prevalence of genotypic drug resistance among a cohort of HIV-infected newborns. *J Acquir Immune Defic Syndr.* 2003;32(3):292-297.
43. Karchava M, Pulver W, Smith L, et al. Prevalence of drug-resistance mutations and non-subtype B strains among HIV-infected infants from New York State. *J Acquir Immune Defic Syndr.* 2006;42(5):614-619.
44. McConnell M, Bakaki P, Eure C, et al. Effectiveness of repeat single-dose nevirapine for prevention of mother-to-child transmission of HIV-1 in repeat pregnancies in Uganda. *J Acquir Immune Defic Syndr.* 2007;46(3):291-296.
45. Martinson NA, Ekouevi DK, Dabis F, et al. Transmission rates in consecutive pregnancies exposed to single-dose nevirapine in Soweto, South Africa and Abidjan, Côte d'Ivoire. *J Acquir Immune Defic Syndr.* 2007;45(2):206-209.
46. Coovadia A, Marais B, Abrams E, et al. Virologic response to NNRTI-treatment among women who took single-dose nevirapine 18-36 months later. Presented at the 13th Conference on Retroviruses and Opportunistic Infections; February 2006; Denver, Co. Abstract 641.
47. Lockman S, Shapiro RL, Smeaton LM, et al. Response to antiretroviral therapy after a single, peripartum dose of nevirapine. *N Engl J Med.* 2007;356(2):135-147.
48. Lockman S and the A5208/OCTANE Study Team. Lopinavir/ritonavir + tenofovir/emtricitabine is superior to nevirapine + tenofovir/emtricitabine for women with prior exposure to single-dose nevirapine: A5208 ("OCTANE"). Paper presented at: 16th Conference on Retroviruses and Opportunistic Infections; February 8-11, 2009; Montreal, Canada.
49. Rouzioux C, Costagliola D, Burgard M, et al. Estimated timing of mother to child human immunodeficiency virus type 1 (HIV-1) transmission by use of a Markov model. *Am J Epidemiol.* 1995;142(12):1330-1337.
50. Kuhn L, Steketee RW, Weedon J, et al. Distinct risk factors for intrauterine and intrapartum human immunodeficiency virus transmission and consequences for disease progression in infected children. *J Infect Dis.* 1999;179(1):52-58.
51. Magder LS, Mofenson LM, Paul ME, et al. Risk factors for in utero and intrapartum transmission of HIV. *J Acquir Immune Defic Syndr.* 2005;38(1):87-95.
52. Sperling RS, Shapiro DE, Coombs RW, et al. Maternal viral load, zidovudine treatment, and the risk of transmission of human immunodeficiency virus type 1 from mother to infant. Pediatric AIDS Clinical Trials Group Protocol 076 Study Group. *N Engl J Med.* 1996;335(22):1621-1629.
53. Wade NA, Birkhead GS, Warren BL, et al. Abbreviated regimens of zidovudine prophylaxis and perinatal transmission of the human immunodeficiency virus. *N Engl J Med.* 1998;339(20):1409-1414.
54. Melvin AJ, Burchett SK, Watts DH, et al. Effect of pregnancy and zidovudine therapy on viral load in HIV-1-infected women. *J Acquir Immune Defic Syndr Hum Retrovirol.* 1997;14(3):232-236.
55. Qian M, Bui T, Ho RJY, Unadkat JD. Metabolism of 3'-azido-3'-deoxythymidine (AZT) in human placental trophoblasts and hofbauer cells. *Biochem Pharmacol.* 1994;48(2):383-389.
56. Sandberg JA, Binienda Z, Lipe G, et al. Placental transfer and fetal disposition of 2',3'-dideoxycytidine and 2',3'-dideoxyinosine in the rhesus monkey. *Drug Metab Dispos.* 1995;23(8):881-884.
57. Dancis J, Lee JD, Mendoza S, Liebes L. Transfer and metabolism of dideoxyinosine by the perfused human placenta. *J Acquir Immune Defic Syndr Hum Retrovirol.* 1993;6(1):2-6.
58. Sandberg JA, Binienda Z, Lipe G, Slikker Jr W. Placental transfer and fetal disposition of dideoxycytidine (ddC) and dideoxyinosine (ddI) [Abstract]. *Toxicologist.* 1994;14:434.
59. Chuachoowong R, Shaffer N, Siriwasin W, et al. Short-course antenatal zidovudine reduces both cervicovaginal human immunodeficiency virus type 1 RNA levels and risk of perinatal transmission. *J Infect Dis.* 2000;181(1):99-106.

60. Si-Mohamed A, Kazatchkine MK, Heard I, et al. Selection of drug-resistant variants in the female genital tract of human immunodeficiency virus type 1-infected women receiving antiretroviral therapy. *J Infect Dis.* 2000;182(1):112-122.
61. Dumond J, Yeh R, Corbett A, et al. First dose and steady state genital tract pharmacokinetics of ten antiretroviral drugs in HIV-infected women: implications for pre- and post-exposure prophylaxis. Presented at the 13th Conference on Retroviruses and Opportunistic Infections; February 5-8, 2006; Denver, Co. Abstract 129.
62. Vourvahis M, Tappouni H, Patterson K, et al. A pharmacologic basis for the use of tenofovir in pre- and post-exposure prophylaxis: intra- and extra-cellular genital tract pharmacokinetics and pharmacodynamics from first dose to steady state in HIV-1-infected men and women. Presented at the 13th Conference on Retroviruses and Opportunistic Infections; February 5-8, 2006; Denver, Co. Abstract 569.
63. Strazielle N, Belin MF, Ghersi-Egea JF. Choroid plexus contrals brain availability of anti-HIV nucleoside analogs via pharmacologically inhibitable organic anion transporters. *AIDS.* 2003;17(10):1473-1485.
64. Thomas SA. Anti-HIV drug distribution to the central nervous system. *Curr Pharmaceut Des.* 2004;10(12):1313-1324.
65. McIntyre JA, Hopley M, Moodley D, et al. Efficacy of short-course AZT plus 3TC to reduce nevirapine resistance in the prevention of mother-to-child HIV transmission: a randomized clinical trial. PLoS Med. 2009;6(10):e1000172.
66. Chaix ML, Ekouevi DK, Rouet F, et al. Low risk of nevirapine resistance mutations in the prevention of mother-to-child transmission of HIV-1: Agence Nationale de Recherches sur le SIDA Ditrame Plus, Abidjan, Cote d'Ivoire. *J Infect Dis.* 2006;193(4):482-487. Epub 2006 Jan 2011.
67. Fox Z, Phillips A, Cohen C, et al. Viral resuppression and detection of drug resistance following interruption of a suppressive non-nucleoside reverse transcriptase inhibitor-based regimen. *AIDS.* 2008;22(17):2279-2289.
68. Sadiq ST, Fredericks S, Khoo SH, et al. Efavirenz detectable in plasma 8 weeks after stopping therapy and subsequent development of non-nucleoside reverse transcriptase inhibitor-associated resistance. *AIDS.* 2005;19(15):1716-1717.

Intrapartum Care (Updated May 24, 2010)

INTRAPARTUM ANTIRETROVIRAL THERAPY/PROPHYLAXIS

Panel's Recommendations:

- ***Intrapartum intravenous zidovudine is recommended for all HIV-infected pregnant women, regardless of their antepartum regimen, to reduce perinatal transmission of HIV (AI).***
- ***For women who are receiving a stavudine-containing antepartum regimen, stavudine should be discontinued during labor while intravenous zidovudine is being administered (AI).***
- ***Women who are receiving an antepartum combination antiretroviral treatment regimen should continue this regimen on schedule as much as possible during labor and prior to scheduled cesarean delivery (AIII).***
- ***Women receiving fixed-dose combination regimens that include zidovudine should have zidovudine administered intravenously during labor while other antiretroviral components are continued orally (AIII).***
- ***For women who have received antepartum antiretroviral drugs but have suboptimal viral suppression near delivery (i.e., >1,000 copies/mL), scheduled cesarean delivery is recommended (AI). The addition of single-dose intrapartum/newborn nevirapine is generally not recommended (AI).***
- ***Women of unknown HIV status who present in labor should have rapid HIV antibody testing performed (AII). If the test is positive, a confirmatory HIV test should be sent as soon as possible and maternal/infant antiretroviral drugs should be initiated without waiting for results of the confirmatory test (AII). If the confirmatory HIV test is positive, antiretroviral drugs should be continued in the infant for 6 weeks (see Neonatal Postnatal Care) (AI); if the test is negative, the infant antiretroviral drugs should be stopped.***
- ***For HIV-infected women in labor who have not received antepartum antiretroviral drugs, intravenous zidovudine during labor and 6 weeks of infant zidovudine are recommended (AII). Some experts would combine the intravenous intrapartum/6-week newborn zidovudine regimen with single-dose intrapartum/newborn nevirapine (CIII).***
- ***If single-dose intrapartum/newborn nevirapine is given, an antiretroviral "tail" should be administered to reduce development of nevirapine resistance (AII).***

Table 7 shows dosing for intravenous intrapartum zidovudine given in continuous infusion during labor and neonatal zidovudine dosing; Table 8 shows intrapartum and neonatal dosing for additional drugs to be considered in certain situations as delineated below.

Women Who Have Received Antepartum Antiretroviral Drugs

Use of Intravenous Zidovudine during Labor

The PACTG 076 results and subsequent epidemiologic studies have proven the efficacy of the three-part zidovudine chemoprophylaxis regimen alone or in combination with other antiretroviral agents. The PACTG 076 zidovudine regimen includes a continuous intravenous infusion of zidovudine during labor (initial loading dose of 2 mg/kg intravenously over 1 hour, followed by continuous infusion of 1 mg/kg/hour until delivery). Therefore, intravenous zidovudine during the intrapartum period should be discussed with and recommended to all HIV-infected pregnant women. For a scheduled cesarean delivery, intravenous zidovudine should begin 3 hours before surgery, according to standard dosing recommendations. Women receiving fixed-dose combination regimens that include zidovudine (e.g., the zidovudine/lamivudine combination) should have zidovudine administered intravenously during labor while other antiretroviral components are continued orally (e.g., if a woman is receiving zidovudine/lamivudine during pregnancy, zidovudine should be given intravenously and lamivudine should be given orally during labor).

If known or suspected zidovudine resistance or toxicity has precluded antenatal use of zidovudine, intrapartum zidovudine according to the PACTG 076 protocol should still be recommended unless a woman has a documented history of hypersensitivity. This intrapartum use of the drug is recommended due to the unique characteristics of zidovudine and its proven record in reducing perinatal transmission (see **Management of Antiretroviral Drug Resistance during Pregnancy**). There is a pharmacologic antagonism between zidovudine and stavudine, and therefore these drugs should not be coadministered during labor. Women who are receiving an antepartum stavudine-containing regimen should discontinue stavudine during labor while intravenous zidovudine is being administered, with other components of the regimen continued orally.

Continuation of Antenatal Antiretroviral Drugs during Labor and Postpartum

Women who are receiving an antepartum combination antiretroviral treatment regimen should continue this regimen on schedule as much as possible during the intrapartum period to provide maximal virologic effect and to minimize the chance of development of drug resistance. When cesarean delivery is planned, oral medications may be continued preoperatively with sips of water. Medications requiring food ingestion for absorption could be taken with liquid dietary supplements, contingent on consultation with the attending anesthesiologist in the preoperative period. If maternal antiretroviral therapy must be interrupted temporarily (i.e., for less than 24 hours) in the peripartum period, all drugs (except for intrapartum intravenous zidovudine) should be stopped and reinstituted simultaneously to minimize the chance of resistance developing.

Women Who Have Received Antepartum Antiretroviral Drugs but Have Suboptimal Viral Suppression near Delivery

Women who have received antiretroviral therapy may not achieve complete viral suppression by the time of delivery due to factors such as poor adherence, viral resistance, or late entry into care. Regardless of the reason, all women who have HIV RNA levels >1,000 copies/mL near the time of delivery should be offered a scheduled cesarean delivery at 38 weeks, which may significantly reduce the risk of transmission (see **Transmission and Mode of Delivery**). The addition of single-dose nevirapine during labor has not been shown to reduce perinatal transmission of HIV in this group of women. The PACTG 316 study, conducted in women in the United States, Europe, Brazil, and the Bahamas who were receiving antiretroviral drugs during pregnancy (primarily combination therapy), showed that the addition of single-dose nevirapine did not reduce the risk of mother-to-child transmission of HIV even in the setting of maternal viremia but was associated with the development of nevirapine resistance in 15% of women with detectable HIV RNA postpartum *[1-2]*. However, the number of women with detectable HIV RNA at delivery, and especially with HIV RNA greater than

10,000 copies/mL, was small and may have been insufficient to allow assessment of a possible benefit of single-dose nevirapine in this subgroup. Given the risk of development of resistance and the lack of data to suggest added efficacy, addition of single-dose nevirapine when a woman has received antepartum drugs is generally not recommended. However, single-dose nevirapine use may be considered in special circumstances, such as in women with high HIV RNA levels at or near the time of delivery, especially if delivery is vaginal rather than a scheduled cesarean delivery. If single-dose nevirapine is administered, the use of maternal postpartum zidovudine/lamivudine for at least 7 days is suggested to prevent the development of nevirapine resistance (see **Choice of Intrapartum/Postpartum Antiretroviral Regimen for Women without Antepartum Antiretroviral Therapy**).

Women Who Have Not Received Antepartum Antiretroviral Drugs

Women Who Present in Labor with No Documentation of HIV Status

Any woman without documented HIV status at the time of labor should be screened with rapid HIV testing unless she declines (opt-out screening). Rapid HIV testing is also recommended for women presenting in labor who tested negative for HIV in early pregnancy but are at increased risk of HIV infection and were not retested in the third trimester *[3]*. Factors increasing risk of infection may include diagnosis of an STD, illicit drug use or exchange of sex for money or drugs, multiple sexual partners during pregnancy, a sexual partner at risk of HIV infection, signs/symptoms of acute HIV infection, or living in a region with an elevated incidence of HIV in women of childbearing age without a repeat HIV test in the third trimester *[3]*.

Rapid HIV antibody testing should be available on a 24-hour basis at all facilities with a maternity service and/or neonatal intensive care unit. Statutes and regulations regarding rapid testing vary from state to state; see **http://www.nccc.ucsf.edu/consultation_library/state_hiv_testing_laws** for a review of state HIV testing laws. Current information on rapid testing should also be available at all facilities with a maternity service and/or neonatal intensive care unit.

A woman with a positive rapid antibody test should be presumed to be infected until standard HIV antibody confirmatory testing clarifies her infection. Along with confirmatory HIV antibody testing, the woman should have appropriate assessments (e.g., CD4 count and HIV RNA copy number) as soon as possible to determine maternal health status and whether antiretroviral therapy is recommended for her own health. Arrangements for establishing HIV care and providing ongoing psychosocial support after discharge should also be provided. All women with a positive rapid HIV test in labor should have intravenous zidovudine started immediately to prevent perinatal transmission of HIV, as discussed below.

Choice of Intrapartum/Postpartum Antiretroviral Regimen for Women without Antepartum Antiretroviral Therapy

All HIV-infected women who have not received antepartum antiretroviral therapy should have intravenous zidovudine started immediately to prevent perinatal transmission of HIV (see **Table 7** for dosing information). Although intrapartum/neonatal antiretroviral medications will not prevent perinatal transmission that occurs before labor, most transmission occurs near to or during labor and delivery. Pre-exposure prophylaxis for the fetus can be provided by giving the mother a drug that rapidly crosses the placenta to produce systemic antiretroviral drug levels in the fetus during intensive exposure to HIV in maternal genital secretions and blood during birth. In general, zidovudine and other NRTI drugs as well as NNRTI drugs cross the placenta well, although PI drugs do not (see **Table 4**).

Epidemiologic data indicate that intravenous maternal intrapartum zidovudine followed by oral zidovudine for 6 weeks for the infant significantly reduces transmission compared to no treatment *[4]*.

In a New York State cohort study, transmission rates were 10% with intrapartum and neonatal zidovudine compared with 27% without zidovudine, a 62% reduction in risk *[4]*. The PETRA study demonstrated that intrapartum prophylaxis alone, without an infant post-exposure prophylaxis component, is not effective in reducing perinatal transmission *[5]*.

Whether the addition of other antiretroviral drugs to the intravenous intrapartum/newborn zidovudine regimen when no maternal antepartum drugs have been received increases efficacy in preventing perinatal transmission has not been directly studied. Several intrapartum/neonatal prophylaxis regimens have been found to be effective in international studies. These include oral zidovudine/lamivudine during labor followed by 1 week of oral zidovudine/lamivudine to the infant and single-dose intrapartum/newborn nevirapine *[5-6]*. However, none of these regimens has been compared to intravenous zidovudine combined with 6 weeks of infant zidovudine prophylaxis.

An ongoing study in the United States, Brazil, Argentina, and South Africa is assessing whether adding drugs to the intravenous intrapartum/newborn zidovudine regimen will enhance efficacy in reducing perinatal transmission. In the absence of data, some experts feel additional drugs may be warranted. One option is to add the single-dose intrapartum/newborn nevirapine regimen to the intravenous/6-week infant zidovudine regimen. Although single-dose nevirapine did not provide additional efficacy when added to antepartum combination antiretroviral regimens in PACTG 316, in this situation, no maternal antepartum therapy has been given. Theoretical advantages of combining the zidovudine and nevirapine intrapartum/neonatal regimens include the known short-term safety of each regimen alone, excellent transplacental passage of both drugs, greater antiviral activity of nevirapine compared to zidovudine, as well as the activity of nevirapine against extracellular and intracellular virus *[7-8]*, and the known synergy of zidovudine and nevirapine in inhibiting HIV replication *in vitro [9]*.

However, single-dose nevirapine is associated with the development of nevirapine -resistant virus (see **Incidence of Antiretroviral Resistance with Perinatal Prophylactic Regimens**) *[2, 10-12]*. Studies have shown that nevirapine resistance after intrapartum administration of single-dose nevirapine can be substantially reduced (but not eliminated) by using a short postpartum course of antiretroviral agents from alternate classes (a “tail”). There is no current consensus about the exact duration or composition of the antiretroviral tail. Several trials in Africa have found 3–7 days of maternal/infant postpartum zidovudine/lamivudine to be effective *[13-15]* (See **Table 8** for dosing information.) Development of resistance to zidovudine or lamivudine given for a short period in this setting is rare *[16-17]*. More recent studies have found that 7 days of tenofovir/emtricitabine *[18]*, 7 days of zidovudine/didanosine/lopinavir-ritonavir *[19]*, and 30 days of zidovudine/didanosine or zidovudine/didanosine/lopinavir-ritonavir *[19-20]* all appear to be effective at reducing the development of nevirapine resistance. In the United States the use of maternal postpartum zidovudine/lamivudine for at least 7 days is suggested as a reasonable tail after intrapartum single-dose nevirapine use (see **Neonatal Postnatal Care** section for discussion of infant regimens). Other tail options may also be considered.

References:

1. Dorenbaum A, Cunningham CK, Gelber RD, et al. Two-dose intrapartum/newborn nevirapine and standard antiretroviral therapy to reduce perinatal HIV transmission: a randomized trial. *JAMA.* 2002;288(2):189-198.
2. Cunningham CK, Chaix ML, Rekacewicz C, et al. Development of resistance mutations in women receiving standard antiretroviral therapy who received intrapartum nevirapine to prevent perinatal human immunodeficiency virus type 1 transmission: a substudy of pediatric AIDS clinical trials group protocol 316. *J Infect Dis.* 2002;186(2):181-188.
3. Centers for Disease Control and Prevention (CDC). Revised recommendations for HIV testing of adults, adolescents, and pregnant women in health-care settings. *MMWR Recomm Rep.* 2006;55(RR-14):1-17; quiz CE11-14.

4. Wade NA, Birkhead GS, Warren BL, et al. Abbreviated regimens of zidovudine prophylaxis and perinatal transmission of the human immunodeficiency virus. *N Engl J Med.* 1998;339(20):1409-1414.
5. Petra Study Team. Efficacy of three short-course regimens of zidovudine and lamivudine in preventing early and late transmission of HIV-1 from mother to child in Tanzania, South Africa, and Uganda (Petra study): a randomised, double-blind, placebo-controlled trial. *Lancet.* 2002;359(9313):1178-1186.
6. Jackson JB, Musoke P, Fleming T, et al. Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: 18-month follow-up of the HIVNET 012 randomised trial. *Lancet.* 2003;362(9387):859-868.
7. Zhang H, Dornadula G, Wu Y, et al. Kinetic analysis of intravirion reverse transcription in the blood plasma of human immunodeficiency virus type 1-infected individuals: direct assessment of resistance to reverse transcriptase inhibitors in vivo. *J Virol.* 1996;70(1):628-634.
8. Musoke P, Guay L, Bagenda D, et al. A phase I/II study of the safety and pharmacokinetics of nevirapine in HIV-1-infected pregnant Ugandan women and their neonates (HIVNET 006). *AIDS.* 1999;13(4):479-486.
9. Koup RA, Brewster F, Grob P, et al. Nevirapine synergistically inhibits HIV-1 replication in combination with zidovudine, interferon or CD4 immunoadhesin. *AIDS.* 1993;7(9):1181-1184.
10. Eshleman SH, Mracna M, Guay LA, et al. Selection and fading of resistance mutations in women and infants receiving nevirapine to prevent HIV-1 vertical transmission (HIVNET 012). *AIDS.* 2001;15(15):1951-1957.
11. Eshleman SH, Guay LA, Mwatha A, et al. Characterization of nevirapine resistance mutations in women with subtype A vs. D HIV-1 6-8 weeks after single-dose nevirapine (HIVNET 012). *J Acquir Immune Defic Syndr.* 2004;35(2):126-130.
12. Jourdain G, Ngo-Giang-Huong N, Le Coeur S, et al. Intrapartum exposure to nevirapine and subsequent maternal responses to nevirapine-based antiretroviral therapy. *N Engl J Med.* 2004;351(3):229-240.
13. McIntyre JA, Hopley M, Moodley D, et al. Efficacy of short-course AZT plus 3TC to reduce nevirapine resistance in the prevention of mother-to-child HIV transmission: a randomized clinical trial. *PLoS Med.* 2009;6(10):e1000172.
14. Chaix ML, Ekouevi DK, Rouet F, et al. Low risk of nevirapine resistance mutations in the prevention of mother-to-child transmission of HIV-1: Agence Nationale de Recherches sur le SIDA Ditrame Plus, Abidjan, Cote d'Ivoire. *J Infect Dis.* 2006;193(4):482-487.
15. Farr S, Nelson J, Ng'ombe3 T, et al. Addition of 7 Days of Zidovudine + Lamivudine to Peripartum Single-dose Nevirapine Effectively Reduces Nevirapine Resistance at 2 and 6 Weeks Post-partum in HIV-infected Mothers: Lilongwe, Malawi. Paper presented at: 16th Conference on Retroviruses and Opportunistic Infections; February 8-11, 2009; Montreal, Canada. Abstract 958b.
16. Mandelbrot L, Landreau-Mascaro A, Rekacewicz C, et al. Lamivudine-zidovudine combination for prevention of maternal-infant transmission of HIV-1. *JAMA.* 2001;285(16):2083-2093.
17. Sullivan J. South African Intrapartum Nevirapine Trial: selection of resistance mutations. Paper presented at: XIV International Conference on AIDS; July 7-12, 2002; Barcelona, Spain. Abstract LbPeB9024.
18. TEmAA ANRS 12109 Study Group. Tolerance and viral resistance after single-dose nevirapine with tenofovir and emtricitabine to prevent vertical transmission of HIV-1. *AIDS.* 2009;23(7):825-833.
19. Van Dyke R, Jourdain G, Shapiro D, et al. A Phase II Study of the Incidence of Nevirapine Resistance Mutations in HIV-infected Thai Women Receiving a Single Intrapartum Dose of NVP followed by a Postpartum Tail of ZDV/ddI or ZDV/ddI/LPV/r: IMPAACT P1032. Paper presented at: 16th Conference on Retroviruses and Opportunistic Infections; February 8-11, 2009; Montreal, Canada. Abstract 95aLB.
20. Lallemant M, Ngo-Giang-Huong N, Jourdain G, et al. Efficacy and safety of 1-month postpartum zidovudine-didanosine to prevent HIV-resistance mutations after intrapartum single-dose nevirapine. *Clin Infect Dis.* 2010;50(6):898-908.

Table 7. Intrapartum Maternal and Neonatal Zidovudine (ZDV) Dosing for Prevention of Mother-to-Child Transmission of HIV

Maternal Intrapartum		
Drug	**Dosing**	**Duration**
ZDV	2 mg per kg body weight intravenously over 1 hour, followed by continuous infusion of 1 mg per kg body weight per hour	Onset of labor until delivery of infant
Neonatal		
Drug	**Dosing**	**Duration**
ZDV	>35 weeks gestation: 2 mg per kg body weight per dose given orally [1, 2] (or 1.5 mg per kg body weight per dose given intravenously) started within 6–12 hours of delivery, then every 6 hours	Birth to 6 weeks
ZDV	<35 to >30 weeks gestation: 2 mg per kg body weight per dose given orally (or 1.5 mg per kg body weight per dose given intravenously) started within 6–12 hours of delivery, then every 12 hours, advanced to every 8 hours at 2 weeks of age	Birth to 6 weeks
ZDV	<30 weeks gestation: 2 mg per kg body weight per dose given orally (or 1.5 mg/kg/dose given intravenously) started within 6–12 hours of delivery, then every 12 hours, advanced to every 8 hours at 4 weeks of age	Birth to 6 weeks

[1] Zidovudine dosing of 4 mg per kg body weight per dose given every 12 hours has been used for infant prophylaxis in some international perinatal studies. Although there are no definitive data to show equivalent pharmacokinetic parameters or efficacy in preventing transmission, a regimen of zidovudine 4 mg per kg body weight per dose given orally twice daily instead of 2 mg per kg body weight per dose given orally 4 times daily may be considered when there are concerns about adherence to drug administration to the infant.

[2] A simplified zidovudine dosing regimen has been developed for use in low resource settings. This regimen consists of 10 mg orally twice daily for infants weighing less than 2.5 kg at birth and 15 mg twice daily for infants weighing more than 2.5 kg at birth. See discussion in **Neonatal Postnatal Care: Infant Antiretroviral Prophylaxis**. This regimen could be considered for infants in higher resource settings born after 35 weeks gestation if simplicity in zidovudine dosing and administration is of prime importance.

Table 8. Intrapartum Maternal and Neonatal Dosing for Additional Antiretroviral Drugs to be Considered Only in Selected Circumstances

*(See **Special Considerations Regarding the Use of Antiretroviral Drugs by HIV-Infected Pregnant Women and their Infants** and **Antiretroviral Drug Resistance and Resistance Testing in Pregnancy** for further discussion.)*

Maternal Intrapartum/Postpartum		
Drug	**Dosing**	**Duration**
NVP (as single dose intrapartum)[1]	200 mg given orally as single dose	Single dose at onset of labor
ZDV + 3TC (given with single dose NVP as "tail" to reduce NVP resistance)	ZDV: intravenously intrapartum as per **Table 7**, then after delivery 300 mg orally twice daily 3TC: 150 mg orally twice daily starting at onset of labor	Through 1 week postpartum
Neonatal		
Drug	**Dosing**	**Duration**
NVP (as single dose)[2]	2 mg per kg body weight given orally as single dose	Single dose between birth and 72 hours of age. If maternal dose is given ≤ 2 hours before delivery or not received, infant dose should be administered as soon as possible following birth.[3]
ZDV + 3TC (given with single dose NVP as "tail" to reduce NVP resistance)	ZDV: neonatal dosing as per **Table 5** 3TC: 2 mg per kg body weight given orally twice daily	ZDV: Birth to 6 weeks 3TC: Birth to 1 week

Key to Abbreviations: NVP = nevirapine, ZDV = zidovudine, 3TC = lamivudine

[1] Given *in addition* to intravenous intrapartum ZDV; if intrapartum single-dose NVP is given to mother, administration of intrapartum oral 3TC followed by administration of ZDV and 3TC for at least 7 days postpartum to reduce development of NVP-resistant virus is recommended.

[2] Given *in addition* to 6 weeks of infant ZDV; addition of at least 7 days of 3TC may be considered to reduce development of NVP-resistant virus.

[3] Some experts recommend a second NVP dose at 48–72 hours of life to babies born in this circumstance.

TRANSMISSION AND MODE OF DELIVERY

Panel's Recommendations:

- ***Scheduled cesarean delivery at 38 weeks gestation is recommended for women with HIV RNA levels >1,000 copies/mL near the time of delivery (whether receiving or not receiving antepartum antiretroviral drugs) and for women with unknown HIV RNA levels near the time of delivery (AII).***
- ***It is not clear whether cesarean delivery after rupture of membranes or onset of labor provides benefit in preventing perinatal transmission. Management of women originally scheduled for cesarean delivery who present with ruptured membranes or in labor must be individualized based on duration of rupture, progress of labor, plasma HIV RNA level, current antiretroviral therapy, and other clinical factors (BII).***
- ***Data are insufficient to evaluate the potential benefit of cesarean delivery for prevention of perinatal transmission in pregnant women receiving combination antiretroviral drugs with plasma HIV RNA levels <1,000 copies/mL near the time of delivery. Given the low rate of transmission among this group, it is unclear whether scheduled cesarean delivery would confer additional benefit in reduction of transmission. Decisions should be individualized based on discussion between the obstetrician and the mother (BII).***
- ***Among HIV-infected women, use of prophylactic antibiotics at the time of cesarean delivery is recommended (AII).***
- ***Women should be informed of the risks associated with cesarean delivery; the risk to the woman should be balanced with potential benefits expected for the neonate (AIII).***

Basis for Current Recommendations

Scheduled cesarean delivery, defined as cesarean delivery performed before the onset of labor and before ruptured membranes, is recommended for women with HIV RNA levels >1,000 copies/mL near the time of delivery and for women with unknown HIV RNA levels *[1]*.

This recommendation is based on the findings from a multi-center randomized clinical trial *[2]* and a large individual patient data meta-analysis *[3]*. These two studies were conducted at a time when the majority of women received no antiretroviral medications or zidovudine as a single drug and before the availability of viral load information. However, study results have been extrapolated to make recommendations regarding the mode of delivery in an era when combination antiretroviral therapy during pregnancy is recommended and viral load information is readily available. In the randomized clinical trial, 1.8% of infants born to women randomized to undergo cesarean delivery were HIV infected compared to 10.5% of infants born to women randomized to deliver vaginally ($p<0.001$). When adjusted for antiretroviral use in pregnancy (zidovudine alone), scheduled cesarean delivery lowered the risk of HIV transmission by 80%, although the results were no longer statistically significant (OR 0.2, 95% CI 0–1.7). When the data were analyzed by the actual mode of delivery, rather than to what group women were allocated, there was still a protective effect of scheduled cesarean delivery (adjusted odds ratio [OR] 0.3; 95% CI 0.1–0.8) but not with emergency cesarean delivery (adjusted OR 1.0; 95% CI 0.3–3.7) *[2]*. Results from a large meta-analysis of individual patient data from 15 prospective cohort studies also demonstrated a benefit of scheduled cesarean delivery with a 50% reduction in risk *[3]*. Primarily based on these data, the American College of

Obstetricians and Gynecologists (ACOG) has recommended consideration of scheduled cesarean delivery for HIV-infected pregnant women since 1999 *[4]*.

HIV RNA Level of 1,000 copies/mL as a Threshold for Recommendation of Cesarean Delivery

The original ACOG committee opinion was updated in 2000 to include further refinements based on HIV RNA levels *[1]*. Currently, ACOG *[1]* recommends that women with HIV RNA >1,000 copies/mL be counseled regarding the potential benefits of scheduled cesarean delivery. Initially, this threshold of 1,000 copies/mL was based largely on data from the Women and Infants Transmission Study (WITS), a large prospective cohort study that reported no HIV transmission among 57 women with HIV RNA levels <1,000 copies/mL *[5]*. Since that time, newer studies have demonstrated that HIV transmission occurred among infants born to women with low viral loads. In an analysis of 957 women with plasma viral loads of <1,000 copies/mL, cesarean delivery (scheduled or urgent) reduced the risk of HIV transmission when adjusting for potential confounders including receipt of maternal antiretroviral therapy, primarily zidovudine alone as prophylaxis (adjusted OR 0.30; p=0.022) *[6]*. Overall, the transmission rate among women with HIV RNA <1,000 copies/mL receiving antiretroviral therapy was 8 (1%) of 834. In a more recent report from a comprehensive national surveillance system in the United Kingdom and Ireland, 3 (0.1%) of 2,309 and 12 (1.2%) of 1,023 infants born to women with HIV RNA of <50 copies/mL and 50–999 copies/mL, respectively, were HIV infected *[7]*. These later studies document that transmission can occur even at very low HIV RNA levels. However, given the low rate of transmission among this group, it is unclear whether scheduled cesarean delivery confers any additional benefit in reduction of transmission. Therefore, decisions about mode of delivery for women with HIV RNA levels <1,000 copies/mL should be individualized based on discussion between the obstetrician and the mother.

Cesarean Delivery in the HAART Era

In surveillance data from the United Kingdom and Ireland, pregnant women receiving combination antiretroviral drugs regimens (e.g., at least 3 drugs) had transmission rates of about 1%, unadjusted for mode of delivery. Pregnant women with undetectable HIV viral load (< 50 copies/mL) had transmission rates of about 0.1% *[7]*. Given the low transmission rates achievable with use of maternal combination antiretroviral therapy or prophylaxis, the benefit of scheduled cesarean delivery is difficult to evaluate. Both the randomized clinical trial *[2]* and meta-analysis *[3]* documenting the benefits of cesarean delivery included mostly women who were receiving either no antiretrovirals or zidovudine only. However, other data partially address this issue. In a report from the European Collaborative Study that included data from 4,525 women, the overall transmission rate among the subset of women on a combination antiretroviral regimen was 11(1.2%) of 918 *[8]*. Among the subset of 560 women with undetectable HIV RNA levels (≤ 50 to ≤200 copies/mL, depending on site), scheduled cesarean delivery was associated with a significant reduction in perinatal transmission in univariate analysis (OR 0.07, 95% CI 0.02–0.31, p=0.0004). However, after adjustment for antiretroviral therapy (none vs. any), the effect was no longer significant (adjusted OR 0.52, 95% CI 0.14–2.03, p=0.359). Similarly, data from a European surveillance study did not demonstrate a statistically significant difference in transmission rates between scheduled cesarean delivery and planned vaginal delivery (adjusted OR 1.24; 95% CI 0.34–4.5) among women on combinational antiretroviral therapy or prophylaxis *[7]*. The transmission rate among all women who received at least 14 days of antiretroviral therapy was 40 (0.8%) of 4,864, regardless of mode of delivery. Therefore, it is not clear whether there is any benefit from scheduled cesarean delivery among women who have been receiving combination antiretroviral therapy for several weeks.

Women Presenting Late in Pregnancy

HIV-infected women who present in late pregnancy and are not receiving antiretroviral drugs may not have HIV RNA results available before delivery. Without current therapy, HIV RNA levels are unlikely to be <1,000 copies/mL at baseline. Even if combination antiretroviral therapy were begun immediately, reduction in plasma HIV RNA to undetectable levels usually takes several weeks, depending on the baseline RNA level *[9]*. In this instance, scheduled cesarean delivery is likely to provide additional benefit in reducing risk of perinatal transmission of HIV for women with unknown HIV RNA levels near the time of delivery.

Timing of Scheduled Cesarean Delivery

In general, for women without HIV infection, ACOG recommends that scheduled cesarean delivery not be performed before 39 weeks gestation due to the risk of iatrogenic prematurity *[10-11]*. However, in cases of cesarean delivery performed to prevent HIV transmission, ACOG recommends scheduling cesarean delivery at 38 weeks gestation in order to decrease the likelihood of onset of labor or rupture of membranes before delivery *[1]*. Among all women undergoing repeat cesarean delivery, the risk of any neonatal adverse event, which includes neonatal death, respiratory complications, hypoglycemia, newborn sepsis, or admission to the neonatal intensive care unit, is 15.3% at 37 weeks, 11.0% at 38 weeks, and 8.0% at 39 weeks *[11]*. Clinicians should recognize that newborn complications may be increased in planned early term births <39 weeks gestation. However, for HIV-infected women the benefits of decreasing HIV transmission by planned delivery at 38 weeks are generally thought to outweigh the risks. Furthermore, gestational age should be determined by last menstrual period and ultrasonography because amniocentesis to document lung maturity should be avoided when possible *[1]*.

Risk of Maternal Complications

Because maternal infectious morbidity is increased with cesarean delivery even among women without HIV infection, use of peri-operative antimicrobial prophylaxis is recommended for all women undergoing cesarean delivery. Most studies have demonstrated that HIV-infected women have increased rates of postoperative complications, mostly infectious, compared to HIV-uninfected women and that the risk of complications is related to the degree of immunosuppression *[12-17]*. Furthermore, a Cochrane review of six studies of HIV-infected women concluded that urgent cesarean delivery was associated with the highest risk of postpartum morbidity, that scheduled cesarean delivery was intermediate in risk, and that vaginal delivery had the lowest risk of morbidity *[18]*. Complication rates in most studies *[2, 19-23]* were within the range reported in populations of HIV-uninfected women with similar risk factors and were not of sufficient frequency or severity to outweigh the potential benefit of reduced transmission. Therefore, HIV-infected women should be counseled regarding the increased risks and potential benefits associated with cesarean delivery based on their HIV RNA levels and current antiretroviral therapy.

Management of Women Who Present in Early Labor or With Ruptured Membranes

Few data are available to address the question of whether performing cesarean delivery after the onset of labor or membrane rupture may decrease the risk of perinatal transmission of HIV. Most studies have shown the risk of transmission with cesarean delivery done after labor and membrane rupture for obstetric indications to be similar to that with vaginal delivery. In one study, the HIV transmission rate among women undergoing emergency cesarean delivery was similar to women delivering vaginally (1.6% vs. 1.9%, respectively) *[7]*. A meta-analysis of women mostly on zidovudine as a single drug or no antiretroviral therapy demonstrated a 2% increased transmission risk for every additional hour of ruptured membranes *[24]*. However, it is not clear how soon after the onset of labor or the rupture of membranes the benefit of cesarean delivery is lost *[25]*. Therefore, the management of women

originally scheduled for cesarean delivery who present with ruptured membranes or in labor must be individualized based on clinical factors such as duration of rupture, progress of labor, plasma RNA level, and current antiretroviral therapy or prophylaxis status. When membrane rupture occurs prior to 37 weeks gestation, decisions about delivery should be based on gestational age, HIV RNA level, current antiretroviral regimen, and evidence of acute infection (e.g., chorioamnionitis); consultation with an expert is recommended. The antiretroviral drug regimen should be continued and consideration given to initiating intravenous zidovudine if imminent delivery seems possible. There are no data to suggest that use of steroids to accelerate fetal lung maturity should be altered among HIV-infected women.

Table 9 provides a summary of recommendations regarding mode of delivery for different clinical scenarios.

Table 9. Clinical Scenarios and Recommendations Regarding Mode of Delivery to Reduce Perinatal Transmission of HIV

Clinical Scenario	Recommendations
HIV-infected woman presenting in late pregnancy (after about 36 weeks gestation), known to be HIV-infected but not receiving antiretroviral therapy, and who has HIV RNA level and CD4 count pending but unlikely to be available before delivery.	• The woman should be started on antiretroviral therapy as per **Table 6**. • The woman should be counseled that scheduled cesarean delivery is likely to reduce the risk of transmission to her infant. She should also be informed of the increased risks to her of cesarean delivery, including increased rates of postoperative infection, anesthesia risks, and other surgical risks. • If cesarean delivery is chosen, the procedure should be scheduled at 38 weeks gestation based on the best available clinical information. • When scheduled cesarean delivery is performed, the woman should receive continuous intravenous zidovudine infusion beginning 3 hours before surgery. • Use of prophylactic antibiotics at the time of cesarean delivery is generally recommended. • Options for continuing or initiating combination antiretroviral therapy after delivery should be discussed with the woman as soon as her viral load and CD4 count results are available. • The infant should receive 6 weeks of zidovudine after birth (see **Table 6**).
HIV-infected woman who initiated prenatal care early in the third trimester, is receiving a combination antiretroviral regimen, and has an initial virologic response but has HIV RNA levels that remain substantially greater than 1,000 copies/mL at 36 weeks gestation.	• The current combination antiretroviral regimen should be continued because the HIV RNA level is dropping appropriately. • The woman should be counseled that although she is responding to the antiretroviral therapy, it is unlikely that her HIV RNA level will fall below 1,000 copies/mL before delivery. Therefore, scheduled cesarean delivery may provide additional benefit in preventing intrapartum transmission of HIV. She should also be informed of the increased risks to her of cesarean delivery, including risks related to anesthesia and surgery and increased rates of postoperative infection. • If the woman chooses scheduled cesarean delivery, the procedure should be performed at 38 weeks gestation as determined by last menstrual period and ultrasonography. Intravenous zidovudine should be started at least 3 hours before surgery. • Other antiretroviral medications should be continued on schedule as much as possible before and after surgery. • Use of prophylactic antibiotics at the time of cesarean delivery is generally recommended. • The importance of adhering to therapy after delivery for the woman's health should be emphasized. • The infant should receive 6 weeks of zidovudine after birth (see **Table 6**).
HIV-infected woman on a combination antiretroviral regimen with an undetectable HIV RNA level at 36 weeks gestation.	• The woman should be counseled that her risk of perinatal transmission of HIV with a persistently undetectable HIV RNA level is low, probably 1% or less, even with vaginal delivery. There is currently no evidence that performing a scheduled cesarean delivery will lower her risk further. • Cesarean delivery has an increased risk of complications for the woman compared to vaginal delivery, and these risks must be balanced against the uncertain benefit of cesarean delivery in this case. • The infant should receive 6 weeks of zidovudine after birth (see **Table 6**).

Clinical Scenario	Recommendations
HIV-infected woman who has elected scheduled cesarean delivery but presents after rupture of membranes at >37 weeks gestation.	• Intravenous zidovudine should be started immediately. • Decision regarding mode of delivery should be individualized and based on clinical factors such as duration of rupture, anticipated progress of labor, plasma RNA level, and current antiretroviral therapy. • If the decision is made to proceed with vaginal delivery, some clinicians may consider administration of oxytocin, if clinically appropriate, in order to expedite delivery. Scalp electrodes and other invasive monitoring and operative delivery should be avoided if possible. • If the decision is made to proceed with cesarean delivery, administration of the loading dose of intravenous zidovudine should be completed prior to cesarean delivery. • The infant should receive 6 weeks of zidovudine after birth (see **Table 6**).

References

1. American College of Obstetricians and Gynecologists. ACOG committee opinion scheduled Cesarean delivery and the prevention of vertical transmission of HIV infection. Number 234, May 2000 (replaces number 219, August 1999). *Int J Gynaecol Obstet.* 2001;73(3):279-281.
2. European Mode of Delivery Collaboration. Elective caesarean-section versus vaginal delivery in prevention of vertical HIV-1 transmission: a randomised clinical trial. The European Mode of Delivery Collaboration. *Lancet.* 1999;353(9158):1035-1039.
3. International Perinatal HIV Group. The mode of delivery and the risk of vertical transmission of human immunodeficiency virus type 1--a meta-analysis of 15 prospective cohort studies. The International Perinatal HIV Group. *N Engl J Med.* 1999;340(13):977-987.
4. American College of Obstetricians and Gynecologists. ACOG committee opinion. Scheduled cesarean delivery and the prevention of vertical transmission of HIV infection. Number 219, August 1999. Committee on Obstetric Practice. American College of Obstetricians and Gynecologists. *Int J Gynaecol Obstet.* 1999;66(3):305-306.
5. Garcia PM, Kalish LA, Pitt J, et al. Maternal levels of plasma human immunodeficiency virus type 1 RNA and the risk of perinatal transmission. Women and Infants Transmission Study Group. *N Engl J Med.* 1999;341(6):394-402.
6. Ioannidis JP, Abrams EJ, Ammann A, et al. Perinatal transmission of human immunodeficiency virus type 1 by pregnant women with RNA virus loads <1000 copies/ml. *J Infect Dis.* 2001;183(4):539-545.
7. Townsend CL, Cortina-Borja M, Peckham CS, et al. Low rates of mother-to-child transmission of HIV following effective pregnancy interventions in the United Kingdom and Ireland, 2000-2006. *AIDS.* 2008;22(8):973-981.
8. European Collaborative Study. Mother-to-child transmission of HIV infection in the era of highly active antiretroviral therapy. *Clin Infect Dis.* 2005;40(3):458-465.
9. European Collaborative Study, Patel D, Cortina-Borja M, et al. Time to undetectable viral load after highly active antiretroviral therapy initiation among HIV-infected pregnant women. *Clin Infect Dis.* 2007;44(12):1647-1656.
10. American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 97: Fetal lung maturity. *Obstet Gynecol.* 2008;112(3):717-726.
11. Tita AT, Landon MB, Spong CY, et al. Timing of elective repeat cesarean delivery at term and neonatal outcomes. *N Engl J Med.* 2009;360(2):111-120.
12. Grubert TA, Reindell D, Kastner R, et al. Complications after caesarean section in HIV-1-infected women not taking antiretroviral treatment. *Lancet.* 1999;354(9190):1612-1613.
13. Maiques-Montesinos V, Cervera-Sanchez J, Bellver-Pradas J, et al. Post-cesarean section morbidity in HIV-positive women. *Acta Obstet Gynecol Scand.* 1999;78(9):789-792.

14. Rodriguez EJ, Spann C, Jamieson D, et al. Postoperative morbidity associated with cesarean delivery among human immunodeficiency virus-seropositive women. *Am J Obstet Gynecol.* 2001;184(6):1108-1111.
15. Semprini AE, Castagna C, Ravizza M, et al. The incidence of complications after caesarean section in 156 HIV-positive women. *AIDS.* 1995;9(8):913-917.
16. Urbani G, de Vries MM, Cronje HS, et al. Complications associated with cesarean section in HIV-infected patients. *Int J Gynaecol Obstet.* 2001;74(1):9-15.
17. Vimercati A, Greco P, Loverro G, et al. Maternal complications after caesarean section in HIV infected women. *Eur J Obstet Gynecol Reprod Biol.* 2000;90(1):73-76.
18. Read JS, Newell MK. Efficacy and safety of cesarean delivery for prevention of mother-to-child transmission of HIV-1. *Cochrane Database Syst Rev.* 2005(4):CD005479.
19. Faucher P, Batallan A, Bastian H, et al. [Management of pregnant women infected with HIV at Bichat Hospital between 1990 and 1998: analysis of 202 pregnancies]. *Gynecol Obstet Fertil.* 2001;29(3):211-225.
20. Fiore S, Newell ML, Thorne C. Higher rates of post-partum complications in HIV-infected than in uninfected women irrespective of mode of delivery. *AIDS.* 2004;18(6):933-938.
21. Marcollet A, Goffinet F, Firtion G, et al. Differences in postpartum morbidity in women who are infected with the human immunodeficiency virus after elective cesarean delivery, emergency cesarean delivery, or vaginal delivery. *Am J Obstet Gynecol.* 2002;186(4):784-789.
22. Read JS, Tuomala R, Kpamegan E, et al. Mode of delivery and postpartum morbidity among HIV-infected women: the women and infants transmission study. *J Acquir Immune Defic Syndr.* 2001;26(3):236-245.
23. Watts DH, Lambert JS, Stiehm ER, et al. Complications according to mode of delivery among human immunodeficiency virus-infected women with CD4 lymphocyte counts of < or = 500/microL. *Am J Obstet Gynecol.* 2000;183(1):100-107.
24. The International Perinatal HIV Group. Duration of ruptured membranes and vertical transmission of HIV-1: a meta-analysis from 15 prospective cohort studies. *AIDS.* 2001;15(3):357-368.
25. Jamieson DJ, Read JS, Kourtis AP, et al. Cesarean delivery for HIV-infected women: recommendations and controversies. *Am J Obstet Gynecol.* 2007;197(3 Suppl):S96-100.

OTHER INTRAPARTUM MANAGEMENT CONSIDERATIONS

Panel's Recommendations:

- ***Artificial rupture of membranes should generally be avoided because of a small but potential increased risk of transmission (BIII).***
- ***Routine use of fetal scalp electrodes for fetal monitoring should be avoided in the setting of maternal HIV infection (BIII).***
- ***Operative delivery with forceps or the vacuum extractor and episiotomy should be performed only in select circumstances (BIII).***
- ***When uterine atony results in excessive postpartum bleeding in women receiving a protease inhibitor or efavirenz, methergine should not be used unless alternative treatments for postpartum hemorrhage are not available and if the need for pharmacologic treatment outweighs the risks. If used, methergine should be administered in the lowest effective dose for the shortest duration possible (BIII).***

If spontaneous rupture of membranes occurs before or early during the course of labor, interventions to decrease the interval to delivery, such as administration of oxytocin, may be considered. For women who present in labor and the decision is made to proceed with vaginal delivery despite detectable viral load, artificial rupture of membranes should be avoided and employed only for a clear obstetric indication. For women with nondetectable viral load and planned vaginal delivery, data are limited, but artificial rupture of membranes should generally still be avoided and be performed only for clear obstetrical indications in order to avoid the small but potential increased risk of HIV transmission.

Obstetric procedures increasing the risk of fetal exposure to maternal blood, such as invasive fetal monitoring, have been implicated in increasing vertical transmission rates by some, but not all, investigators *[1-4]*. Although data are limited, the routine use of fetal scalp electrodes in labor should be avoided in the setting of maternal HIV infection because of the potential risk of disruption of fetal skin.

Operative vaginal delivery with forceps or the vacuum extractor and/or use of episiotomy theoretically may increase the risk of transmission but should not be delayed if there are clear obstetric indications *[2, 4]*.

Postpartum Hemorrhage, Antiretroviral Drugs, and Methergine Use

Women experiencing postpartum hemorrhage due to uterine atony are often managed with oral or parenteral methergine or other ergot alkaloids as a first-line agent. However, methergine should not be coadministered with drugs that are potent CYP3A4 enzyme inhibitors, including protease inhibitors. The concomitant use of ergotamines (e.g., methergine) and protease inhibitors has been associated with exaggerated vasoconstrictive responses. When uterine atony results in excessive postpartum bleeding in women receiving protease inhibitors or efavirenz as a component of an antiretroviral regimen, methergine should not be used unless alternative treatments (e.g., prostaglandin F 2 alpha, misoprostol, or oxytocin) are not available. If there are no alternative medications available and the need for pharmacologic treatment outweighs the risks, methergine should be used in as low a dosage and for as short a duration as possible. When other antiretroviral agents are used that are CYP3A4 inducers, there is the potential for decreased methergine levels and inadequate treatment effect; therefore, additional uterotonic agents may be needed.

References

1. Boyer PJ, Dillon M, Navaie M, et al. Factors predictive of maternal-fetal transmission of HIV-1. Preliminary analysis of zidovudine given during pregnancy and/or delivery. *JAMA.* 1994;271(24):1925-1930.
2. Mandelbrot L, Mayaux MJ, Bongain A, et al. Obstetric factors and mother-to-child transmission of human immunodeficiency virus type 1: the French perinatal cohorts. SEROGEST French Pediatric HIV Infection Study Group. *Am J Obstet Gynecol.* 1996;175(3 Pt 1):661-667.
3. Mofenson LM, Lambert JS, Stiehm ER, et al. Risk factors for perinatal transmission of human immunodeficiency virus type 1 in women treated with zidovudine. Pediatric AIDS Clinical Trials Group Study 185 Team. *N Engl J Med.* 1999;341(6):385-393.
4. Shapiro DE, Sperling RS, Mandelbrot L, et al. Risk factors for perinatal human immunodeficiency virus transmission in patients receiving zidovudine prophylaxis. Pediatric AIDS Clinical Trials Group protocol 076 Study Group. *Obstet Gynecol.* 1999;94(6):897-908.

Postpartum Care (Updated May 24, 2010)

POSTPARTUM FOLLOW-UP OF HIV-INFECTED WOMEN

Panel's Recommendations:

• The decision to continue antiretroviral therapy after delivery should be based on the nadir CD4 count, clinical symptoms/disease stage, presence of other indications for antiretroviral therapy, and patient and provider preference (AI).

• The immediate postpartum period poses unique challenges for adherence; new or continued supportive services should be assured prior to hospital discharge (AII).

• Women with a positive rapid HIV antibody test during labor require comprehensive follow-up, including confirmation of HIV infection and, if infection is confirmed, a full health assessment including evaluation for associated medical conditions, counseling related to newly diagnosed HIV infection, and assessment of need for antiretroviral therapy and opportunistic infection prophylaxis (AII).

• Breastfeeding is not recommended for HIV-infected women in the United States (AI).

• Contraceptive counseling should be included as a critical aspect of postpartum care (AIII).

Comprehensive care and support services are particularly important for women with HIV infection and their families, who often face multiple medical and social challenges. Components of comprehensive care include the following medical and supportive care services as needed:

- primary, gynecologic/obstetric, and HIV specialty care for the HIV-infected woman;
- pediatric care for her infant;
- family planning services;
- mental health services;
- substance abuse treatment;
- support services; and
- coordination of care through case management for the woman, her child(ren), and other family members.

Support services should be tailored to the individual woman's needs and may include case management, child care, respite care, assistance with basic life needs (e.g., housing, food, transportation), peer counseling, and legal and advocacy services. Ideally, this care should begin before pregnancy and should be continued throughout pregnancy and the postpartum period.

Maternal medical services during the postpartum period must be coordinated between obstetric care providers and HIV specialists. It is especially critical to ensure continuity of antiretroviral treatment when such treatment is required for the woman's health. The decision whether to continue antiretroviral therapy after delivery will depend on the woman's nadir CD4 count; clinical symptoms/disease stage; presence of other indications for antiretroviral therapy, such as chronic hepatitis B; and patient and provider preference. Ideally, a discussion of these factors should occur well before delivery.

Concerns have been raised about adherence to antiretroviral regimens during the postpartum period. Women should be counseled that the physical and psychological changes of the postpartum period, as well as the stresses and demands of caring for a new baby, might make adherence more difficult and that additional support may be needed to maintain good adherence during this period *[1-3]*. The health care provider should

be vigilant for signs of depression and illicit drug or alcohol use, which may require assessment and treatment and which may interfere with adherence. Poor adherence has been shown to be associated with virologic failure, development of resistance, and decreased long-term effectiveness of antiretroviral therapy *[4-6]*. Efforts to maintain adequate adherence during the postpartum period might prolong the effectiveness of therapy. See the section on *Adherence* in the ***Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents***.

Women with nadir CD4 counts less than the currently recommended threshold for institution of antiretroviral therapy *[7]* and/or symptomatic HIV infection should be encouraged to continue their antiretroviral regimens postpartum with no interruption. For women who began antiretroviral drugs for prophylaxis of transmission with a nadir CD4+ cell count greater than that currently recommended for treatment *[7]*, the decision of whether to continue therapy after delivery should be made in consultation with the HIV provider, taking into account current and nadir CD4+ lymphocyte counts and trajectory, HIV RNA levels, and patient preference.

For women whose antepartum regimen included an NNRTI and who plan to stop antiretroviral prophylaxis after delivery, consideration should be given to stopping the NNRTI and continuing the other antiretroviral drugs or switching from an NNRTI to a PI prior to interruption and continuing the PI with the other antiretroviral drugs for a period of time before electively stopping. The optimal interval between stopping an NNRTI and the other antiretroviral drugs is not known; at least 7 days is recommended. Given the potential of prolonged detectable NNRTI concentrations for more than 3 weeks in patients receiving efavirenz-based therapy, some experts recommend continuing the other antiretroviral agents or substituting a PI plus two other agents for up to 30 days. (See **Stopping Antiretroviral Therapy during Pregnancy** and **Prevention of Antiretroviral Drug Resistance**).

Among women with indications for continued antiretroviral therapy postpartum, planned interruption of antiretroviral therapy for several weeks or months has not been studied prospectively and cannot be recommended. However, women may be at increased risk of decreased adherence during the postpartum period. Intermittent adherence increases the risk of developing HIV resistance, so every effort should be made to maximize adherence. Simplification of an antiretroviral regimen (for example, to once-daily medications) could be considered. If a woman is unable to adhere to her regimen, it may be preferable to temporarily interrupt antiretroviral therapy while she works with her provider on strategies to improve adherence.

Data on follow-up of women from PACTG 076 who received antepartum and intrapartum zidovudine prophylaxis with discontinuation of the drug after delivery (median follow-up 4 years) demonstrated no difference in clinical, immunologic, virologic, and resistance status compared to women who received placebo *[8]*. Among women with CD4 cell counts >350 cells/mm^3 followed in the Women and Infants Transmission Study (WITS) cohort, there were no significant differences in CD4 count or disease progression among those who did or did not continue antiretroviral treatment after delivery *[9]*. However, for women receiving current combination antiretroviral prophylaxis regimens with no indication to continue antiretroviral therapy postpartum, the effect of limited-duration, fully suppressive antiretroviral prophylaxis in pregnancy on future treatment efficacy is unknown, and further research is needed. Such women may eventually require antiretroviral therapy again in the context of subsequent pregnancies or for advancing HIV disease.

Women with a positive rapid HIV antibody test during labor or at delivery require comprehensive medical assessment, counseling, and follow-up. Confirmatory HIV antibody testing should be performed as soon as possible after an initial positive rapid test to minimize the delay for definitive diagnosis *[10]*. Women with a positive rapid HIV antibody test should not breastfeed unless the confirmatory HIV test is negative. Women with a new HIV diagnosis postpartum should receive the same thorough evaluation as other newly identified infected patients, including consideration of antiretroviral therapy and opportunistic infection prophylaxis as indicated. Her other children and partner(s) should be referred for HIV testing.

In the United States and other parts of the world where replacement feeding is affordable, feasible, acceptable, sustainable, and safe, breastfeeding by HIV-infected women (including those receiving antiretroviral drugs) is

not recommended. Postpartum HIV transmission via breast milk is well documented and the risk of transmission is related to a variety of factors, including maternal health status and breast milk cell-free and cell-associated viral load *[11]*. There are no safe methods to treat breast milk that will completely eliminate the risk of HIV transmission associated with breastfeeding. Data are limited regarding the penetration of antiretroviral drugs into breast milk. The available data indicate that there is differential penetration of drugs into milk, with some drugs having high levels while others may have low or undetectable levels in breast milk, which raises concerns regarding both infant toxicity and selection of drug-resistant virus within breast milk *[12-13]*. Three studies have found multi-class drug resistance in breastfeeding infants who have become infected despite maternal triple antiretroviral drug prophylaxis *[14-16]*. Additionally, drug levels in the neonate from ingested breast milk may be subtherapeutic and cannot be relied on to interrupt transmission of HIV via breast milk.

Contraceptive counseling is a critical aspect of postpartum care. Although condoms are universally recommended for prevention of STD/HIV transmission, the unintended pregnancy rate even with consistent condom use alone is estimated at 10%–15% annually. Women should be educated about the risk of unintended pregnancy when condoms are the sole contraceptive method used. If another pregnancy is not desired in the near future and/or if the antiretroviral regimen contains potentially teratogenic agents such as efavirenz, women should be offered dual-method contraception *[17]*. Reversible options include intrauterine devices, which have been shown to be safe and effective in HIV-infected women *[18]*, and hormonal methods. Emergency contraception should not be recommended for routine use as a form of contraception but should be provided for use within 72 hours after an episode of unprotected intercourse or broken condom for women declining additional contraception.

Drug interactions have been documented between oral contraceptives and many antiretrovirals (see the ***Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents***, Tables 13, 14a, and 14b) *[7]*. These interactions do not necessarily rule out the use of hormonal contraceptive methods because there is no clear evidence of an effect on contraceptive or antiretroviral efficacy or toxicity. However, amprenavir/fosamprenavir levels are significantly lowered by oral contraceptives and co-administration is not recommended; it is not known if low-dose ritonavir boosting raises amprenavir levels sufficiently to allow co-administration. Depot medroxyprogesterone acetate (Depo-Provera, DMPA) pharmacokinetics are not significantly affected by nevirapine, efavirenz, or nelfinavir, and levels of these drugs were not significantly altered by DMPA *[19]*. Potential interactions between antiretroviral agents and the transdermal contraceptive patch, vaginal ring, and other implantable forms of contraception have not yet been defined. Permanent sterilization is an appropriate option only for those women who are certain they do not desire future childbearing. Advance counseling and discussion about sterilization is strongly encouraged in order to enable the woman to make a well-informed choice.

The postpartum period provides an opportunity to review and optimize women's health care; this should include cervical cancer screening and routine immunizations. This period also provides an opportunity to assess the need for behavioral health interventions; this should include mental health screening, including an assessment for signs of postpartum depression, and substance abuse treatment as indicated. Providers should also re-emphasize the importance of safer sex practices.

References

1. Cohn SE, Umbleja T, Mrus J, et al. Prior illicit drug use and missed prenatal vitamins predict nonadherence to antiretroviral therapy in pregnancy: adherence analysis A5084. *AIDS Patient Care STDS.* 2008;22(1):29-40.
2. Ickovics JR, Wilson TE, Royce RA, et al. Prenatal and postpartum zidovudine adherence among pregnant women with HIV: results of a MEMS substudy from the Perinatal Guidelines Evaluation Project. *J Acquir Immune Defic Syndr.* 2002;30(3):311-315.

3. Bardeguez AD, Lindsey JC, Shannon M, et al. Adherence to antiretrovirals among US women during and after pregnancy. *J Acquir Immune Defic Syndr.* 2008;48(4):408-417.
4. Paterson DL, Swindells S, Mohr J, et al. Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. *Ann Intern Med.* 2000;133(1):21-30.
5. Le Moing V, Chene G, Carrieri MP, et al. Clinical, biologic, and behavioral predictors of early immunologic and virologic response in HIV-infected patients initiating protease inhibitors. *J Acquir Immune Defic Syndr.* 2001;27(4):372-376.
6. Murri R, Ammassari A, Gallicano K, et al. Patient-reported nonadherence to HAART is related to protease inhibitor levels. *J Acquir Immune Defic Syndr.* 2000;24(2):123-128.
7. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. December 1, 2009:1-161. http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf.
8. Bardeguez AD, Shapiro DE, Mofenson LM, et al. Effect of cessation of zidovudine prophylaxis to reduce vertical transmission on maternal HIV disease progression and survival. *J Acquir Immune Defic Syndr.* 2003;32(2):170-181.
9. Watts DH, Lu M, Thompson B, et al. Treatment interruption after pregnancy: effects on disease progression and laboratory findings. *Infect Dis Obstet Gynecol.* 2009;2009:456717.
10. Centers for Disease Control and Prevention (CDC). Rapid HIV-1 antibody testing during labor and delivery for women of unknown HIV status: a practical guide and model protocol. 2004; www.cdc.gov/hiv/topics/testing/resources/guidelines/pdf/Labor&DeliveryRapidTesting.pdf.
11. Rousseau CM, Nduati RW, Richardson BA, et al. Longitudinal analysis of human immunodeficiency virus type 1 RNA in breast milk and of its relationship to infant infection and maternal disease. *J Infect Dis.* 2003;187(5):741-747.
12. Shapiro RL, Holland DT, Capparelli E, et al. Antiretroviral concentrations in breast-feeding infants of women in Botswana receiving antiretroviral treatment. *J Infect Dis.* 2005;192(5):720-727.
13. Mirochnick M, Thomas T, Capparelli E, et al. Antiretroviral concentrations in breast-feeding infants of mothers receiving highly active antiretroviral therapy. *Antimicrob Agents Chemother.* 2009;53(3):1170-1176.
14. Lidstrom J, Kumwenda N, Kafulafula G, et al. Antiretroviral treatment of HIV-infected women can induce multi-class drug resistance in their breastfeeding infants. *Antiviral Ther.* 2009;14 Suppl 1:A158.
15. Lidstrom J, Guay L, Musoke P, et al. Multi-class drug resistance arises frequently in HIV-infected breastfeeding infants whose mothers initiate HAART postpartum. Paper presented at: 17th Conference on Retroviruses and Opportunistic Infections; February 16-19, 2010; San Francisco, CA. Abstract 920.
16. Zeh C, Weidle P, Nafisa L, et al. Emergence of HIV-1 Drug Resistance among Breastfeeding Infants Born to HIV-infected Mothers Taking Antiretrovirals for Prevention of Mother-to-Child Transmission of HIV: The Kisumu Breastfeeding Study, Kenya. Paper presented at: 15th Conference on Retroviruses and Opportunistic Infections; February 3-6, 2008; Boston, MA. Abstract 84LB.
17. Cates W, Jr., Steiner MJ. Dual protection against unintended pregnancy and sexually transmitted infections: what is the best contraceptive approach? *Sex Transm Dis.* 2002;29(3):168-174.
18. Stringer EM, Kaseba C, Levy J, et al. A randomized trial of the intrauterine contraceptive device vs hormonal contraception in women who are infected with the human immunodeficiency virus. *Am J Obstet Gynecol.* 2007;197(2):144 e141-148.
19. Cohn SE, Park JG, Watts DH, et al. Depo-medroxyprogesterone in women on antiretroviral therapy: effective contraception and lack of clinically significant interactions. *Clin Pharmacol Ther.* 2007;81(2):222-227.

Neonatal Postnatal Care (Updated May 24, 2010)

INFANTS BORN TO MOTHERS WITH UNKNOWN HIV INFECTION STATUS

Panel's Recommendations:

- ***For infants born to mothers with unknown HIV status, rapid HIV antibody testing of the mother and/or infant is recommended as soon as possible after birth, with initiation of infant antiretroviral prophylaxis immediately if the rapid test is positive (AII).***
- ***If the rapid HIV antibody test is positive, standard antibody confirmatory testing (e.g., Western blot) should be performed on the mother (or her infant) as soon as possible. If the confirmatory test is negative, antiretroviral prophylaxis can be discontinued (AIII).***
- ***If the HIV antibody confirmatory test is positive, a newborn HIV DNA PCR should be obtained (AIII).***
- ***If the newborn HIV DNA PCR is positive, antiretroviral prophylaxis should be discontinued and the infant promptly referred to a pediatric HIV specialist for confirmation of the diagnosis and treatment of HIV infection with standard combination antiretroviral therapy (AI). The HIV-infected infant should also receive chemoprophylaxis against Pneumocystis jirovecci pneumonia (PCP) with oral trimethoprim-sulfamethoxazole according to guidelines (AII).***

If maternal HIV status is unknown and a rapid HIV antibody test was not performed on the mother during labor, rapid HIV antibody testing of the mother and/or infant is recommended as soon as possible after birth, with initiation of antiretroviral prophylaxis for the infant immediately if the rapid test is positive. Rapid HIV antibody testing should be available on a 24-hour basis at all facilities with a maternity service and/or neonatal intensive care or newborn nursery. A positive rapid antibody test on the mother or the infant should be presumed to indicate maternal HIV infection until standard antibody confirmatory testing clarifies maternal status. A standard confirmatory test (e.g., Western blot) should be performed on the mother (or her infant) as soon as possible after the initial positive rapid test *[1]*. A positive HIV antibody test in the infant indicates maternal but not necessarily infant HIV infection. Diagnosing HIV infection in infants <18 months of age requires virologic testing. If the confirmatory test on the mother (or infant) is negative, antiretroviral prophylaxis can be discontinued. If the confirmatory test is positive, an HIV DNA PCR should be obtained urgently from the newborn. If the HIV DNA PCR is positive, antiretroviral prophylaxis should be promptly discontinued and the infant should receive treatment for HIV infection with standard combination antiretroviral therapy according to established Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection developed by The Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children (**http://aidsinfo.nih.gov/contentfiles/PediatricGuidelines.pdf**). In addition, all newly diagnosed HIV-infected infants should receive chemoprophylaxis to prevent *Pneumocystis jirovecii* pneumonia (PCP) with oral trimethoprim-sulfamethoxazole beginning at 4–6 weeks of age *[2]*.

INFANT ANTIRETROVIRAL PROPHYLAXIS

Panel's Recommendations:

- ***The 6-week neonatal component of the zidovudine chemoprophylaxis regimen is recommended for all HIV-exposed neonates to reduce perinatal HIV transmission (AI).***
- ***Zidovudine should be initiated as close to the time of birth as possible, preferably within 6 to 12 hours of delivery (AII).***
- ***The 6-week zidovudine prophylaxis regimen is recommended at gestational age-appropriate doses; zidovudine should be dosed differently for premature infants <35 weeks than for infants ≥35 weeks (see text) (AII).***
- ***In the United States, the use of antiretroviral drugs other than zidovudine cannot be recommended in premature infants due to lack of dosing and safety data (BIII).***
- ***The use of intrapartum/neonatal zidovudine is recommended regardless of maternal zidovudine resistance history (BIII).***
- ***The decision to combine additional drugs with the 6-week zidovudine regimen should be accompanied by consultation with a pediatric HIV specialist and a discussion of the potential risks and benefits of this approach with the mother, preferably before delivery (BIII).***
- ***Some experts consider the use of zidovudine in combination with other antiretroviral drugs in certain situations, although the optimal prophylactic regimen for infants born to women in these circumstances is unknown (CIII).***
- ***Decisions regarding the use of additional drugs for the neonate will depend on the history of maternal past and current antiretroviral drug exposure, maternal HIV RNA level at or near delivery, current and previous maternal resistance testing, and availability of drug formulation and dosing information in the infant. If additional drugs are used, choice of drugs and dosing recommendations should be determined in consultation with a pediatric HIV specialist (CIII).***
- ***The National Perinatal HIV Hotline (1-888-448-8765) provides free clinical consultation on all aspects of perinatal HIV including infant care.***

Zidovudine Dosing

All HIV-exposed infants should receive postpartum antiretroviral drugs to reduce perinatal HIV transmission. The 6-week neonatal zidovudine chemoprophylaxis regimen is recommended for all HIV-exposed infants *[3-4]*. **Table 7** shows dosing for intravenous intrapartum zidovudine given in continuous infusion during labor and neonatal zidovudine dosing. **Table 8** shows intrapartum and neonatal dosing for additional drugs to be considered in certain situations as delineated below.

The recommended dose of zidovudine for post-exposure prophylaxis in full-term neonates is 2 mg/kg body weight orally every 6 hours for the first 6 weeks of life, starting as close to the time of birth as possible, preferably within 6 to 12 hours of delivery. If given intravenously, the dose is 1.5 mg/kg body weight every 6 hours. However, some international studies have used an oral infant zidovudine dose of 4 mg/kg body weight twice daily for prophylaxis *[5-9]*. Zidovudine is now approved for two or three times a day dosing when used for treatment of HIV-infected children aged 4 weeks or older and weighing 4 kg or greater. Although there are no definitive data to show pharmacokinetic equivalence of giving double the standard dose at a longer interval when using zidovudine for prophylaxis or whether such dosing has equivalent efficacy in reducing perinatal transmission, a regimen of dosing twice instead of four times daily may increase adherence to the regimen and could be considered when there are concerns about adherence to drug administration to the infant. However, there is inadequate hematologic safety data with administration of double the standard dose of zidovudine

twice daily in infants younger than 1 month of age. Frequent hematological monitoring is recommended in this instance.

A simplified zidovudine dosing regimen has been developed for use in low resource settings. This regimen consists of 10 mg given twice daily for infants weighing less than 2.5 kg at birth and 15 mg given twice daily for infants weighing more than 2.5 kg at birth. The advantage of this simplified regimen is that it avoids the need for dosing calculations and involves administration of either 1.0 or 1.5 mL of zidovudine syrup. The disadvantage of this dosing regimen is that, compared to mg-per-kg dosing, infants with birth weight greater than 3.75 kg will receive a smaller zidovudine dose and infants less than 3.75 kg will receive a larger zidovudine dose. This regimen could be used for infants in higher resource settings born after 35 weeks gestation if simplicity in zidovudine dosing and administration is of prime importance.

The zidovudine dosing requirements differ for premature infants and term infants. Zidovudine is primarily cleared through hepatic glucuronidation to an inactive metabolite; this metabolic pathway is immature in neonates, leading to prolonged zidovudine half-life and clearance compared to older infants. Because premature infants have even greater immaturity in hepatic metabolic function than full-term infants, further prolongation of clearance is seen *[10-11]*. The recommended zidovudine dosage for infants <35 weeks gestation is 2 mg/kg body weight per dose orally every 12 hours (or 1.5 mg/kg body weight intravenously per dose every 12 hours), increasing to 2 mg/kg body weight per dose every 8 hours at 2 weeks of age if ≥30 weeks gestation at birth or at 4 weeks of age if <30 weeks gestation at birth.

A 4-week neonatal chemoprophylaxis regimen is recommended in the United Kingdom *[12-13]*. This approach may be considered if there are concerns about adherence or toxicity with the 6-week regimen. An observational study in Ireland, where 4 weeks of infant zidovudine post-exposure chemoprophylaxis is standard (given in combination with maternal antiretroviral prophylaxis), reported a transmission rate of 1% in 835 HIV-exposed infants, which may be similar to transmission rates observed in the United States where 6 weeks of infant zidovudine prophylaxis is standard *[13]*. However, the optimal duration of neonatal zidovudine chemoprophylaxis has not been established in clinical trials and in the United States, when there are not concerns about adherence or toxicity, the standard 6-week infant zidovudine regimen is recommended.

General Considerations for Choice of Infant Prophylaxis

In certain situations, some experts combine the 6-week infant zidovudine prophylaxis regimen with additional antiretroviral drugs. Whether combining zidovudine with other antiretroviral drugs provides additional efficacy for prevention of transmission has not been proven in clinical trials. Additionally, appropriate drug formulations and dosing regimens for neonates are incompletely defined and there are minimal data about the safety of combination drugs in the neonate (see **Short-Term Antiretroviral Drug Safety and Choice for Neonatal Prophylaxis** and the ***Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection***). Therefore, the use of combination antiretroviral prophylaxis for the infant involves balancing potential benefits (in terms of preventing perinatal HIV transmission) with risks (in terms of toxicity to the infant).

Infants born to mothers who have received standard antepartum and intrapartum antiretroviral prophylaxis and have undetectable viral load are at very low risk of HIV transmission. However, the risk of transmission is increased when the mother has high viral load at delivery or when the mother has not received the full antepartum and/or intrapartum prophylaxis regimen. In such situations, some experts feel that the potential benefit of combining zidovudine infant prophylaxis with additional antiretroviral drugs may exceed the risk of multiple drug exposure to the infant. These situations include:

a. infants born to mothers who received antepartum and intrapartum antiretroviral drugs but who had suboptimal viral suppression at delivery, particularly if the infant was delivered vaginally;

b. infants born to mothers who received only intrapartum antiretroviral drugs;

c. infants born to mothers who received no antepartum or intrapartum antiretroviral drugs; and

d. infants born to mothers with known antiretroviral drug-resistant virus.

In each of these situations, there is a spectrum of transmission risk that will depend on a number of maternal and infant factors (e.g., maternal viral load, mode of delivery, gestational age at delivery); the risks and benefits of infant exposure to antiretroviral drugs in addition to zidovudine will differ depending on where the mother/child falls in that risk spectrum. For example, an infant born vaginally to a mother with a delivery HIV RNA level of ≥100,000 copies/mL has a higher risk of acquiring HIV infection than an infant born by cesarean delivery to a mother with a delivery HIV RNA level of approximately 10,000 copies/mL. Thus, a generic recommendation regarding use of combination drug regimens in these situations cannot be made and each situation needs to be considered individually. There are no data evaluating the efficacy of specific combination regimens in this situation and the choice of drugs in the neonate is limited (see **Short-Term Antiretroviral Drug Safety and Choice for Neonatal Prophylaxis**). Decisions to use combination infant antiretroviral prophylaxis should be made in consultation with a pediatric HIV specialist before delivery and should be accompanied by a discussion with the mother of the potential risks and benefits of this approach.

Antiretroviral combinations with the greatest experience in neonates are zidovudine in combination with single-dose nevirapine and the dual NRTI combination of zidovudine and lamivudine combined with and/or without the NNRTI nevirapine. Newborn and neonatal dosing information is not available for either nelfinavir or the currently available boosted PIs. Caution should be exercised when using ritonavir or boosted PIs in neonates because both ritonavir and lopinavir/ritonavir have been reported to cause heart block. Careful infant monitoring is needed if combination drugs are provided (see **Long-Term Follow-Up of Antiretroviral Drug-Exposed Infants**).

The National Perinatal HIV Hotline (1-888-448-8765)

The **National Perinatal HIV Hotline** is a federally funded service providing free clinical consultation to providers caring for HIV-infected pregnant women and their infants.

Infant Antiretroviral Prophylaxis Recommendations for Specific Clinical Situations

Infants Born to Mothers Who Received Antepartum/Intrapartum Antiretroviral Drugs with Effective Viral Suppression

Infants born to women who received standard antiretroviral prophylaxis regimens during pregnancy and labor and had undetectable viral load at delivery, or born to mothers with low viral load at delivery and delivered by cesarean section, have a very small risk of HIV acquisition. For example, in PACTG 316, the infection rate in infants born to women receiving antepartum PI-based therapy was 0.7% of 269 infants if delivery HIV RNA was <400 copies/mL *[4]*. Such infants should receive the 6-week zidovudine infant prophylaxis regimen. The benefit of combining zidovudine with additional antiretroviral drugs in reducing transmission in this situation would be very limited and this combination is not recommended.

Infants Born to Mothers Who Have Received Antepartum/Intrapartum Antiretroviral Drugs but Have Suboptimal Viral Suppression near Delivery

The risk of perinatal transmission is related to maternal antepartum viral load in women receiving antiretroviral drugs as well as in antiretroviral-naïve women *[14-16]*. Scheduled cesarean delivery is recommended for prevention of perinatal transmission for women who have received antepartum antiretroviral drugs but have detectable viremia near the time of delivery (i.e., HIV RNA >1,000 copies/mL) (see **Intrapartum Care** and **Transmission and Mode of Delivery**). In PACTG 316, transmission occurred in 0% of 17 infants when maternal delivery HIV RNA was >10,000 copies/mL and the infant was born by scheduled cesarean delivery *[4]*. However, not all women with detectable viremia near delivery will undergo cesarean delivery. Infants born to mothers with higher viral load near delivery, particularly if delivered vaginally, will have a greater risk

of HIV acquisition. There is a gradient of transmission risk based on HIV RNA levels as well as type of maternal antiretroviral therapy. In the Women and Infants Transmission Study, the risk of HIV transmission in women receiving triple combination antiretroviral prophylaxis was ≤1.8% in women with delivery HIV RNA <30,000 copies/mL and increased to 4.8% in women with HIV RNA ≥30,000 copies/mL *[16]*.

There are no data to address whether a more intensive combination infant prophylaxis regimen when the mother has detectable viremia near delivery provides further protection against transmission or at what level of viremia this risk becomes significant enough to outweigh the potential risks of infant combination antiretroviral exposure.

All infants should receive zidovudine for 6 weeks. As discussed earlier (see **Intrapartum Care**), in the PACTG 316 study, the addition of single-dose maternal/infant nevirapine did not reduce the risk of transmission among women who were receiving primarily combination therapy during pregnancy; there were no significant differences in transmission rates between the single-dose nevirapine or placebo groups in any HIV RNA subgroup, although only a small proportion (11%) of the women had HIV RNA levels >10,000 copies/mL at delivery. Given the lack of additional efficacy of single-dose nevirapine in this study and the risk of nevirapine resistance in the mother (and the infant should the infant become infected despite prophylaxis), addition of maternal/infant single-dose nevirapine is not recommended in this situation. Some experts would consider the use of dual or triple antiretroviral drug infant prophylaxis in selected circumstances (e.g., infants born vaginally to mothers with very high viral load near delivery).

Infants Born to Mothers Who Received Only Intrapartum Antiretroviral Drugs

All infants whose mothers have received only intrapartum antiretroviral drugs should be given zidovudine for 6 weeks. The post-exposure prophylaxis provided by the 6-week course of infant zidovudine treatment is a critical component of prevention when no maternal antepartum antiretroviral drugs have been received. The PETRA study demonstrated that intrapartum prophylaxis alone, without an infant post-exposure prophylaxis component, is not effective in reducing perinatal transmission *[5]*. Additionally, a study in Thailand indicated that when the mother has <4 weeks of antenatal zidovudine, longer infant zidovudine prophylaxis (6 weeks compared to 3 days) is required for optimal efficacy *[17]*.

As discussed in the **Intrapartum Care** section, in this situation, some experts would add maternal/infant single-dose nevirapine to the standard intravenous intrapartum/6-week infant zidovudine regimen. This situation differs from that studied in PACTG 316 because, in this circumstance, the mother has received no antepartum antiretroviral drugs. Nevirapine resistance can occur in infants exposed to single-dose nevirapine who become infected despite prophylaxis. The addition of at least 7 days of lamivudine to the 6-week infant zidovudine regimen may reduce the development of nevirapine resistance in such infants, similar to what is recommended for women receiving single-dose nevirapine (see **Intrapartum Care** and **Table 7**) *[18-19]*. However, although all HIV-infected mothers exposed to single-dose nevirapine are at risk of resistance, only a small proportion of infants exposed to single-dose nevirapine become infected and would benefit from the addition of lamivudine. Combination zidovudine/lamivudine may be associated with more severe hematologic toxicity than zidovudine alone (see **Short-Term Antiretroviral Drug Safety and Choice for Neonatal Prophylaxis** and see **Table 8** for dosing information), and more frequent hematologic monitoring of infants receiving this combination is recommended, particularly if it is given for more than 1 week *[20]*.

Although controversial, other experts might consider use of dual or triple antiretroviral drug infant prophylaxis for 6 weeks in this situation because maternal viral load at delivery will not be known and no antenatal therapy has been administered.

Infants Born to Mothers Who Did Not Receive Antepartum or Intrapartum Antiretroviral Drugs

Infants of HIV-infected mothers who have received neither antepartum nor intrapartum antiretroviral drugs should be started on prophylactic zidovudine as soon as possible after delivery. Observational studies suggest that post-exposure prophylaxis to the infant alone may be helpful in preventing HIV transmission. Epidemiologic data from a New York State study indicate a decline in transmission when infants were given zidovudine for the first 6 weeks of life compared to no prophylaxis *[21]*. Transmission rates were 9% (95% CI = 4.1%–17.5%) with zidovudine prophylaxis of newborns only (initiated within 48 hours after birth) versus 27% (95% CI = 21%–33%) with no zidovudine prophylaxis. For most infants in this study, prophylaxis was initiated within 12 hours *[22]*. Thus, when no maternal antepartum or intrapartum antiretroviral drugs have been received, the 6-week infant zidovudine prophylaxis regimen should be initiated as soon as possible after birth.

The interval during which post-exposure prophylaxis can be initiated and still be of benefit is undefined. When prophylaxis was delayed beyond 48 hours after birth in the New York State study, no efficacy could be demonstrated. Data from studies of animals indicate that the longer the delay in institution of prophylaxis, the less likely that infection will be prevented. In most studies of animals, antiretroviral prophylaxis initiated 24 to 36 hours after exposure has usually not been effective for preventing infection, although later administration has been associated with decreased viremia *[23-25]*. Initiation of post-exposure prophylaxis after 2 days of age is not likely to be efficacious in preventing transmission and, by age 14 days, infection would already be established in most infants *[26]*.

Some clinicians view this situation as analogous to nosocomial post-exposure prophylaxis *[27]* and may decide to provide zidovudine in combination with one or more other antiretroviral agents. However, there are no clinical trial data to demonstrate increased efficacy of combination antiretroviral drugs with 6-week zidovudine for infant-only post-exposure prophylaxis in nonbreastfeeding populations, although there is a clinical trial ongoing in the United States, South America, and South Africa.

Data are not available to demonstrate that 6 weeks of infant zidovudine combined with infant single-dose nevirapine at birth is superior to 6 weeks of zidovudine alone. A clinical trial of infant post-exposure prophylaxis in breastfeeding infants in Malawi (see **Lessons from International Clinical Trials of Short-Course Regimens for Prevention of HIV Perinatal Transmission** and **Table 3**) showed that the addition of 1 week of zidovudine to single-dose infant nevirapine was 36% more effective in reducing perinatal transmission compared to single-dose infant nevirapine alone *[7]*. Although this situation is not analogous to adding nevirapine to 6 weeks of zidovudine, particularly in formula-fed infants, some experts would provide single-dose nevirapine at birth to the infant in this situation with the addition of at least 7 days of lamivudine to reduce the risk of nevirapine resistance should the infant become infected (see **Table 8** for dosing information).

Although controversial, other experts might consider use of triple drug combination therapy in the infant for the 6-week prophylaxis period, similar to occupational post-exposure prophylaxis.

Infants Born to Mothers with Antiretroviral Drug-Resistant Virus

The optimal prophylactic regimen for newborns of women with antiretroviral drug-resistant virus is unknown. Antiretroviral prophylaxis for an infant born to a woman with known or suspected drug resistance should be determined in consultation with a pediatric HIV specialist before delivery.

Data from the Women and Infants Transmission Study (WITS) suggest that in women who have mixed zidovudine-resistant and zidovudine-sensitive viral populations, the zidovudine-sensitive rather than -resistant virus may be preferentially transmitted *[28-29]* (see **Table 7**). Thus, the 6-week infant zidovudine prophylaxis (along with maternal intravenous intrapartum zidovudine prophylaxis) continues to be recommended even when maternal zidovudine-resistant virus with thymidine-associated mutations (TAMs) is identified.

There have been some studies suggesting that antiretroviral drug-resistant virus may have decreased replicative capacity (reduced viral fitness) and transmissibility *[29]*. However, transmission of multi-drug resistant virus from mother to child has been reported *[30-32]*.

The use of zidovudine in combination with other antiretroviral drugs selected on the basis of maternal virus resistance testing may be considered for these newborns. The efficacy of this approach for prevention of transmission has not been proven in clinical trials, and appropriate dosing regimens for neonates are incompletely defined for many drugs. Decisions regarding use of additional drugs will depend on the history of maternal past and current antiretroviral drug exposure, HIV RNA level at or near delivery, current and previous maternal resistance testing, and availability of drug formulation and dosing information in the infant. Additional antiretroviral drugs that can be added to zidovudine include lamivudine and nevirapine.

Short-Term Antiretroviral Drug Safety and Choice for Neonatal Prophylaxis

Short-term toxicity of infant zidovudine prophylaxis has been minimal, consisting primarily of transient hematologic toxicity, mainly anemia, which generally resolves by age 12 weeks. Data on the toxicity of multiple antiretroviral drug exposure for the infant are limited.

The latest information on neonatal dosing for antiretroviral drugs can be found in the ***Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection***. Other than zidovudine, the NRTI with the most experience in use for neonatal prophylaxis is lamivudine, although neonatal exposure to combination zidovudine/lamivudine has generally been limited to 1 week *[5-6, 33]*. Six weeks of infant zidovudine/lamivudine exposure has been reported in a few studies; these studies suggest that hematologic toxicity may be increased over that seen with zidovudine alone, although the infants also had *in utero* exposure to maternal combination therapy. In a French study where 6 weeks of zidovudine/lamivudine was provided for infant prophylaxis in infants who were also exposed to antepartum zidovudine/lamivudine, more severe anemia and neutropenia were observed than in a historical cohort exposed only to zidovudine; anemia was observed in 15% and neutropenia in 18% of infants exposed to zidovudine/lamivudine, with 2% of infants requiring blood transfusion and 4% requiring treatment discontinuation for toxicity *[34]*. Similarly, in a Brazilian study using maternal antepartum and 6-week infant zidovudine/lamivudine prophylaxis, neonatal hematologic toxicity was common, with anemia seen in 69% and neutropenia in 13% of infants *[35]*. In a Phase I study of stavudine in pregnant women, infants received 6 weeks of zidovudine/lamivudine and a single dose of stavudine at age 1 and 6 weeks; 43% of 14 infants experienced grade 3 hematologic toxicity after birth (36% neutropenia and 7% anemia) *[36]*. Finally, in 3 Phase I studies of PIs (saquinavir/ritonavir, indinavir, or nelfinavir) in pregnancy, a total of 52 infants received 6 weeks of zidovudine/lamivudine (in 26 infants, zidovudine/lamivudine was combined with nelfinavir); grade 2 or higher hematologic toxicity was observed in 46% to 62% of infants *[37-39]*. Experience with other NRTI drugs for neonatal prophylaxis is more limited *[40-41]*. Hematologic and mitochondrial toxicity may be more common with exposure to multiple versus single NRTI drugs *[34, 42-45]*.

Nevirapine is the only NNRTI drug with a pediatric drug formulation and neonatal dosing information (see ***Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection***). Chronic, multiple-dose nevirapine can be rarely associated with severe and potentially life-threatening rash and hepatic toxicity. These toxicities have not been observed in infants receiving single-dose nevirapine or in breastfeeding infants receiving 6 to 14 weeks of daily infant nevirapine prophylaxis to prevent transmission of HIV via breast milk *[46-47]*. However, nevirapine drug resistance may occur with exposure to single-dose nevirapine should the infant become infected despite prophylaxis (see **Table 7**). If multiple-dose daily nevirapine is used as part of a combination infant prophylaxis regimen, some experts would stop nevirapine first and continue the other drugs for a period of time (e.g., at least 7 days). This drug administration strategy is adopted because the prolonged half-life of nevirapine in infants results in a period of persistent subtherapeutic level of nevirapine if all drugs are stopped simultaneously, resulting in a risk of nevirapine resistance should the infant become infected

despite prophylaxis. Antiretroviral drug resistance testing is recommended prior to initiation of antiretroviral therapy in all HIV-infected infants (see ***Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection***).

Of the PIs, nelfinavir, lopinavir/ritonavir, ritonavir, tipranavir, and fosamprenavir have pediatric drug formulations. However, dosing information for newborn infants is available only for nelfinavir, which has highly variable levels in neonates and requires high doses (more than 45 mg/kg body weight twice daily and possibly as high as 75 mg/kg body weight twice daily) to achieve target levels (see ***Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection***) *[39, 41]*. Pharmacokinetic data for treatment of HIV-infected infants aged 2 to 6 weeks of age with lopinavir/ritonavir are available. Although the lopinavir area under the curve with dosing 300 mg lopinavir/75 mg ritonavir per meter^2 body surface area twice daily was significantly lower than observed for infants older than 6 weeks, treatment was well tolerated, and 80% of 10 infants had viral control at 6 months *[48]*. Although under study, data are not yet available for infants younger than 2 weeks of age. However, there have been 4 premature infants (2 sets of twins) started on lopinavir/ritonavir from birth who developed heart block that resolved following discontinuation of the drug *[49-50]*. In studies of adults, both ritonavir and lopinavir/ritonavir cause dose-dependent prolongation of the PR interval and cases of significant heart block, including complete heart block, have been reported.

Dosing for premature infants is only available for zidovudine (see **Table 7**), making use of additional antiretroviral drugs more problematic in this group. Renal and hepatic metabolism is immature in preterm infants, which increases the risk of overdosing and toxicity. Additionally, zidovudine is the only antiretroviral drug available in intravenous formulation. Therefore, the 6-week zidovudine prophylaxis regimen is recommended for preterm infants at gestational age-appropriate doses. Use of antiretroviral drugs other than zidovudine cannot be recommended in premature infants due to lack of dosing and safety data.

Initial Postnatal Management of the HIV-Exposed Neonate

Panel's Recommendations:

- ***A complete blood count (CBC) and differential should be performed on the newborn as a baseline evaluation (BIII).***
- ***Decisions about the timing of subsequent monitoring of the hematologic parameters in the infant will depend on baseline hematologic values, gestational age at birth, clinical condition of the infant, dose of zidovudine being administered, receipt of concomitant medications, and maternal antepartum therapy (CIII).***
- ***Some experts recommend more intensive monitoring of hematologic and serum chemistry and liver function assays during the first few weeks of life for infants exposed to combination antiretroviral therapy in utero or during the neonatal period (CIII).***
- ***If hematologic abnormalities are identified while the infant is receiving prophylaxis, decisions on whether to continue infant antiretroviral prophylaxis need to be individualized. Consultation with an expert in pediatric HIV infection is advised if discontinuation of prophylaxis is considered (CIII).***
- ***Routine measurement of serum lactate is not recommended. However, measurement of serum lactate may be considered if an infant develops severe clinical symptoms of unknown etiology (particularly neurologic symptoms) (CIII).***
- ***Virologic tests are required to diagnose HIV infection in infants <18 months of age and should be performed at a minimum at ages 14 to 21 days, 1 to 2 months, and 4 to 6 months (AII).***
- ***To prevent Pneumocystis jirovecci pneumonia (PCP), all infants born to women with HIV infection should begin PCP prophylaxis at age 4–6 weeks, after completion of the zidovudine prophylaxis regimen, unless there is adequate test information to presumptively exclude HIV infection (see USPHS/IDSA Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Exposed and Infected Children) (AIII).***

A CBC and differential should be performed on the newborn as a baseline evaluation before administration of zidovudine. Anemia has been the primary complication of the 6-week zidovudine regimen in the neonate. In PACTG 076, infants in the zidovudine group had lower hemoglobin at birth than infants in the placebo group, with the maximal difference (1 gm/dL) occurring at age 3 weeks *[3]*. The lowest mean value for hemoglobin (10 gm/dL) occurred at 6 weeks of age in the zidovudine group. By 12 weeks of age, hemoglobin values in both groups were similar. No significant differences in other laboratory parameters were observed between groups.

Decisions about the timing of subsequent hematologic monitoring of infants following birth will depend on a number of factors, including baseline hematologic values, gestational age at birth, clinical condition of the infant, dose of zidovudine being administered, receipt of concomitant medications, and maternal antepartum therapy. Some experts re-check hematologic values in healthy infants receiving zidovudine prophylaxis only if the child is symptomatic, although others re-check hemoglobin and neutrophil count after 4 weeks of zidovudine prophylaxis.

If hematologic abnormalities are found, decisions on whether to continue infant antiretroviral prophylaxis need to be individualized. Considerations include the extent of the abnormality, whether the infant has related symptoms, duration of infant prophylaxis received, the risk of HIV infection in the infant (as assessed by whether the mother had received antiretroviral prophylaxis, her viral load near delivery, and mode of delivery), and availability of alternative interventions (e.g., erythropoietin, transfusion). Consideration may be given to reducing the duration of infant prophylaxis from 6 to 4 weeks. Consultation with an expert in pediatric HIV infection is advised if discontinuation of prophylaxis is considered.

Data are limited concerning potential toxicities in infants whose mothers have received combination antiretroviral therapy or when the infant receives more than zidovudine prophylaxis. Some studies suggest a higher incidence of anemia and/or neutropenia in infants who receive zidovudine prophylaxis but are born to mothers who received combination therapy compared to infants born to mothers who received only zidovudine during pregnancy *[45, 51-52]*. In PACTG 316, where 77% of mothers received antenatal combination therapy, significant grade 3 or higher anemia was seen in 13% and neutropenia in 12% of infants. Additionally, as discussed earlier, higher rates of hematologic toxicity have been observed in infants receiving zidovudine/lamivudine combination prophylaxis than in those receiving zidovudine alone.

Thus, more intensive monitoring of hematologic values and serum chemistry and liver function assays during the first few weeks of life is advised for these infants, based on what is known about the side effects of the drugs. For example, because hepatic toxicity is observed with most of the antiretroviral drugs, measurement of baseline liver transaminase levels in infants with exposure to multiple antiretroviral drugs *in utero* or receiving infant combination drug prophylaxis might be considered. Hematologic toxicity appears to be more significant in infants who receive both zidovudine and lamivudine as infant prophylaxis for 6 weeks and who were exposed to antepartum zidovudine/lamivudine. More frequent monitoring of hematologic values in these infants versus in infants who receive only zidovudine prophylaxis might be considered *[34]*. Additionally, as previously stated, hematologic safety data with administration of double the standard dose of zidovudine twice daily in infants under a month of age are inadequate. More frequent hematological monitoring is also recommended in this instance.

Although hyperlactatemia has been reported in infants with *in utero* antiretroviral exposure, this appears transient and in most cases asymptomatic *[53-54]*. Routine measurement of serum lactate in asymptomatic neonates to assess for potential mitochondrial toxicity is not recommended because the clinical relevance is unknown and predictive value for toxicity appears poor *[53-54]*. However, should an infant develop severe clinical symptoms of unknown etiology, particularly neurologic symptoms, obtaining serum lactate should be considered. If serum lactate is significantly abnormal (>5 mmol/L) in an infant with symptoms, antiretroviral prophylaxis should be discontinued and an expert in pediatric HIV infection should be consulted regarding potential alternate prophylaxis.

To prevent *Pneumocystis jirovecii* pneumonia (PCP), all infants born to women with HIV infection should begin trimethoprim-sulfamethoxazole prophylaxis at age 6 weeks, after completion of the zidovudine prophylaxis, unless there is adequate virologic test information to presumptively exclude HIV infection (see ***USPHS/IDSA Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Exposed and Infected Children***) *[2]*.

HIV infection in infants should be diagnosed using HIV DNA PCR or RNA virologic assays. Maternal HIV antibody crosses the placenta and will be detectable in all HIV-exposed infants up to 18 months of age; therefore, standard antibody tests should not be used for HIV diagnosis in newborns. HIV virologic testing should be performed at a minimum at ages 14 to 21 days, 1 to 2 months, and 4 to 6 months *[55]*. Some experts also perform a virologic test at birth, especially if the woman has not had good virologic control during pregnancy or if adequate follow-up of the infant may not be assured. A positive HIV virologic test should be confirmed as soon as possible with a second HIV virologic test on a different specimen. Two positive HIV tests constitute a diagnosis of HIV infection. Data do not indicate any delay in HIV diagnosis with HIV DNA PCR assays in infants who have received the zidovudine regimen *[3, 56]*. However, the effect of combination antiretroviral therapy in the mother or newborn on the sensitivity of infant virologic diagnostic testing, particularly using HIV RNA assays, is unknown. Therefore, although HIV RNA assays may be acceptable for diagnosis (particularly in older infants), HIV DNA PCR assays may be more optimal for diagnosing infection in the neonatal period.

HIV may be presumptively excluded with two or more negative tests with one at ≥14 days and another at ≥1 month of age. Definitive exclusion of HIV in nonbreastfed infants may be based on two negative virologic

tests at ≥1 month and ≥4 months of age. Many experts confirm HIV-negative status with an HIV antibody test at age 12 to 18 months. (Alternative algorithms exist for presumptive and definitive HIV exclusion *[55]*.)

Following birth, HIV-exposed infants should have a detailed physical examination and a thorough maternal history should be obtained. The HIV-infected mother may be coinfected with other pathogens that can be transmitted from mother to child, such as cytomegalovirus, herpes simplex virus, hepatitis B, hepatitis C, syphilis, toxoplasmosis, or tuberculosis. Infants born to mothers with such coinfections should undergo appropriate evaluation as indicated by maternal CD4 count and evidence of disease activity to rule out transmission of additional infectious agents. HIV-exposed infants born to HIV-infected mothers should follow the routine primary immunization schedule. Infants with known HIV infection may require modifications in the schedule for live virus vaccines (see ***USPHS/IDSA Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Exposed and Infected Children***).

Infant Feeding Practices and the Risk of HIV Transmission

In the United States, where safe infant feeding alternatives are available and free for women in need, HIV-infected women should not breastfeed their infants. Postnatally, mothers should be advised that although antiretroviral therapy is likely to reduce free virus in the plasma, the presence of cell-associated virus (intracellular HIV DNA) remains unaffected and may therefore continue to pose a transmission risk *[57]*.

Late HIV transmission events in infancy have recently been reported from three HIV-infected children. In each case HIV infection is suspected to have occurred as a result of infant consumption of premasticated food given to them from their caregivers. Phylogenetic comparisons of virus from cases and suspected sources and supporting clinical history and investigations identified the practice of feeding premasticated foods to infants as a potential risk factor for HIV transmission. Health care providers should routinely inquire about this feeding practice and instruct HIV-infected caregivers on safer feeding options *[58]*.

Long-Term Follow-Up of Antiretroviral Drug-Exposed Infants

Panel's Recommendations:

- ***Children with in utero/neonatal antiretroviral exposure who develop significant organ system abnormalities of unknown etiology, particularly of the nervous system or heart, should be evaluated for potential mitochondrial dysfunction (CIII).***
- ***Follow-up of children with antiretroviral exposure should continue into adulthood because of the theoretical concerns regarding the potential for carcinogenicity of the nucleoside analogue antiretroviral drugs (CIII).***

Data remain insufficient to address the effect that exposure to zidovudine or other antiretroviral agents *in utero* might have on long-term risk of neoplasia or organ system toxicities in children. Data from follow-up of PACTG 076 infants through age 6 years do not indicate any differences in immunologic, neurologic, and growth parameters between infants who were exposed to the zidovudine regimen and those who received placebo, and no malignancies have been seen *[59-61]*. As discussed earlier in the section on **NRTI Drugs and Mitochondrial Toxicity**, there are conflicting data regarding whether mitochondrial dysfunction is associated with perinatal antiretroviral exposure. Mitochondrial dysfunction should be considered in uninfected children with perinatal antiretroviral exposure who present with severe clinical findings of unknown etiology, particularly neurologic findings.

Continued evaluation of early and late effects of *in utero* antiretroviral exposure is ongoing through several mechanisms, including the Pediatric HIV/AIDS Cohort Study (PHACS), Surveillance Monitoring of Antiretroviral Toxicity Study, natural history studies, and HIV/AIDS surveillance conducted by state health departments and CDC. Because most of the available follow-up data relate to *in utero* exposure to antenatal

zidovudine alone and most pregnant women with HIV infection currently receive combination therapy, it is critical that studies to evaluate potential adverse effects of *in utero* drug exposure continue to be supported.

Innovative methods are needed to provide follow-up of infants with *in utero* exposure to antiretroviral drugs. Information regarding such exposure should be part of the ongoing permanent medical record of the child, particularly for uninfected children. Children with *in utero* antiretroviral exposure who develop significant organ system abnormalities of unknown etiology, particularly of the nervous system or heart, should be evaluated for potential mitochondrial dysfunction *[62-64]*. Follow-up of children with antiretroviral exposure should continue into adulthood because of the theoretical concerns regarding the potential for carcinogenicity of the nucleoside analogue antiretroviral drugs. Long-term follow-up should include yearly physical examinations of all children exposed to antiretroviral drugs.

HIV surveillance databases from states that require HIV reporting provide an opportunity to collect population-based information concerning *in utero* antiretroviral exposure. To the extent permitted by federal law and regulations, data from these confidential registries can be used to compare with information from birth defect and cancer registries to identify potential adverse outcomes.

References

1. Centers for Disease Control and Prevention (CDC). Rapid HIV-1 antibody testing during labor and delivery for women of unknown HIV status: a practical guide and model protocol. 2004; www.cdc.gov/hiv/topics/testing/resources/guidelines/pdf/Labor&DeliveryRapidTesting.pdf.
2. Centers for Disease Control and Prevention (CDC). Guidelines for the Prevention and Treatment of Opportunistic Infections among HIV-exposed and HIV-infected children. *MMWR.* 2009;58(RR-11):1-176.
3. Connor EM, Sperling RS, Gelber R, et al. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. *N Engl J Med.* 1994;331(18):1173-1180.
4. Dorenbaum A, Cunningham CK, Gelber RD, et al. Two-dose intrapartum/newborn nevirapine and standard antiretroviral therapy to reduce perinatal HIV-1 transmission: a randomized trial. *JAMA.* 2002;288(2):189-198.
5. Petra Study Team. Efficacy of three short-course regimens of zidovudine and lamivudine in preventing early and late transmission of HIV-1 from mother to child in Tanzania, South Africa, and Uganda (Petra study): a randomised, double-blind, placebo-controlled trial. *Lancet.* 2002;359(9313):1178-1186.
6. Moodley D, Moodley J, Coovadia H, et al. A multicenter randomized controlled trial of nevirapine versus a combination of zidovudine and lamivudine to reduce intrapartum and early postpartum mother-to-child transmission of human immunodeficiency virus type 1. *J Infect Dis.* 2003;187(5):725-735.
7. Taha TE, Kumwenda NI, Gibbons A, et al. Short postexposure prophylaxis in newborn babies to reduce mother-to-child transmission of HIV-1: NVAZ randomised clinical trial. *Lancet.* 2003;362(9391):1171-1177.
8. Taha TE, Kumwenda NI, Hoover DR, et al. Nevirapine and zidovudine at birth to reduce perinatal transmission of HIV in an African setting: a randomized controlled trial. *JAMA.* 2004;292(2):202-209.
9. Shapiro RL, Thior I, Gilbert PB, et al. Maternal single-dose nevirapine versus placebo as part of an antiretroviral strategy to prevent mother-to-child HIV transmission in Botswana. *AIDS.* 2006;20(9):1281-1288.
10. Capparelli E, Mirochnick M, Dankner WM, et al. Pharmacokinetics and tolerance of zidovudine in preterm infants. *J Pediatr.* 2003;142(1):47-52.
11. Mirochnick M, Capparelli E, Connor J. Pharmacokinetics of zidovudine in infants: a population analysis across studies. *Clin Pharmacol Ther.* 1999;66(1):16-24.
12. de Ruiter A, Mercey D, Anderson J, et al. British HIV Association and Children's HIV Association guidelines for the management of HIV infection in pregnant women 2008. *HIV Med.* 2008;9(7):452-502.
13. Ferguson W, Good M, Walksh A, et al. Four weeks of neonatal antiretroviral therapy (ART) is sufficient to optimally prevent mother to child transmission (PMTCT) of HIV. 48th Annual ICAAC/IDSA 46th Annual Meeting, October 25-28, 2008; Washington, DC. Abstract H-459, page 400.

14. Mofenson LM, Lambert JS, Stiehm ER, et al. Risk factors for perinatal transmission of human immunodeficiency virus type 1 in women treated with zidovudine. Pediatric AIDS Clinical Trials Group Study 185 Team. *N Engl J Med.* 1999;341(6):385-393.
15. Garcia PM, Kalish LA, Pitt J, et al. Maternal levels of plasma human immunodeficiency virus type 1 RNA and the risk of perinatal transmission. *N Engl J Med.* 1999;341(6):394-402.
16. Cooper ER, Charurat M, Mofenson LM, et al. Combination antiretroviral strategies for the treatment of pregnant HIV-1 infected women and prevention of perinatal HIV-1 transmission. *J Acquir Immune Defic Syndr Hum Retrovirol.* 2002;29(5):484-494.
17. Lallemant M, Jourdain G, Le Coeur S, et al. A trial of shortened zidovudine regimens to prevent mother-to-child transmission of human immunodeficiency virus type 1. Perinatal HIV Prevention Trial (Thailand) Investigators. *N Engl J Med.* 2000;343(14):982-991.
18. Chaix ML, Ekouevi DK, Rouet F, et al. Low risk of nevirapine resistance mutations in the prevention of mother-to-child transmission of HIV-1: Agence Nationale de Recherches sur le SIDA Ditrame Plus, Abidjan, Cote d'Ivoire. *J Infect Dis.* 2006;193(4):482-487. Epub 2006 Jan 2011.
19. McIntyre JA, Hopley M, Moodley D, et al. Efficacy of short-course AZT plus 3TC to reduce nevirapine resistance in the prevention of mother-to-child HIV transmission: a randomized clinical trial. *PLoS Med.* 2009;6(10):e1000172.
20. Mandelbrot L, Landreau-Mascaro A, Rekacewicz C, et al. Lamivudine-zidovudine combination for prevention of maternal-infant transmission of HIV-1. *JAMA.* 2001;285(16):2083-2093.
21. Wade NA, Birkhead GS, Warren BL, et al. Abbreviated regimens of zidovudine prophylaxis and perinatal transmission of the human immunodeficiency virus. *N Engl J Med.* 1998;339(20):1409-1414.
22. Wade NA, Birkhead GS, French PT. Short courses of zidovudine and perinatal transmission of HIV (letter). *N Engl J Med.* 1999;340(13):1040-1043.
23. Van Rompay KK, Otsyula MG, Marthas ML, et al. Immediate zidovudine treatment protects simian immunodeficiency virus-infected newborn macaques against rapid onset of AIDS. *Antimicrob Agents Chemother.* 1995;39(1):125-131.
24. Tsai CC, Follis KE, Sabo A, et al. Prevention of SIV infection in macaques by (R)-9-(2-phosphonylmethoxypropyl)adenine. *Science.* 1995;270(5239):1197-1199.
25. Bottiger D, Johansson NG, Samuelsson B, et al. Prevention of simian immunodeficiency virus, SIVsm, or HIV-2 infection in cynomolgus monkeys by pre- and postexposure administration of BEA-005. *AIDS.* 1997;11(2):157-162.
26. Dunn DT, Brandt CD, Krivine A, et al. The sensitivity of HIV-1 DNA polymerase chain reaction in the neonatal period and the relative contributions of intra-uterine and intra-partum transmission. *AIDS.* 1995;9(9):F7-11.
27. Panlilio AL, Cardo DM, Grohskopf LA, et al. Updated U.S. Public Health Service guidelines for the management of occupational exposures to HIV and recommendations for postexposure prophylaxis. *MMWR Recomm Rep.* 2005;54(RR-9):1-17.
28. Colgrove RC, Pitt J, Chung PH, et al. Selective vertical transmission of HIV-1 antiretroviral resistance mutations. *AIDS.* 1998;12(17):2281-2288.
29. Bauer GR, Colgrove RC, Larussa PS, et al. Antiretroviral resistance in viral isolates from HIV-1-transmitting mothers and their infants. *AIDS.* 2006;20(13):1707-1712.
30. Cohan D, Feakins C, Wara D, et al. Perinatal transmission of multidrug-resistant HIV-1 despite viral suppression on an enfuvirtide-based treatment regimen. *AIDS.* 2005;19(9):989-990.
31. Desai N, Mathur M. Selective transmission of multidrug resistant HIV to a newborn related to poor maternal adherence. *Sex Transm Infect.* 2003;79(5):419-421.
32. De Jose MI, Ramos JT, Alvarez S, et al. Vertical transmission of HIV-1 variants resistant to reverse transcriptase and protease inhibitors. *Arch Intern Med.* 2001;161(22):2738-2739.
33. Moodley J, Moodley D, Pillay K, et al. Pharmacokinetics and antiretroviral activity of lamivudine alone or when coadministered with zidovudine in human immunodeficiency virus type 1-infected pregnant women and their offspring. *J Infect Dis.* 1998;178(5):1327-1333.
34. Mandelbrot L, Landreau-Mascaro A, Rekacewicz C, et al. Lamivudine-zidovudine combination for prevention of maternal-infant transmission of HIV-1. *JAMA.* 2001;285(16):2083-2093.
35. Lambert JS, Nogueira SA, Abreu T, et al. A pilot study to evaluate the safety and feasibility of the administration of AZT/3TC fixed dose combination to HIV infected pregnant women and their infants in Rio de Janeiro, Brazil. *Sex Transm Infect.* 2003;79(6):448-452.

36. Wade NA, Unadkat JD, Huang S, et al. Pharmacokinetics and safety of stavudine in HIV-infected pregnant women and their infants: Pediatric AIDS Clinical Trials Group protocol 332. *J Infect Dis.* 2004;190(12):2167-2174.
37. Zorrilla CD, Van Dyke R, Bardeguez A, et al. Clinical response and tolerability to and safety of saquinavir with low-dose ritonavir in human immunodeficiency virus type 1-infected mothers and their infants. *Antimicrob Agents Chemother.* 2007;51(6):2208-2210.
38. Unadkat JD, Wara DW, Hughes MD, et al. Pharmacokinetics and safety of indinavir in human immunodeficiency virus-infected pregnant women. *Antimicrob Agents Chemother.* 2007;51(2):783-786.
39. Mirochnick M, Stek A, Acevedo M, et al. Safety and pharmacokinetics of nelfinavir coadministered with zidovudine and lamivudine in infants during the first 6 weeks of life. *J Acquir Immune Defic Syndr.* 2005;39(2):189-194.
40. Gray G, Violari A, McIntyre J, et al. Antiviral activity of nucleoside analogues during short-course monotherapy or dual therapy: its role in preventing HIV infection in infants. *J Acquir Immune Defic Syndr.* 2006;42(2):169-176.
41. Rongkavilit C, van Heeswijk RP, Limpongsanurak S, et al. Dose-escalating study of the safety and pharmacokinetics of nelfinavir in HIV-exposed neonates. *J Acquir Immune Defic Syndr.* 2002;29(5):455-463.
42. Torres SM, Walker DM, Carter MM, et al. Mutagenicity of zidovudine, lamivudine, and abacavir following in vitro exposure of human lymphoblastoid cells or in utero exposure of CD-1 mice to single agents or drug combinations. *Environ Mol Mutagen.* 2007;48(3-4):224-238.
43. Le Chenadec J, Mayaux MJ, Guihenneuc-Jouyaux C, et al. Perinatal antiretroviral treatment and hematopoiesis in HIV-uninfected infants. *AIDS.* 2003;17(14):2053-2061.
44. Pacheco SE, McIntosh K, Lu M, et al. Effect of perinatal antiretroviral drug exposure on hematologic values in HIV-uninfected children: An analysis of the women and infants transmission study. *J Infect Dis.* 2006;194(8):1089-1097.
45. Feiterna-Sperling C, Weizsaecker K, Bührer C, et al. Hematologic effects of maternal antiretroviral therapy and transmission prophylaxis in HIV-1-exposed uninfected newborn infants. *J Acquir Immune Defic Syndr.* 2007;45(1):43-51.
46. Six Week Extended-Dose Nevirapine (SWEN) Study Team, Bedri A, Gudetta B, et al. Extended-dose nevirapine to 6 weeks of age for infants to prevent HIV transmission via breastfeeding in Ethiopia, India, and Uganda: an analysis of three randomised controlled trials. *Lancet.* 2008;372(9635):300-313.
47. Kumwenda NI, Hoover DR, Mofenson LM, et al. Extended antiretroviral prophylaxis to reduce breast-milk HIV-1 transmission. *N Engl J Med.* 2008;359(2):119-129.
48. Chadwick EG, Pinto J, Yogev R, et al. Early initiation of lopinavir/ritonavir in infants less than 6 weeks of age: pharmacokinetics and 24-week safety and efficacy. *Pediatr Infect Dis J.* 2009;28(3):215-219.
49. Lopriore E, Rozendaal L, Gelinck LB, et al. Twins with cardiomyopathy and complete heart block born to an HIV-infected mother treated with HAART. *AIDS.* 2007;21(18):2564-2565.
50. McArthur MA, Kalu SU, Foulks AR, et al. Twin preterm neonates with cardiac toxicity related to lopinavir/ritonavir therapy. *Pediatr Infect Dis J.* 2009;28(12):1127-1129.
51. El Beitune P, Duarte G. Antiretroviral agents during pregnancy: consequences on hematologic parameters in HIV-exposed, uninfected newborn infant. *Eur J Obstet Gynecol Reprod Biol.* 2006;128(1-2):59-63.
52. Watson WJ, Stevens TP, Weinberg GA. Profound anemia in a newborn infant of a mother receiving antiretroviral therapy. *Pediatr Infect Dis J.* 1998;17(5):435-436.
53. Ekouevi DK, Touré R, Becquet R, et al. Serum lactate levels in infants exposed peripartum to antiretroviral agents to prevent mother-to-child transmission of HIV: Agence Nationale de Recherches Sur le SIDA et les Hépatites Virales 1209 study, Abidjan, Ivory Coast. *Pediatrics.* 2006;118(4):e1071-1077.
54. Noguera A, Fortuny C, Muñoz-Almagro C, et al. Hyperlactatemia in human immunodeficiency virus-uninfected infants who are exposed to antiretrovirals. *Pediatrics.* 2004;114(5):e598-603.
55. Centers for Disease Control and Prevention (CDC). Revised surveillance case definitions for HIV infection among adults, adolescents, and children aged <18 months and for HIV infection and AIDS among children aged 18 months to <13 years--United States, 2008. *MMWR Recomm Rep.* 2008;57(RR-10):1-12.
56. Kovacs A, Xu J, Rasheed S, et al. Comparison of a rapid nonisotopic polymerase chain reaction assay with four commonly used methods for the early diagnosis of human immunodeficiency virus type 1 infection in neonates and children. *Pediatr Infect Dis J.* 1995;14(11):948-954.

57. Gaillard P, Fowler MG, Dabis F, et al. Use of antiretroviral drugs to prevent HIV-1 transmission through breast-feeding: from animal studies to randomized clinical trials. *J Acquir Immune Defic Syndr.* 2004;35(2):178-187.
58. Gaur AH, Dominguez KL, Kalish ML, et al. Practice of feeding premasticated food to infants: a potential risk factor for HIV transmission. *Pediatrics.* 2009;124(2):658-666.
59. Culnane M, Fowler MG, Lee SS, et al. Lack of long-term effects of in utero exposure to zidovudine among uninfected children born to HIV-infected women. *JAMA.* 1999;281(2):151-157.
60. Hanson IC, Antonelli TA, Sperling RS, et al. Lack of tumors in infants with perinatal HIV-1 exposure and fetal/neonatal exposure to zidovudine. *J Acquir Immune Defic Syndr Hum Retrovirol.* 1999;20(5):463-467.
61. Brogly S, Williams P, Seage G, 3rd,, et al. In utero nucleoside reverse transcriptase inhibitor exposure and cancer in HIV-uninfected children: an update from the pediatric AIDS clinical trials group 219 and 219C cohorts. *J Acquir Immune Defic Syndr.* 2006;41(4):535-536.
62. Blanche S, Tardieu M, Rustin P, et al. Persistent mitochondrial dysfunction and perinatal exposure to antiretroviral nucleoside analogues. *Lancet.* 1999;354(9184):1084-1089.
63. Barret B, Tardieu M, Rustin P, et al. Persistent mitochondrial dysfunction in HIV-1-exposed but uninfected infants: clinical screening in a large prospective cohort. *AIDS.* 2003;17(12):1769-1785.
64. Spector SA, Saitoh A. Mitochondrial dysfunction: prevention of HIV-1 mother-to-infant transmission outweighs fear. *AIDS.* 2006;20(13):1777-1778.

Appendix: Financial Disclosure for Members of HHS Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission – January 2010

Name	Panel Status*	Company	Relationship
Erika Aaron	M	Gilead Pharmaceuticals Tibotec	Research Support Research Support
Elaine Abrams	M	NONE	N/A
Jean Anderson	M	Abbott Tibotec	Honoraria, Funded printing of provider tool for preconception care Honoraria, Advisory Board
Dawn Averitt Bridge	M	Boehringer Ingelheim Bristol-Myers Squibb Gilead Merck Tibotec	Consultant Advisory Board, Consultant Advisory Board Advisory Board, Honoraria, Consultant Consultant
Rana Chakraborty	M	NONE	N/A
Susan E. Cohn		Tibotec	Advisory Board
Amanda Cotter	M	NONE	N/A
Susan Cu-Uvin	M	Bristol-Myers Squibb Family Health International (FHI) and the Contraceptive Research and Development Program (CONRAD)	Research Support Advisory Board
Judith Feinberg	M	Bristol-Meyers Squibb Glaxo Smith Kline Merck Pfizer Tibotec	Advisory Board, Research Support, Speakers' Bureau Speakers' Bureau Advisory Board, Speakers' Bureau Research Support, Speakers' Bureau Advisory Board, Research Support, Speakers' Bureau
Patricia Flynn	M	Tibotec	Clinical trials agreement
Mary Glenn Fowler	M	NONE	N/A
Robert Maupin	M	NONE	N/A
Howard Minkoff	M	NONE	N/A
Mark Mirochnick	M	NONE	N/A
Fatima Y. Prioleau	M	New York State Education	Stockholder
Stephen Spector	M	Pfizer Sanofi Pasteur	Stockholder Stockholder
Ruth Tuomala	M	NONE	N/A
Geoffrey A. Weinberg	M	Medimmune, Inc. Merck Vaccines Sanofi Pasteur Vaccines Glaxo Smith Kline Vaccines	Advisory Board Speaker's Bureau Speaker's Bureau Speaker's Bureau

Name	Panel Status*	Company	Relationship
Federal Government Representatives			
Songhai Barclift	GR	NONE	N/A
Brian Feit	GR	NONE	N/A
Edward Handelsman	GR	NONE	N/A
Denise Jamieson	GR	NONE	N/A
Lynne Mofenson	GR	NONE	N/A
Alan Shaprio	GR	NONE	N/A
Heather D. Watts	GR	NONE	N/A

* M = Member; GR = government representative; N/A = not applicable

Supplement: Safety and Toxicity of Individual Antiretroviral Agents in Pregnancy

(Updated May 24, 2010)

Glossary of Terms for Supplement

Clastogenic: causing disruption or breakages of chromosomes

Mutagenic: inducing or capable of inducing genetic mutation

Genotoxic: damaging to genetic material (e.g., DNA, chromosomes)

Carcinogenic: producing or tending to produce cancer

Notes: (1) Some agents (e.g., certain chemicals or forms of radiation) are both mutagenic and clastogenic. (2) Genetic mutations and/or chromosome damage can contribute to cancer formation.

NUCLEOSIDE AND NUCLEOTIDE ANALOGUE REVERSE TRANSCRIPTASE INHIBITORS

Six nucleoside analogue reverse transcriptase inhibitors are currently approved (zalcitabine is no longer available in the United States). Data are available from clinical trials in human pregnancy for zidovudine, abacavir, lamivudine, didanosine, emtricitabine, and stavudine. Tenofovir disoproxil fumarate is the first nucleotide analogue reverse transcriptase inhibitor. The nucleoside analogue drugs require three intracellular phosphorylation steps to form the triphosphate nucleoside, which is the active drug moiety. Tenofovir, an acyclic nucleotide analogue drug, contains a monophosphate component attached to the adenine base, and hence only requires two phosphorylation steps to form the active moiety.

For information regarding the nucleoside analogue drug class and potential mitochondrial toxicity in pregnancy and to the infant, see **NRTI Drugs and Mitochondrial Toxicity** in the Perinatal Guidelines.

Abacavir (Ziagen, ABC) is classified as FDA pregnancy category C.

- Animal carcinogenicity studies
  Abacavir is mutagenic and clastogenic in some *in vitro* and *in vivo* assays. In long-term carcinogenicity studies in mice and rats, malignant tumors of the preputial gland of males and the clitoral gland of females were observed in both species, and malignant hepatic tumors and nonmalignant hepatic and thyroid tumors were observed in female rats. The tumors were seen in rodents at doses that were 6 to 32 times that of human therapeutic exposure.
- Reproduction/fertility
  No effect of abacavir on reproduction or fertility in male and female rodents has been seen at doses of up to 500 mg/kg/day (about 8 times that of human therapeutic exposure based on body surface area).
- Teratogenicity/developmental toxicity
  Abacavir is associated with developmental toxicity (decreased fetal body weight and reduced crown-rump length) and increased incidence of fetal anasarca and skeletal malformations in rats treated with abacavir

during organogenesis at doses of 1,000 mg/kg (about 35 times that of human therapeutic exposure based on area under the curve [AUC]). Toxicity to the developing embryo and fetus (increased resorptions and decreased fetal body weight) occurred with abacavir administration of 500 mg/kg/day to pregnant rodents. The offspring of female rats treated with 500 mg/kg of abacavir beginning at embryo implantation and ending at weaning had an increased incidence of stillbirth and lower body weight throughout life. However, in the rabbit, no evidence of drug-related developmental toxicity was observed and no increase in fetal malformations was observed at doses up to 700 mg/kg (about 8.5 times that of human therapeutic exposure).

In the Antiretroviral Pregnancy Registry, sufficient numbers of first-trimester exposures to abacavir in humans have been monitored to be able to detect at least a 2-fold increase in risk of overall birth defects. No such increase in birth defects has been observed with abacavir. The prevalence of birth defects with first-trimester abacavir exposure was 3.0% (19/628, 95% CI: 1.8%–4.7%) comparedto total prevalence of birth defects in the U.S. population based on Centers for Disease Control and Prevention (CDC) surveillance of 2.7% *[1]*.

- Placental and breast milk passage
  Abacavir crosses the placenta and is excreted into the breast milk of lactating rats.
- Human studies in pregnancy
  A Phase I study of abacavir in pregnant women indicates that the AUC drug concentration during pregnancy was similar to that at 6 to 12 weeks postpartum and to nonpregnant individuals *[2]*. Thus, no dose adjustment for abacavir is needed during pregnancy. Serious hypersensitivity reactions have been associated with abacavir therapy in nonpregnant adults and have rarely been fatal; symptoms include fever, skin rash, fatigue, and gastrointestinal symptoms such as nausea, vomiting, diarrhea, or abdominal pain. Abacavir should not be restarted following a hypersensitivity reaction because more severe symptoms will recur within hours and may include life-threatening hypotension and death.

References

1. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral pregnancy registry international interim report for 1 Jan 1989 – 31 July 2009. Wilmington, NC: Registry coordinating center; 2009.
2. Best BM, Mirochnick M, Capparelli EV, et al. Impact of pregnancy on abacavir pharmacokinetics. *AIDS*, 2006. 20(4):553-60. http://www.ncbi.nlm.nih.gov/pubmed/16470119

Didanosine (Videx, ddI) is classified as FDA pregnancy category B.

- Animal carcinogenicity studies
  Didanosine is both mutagenic and clastogenic in several *in vitro* and *in vivo* assays. Long-term animal carcinogenicity screening studies at human exposures of 0.7 to 1.7- and 3- times in mice and rats, respectively, have been negative.
- Reproduction/fertility
  At approximately 12 times the estimated human exposure, didanosine was slightly toxic to female rats and their pups during mid- and late- lactation. These rats showed reduced food intake and body weight gains; however, the physical and functional development of the offspring was not impaired and there were no major changes in the F2 generation.
- Teratogenicity/developmental toxicity
  No evidence of teratogenicity or toxicity was observed with administration of didanosine at 12- and 14-times human exposure in pregnant rats and rabbits, respectively. Among cases of first-trimester didanosine exposure reported to the Antiretroviral Pregnancy Registry, defects have been noted in 4.6% (17/370, 95% CI: 2.7%–7.3%) compared to total prevalence of birth defects in the U.S. population based on CDC surveillance of 2.7% *[1]*. All defects were reviewed in detail by the Registry, and no pattern of defects was discovered. The rate and types of defects will continue to be monitored closely.

- Placental and breast milk passage
  Placental transfer of didanosine was limited in a Phase I/II safety and pharmacokinetic study *[2]*. This was confirmed in a study of 100 HIV-infected pregnant women who were receiving NRTIs (generally as part of a two- or three- drug combination antiretroviral regimen). At the time of delivery, cord-to-maternal blood ratio for didanosine (n=10) was 0.38 (range 0.0–2.00) and in 15/24 samples (62%), cord blood concentrations for didanosine were below the limits of detection *[3]*. A study in rats showed that didanosine and/or its metabolites are transferred to the fetus through the placenta. It is not known if didanosine is excreted in human breast milk.

- Human studies in pregnancy
  A Phase I study (PACTG 249) of didanosine was conducted in 14 HIV-infected pregnant women enrolled at gestational age 26 to 36 weeks and treated through 6 weeks postpartum *[2]*. The drug was well tolerated during pregnancy by the women and the fetuses. Pharmacokinetic parameters after oral administration were not significantly affected by pregnancy, and dose modification from the usual adult dosage is not needed.

  Cases of lactic acidosis, in some cases fatal, have been described in pregnant women receiving the combination of didanosine and stavudine along with other antiretroviral agents *[4-6]*; the FDA and Bristol-Myers Squibb have issued a warning to health care professionals that pregnant women may be at increased risk of fatal lactic acidosis when prescribed the combination of didanosine and stavudine (see **NRTI Drugs and Mitochondrial Toxicity** in Perinatal Guidelines). The combination of these two drugs should be prescribed for pregnant women only when the potential benefit clearly outweighs the potential risk. Clinicians should prescribe this antiretroviral combination during pregnancy with caution and generally only when other nucleoside analog drug combinations have failed or have caused unacceptable toxicity or side effects.

References

1. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral pregnancy registry international interim report for 1 Jan 1989 – 31 July 2009. Wilmington, NC: Registry coordinating center; 2009.
2. Wang Y, Livingston E, Patil S, et al. Pharmacokinetics of didanosine in antepartum and postpartum human immunodeficiency virus-infected pregnant women and their neonates: an AIDS clinical trials group study. *J Infect Dis,* 1999. 180(5):1536-41. http://www.ncbi.nlm.nih.gov/pubmed/10515813
3. Chappuy H, Tréluyer JM, Jullien V, et al. Maternal-fetal transfer and amniotic fluid accumulation of nucleoside analogue reverse transcriptase inhibitors in human immunodeficiency virus-infected pregnant women. *Antimicrob Agents Chemother,* 2004. 48(11):4332-6. http://www.ncbi.nlm.nih.gov/pubmed/15504861
4. Bristol-Myers Squibb Company. Healthcare Provider Important Drug Warning Letter. January 5, 2001.
5. Sarner L, Fakoya A. Acute onset lactic acidosis and pancreatitis in the third trimester of pregnancy in HIV-1 positive women taking antiretroviral medication. *Sex Transm Inf,* 2002. 78(1):58-9. http://www.ncbi.nlm.nih.gov/pubmed/11872862
6. Mandelbrot L, Kermarrec N, Marcollet A, et al. Case report: nucleoside analogue-induced lactic acidosis in the third trimester of pregnancy. *AIDS,* 2003. 17(2):272-3. http://www.ncbi.nlm.nih.gov/pubmed/12545093

Emtricitabine (Emtriva, FTC) is classified as FDA pregnancy category B.

- Animal carcinogenicity studies
  Emtricitabine was neither mutagenic nor clastogenic in a series of *in vitro* and animal *in vivo* screening tests. In long-term oral carcinogenicity studies of emtricitabine, no drug-related increases in tumor incidence were found in mice at doses up to 26 times the human systemic exposure at the therapeutic dose of 200 mg/day or in rats at doses up to 31 times the human systemic exposure at the therapeutic dose.

- Reproduction/fertility
  No effect of emtricitabine on reproduction or fertility was observed with doses that produced systemic drug exposures (as measured by AUC approximately 60-fold higher in female mice and 140-fold higher in male mice than observed with human exposure at the recommended therapeutic dose.

- Teratogenicity/developmental toxicity
  The incidence of fetal variations and malformations was not increased with emtricitabine dosing in mice resulting in systemic drug exposure 60-fold higher than observed with human exposure at recommended doses, or in rabbits with dosing resulting in drug exposure 120-fold higher than human exposure.

  In the Antiretroviral Pregnancy Registry, sufficient numbers of first-trimester exposures to emtricitabine in humans have been monitored to be able to detect at least a 2-fold increase in risk of overall birth defects. No such increase in birth defects has been observed with emtricitabine. The prevalence of birth defects with first-trimester emtricitabine exposure was 2.9% (11/384, 95% CI: 1.4%–5.1%) compared to total prevalence of birth defects in the U.S. population based on CDC surveillance of 2.7% *[1]*.

- Placental and breast milk passage
  Emtricitabine has been shown to cross the placenta in mice and rabbits; the average fetal/maternal drug concentration was 0.4 in mice and 0.5 in rabbits *[2]*. Emtricitabine has been shown to have good placental transfer in pregnant women. In 18 women who received 200 mg emtricitabine daily during pregnancy, mean cord blood concentration was 300 ± 268 ng/mL and mean ratios of cord blood/maternal emtricitabine concentrations were 1.17 ± 0.6 (n=9) *[3]*. When 35 women were administered 400 mg of emtricitabine in combination with tenofovir at delivery, median maternal and cord concentrations were 1.02 (0.034–2.04) and 0.74 (0.0005–1.46) mg/L, respectively *[4]*. It is unknown if emtricitabine is excreted in human milk.

- Human studies in pregnancy
  Emtricitabine pharmacokinetics have been evaluated in 18 HIV-infected pregnant women receiving combination antiretroviral therapy including emtricitabine (200 mg once daily) at 30 to 36 weeks gestation and 6 to 12 weeks postpartum *[3]*. Emtricitabine exposure was modestly lower during the third trimester (8.6 µg*h/mL [5.2–15.9]) compared to the postpartum period (9.8 µg*h/mL [7.4–30.3]). Two-thirds (12/18) of pregnant women versus 100% (14/14) of postpartum women met the AUC target (10^{th} percentile in nonpregnant adults). Trough emtricitabine levels were also lower during pregnancy (C_{min} 52 ng/mL [14 – 180]) compared to the postpartum period (86 ng/mL [<10 – 306]). In another study of 35 women who received 400 mg of emtricitabine with tenofovir at delivery, median population AUC, C_{max}, and C_{min} were 14.3 µg*h/mL; 1,680 ng/mL; and 76 ng/mL, respectively *[4]*.

References

1. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral pregnancy registry international interim report for 1 Jan 1989 – 31 July 2009. Wilmington, NC: Registry coordinating center; 2009.
2. Szczech GM, Wang LH, Walsh JP, et al. Reproductive toxicology of emtricitabine in mice and rabbits. Reproductive Toxicol 2003;17:95-108. *Reproductive Toxicol*, 2003. 17(1):95-108. http://www.ncbi.nlm.nih.gov/pubmed/12507664
3. Hirt D, Urien S, Rey E, et al. Population pharmacokinetics of emtricitabine in HIV-infected pregnant women and their neonates: TEmAA ANRS 12109. 15^{th} Conference on Retroviruses and Opportunistic Infections; February 3-6, 2008; Boston, MA Abstract 626. http://www.retroconference.org/2008/PDFs/626.pdf
4. Best B, Stek A, Hu C, et al. for the PACTG/IMPAACT P1026S team. High-dose lopinavir and standard-dose emtricitabine pharmacokinetics during pregnancy and postpartum. 15^{th} Conference on Retroviruses and Opportunistic Infections, February 3-8, 2008; Boston, MA. Abstract 629. http://www.retroconference.org/2008/PDFs/629.pdf

Lamivudine (Epivir, 3TC) is classified as FDA pregnancy category C.

- Animal carcinogenicity studies
  Lamivudine has weak mutagenic activity in 1 *in vitro* assay but no evidence of *in vivo* genotoxicity in rats at 35–45 times human exposure. Long-term animal carcinogenicity screening studies at 10- and 58- times human exposure have been negative in mice and rats, respectively.

- Reproduction/fertility
  Lamivudine administered to rats at doses up to 4,000 mg/kg/day, producing plasma levels 47- to 70- times those in humans, revealed no evidence of impaired fertility and no effect on the survival, growth, and development to weaning of the offspring.

- Teratogenicity/developmental toxicity studies
  There is no evidence of lamivudine-induced teratogenicity at 35 times human plasma levels in rats and rabbits. Early embryolethality was seen in rabbits at doses similar to human therapeutic exposure but not in rats at 35 times the human exposure level.

  In the Antiretroviral Pregnancy Registry, sufficient numbers of first-trimester exposures to lamivudine in humans have been monitored to detect at least a 1.5-fold increase in risk of overall birth defects and a 2-fold increase in the most commonly occurring birth defects (e.g., defects of the cardiovascular and genitourinary systems). No such increase in birth defects has been observed with lamivudine. The prevalence of birth defects with first-trimester lamivudine exposure was 2.9% (96/3,314, 95% CI: 2.3%–3.5%) compared to total prevalence of birth defects in the U.S. population based on CDC surveillance of 2.7% *[1]*.

- Placental and breast milk passage
  Lamivudine readily crosses the placenta in humans, achieving comparable cord blood and maternal concentrations*[2]*. Lamivudine is excreted into human breast milk. In a study in Kenya of 67 HIV-infected nursing mothers receiving a combination regimen of zidovudine, lamivudine, and nevirapine, the median breast milk lamivudine concentration was 1,214 ng/mL and the median ratio of lamivudine concentration in breast milk to that in plasma was 2.56 *[3]*. Their infants, who only received lamivudine via breast milk, had a median plasma lamivudine concentration of 23 ng/mL (IC_{50} of wild-type HIV against lamivudine = 0.6 – 21 ng/mL).

- Human studies in pregnancy
  A small Phase I study in South Africa evaluated the safety and pharmacokinetics of lamivudine alone or in combination with zidovudine in 20 HIV-infected pregnant women; therapy was started at 38 weeks gestation, continued through labor, and given for 1 week following birth to the infants*[2]*. The drug was well tolerated in the women at the recommended adult dose of 150 mg orally twice daily; pharmacokinetics were similar to those observed in nonpregnant adults, and no pharmacokinetic interaction with zidovudine was observed.

  Zidovudine and lamivudine, given in combination orally intrapartum, were well-tolerated. Lamivudine was well tolerated in the neonates, but clearance was about 50% that of older children, requiring a reduced dosing regimen (4 mg/kg/day in neonates compared to 8 mg/kg/day for infants older than 3 months). There are currently no data on the pharmacokinetics of lamivudine between 2 and 6 weeks of age, and the exact age at which lamivudine clearance begins to approximate that in older children is not known.

References

1. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral pregnancy registry international interim report for 1 Jan 1989 – 31 July 2009. Wilmington, NC: Registry coordinating center; 2009.
2. Moodley J, Moodley D, Pillay K, et al. Pharmacokinetics and antiretroviral activity of lamivudine alone or when coadministered with zidovudine in human immunodeficiency virus type 1-infected pregnant women and their offspring. *J Infect Dis*, 1998. 178(5):1327-33. http://www.ncbi.nlm.nih.gov/pubmed/9780252
3. Mirochnick M, Thomas T, Capparelli E, et al. Antiretroviral concentrations in breast-feeding infants of mothers receiving highly active antiretroviral therapy. *Antimicrob Agents Chemother*, 2009. 53(3):1170-6. http://www.ncbi.nlm.nih.gov/pubmed/19114673

Stavudine (Zerit, d4T) is classified as FDA pregnancy category C.

- Animal carcinogenicity studies
  Stavudine is clastogenic in *in vivo* and *in vivo* assays but not mutagenic in *in vitro* assays. In 2-year carcinogenicity studies in mice and rats, stavudine was noncarcinogenic in doses producing exposures 39 (mice) and 168 (rats) times human exposure at the recommended therapeutic dose. At higher levels of exposure (250 [mice] and 732 [rats] times human exposure at therapeutic doses), benign and malignant liver tumors occurred in mice and rats and urinary bladder tumors occurred in male rats.

- Reproduction/fertility
  No effect of stavudine on reproduction or fertility in rodents has been seen. A dose-related cytotoxic effect has been observed on preimplantation mouse embryos, with inhibition of blastocyst formation at a concentration of stavudine of 100 µM and of postblastocyst development at 10 µM *[1]*.

- Teratogenicity/developmental toxicity studies
  No evidence of teratogenicity was noted in rats or rabbits with exposures (based on C_{max}) up to 399 and 183 times, respectively, of that seen at a clinical dosage of 1 mg/kg/day. The incidence in fetuses of a common skeletal variation, unossified or incomplete ossification of sternebra, was increased in rats at 399 times human exposure, although no effect was observed at 216 times human exposure. A slight post-implantation loss was noted at 216 times the human exposure with no effect noted at approximately 135 times the human exposure. An increase in early rat neonatal mortality (birth to 4 days of age) occurred at 399 times the human exposure, although survival of neonates was unaffected at approximately 135 times the human exposure. A study in rats showed that stavudine is transferred to the fetus through the placenta. The concentration in fetal tissue was approximately one-half the concentration in maternal plasma.

  In the Antiretroviral Pregnancy Registry, sufficient numbers of first-trimester exposures to stavudine in humans have been monitored to be able to detect at least a 2-fold increase in risk of overall birth defects. No such increase in birth defects has been observed with stavudine. The prevalence of birth defects with first-trimester stavudine exposure was 2.5% (19/771, 95% CI: 1.5%–3.8%) compared with total prevalence of birth defects in the U.S. population based on CDC surveillance of 2.7% *[2]*.

- Placental and breast milk passage
  Stavudine crosses the rat placenta *in vivo* and the human placenta *ex vivo*, resulting in a fetal/maternal concentration of approximately 0.50. In primates (pigtailed macaques), fetal/maternal plasma concentrations were approximately 0.80 *[3]*. Stavudine is excreted into the breast milk of lactating rats.

- Human studies in pregnancy
  A Phase I/II safety and pharmacokinetic study of combination stavudine and lamivudine in pregnant HIV-infected women and their infants has been conducted (PACTG 332). Both drugs were well tolerated, with pharmacokinetics similar to those in nonpregnant adults *[4]*. Data from primate studies also indicated that pregnancy did not affect the pharmacokinetics of stavudine *[5]*.

  Cases of lactic acidosis, in some cases fatal, have been described in pregnant women receiving the combination of didanosine and stavudine along with other antiretroviral agents *[6-8]*. The FDA and Bristol-Myers Squibb have issued a warning to health care professionals that pregnant women may be at increased risk of fatal lactic acidosis when prescribed the combination of didanosine and stavudine (see **NRTI Drugs and Mitochondrial Toxicity** in the Perinatal Guidelines). The combination of these two drugs should be prescribed for pregnant women only when the potential benefit clearly outweighs the potential risk. Clinicians should prescribe this antiretroviral combination during pregnancy with caution and generally only when other nucleoside analog drug combinations have failed or have caused unacceptable toxicity or side effects.

References

1. Toltzis P, Mourton T and Magnuson T. Comparative embryonic cytotoxicity of antiretroviral nucleosides. *J Infect Dis,* 1994. 169(5):1100-2. http://www.ncbi.nlm.nih.gov/pubmed/8169400

2. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral pregnancy registry international interim report for 1 Jan 1989 – 31 July 2009. Wilmington, NC: Registry coordinating center; 2009.
3. Odinecs A, Nosbisch C, Keller RD, et al. In vivo maternal-fetal pharmacokinetics of stavudine (2',3'-didehydro-3'-deoxythymidine) in pigtailed macaques (*Macaca nemestrina*). *Antimicrob Agents Chemother*, 1996. 40(1):196-202. http://www.ncbi.nlm.nih.gov/pubmed/8787905
4. Wade NA, Unadkat JD, Huang S, et al. Pharmacokinetics and safety of stavudine in HIV-infected pregnant women and their infants: Pediatric AIDS Clinical Trials Group protocol 332. *J Infect Dis*, 2004. 190(12):2167-74. http://www.ncbi.nlm.nih.gov/pubmed/15551216
5. Odinecs A, Pereira C, Nosbisch C, et al. Prenatal and postpartum pharmacokinetics of stavudine (2',3'-didehydro- 3'-deoxythymidine) and didanosine (dideoxyinosine) in pigtailed macaques (*Macaca nemestrina*). *Antimicrob Agents Chemother*, 1996. 40(10):2423-5. http://www.ncbi.nlm.nih.gov/pubmed/8891157
6. Bristol-Myers Squibb Company. Healthcare Provider Important Drug Warning Letter. January 5, 2001.
7. Sarner L, Fakoya A. Acute onset lactic acidosis and pancreatitis in the third trimester of pregnancy in HIV-1 positive women taking antiretroviral medication. *Sex Transm Inf*, 2002. 78(1):58-9. http://www.ncbi.nlm.nih.gov/pubmed/11872862
8. Mandelbrot L, Kermarrec N, Marcollet A, et al. Case report: nucleoside analogue-induced lactic acidosis in the third trimester of pregnancy. *AIDS*, 2003. 17(2):272-3. http://www.ncbi.nlm.nih.gov/pubmed/12545093

Tenofovir disoproxil fumarate (Viread, TDF) is classified as FDA pregnancy category B.

- Animal carcinogenicity studies
  Tenofovir is mutagenic in one of two *in vitro* assays and has no evidence of clastogenic activity. Long-term oral carcinogenicity studies of tenofovir DF in mice and rats were carried out at 16 times (mice) and 5 times (rats) human exposure. In female mice, liver adenomas were increased at exposures 16 times that observed in humans at therapeutic doses. In rats, the study was negative for carcinogenic findings at exposures up to 5 times that observed in humans at the therapeutic dose.

- Reproduction/fertility
  Reproduction studies have been performed in rats and rabbits at doses up to 14 and 19 times the human dose based on body surface area comparisons and revealed no evidence of impaired fertility or harm to the fetus due to tenofovir. There were also no effects on fertility, mating performance, or early embryonic development when tenofovir disoproxil fumarate was administered to male rats (600 mg/kg/day; equivalent to 10 times the human dose based on body surface area) for 28 days prior to mating and to female rats for 15 days prior to mating through Day 7 of gestation. There was, however, an alteration of the estrous cycle in female rats administered 600 mg/kg/day.

- Teratogenicity/developmental toxicity
  Chronic exposure of fetal monkeys to tenofovir at a high dose of 30 mg/kg (exposure equivalent to 25 times the AUC achieved with therapeutic dosing in humans) from Days 20–150 of gestation did not result in gross structural abnormalities *[1]*. However, significantly lower fetal circulating insulin-like growth factor (IGF)-1 (a primary regulator of linear growth) and higher IGF binding protein (IGFBP)-3 levels were shown and were associated with overall body weights approximately 13% lower than untreated controls. A slight reduction in fetal bone porosity was also observed. Effects on these parameters were observed within 2 months of maternal treatment. Significant changes in maternal monkey bone biomarkers were noted but were primarily limited to the treatment period and were reversible.

  Continued administration of tenofovir at 30 mg/kg/day to the infant monkey postnatally resulted in significant growth restriction and severe bone toxicity in 25% of 8 infants and effects on bone biomarkers and defective bone mineralization in all animals. Chronic administration of tenofovir to immature animals of multiple species has resulted in reversible bone abnormalities; these effects were dose-, exposure-, age-, and species specific. Abnormalities ranged from minimal decrease in bone mineral density and content (with oral dosing in rats and dogs that achieved drug exposures 6 to 10 times that achieved with therapeutic dosing in

humans) to severe, pathologic osteomalacia (with subcutaneous dosing given to monkeys). Juvenile monkeys given chronic subcutaneous tenofovir at 30 mg/kg/day (exposure equivalent to 25 times the AUC achieved with therapeutic dosing in humans) developed osteomalacia, bone fractures, and marked hypophosphatemia. However, no clinical or radiologic bone toxicity was seen when juvenile monkeys received subcutaneous dosing of 10 mg/kg/day (exposure equivalent to 8 times the AUC achieved with therapeutic dosing in humans). Evidence of nephrotoxicity was observed in newborn and juvenile monkeys given tenofovir in doses resulting in exposures 12 to 50 times higher than the human dose based on body surface area comparisons.

In the Antiretroviral Pregnancy Registry, sufficient numbers of first-trimester exposures to tenofovir in humans have been monitored to be able to detect at least a 2-fold increase in risk of overall birth defects. No such increase in birth defects has been observed with tenofovir. The prevalence of birth defects with first-trimester tenofovir exposure was 2.4% (18/756, 95% CI: 1.4%–3.7%) compared to total prevalence of birth defects in the U.S. population based on CDC surveillance of 2.7% *[2]*.

- Placental and breast milk passage
  Studies in rats have demonstrated that tenofovir is secreted in milk. Intravenous administration of tenofovir to pregnant cynomolgus monkeys resulted in a fetal/maternal concentration of 17%, demonstrating that tenofovir does cross the placenta *[3]*. In 3 studies of pregnant women, the cord-to-maternal blood ratio ranged from 0.60 to 0.99, indicating high placental transfer*[4-6]*. In 2 studies including 21 pregnant women receiving tenofovir-based therapy, the cord-to-maternal blood ratio ranged from 0.95 to 0.99 *[4,5]*. There are no data on whether tenofovir is excreted in breast milk in humans.

- Human studies in pregnancy
  Tenofovir pharmacokinetics were evaluated in 19 pregnant women receiving tenofovir-based combination therapy in study P1026s at 30 to 36 weeks gestation and 6 to 12 weeks postpartum *[4]*. The percent of women with tenofovir AUC exceeding the target of 2 μg*hour/mL (the 10th percentile in nonpregnant adults) was lower in women in the third trimester (74%, 14/19) than postpartum (86%, 12/14) (p = 0.02); however, trough levels were similar in the third trimester and postpartum.

  A recent case series found tenofovir to be well tolerated among 76 pregnant women, with 2 stopping therapy, 1 for rash and 1 for nausea. All 78 infants were healthy with no signs of toxicity, and all were HIV-uninfected *[7]*. A retrospective review of 16 pregnancy outcomes among 15 heavily antiretroviral experienced women demonstrated that tenofovir was well-tolerated by the women and associated with normal growth and development in the infants *[8]*.

References

1. Tarantal AF, Castillo A, Ekert JE, et al. Fetal and maternal outcome after administration of tenofovir to gravid rhesus monkeys (*Macaca mulatta*). *J Acquir Immune Defic Syndr*, 2002. 29(3):207-20. http://www.ncbi.nlm.nih.gov/pubmed/11873070
2. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral pregnancy registry international interim report for 1 Jan 1989 – 31 July 2009. Wilmington, NC: Registry coordinating center; 2009.
3. Tarantal AF, Marthas ML, Shaw JP, et al. Administration of 9-[2-(R)-(phosphonomethoxy)propyl]adenine (PMPA) to gravid and infant rhesus macaques (*Macaca mulatta*): safety and efficacy studies. *J Acquir Immune Defic Syndr Hum Retrovirol*, 1999. 20(4):323-33. http://www.ncbi.nlm.nih.gov/pubmed/10096575
4. Burchett S, Best B, Mirochnick M, et al. Tenofovir pharmacokinetics during pregnancy, at delivery, and postpartum. 14th Conference on Retoviruses and Opportunistic Infections; February 25-28, 2007; Los Angeles, CA. Abstract 738b. http://www.retroconference.org/2007/Abstracts/30641.htm
5. Bonora S, de Requena DG, Chiesa E, et al. Transplacental passage of tenofovir and other ARVs at delivery. 14th Conference on Retoviruses and Opportunistic Infections; February 25-28, 2007; Los Angeles, CA. Abstract 738a. http://www.retroconference.org/2007/PDFs/738a.pdf

6. Hirt D, Urien S, Rey E, et al. Population pharmacokinetics of tenofovir in HIV-infected pregnant women and their neonates: TemAA ANRS 12109. 15th Conference on Retroviruses and Opportunistic Infections; February 3-6, 2008; Boston, MA Abstract 47LB. http://www.retroconference.org/2008/Abstracts/33470.htm
7. Habert A, Linde R, Reittner A, et al. Safety and efficacy of tenofovir in pregnant women. 15th Conference on Retroviruses and Opportunistic Infections; February 3-6, 2008; Boston, MA. Abstract 627a. http://www.retroconference.org/2008/PDFs/627a.pdf
8. Nurutdinova D, Onen NF, Hayes E, et al. Adverse effects of tenofovir use in HIV-infected pregnant women and their infants. *Ann Pharmacother*, 2008. 42(11):1581-5. http://www.ncbi.nlm.nih.gov/pubmed/18957630

Zalcitabine (HIVID, ddC) is no longer available in the United States.

Zidovudine (Retrovir, AZT, ZDV) is classified as FDA pregnancy category C.

- Animal carcinogenicity studies

  Zidovudine is mutagenic in 2 *in vitro* assays, clastogenic in 1 *in vitro* and 2 *in vivo* assays, but not cytogenic in a single-dose *in vivo* rat study. Long-term carcinogenicity studies have been performed with zidovudine in mice and rats *[1]*. In mice, 7 late-appearing (after 19 months) vaginal neoplasms (5 nonmetastasizing squamous cell carcinomas, 1 squamous cell papilloma, and 1 squamous polyp) occurred in animals given the highest dose. One late-appearing squamous cell papilloma occurred in the vagina of an animal given an intermediate dose. No vaginal tumors were found at the lowest dose. In rats, 2 late-appearing (after 20 months), nonmetastasizing vaginal squamous cell carcinomas occurred in animals given the highest dose. No vaginal tumors occurred at the low or middle dose in rats. No other drug-related tumors were observed in either sex of either species. At doses that produced tumors in mice and rats, the estimated drug exposure (as measured by AUC) was approximately 3 times (mouse) and 24 times (rat) the estimated human exposure at the recommended therapeutic dose of 100 mg every 4 hours. It is not known how predictive the results of rodent carcinogenicity studies may be for humans.

  Two transplacental carcinogenicity studies were conducted in mice *[2,3]*. One study administered zidovudine at doses of 20 mg/kg/day or 40 mg/kg/day from gestation Day 10 through parturition and lactation with dosing continuing in offspring for 24 months postnatally *[3]*. The doses of zidovudine administered in this study produced zidovudine exposures approximately 3 times the estimated human exposure at recommended doses. After 24 months, an increase in incidence of vaginal tumors was noted with no increase in tumors in the liver or lung or any other organ in either gender. These findings are consistent with results of the standard oral carcinogenicity study in mice, as described earlier. A second study administered zidovudine at maximum tolerated doses of 12.5 mg/day or 25 mg/day (~1,000 mg/kg nonpregnant body weight or ~450 mg/kg of term body weight) to pregnant mice from Days 12 through 18 of gestation *[2]*. There was an increase in the number of tumors in the lung, liver, and female reproductive tracts in the offspring of mice receiving the higher dose level of zidovudine.

- Reproduction/fertility

  Zidovudine, administered to male and female rats at doses up to 7 times the usual adult dose based on body surface area, had no effect on fertility judged by conception rates.

  No effect of zidovudine on reproduction or fertility in rodents has been seen. A dose-related cytotoxic effect on preimplantation mouse embryos can occur, with inhibition of blastocyst and postblastocyst development at zidovudine concentrations similar to levels achieved with human therapeutic doses *[4]*.

- Teratogenicity/developmental toxicity

  Oral teratology studies in the rat and in the rabbit at doses up to 500 mg/kg/day revealed no evidence of teratogenicity with zidovudine. Zidovudine treatment resulted in embryo/fetal toxicity as evidenced by an increase in the incidence of fetal resorptions in rats given 150 or 450 mg/kg/day and rabbits given 500 mg/kg/day. The doses used in the teratology studies resulted in peak zidovudine plasma concentrations (after

one-half of the daily dose) in rats 66 to 226 times, and in rabbits 12 to 87 times, mean steady-state peak human plasma concentrations (after one-sixth of the daily dose) achieved with the recommended daily dose (100 mg every 4 hours). In an *in vitro* experiment with fertilized mouse oocytes, zidovudine exposure resulted in a dose-dependent reduction in blastocyst formation. In an additional teratology study in rats, a dose of 3,000 mg/kg/day (very near the oral median lethal dose in rats of 3,683 mg/kg) caused marked maternal toxicity and an increase in the incidence of fetal malformations. This dose resulted in peak zidovudine plasma concentrations 350 times peak human plasma concentrations (estimated AUC in rats at this dose level was 300 times the daily AUC in humans given 600 mg/day). No evidence of teratogenicity was seen in this experiment at doses of 600 mg/kg/day or less.

Increased fetal resorptions occurred in pregnant rats and rabbits treated with doses of zidovudine that produced drug plasma concentrations 66 to 226 times (rats) and 12 to 87 times (rabbits) the mean steady-state peak human plasma concentration following a single 100-mg dose of zidovudine. There were no other reported developmental anomalies. In another developmental toxicity study, pregnant rats received zidovudine up to near-lethal doses that produced peak plasma concentrations 350 times peak human plasma concentrations (300 times the daily AUC in humans given 600 mg/day zidovudine). This dose was associated with marked maternal toxicity and an increased incidence of fetal malformations. However, there were no signs of teratogenicity at doses up to one-fifth the lethal dose.

In humans, in the placebo-controlled perinatal trial PACTG 076, the incidence of minor and major congenital abnormalities was similar between zidovudine and placebo groups and no specific patterns of defects were seen *[5,6]*. A report from the Women and Infants Transmission Study (WITS), a cohort study enrolling women during pregnancy, described an association between first-trimester exposure to zidovudine and a 10-fold increased risk of hypospadius *[7]*. However, in the Antiretroviral Pregnancy Registry, sufficient numbers of first-trimester exposures to zidovudine have been monitored to be able to detect at least a 1.5-fold increase in risk of overall birth defects and a 2-fold increase in defects in the more common classes, defects of the cardiovascular and genitourinary systems. No such increase in birth defects has been observed with zidovudine. The prevalence of birth defects with first-trimester zidovudine exposure was 3.1% (97/3,167, 95% CI: 2.5%–3.7%) compared to total prevalence of birth defects in the U.S. population based on CDC surveillance of 2.7% *[8]*.

- Placental and breast milk passage
  Zidovudine rapidly crosses the human placenta, achieving cord-to-maternal blood ratios of about 0.80. Zidovudine is excreted into human breast milk. In 1 study in Kenya in 67 mothers receiving a combination regimen of zidovudine, lamivudine, and nevirapine, zidovudine concentration in the breast milk of mothers averaged 9 ng/mL and the ratio of breast milk to maternal plasma zidovudine concentration averaged 44% *[9]*. No zidovudine was detectable in the plasma of their nursing infants, who only received zidovudine via breast milk.

- Human studies in pregnancy
  Zidovudine is well tolerated in pregnancy at recommended adult doses and in the full-term neonate at 2 mg/kg body weight orally every 6 hours *[5,10]*. Long-term data on the safety of *in utero* drug exposure in humans are not available for any antiretroviral drug; however, short-term data on the safety of zidovudine are reassuring. No difference in disease progression between women in PACTG 076 who received zidovudine and those who received placebo has been seen in follow-up through 4 years postpartum *[11]*. Infants with *in utero* zidovudine exposure followed for nearly 6 years have shown no significant differences from those who received placebo in immunologic, neurologic, and growth parameters*[6,12]*; follow-up of these infants is continuing.

References

1. Ayers KM, Clive D, Tucker WE, Jr., et al. Nonclinical toxicology studies with zidovudine: genetic toxicity tests and carcinogenicity bioassays in mice and rats. *Fundam Appl Toxicol*, 1996. 32(2):148-58. http://www.ncbi.nlm.nih.gov/pubmed/8921318

2. Olivero OA, Anderson LM, Diwan BA, et al. Transplacental effects of 3'-azido-2',3'-dideoxythymidine (AZT): tumorigenicity in mice and genotoxicity in mice and monkeys. *J Natl Cancer Inst,* 1997. 89(21):1602-8. http://www.ncbi.nlm.nih.gov/pubmed/9362158
3. Ayers KM, Torrey CE and Reynolds DJ. A transplacental carcinogenicity bioassay in CD-1 mice with zidovudine. *Fundam Appl Toxicol,* 1997. 38(2):195-8. http://www.ncbi.nlm.nih.gov/pubmed/9299194
4. Toltzis P, Marx CM, Kleinman N, et al. Zidovudine-associated embryonic toxicity in mice. *J Infect Dis,* 1991. 163(6):1212-8. http://www.ncbi.nlm.nih.gov/pubmed/2037787
5. Connor EM, Sperling RS, Gelber R, et al. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. Pediatric AIDS Clinical Trials Group Protocol 076 Study Group. *N Engl J Med,* 1994. 331(18):1173-80. http://www.ncbi.nlm.nih.gov/pubmed/7935654
6. Sperling RS, Shapiro DE, McSherry GD, et al. Safety of the maternal-infant zidovudine regimen utilized in the Pediatric AIDS Clinical Trial Group 076 Study. *AIDS,* 1998. 12(14):1805-13. http://www.ncbi.nlm.nih.gov/pubmed/9792381
7. Watts DH, Li D, Handelsman E, et al. Assessment of birth defects according to maternal therapy among infants in the Women and Infants Transmission Study. *J Acquir Immune Defic Syndr,* 2007. 44(3):299-305. http://www.ncbi.nlm.nih.gov/pubmed/17159659
8. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral pregnancy registry international interim report for 1 Jan 1989 – 31 July 2009. Wilmington, NC: Registry coordinating center; 2009.
9. Mirochnick M, Thomas T, Capparelli E, et al. Antiretroviral concentrations in breast-feeding infants of mothers receiving highly active antiretroviral therapy. *Antimicrob Agents Chemother,* 2009. 53(3):1170-6. http://www.ncbi.nlm.nih.gov/pubmed/19114673
10. O'Sullivan MJ, Boyer PJ, Scott GB, et al. The pharmacokinetics and safety of zidovudine in the third trimester of pregnancy for women infected with human immunodeficiency virus and their infants: phase I acquired immunodeficiency syndrome clinical trials group study (protocol 082). Zidovudine Collaborative Working Group. *Am J Obstet Gynecol,* 1993. 168(5):1510-6. http://www.ncbi.nlm.nih.gov/pubmed/8098905
11. Bardeguez AD, Shapiro D, Mofenson LM, et al. Effect of cessation of zidovudine prophylaxis to reduce vertical transmission on maternal HIV disease progression and survival. *JAIDS,* 2003. 32(2):170-81. http://www.ncbi.nlm.nih.gov/pubmed/12571527
12. Culnane M, Fowler M, Lee SS, et al. Lack of long-term effects of *in utero* exposure to zidovudine among uninfected children born to HIV-infected women. Pediatric AIDS Clinical Trials Group Protocol 219/076 Teams. *JAMA,* 1999. 281(2):151-7. http://www.ncbi.nlm.nih.gov/pubmed/9917118

NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS

For information regarding potential interaction of the non-nucleoside reverse transcriptase inhibitor drug class and methergine, see **Postpartum Hemorrhage, Antiretroviral Drugs, and Methergine Use** in the Perinatal Guidelines. For more information regarding nevirapine hepatic/rash toxicity, see **Nevirapine and Hepatic/Rash Toxicity** in the Perinatal Guidelines.

Delavirdine (Rescriptor, DLV) is no longer available in the United States.

Efavirenz (Sustiva, EFV) is classified as FDA pregnancy category D.

- Animal carcinogenicity studies
  Efavirenz was neither mutagenic nor clastogenic in a series of *in vitro* and animal *in vivo* screening tests. Long-term animal carcinogenicity studies with efavirenz in mice and rats have been completed. At systemic drug exposures approximately 1.7-fold higher than in humans receiving standard therapeutic doses, no increase in tumor incidence above background was observed in male mice but an increase in hepatocellular adenomas and carcinomas and pulmonary alveolar/bronchiolar adenomas above background were found in

female mice. In male and female rats administered systemic drug exposures lower than that in humans receiving therapeutic doses, no increase in tumor incidence above background was observed.

- Reproduction/fertility animal studies
  No effect of efavirenz on reproduction or fertility in rodents has been seen.

- Teratogenicity/developmental toxicity
  An increase in fetal resorptions was observed in rats at efavirenz doses that produced peak plasma concentrations and AUC values in female rats equivalent to or lower than those achieved in humans at the recommended human dose (600 mg once daily). Efavirenz produced no reproductive toxicities when given to pregnant rabbits at doses that produced peak plasma concentrations similar to and AUC values approximately half of those achieved in humans administered efavirenz (600 mg once daily). Central nervous system (CNS) malformations were observed in 3 of 20 infants born to pregnant cynomolgus monkeys receiving efavirenz from gestational Days 20 to 150 at a dose of 30 mg/kg twice daily (resulting in plasma concentrations comparable to systemic human therapeutic exposure) *[1]*. The malformations included anencephaly and unilateral anophthalmia in 1 fetus, microphthalmia in another fetus, and cleft palate in a third fetus.

  In prospectively reported pregnancies with exposure to efavirenz-based regimens in the Antiretroviral Pregnancy Registry through July 2009, birth defects were observed in 14 (2.8%) of 501 (95% CI: 1.5%–4.7%) live births with first-trimester exposure. Defects reported prospectively after first-trimester efavirenz exposure included a case of sacral aplasia, myelomeningocele, and hydrocephalus with fetal alcohol syndrome and a case of bilateral facial clefts, anophthalmia, and amniotic band *[2]*. Other defects reported included polydactyly (3 cases), hydronephrosis, bilateral hip dislocation and umbilical hernia, bilateral hip dislocation, urinary obstruction with duplicated right collecting system, long bone malformation, shortening of right leg, cutis aplasia, hip dysplasia with pulmonary stenosis, and unspecified heart anomaly. In retrospective case reports, there are 6 reports of central nervous system defects, including 3 cases of meningomyelocele in infants born to mothers receiving efavirenz during the first trimester [Bristol-Myers Squibb April 14 2010, De Santis M, Arch Intern Med, 2002; Fundaro C, AIDS, 2002]. Although a causal relationship of these events to the use of efavirenz has not been established, similar defects have been observed in preclinical studies of efavirenz.

- Placental and breast milk passage
  Efavirenz crosses the placenta in rats, rabbits, and primates, producing cord blood concentrations similar to concentrations in maternal plasma. In a study of 13 women in Rwanda, efavirenz was given during the last trimester of pregnancy and for 6 months after delivery *[6]*. Efavirenz concentrations were measured in maternal plasma, breast milk, and infant plasma. Efavirenz passed into breast milk with a ratio of 0.54 (mean breast milk to mean maternal plasma concentration) and 4.08 (mean skim milk to mean newborn plasma concentration). Mean infant plasma efavirenz concentrations were 13.1% of maternal plasma levels. No data about efavirenz in neonates are currently available.

- Human studies in pregnancy
  Limited data on use of efavirenz in pregnancy are available. In 1 study of 71 pregnancies occurring among women in a primary therapy study, the rate of early losses and stillbirths did not differ among women on efavirenz or other drugs *[7]*. Among 22 livebirths to women exposed to efavirenz in the first trimester, 1 (4.5%) infant had an abnormality, right limb shortening.

  Efavirenz is classified as FDA Pregnancy Category D and may cause fetal harm when administered to a pregnant woman during the first trimester. Because of the potential for teratogenicity, pregnancy should be avoided in women receiving efavirenz, and treatment with efavirenz should be avoided during the first trimester, which is the primary period of fetal organogenesis. Women of childbearing potential should undergo pregnancy testing prior to initiation of efavirenz and should be counseled about the potential risk to the fetus and need to avoid pregnancy. Different types of contraception have known failure rates in women not receiving antiretroviral drugs; these failure rates may increase with drug interactions between estrogen-progesterone hormonal contraceptives and some antiretroviral drugs, including efavirenz. Alternate

antiretroviral regimens that do not include efavirenz should be strongly considered in women who are planning to become pregnant or who are sexually active and not using effective contraception. Barrier contraception should always be used in combination with other methods of contraception (e.g., hormonal contraceptives, intrauterine device). A study evaluating the interaction between efavirenz and depomedroxyprogesetrone (DMPA) in 17 women found no change in the pharmacokinetic profile of either efaviraenz or DMPA with concomitant use *[8]*. DMPA levels remained above the level needed for inhibition of ovulation throughout the dosing interval.

References

1. Nightingale SL. From the Food and Drug Administration. *JAMA*, 1998. 280(17):1472. http://www.ncbi.nlm.nih.gov/pubmed/9809716
2. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral pregnancy registry international interim report for 1 Jan 1989 – 31 July 2009. Wilmington, NC: Registry coordinating center; 2009.
3. Bristol-Myers Squibb Company. Efavirenz drug label. Revised August 2008.
4. De Santis M, Carducci B, De Santis L, et al. Periconceptional exposure to efavirenz and neural tube defects. *Arch Intern Med*, 2002. 162(3):355. http://www.ncbi.nlm.nih.gov/pubmed/11822930
5. Fundaro C, Genovese O, Rendeli C, et al. Myelomeningocele in a child with intrauterine exposure to efavirenz. *AIDS*, 2002. 16(2):299-300. http://www.ncbi.nlm.nih.gov/pubmed/11807320
6. Schneider S, Peltier A, Gras A, et al. Efavirenz in human breast milk, mothers', and newborns' plasma. *J Acquir Immune Defic Syndr*, 2008. 48(4):450-4. http://www.ncbi.nlm.nih.gov/pubmed/18614925
7. Bussmann H, Wester CW, Wester CN, et al. Pregnancy rates and birth outcomes among women on efavirenz-containing highly active antiretroviral therapy in Botswana. *J Acquir Immune Defic Syndr*, 2007. 45(3):269-73. http://www.ncbi.nlm.nih.gov/pubmed/17450102
8. Cohn SE, Park JG, Watts DH, et al. Depo-medroxyprogesterone in women on antiretroviral therapy: effective contraception and lack of clinically significant interactions. *Clin Pharmacol Ther*, 2007. 81(2):222-7. http://www.ncbi.nlm.nih.gov/pubmed/17192768

Etravirine (Intelence, ETV) is classified as FDA pregnancy category B.

- Animal carcinogenicity studies
  Etravirine was neither mutagenic nor clastogenic in a series of *in vitro* and animal *in vivo* screening tests. Carcinogenicity studies of etravirine in rodents are ongoing.

- Reproduction/fertility
  No effect on fertility and early embryonic development was observed when etravirine was tested in rats at maternal doses up to 500 mg/kg/day, resulting in systemic drug exposure equivalent to the recommended human dose (400 mg/day).

- Teratogenicity/developmental toxicity
  Animal reproduction studies in rats and rabbits at systemic exposures equivalent to those at the recommended human dose of 400 mg/day revealed no evidence of fetal toxicity or altered development. Developmental toxicity studies were performed in rabbits (at oral doses up to 375 mg/kg/day) and rats (at oral doses up to 1,000 mg/kg/day). In both species, no treatment-related embryo-fetal effects including malformations were observed. In addition, no treatment effects were observed in a separate pre- and postnatal study performed in rats at oral doses up to 500 mg/kg/day. The systemic exposures achieved in these animal studies were equivalent to those at the recommended human dose (400 mg/day).

- Placental and breast milk passage
  There are no data on whether etravirine crosses the placenta or is excreted in breast milk in humans.

- Human studies in pregnancy
  No adequate and well-controlled studies of etravirine use in pregnant women have been conducted. In addition, no pharmacokinetic studies have been conducted in pregnant patients.

Nevirapine (Viramune, NVP) is classified as FDA pregnancy category B.

- Animal carcinogenicity studies
  Nevirapine showed no evidence of mutagenic or clastogenic activity in a battery of *in vitro* and *in vivo* studies. Hepatocellular adenomas and carcinomas were increased at all doses in male mice and rats, and at higher doses in female mice and rats. Systemic exposure at all doses studied was lower than systemic exposure in humans receiving therapeutic nevirapine doses. Given the lack of genotoxic activity of nevirapine, the relevance to humans of hepatocellular neoplasms in nevirapine-treated mice and rats is not known.

- Reproduction/fertility
  Evidence of impaired fertility was seen in female rats at nevirapine doses providing systemic exposure comparable to human therapeutic exposure.

- Teratogenicity/developmental toxicity
  Teratogenic effects of nevirapine have not been observed in reproductive studies with rats and rabbits at systemic exposures approximately equivalent to or 50% greater than the recommended human dose (based on AUC). In rats, however, a significant decrease in fetal weight occurred at doses producing systemic concentrations approximately 50% higher than human therapeutic exposure.

  In the Antiretroviral Pregnancy Registry, sufficient numbers of first-trimester exposure to nevirapine in humans have been monitored to be able to detect at least a 2-fold increase in risk of overall birth defects. No such increase in birth defects has been observed with nevirapine. The prevalence of birth defects with first-trimester nevirapine exposure was 2.1% (18/842, 95% CI: 1.3%–3.4 %) compared to total prevalence of birth defects in the U.S. population based on CDC surveillance of 2.7% *[1]*.

- Placental and breast milk passage
  Nevirapine crosses the placenta and achieves neonatal blood concentrations equivalent to that in the mother (cord-to-maternal blood ratio approximately 0.90) *[2]*. Nevirapine is excreted into human breast milk; the median concentration in 4 breast milk samples obtained from 3 women during the first week after delivery was approximately 76% (range 54%–104%) of serum levels *[2]*. In 19 women receiving combination therapy with nevirapine, lamivudine, and zidovudine, breast milk nevirapine concentration was 6,795 ng/mL, which was 0.67 times that of maternal serum *[3]*. In a larger study, 67 HIV-infected nursing mothers receiving a combination regimen of zidovudine, lamivudine, and nevirapine in Kenya; median nevirapine breast milk concentration was 4,564 ng/mL *[4]*. Their infants, who only received nevirapine via breast milk, had a median nevirapine concentration of 734 ng/mL.

- Human studies in pregnancy

  Short-Term Peripartum Prophylaxis:

  A Phase I study (PACTG 250) evaluated the safety and pharmacokinetics of nevirapine administered to infected pregnant women as a single 200-mg dose at the onset of labor and as a single 2-mg/kg dose to the infant at age 48 to 72 hours *[2]*. No adverse effects were seen in the women or the infants.

Pharmacokinetic parameters in pregnant women receiving intrapartum nevirapine were similar although somewhat more variable than in nonpregnant adults, possibly due to incomplete drug absorption associated with impaired gastrointestinal function during labor. Nevirapine elimination was prolonged in the infants. The regimen maintained serum concentrations associated with antiviral activity in the infants for the first week of life.

The safety, toxicity, and pharmacokinetics of nevirapine were also studied in HIV-infected pregnant women beginning chronic therapy late in the third trimester and their infants *[5]*. Initial dose pharmacokinetic profiles in pregnant women were similar to those seen in nonpregnant adults. Serum nevirapine concentrations fell below the 100 ng/mL target concentration by Day 7 of life in 4 of 8 infants, suggesting that nevirapine elimination was accelerated in infants whose mother received chronic nevirapine administration compared to newborns whose mothers received only a single intrapartum nevirapine dose.

The HIVNET 012 study in Uganda compared nevirapine (200 mg orally to the mother at the onset of labor and 2 mg/kg to the neonate within 72 hours of birth) to zidovudine (600 mg orally to the mother at the onset of delivery and 300 mg every 3 hours until delivery, and 4 mg/kg orally twice daily for the first 7 days of life to the neonate). In this study, nevirapine lowered the risk of HIV transmission by nearly 50% during the first 14 to 16 weeks of life compared to zidovudine *[6]*. However, the women in this African trial were not receiving any other antiretroviral therapy.

In the United States, most infected women who know their HIV status during pregnancy receive combination antiretroviral therapy, usually including zidovudine, as well as intravenous zidovudine during delivery, with 6 weeks of zidovudine given to their infant. A Phase III perinatal trial (PACTG 316) conducted in the United States, Europe, the Bahamas, and Brazil evaluated whether the HIVNET 012 single-dose nevirapine regimen in combination with standard antiretroviral therapy (at minimum the PACTG 076 zidovudine regimen; 77% of women in the trial received combination therapy) would provide additional benefits in reducing transmission. Transmission was not significantly different between those who had the addition of single-dose nevirapine (1.4%) and those who did not (1.6%) *[7]*.

Nevirapine resistance can be induced by a single mutation. As a result of its long half-life, nevirapine can be detected in plasma up to 3 weeks after administration of a single intrapartum dose *[8]*. This period of persistent subtherapeutic drugs levels exerts selective pressure that predisposes to the development of resistant strains of HIV *[9]*. Nevirapine resistance mutations were detected at 6 weeks postpartum in 19% of antiretroviral-naïve women in HIVNET 012 and 15% of a subset of women receiving additional antiretroviral drugs during pregnancy in PACTG 316 who received single-dose nevirapine during labor *[10-11]*. The clinical implications of the presence of nevirapine-resistant HIV are unclear. In HIVNET 012, these mutations were no longer detectable in plasma virus in women at 13 to 18 months postpartum *[12]*. Evaluation at later time points was not done in PACTG 316. Single-dose nevirapine appears to be as effective in preventing HIV transmission in subsequent pregnancies as when it is used for the first time*[13-14]*. Several studies have suggested that there is no decrease in efficacy when nevirapine-based combination therapy is started at least 6 to 12 months after delivery*[15-18]*. Administration of postpartum antiretrovirals to the mother can reduce the frequency of detection of nevirapine-resistant strains*[9, 19-21]*.

Longer Term Antenatal Combination Therapy:

The pharmacokinetics of nevirapine have been evaluated in pregnant women receiving nevirapine as part of combination antiretroviral therapy during pregnancy. A study that determined nevirapine pharmacokinetics in 26 women during pregnancy (7 second trimester, 19 third trimester) and again in the same women 4 to 12 weeks after delivery found that pregnancy did not alter nevirapine pharmacokinetic parameters *[22]*. In contrast, in nevirapine pharmacokinetic data from a therapeutic drug monitoring program that included 12-hour sampling, nevirapine clearance was 20% greater, AUC was 28% lower, and C_{max} was 30% lower in 16 pregnant women compared to 13 nonpregnant women *[23]*.

Severe, life-threatening, and in some cases, fatal hepatotoxicity, including fulminant and cholestatic hepatitis, hepatic necrosis, and hepatic failure, and severe, life-threatening hypersensitivity skin reactions, including Stevens-Johnson syndrome, have been reported in HIV-infected patients receiving nevirapine in combination with other drugs for treatment of HIV disease and in a small number of individuals receiving nevirapine as part of a combination regimen for post-exposure prophylaxis of nosocomial or sexual HIV exposure *[24]*. These toxicities have not been reported in women or infants receiving two-dose nevirapine (the HIVNET 012 regimen) for prevention of perinatal transmission. The greatest risk of severe rash or hepatic events occurs during the first 6 to 18 weeks of therapy, although the risk of toxicity continues past this period and monitoring should continue at frequent intervals.

The development of severe nevirapine-associated skin rash has been reported to be 5.5 to 7.3 times more common in women than men, and has been reported in pregnant women *[25-27]*. Other studies have found that hepatic adverse events with systemic symptoms (often rash) were 3.2-fold more common in women than men *[28]*. The degree of risk of hepatic toxicity varies with CD4 cell count. In a summary analysis of data from 17 clinical trials of nevirapine therapy, women with CD4 counts >250 cells/mm^3 were 9.8 times more likely than women with lower CD4 counts to experience symptomatic, often rash-associated, nevirapine-related hepatotoxicity *[28]*. Higher CD4 cell counts have also been associated with increased risk of severe nevirapine-associated skin rash *[26]*. In controlled clinical trials, clinical hepatic events, regardless of severity, occurred in 4.0% (range 2.5% – 11.0%) of patients who received nevirapine; however, the risk of nevirapine-associated liver failure or hepatic mortality has been lower, in the range of 0.04%–0.40% *[28-29]*. Severe or life-threatening rash occurs in approximately 2% of patients receiving nevirapine *[29]*.

Although deaths due to hepatic failure have been reported in HIV-infected pregnant women receiving nevirapine as part of a combination antiretroviral regimen, it is unknown if pregnancy increases the risk of hepatotoxicity in women receiving nevirapine or other antiretroviral drugs *[30-31]*. In an analysis of two multi-center prospective cohorts, pregnancy itself was a risk factor for liver enzyme elevations (RR 4.7; 95% CI: 3.4–6.5), although nevirapine use was not, regardless of pregnancy status *[32]*. Further data from the same cohorts did not show any increased risk of hepatotoxicity in HIV-infected pregnant women receiving nevirapine-based combination antiretroviral therapy versus non-nevirapine-based combination antiretroviral therapy *[33]*. These data suggest that nevirapine is no more toxic in pregnant women than in nonpregnant women. Women initiating nevirapine with CD4 counts >250 cells/mm^3, including pregnant women receiving antiretroviral drugs solely for prevention of transmission, have an increased risk of developing symptomatic, often rash-associated, nevirapine-related hepatotoxicity, which can be severe, life-threatening, and in some cases fatal *[34]*. Nevirapine should therefore be used as a component of a combination regimen in this setting only if the benefit clearly outweighs the risk. Women with CD4 counts less than 250/mm^3 can receive nevirapine-based regimens, and women who enter pregnancy on nevirapine regimens and are tolerating the regimens well may continue therapy, regardless of CD4 count. Hepatic toxicity has not been seen in women receiving single-dose nevirapine during labor for prevention of perinatal transmission of HIV.

Because pregnancy itself can mimic some of the early symptoms of hepatotoxicity, health care providers caring for women receiving nevirapine during pregnancy should be aware of this potential complication and conduct frequent and careful monitoring of clinical symptoms and hepatic transaminases (i.e., alanine aminotransferase [ALT] and aspartate aminotransferase [AST]), particularly during the first 18 weeks of therapy. Some clinicians measure serum transaminases at baseline, every 2 weeks for the first month, monthly through 4 months, and every 1 to 3 months thereafter (**Adult Antiretroviral Guidelines**); in patients with pre-existing liver disease, monitoring should be performed more frequently when initiating therapy and then monthly *[35]*. Transaminase levels should be checked in all women who develop a rash while receiving nevirapine. Patients who develop suggestive clinical symptoms accompanied by elevation in serum transaminase levels (ALT and/or AST) or have asymptomatic but severe transaminase elevations should stop nevirapine and not receive nevirapine therapy in the future.

References

1. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral pregnancy registry international interim report for 1 Jan 1989 – 31 July 2009. Wilmington, NC: Registry coordinating center; 2009.
2. Mirochnick M, Fenton T, Gagnier P, et al. Pharmacokinetics of nevirapine in human immunodeficiency virus type 1-infected pregnant women and their neonates. Pediatric AIDS Clinical Trials Group Protocol 250 Team. *J Infect Dis.* 1998;178(2):368-374.
3. Shapiro RL, Holland DT, Capparelli E, et al. Antiretroviral concentrations in breast-feeding infants of women in Botswana receiving antiretroviral treatment. *J Infect Dis.* 2005;192(5):720-727.
4. Mirochnick M, Thomas T, Capparelli E, et al. Antiretroviral concentrations in breast-feeding infants of mothers receiving highly active antiretroviral therapy. *Antimicrob Agents Chemother.* 2009;53(3):1170-1176.
5. Mirochnick M, Siminski S, Fenton T, et al. Nevirapine pharmacokinetics in pregnant women and in their infants after in utero exposure. *Pediatr Infect Dis J.* 2001;20(8):803-805.
6. Guay LA, Musoke P, Fleming T, et al. Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: HIVNET 012 randomised trial. *Lancet.* 1999;354(9181):795-802.
7. Dorenbaum A, Cunningham CK, Gelber RD, et al. Two-dose intrapartum/newborn nevirapine and standard antiretroviral therapy to reduce perinatal HIV transmission: a randomized trial. PACTG 316. *JAMA.* 2002;288(2):189-198.
8. Cressey TR, Jourdain G, Lallemant MJ, et al. Persistence of nevirapine exposure during the postpartum period after intrapartum single-dose nevirapine in addition to zidovudine prophylaxis for the prevention of mother-to-child transmission of HIV-1. *J Acquir Immune Defic Syndr.* 2005;38(3):283-288.
9. Arrivé E, Newell ML, Ekouevi DK, et al. Prevalence of resistance to nevirapine in mothers and children after single-dose exposure to prevent vertical transmission of HIV-1: a meta-analysis. *Int J Epidemiol.* 2007;36(5):1009-1021.
10. Cunningham CK, Chaix ML, Rekacewicz C, et al. Development of resistance mutations in women receiving standard antiretroviral therapy who received intrapartum nevirapine to prevent perinatal human immunodeficiency virus type 1 transmission: a substudy of pediatric AIDS clinical trials group protocol 316. *J Infect Dis.* 2002;186(2):181-188.
11. Eshleman SH, Mracna M, Guay LA, et al. Selection and fading of resistance mutations in women and infants receiving nevirapine to prevent HIV-1 vertical transmission (HIVNET 012). *AIDS.* 2001;15(15):1951-1957.
12. Jackson JB, Becker-Pergola G, Guay LA, et al. Identification of the K103N resistance mutation in Ugandan women receiving nevirapine to prevent HIV-1 vertical transmission. *AIDS.* 2000;14(11):F111-115.
13. McConnell M, Bakaki P, Eure C, et al. Effectiveness of repeat single-dose nevirapine for prevention of mother-to-child transmission of HIV-1 in repeat pregnancies in Uganda. *J Acquir Immune Defic Syndr.* 2007;46(3):291-296.
14. Martinson NA, Ekouevi DK, Dabis F, et al. Transmission rates in consecutive pregnancies exposed to single-dose nevirapine in Soweto, South Africa and Abidjan, Côte d'Ivoire. *J Acquir Immune Defic Syndr.* 2007;45(2):206-209.
15. Lockman S, Shapiro RL, Smeaton LM, et al. Response to antiretroviral therapy after a single, peripartum dose of nevirapine. *N Engl J Med.* 2007;356(2):135-147.
16. Chi BH, Sinkala M, Stringer EM, et al. Early clinical and immune response to NNRTI-based antiretroviral therapy among women with prior exposure to single-dose nevirapine. *AIDS.* 2007;21(8):957-964.
17. Jourdain G, Ngo-Giang-Huong N, Le Coeur S, et al. Intrapartum exposure to nevirapine and subsequent maternal responses to nevirapine-based antiretroviral therapy. *N Engl J Med.* 2004;351(3):229-240.
18. Coffie PA, Ekouevi DK, Chaix ML, et al. Maternal 12-month response to antiretroviral therapy following prevention of mother-to-child transmission of HIV type 1, Ivory Coast, 2003-2006. *Clin Infect Dis.* 2008;46(4):611-621.
19. Chaix ML, Ekouevi DK, Rouet F, et al. Low risk of nevirapine resistance mutations in the prevention of mother-to-child transmission of HIV-1: Agence Nationale de Recherches sur le SIDA Ditrame Plus, Abidjan, Cote d'Ivoire. *J Infect Dis.* 2006;193(4):482-487. Epub 2006 Jan 2011.
20. McIntyre JA, Hopley M, Moodley D, et al. Efficacy of short-course AZT plus 3TC to reduce nevirapine resistance in the prevention of mother-to-child HIV transmission: a randomized clinical trial. PLoS Med. 2009;6(10):e1000172.

21. Chi BH, Sinkala M, Mbewe F, et al. Single-dose tenofovir and emtricitabine for reduction of viral resistance to non-nucleoside reverse transcriptase inhibitor drugs in women given intrapartum nevirapine for perinatal HIV prevention: an open-label randomised trial. *Lancet.* 2007;370(9600):1698-1705.
22. Capparelli EV, Aweeka F, Hitti J, et al. Chronic administration of nevirapine during pregnancy: impact of pregnancy on pharmacokinetics. *HIV Med.* 2008;9(4):214-220.
23. von Hentig N, Carlebach A, Gute P, et al. A comparison of the steady-state pharmacokinetics of nevirapine in men, nonpregnant women and women in late pregnancy. *BR J Clin Pharmacol.* 2006;62(5):552-559.
24. Patel SM, Johnson S, Belknap SM, et al. Serious adverse cutaneous and hepatic toxicities associated with nevirapine use by non-HIV-infected individuals. *J Acquir Immune Defic Syndr.* 2004;35(2):120-125.
25. Mazhude C, Jones S, Murad S, et al. Female sex but not ethnicity is a strong predictor of non-nucleoside reverse transcriptase inhibitor-induced rash. *AIDS.* 2002;16(11):1566-1568.
26. Bersoff-Matcha SJ, Miller WC, Aberg JA, et al. Sex differences in nevirapine rash. *Clin Infect Dis.* 2001;32(1):124-129.
27. Knudtson E, Para M, Boswell H, et al. Drug rash with eosinophilia and systemic symptoms syndrome and renal toxicity with a nevirapine-containing regimen in a pregnant patient with human immunodeficiency virus. *Obstet Gynecol.* 2003;101(5 Pt 2):1094-1097.
28. Stern JO, Robinson PA, Love J, et al. A comprehensive hepatic safety analysis of nevirapine in different populations of HIV infected patients. *J Acquir Immune Defic Syndr.* 2003;34 Suppl 1:S21-33.
29. Boehringer-Ingelheim Pharmaceuticals Inc. Viramune drug label. Revised January 2005.
30. Lyons F, Hopkins S, Kelleher B, et al. Maternal hepatotoxicity with nevirapine as part of combination antiretroviral therapy in pregnancy. *HIV Med.* 2006;7(4):255-260.
31. Hitti J, Frenkel LM, Stek AM, et al. Maternal toxicity with continuous nevirapine in pregnancy: results from PACTG 1022. *J Acquir Immune Defic Syndr.* 2004;36(3):772-776.
32. Ouyang DW, Shapiro DE, Lu M, et al. Increased risk of hepatotoxicity in HIV-infected pregnant women receiving antiretroviral therapy independent of nevirapine exposure. *AIDS.* 2009;23(18):2425-2430.
33. Ouyang DW, Brogly SB, Lu M, et al. Lack of increased hepatotoxicity in HIV-infected pregnant women receiving nevirapine compared with other antiretrovirals. *AIDS.* 2010;24(1):109-114.
34. Grimbert S, Fisch C, Deschamps D, et al. Effects of female sex hormones on mitochondria: possible role in acute fatty liver of pregnancy. *Am J Physiol.* 1995;268(1 Pt 1):G107-115.
35. Kontorinis N, Dieterich DT. Toxicity of non-nucleoside analogue reverse transcriptase inhibitors. *Semin Liver Dis.* 2003;23(2):173-182.

PROTEASE INHIBITORS

For information regarding the protease inhibitor (PI) class of drugs and potential metabolic complications during pregnancy and pregnancy outcome, see **Protease Inhibitor Therapy and Hyperglycemia** and **Combination Antiretroviral Therapy and Pregnancy Outcome** in the Perinatal Guidelines.

Amprenavir (Agenerase, APV) is no longer available in the United States.

Atazanavir (Reyataz, ATV) is classified as FDA pregnancy category B.

- Animal carcinogenicity studies
  In *in vitro* and *in vivo* assays, atazanavir shows evidence of clastogenicity but not mutagenicity. Two-year carcinogenicity studies in mice and rats were conducted with atazanavir. In female mice, the incidence of benign hepatocellular adenomas was increased at systemic exposures 7.2-fold higher than those in humans at the recommended therapeutic dose (400 mg once daily). There were no increases in the incidence of tumors in male mice at any dose. In rats, no significant positive trends in the incidence of neoplasms occurred at systemic exposures up to 5.7-fold higher than those in humans at the recommended therapeutic dose.

- Reproduction/fertility
  No effect of atazanavir on reproduction or fertility in male and female rodents was seen at systemic drug exposures (AUC up to 2 times those achieved in humans at the recommended therapeutic dose).

- Teratogenicity/developmental toxicity
  Atazanavir did not produce teratogenic effects in rabbits with maternal dosing producing systemic drug exposure equivalent to (rabbits) or 2-times that (rats) achieved in humans at the recommended therapeutic dose (400 mg once daily). In developmental toxicity studies in rats, maternal dosing that resulted in maternal toxicity and produced systemic drug exposure 2-times the human exposure also resulted in weight loss or suppression of weight gain in the offspring. However, offspring were unaffected at lower maternal doses that produced systemic drug exposure equivalent to that observed in humans at the recommended therapeutic dose.

  In a retrospective analysis from London of atazanavir used in 31 women during 33 pregnancies (20 of whom were receiving atazanavir at conception), there were 2 miscarriages at 12 and 16 weeks, 26 infants born, and 5 women still pregnant *[1]*. No infant required phototherapy and no birth defects were seen; none of the infants were HIV infected. In the Antiretroviral Pregnancy Registry, sufficient numbers of first-trimester exposure to atazanavir in humans have been monitored to be able to detect at least a 2-fold increase in risk of overall birth defects. No such increase in birth defects has been observed with atazanavir. The prevalence of birth defects with first-trimester atazanavir exposure was 2.6% (9/343, 95% CI: 1.2%–4.9%) compared to total prevalence of birth defects in the U.S. population based on CDC surveillance of 2.7% *[2]*.

  Elevation in indirect (unconjugated) bilirubin attributable to atazanavir-related inhibition of hepatic uridine diphosphate glucuronosyltransferase enzyme occurs frequently during treatment with atazanavir. Studies have demonstrated that infants born to mothers who received atazanavir during pregnancy do not have pathologic or dangerous bilirubin elevations in the newborn period *[1,3-5]*.

- Placental and breast milk passage
  In studies of women receiving atazanavir/ritonavir-based combination therapy during pregnancy, cord blood atazanavir concentration averaged 13%–16% of maternal serum levels at delivery *[3,5]*. Atazanavir is excreted in the milk of lactating rats. In a small study of 3 women, the median ratio of breast milk atazanavir concentration to that in plasma was 13% *[6]*.

- Human studies in pregnancy
  The pharmacokinetics of atazanavir 300 mg when administered once daily during pregnancy with ritonavir 100 mg have been investigated in 4 studies. In a retrospective study, trough atazanavir concentrations were measured in 19 pregnant women at a median of 30 weeks gestation (14 in third trimester); all but 2 women had a trough atazanavir concentration greater than 100 ng/mL *[1]*. Full pharmacokinetic profiles of atazanavir when administered daily as 300 mg with 100 mg ritonavir during pregnancy have been evaluated in 3 studies. In a study of 17 pregnant women, atazanavir AUC was not different during pregnancy compared to 1–6 months postpartum (28.5 µg*hr/mL vs. 30.5 µg*hr/mL, respectively) *[3]*. In contrast, another study determined atazanavir pharmacokinetics in 12 pregnant women and found reductions in atazanavir concentrations of more than 50% during pregnancy, with a mean AUC of 26.6 µg*hr/mL during the third trimester compared to 57.0 µg*hr/mL at 4 weeks postpartum. All subjects had trough atazanavir concentrations greater than 150 ng/mL *[4]*. Similar results were found in another study of atazanavir pharmacokinetics in 18 women not receiving tenofovir, with median AUC of 41.9 µg*hr/mL during pregnancy versus 58.0µ g*hr/mL at 6–12 weeks postpartum *[5]*. Atazanavir AUC was further reduced in 15 women also receiving tenofovir, with median AUC of 30.5 µg*hr/mL during pregnancy compared to 44.1 µg*hr/mL postpartum. Mean atazanavir AUC in nonpregnant adults receiving 300 mg plus 100 mg ritonavir daily dosing is 57.0 µg*hr/mL and is reduced by about 25% in adults receiving concomitant tenofovir *[7,8]*. Investigations of atazanavir exposure with the use of an increased dose of 400 mg in combination with 100 mg ritonavir during pregnancy are under way.

References

1. Natha M, Hay P, Taylor G, et al. Atazanavir use in pregnancy: a report of 33 cases. 14th Conference on Retoviruses and Opportunistic Infections; February 25-28, 2007; Los Angeles, CA. Abstract 750. http://www.retroconference.org/2007/Abstracts/28351.htm
2. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral pregnancy registry international interim report for 1 Jan 1989 – 31 July 2009. Wilmington, NC: Registry coordinating center; 2009.
3. Ripamonti D, Cattaneo D, Maggiolo F, et al. Atazanavir plus low-dose ritonavir in pregnancy: pharmacokinetics and placental transfer. *AIDS*, 2007. 21(18):2409-15. http://www.ncbi.nlm.nih.gov/pubmed/18025877
4. Eley T, Vandeloise E, Child M, et al. Steady State Pharmacokinetics and Safety of Atazanavir after Treatment with ATV 300 mg Once Daily/Ritonavir 100 mg Once Daily + ZDV/3TC during the Third Trimester in HIV+ Women. 15th Conference on Retoviruses and Opportunistic Infections; February 3-6, 2008; Boston, MA. http://www.retroconference.org/2008/PDFs/624.pdf
5. Mirochnick M, Stek A, Capparelli E, et al. Atazanavir Pharmacokinetics with and without Tenofovir during Pregnancy. 16th Conference on Retroviruses and Opportunistic Infections; February, 2009; Montreal, Canada. http://www.retroconference.org/2009/Abstracts/34312.htm
6. Spencer L, Neely M, Mordwinkin N, et al. Intensive Pharmacokinetics of Zidovudine, Lamivudine, and Atazanavir and HIV-1 Viral Load in Breast Milk and Plasma in HIV+ Women Receiving HAART. 16th Conference on Retroviruses and Opportunistic Infections; February, 2009; Montreal, Canada. http://www.retroconference.org/2009/PDFs/942.pdf
7. Reyataz pacakage insert. Bristol-Myers Squibb Co., Princeton, NJ. September, 2008. Accessed on November 21, 2008 at http://www.fda.gov/cder/foi/label/2008/021567s017lbl.pdf.
8. Taburet AM, Piketty C, Chazallon C, et al. Interactions between atazanavir-ritonavir and tenofovir in heavily pretreated human immunodeficiency virus-infected patients. *Antimicrob Agents Chemother*, 2004. 48(6):2091-6. http://www.ncbi.nlm.nih.gov/pubmed/15155205

Darunavir (Prezista, DRV) is classified as FDA pregnancy category C.

- Animal carcinogenicity studies
  Darunavir was neither mutagenic nor clastogenic in a series of *in vitro* and animal *in vivo* screening tests. A dose-related increase in the incidence of hepatocellular adenomas and carcinomas was observed in males and females of both mice and rats as well as an increase in thyroid follicular cell adenomas in male rats. The observed hepatocellular findings in rodents are considered to be of limited relevance to humans. Repeated administration of darunavir to rats caused hepatic microsomal enzyme induction and increased thyroid hormone elimination, which predispose rats, but not humans, to thyroid neoplasms. At the highest tested doses, the systemic exposures to darunavir (based on AUC) were between 0.4- and 0.7-fold (mice) and 0.7- and 1-fold (rats) of those observed in humans at the recommended therapeutic doses (600/100 mg twice daily or 800/100 mg once daily).
- Reproduction/fertility
  No effects on fertility and early embryonic development were seen with darunavir in rats.
- Teratogenicity/developmental toxicity
  No embryotoxicity or teratogenicity was seen in mice, rats, or rabbits. Because of limited bioavailability of darunavir in animals and dosing limitation, the plasma exposures were approximately 50% (mice and rats) and 5% (rabbits) of those obtained in humans. In the rat pre- and postnatal development study, a reduction in pup weight gain was observed with darunavir alone or with ritonavir during lactation due to exposure of pups to drug substances via the milk. In juvenile rats single doses of darunavir (20 mg/kg to 160 mg/kg at ages 5 to 11 days) or multiple doses of darunavir (40 mg/kg to 1,000 mg/kg at age 12 days) caused mortality. The mortalities were associated with convulsions in some of the animals. Within this age range, exposures in

plasma, liver, and brain were dose and age dependent and were considerably greater than those observed in adult rats. These findings were attributed to the ontogeny of the CYP450 liver enzymes involved in the metabolism of darunavir and the immaturity of the blood-brain barrier. Sexual development, fertility, or mating performance of offspring were not affected by maternal treatment. No data are available in humans.

- Placental and breast milk passage
  No animal studies of placental passage of darunavir have been reported. As noted above, passage of darunavir into breast milk has been noted in rats. It is unknown if placental or breast milk passage of darunavir occurs in humans.
- Human studies in pregnancy
  No studies of darunavir have been conducted in pregnant women or neonates. Darunavir is not recommended for children younger than 3 years.

Fosamprenavir (Lexiva, f-APV) is classified as FDA pregnancy category C.

- Animal carcinogenicity studies
  Fosamprenavir and amprenavir were neither mutagenic nor clastogenic in a series of *in vitro* and animal *in vivo* screening tests. Carcinogenicity studies of fosamprenavir showed an increase in the incidence of hepatocellular adenomas and hepatocellular carcinomas at all doses tested in male mice and at the highest dose tested in female mice. In rats, the incidence of hepatocellular adenomas and thyroid follicular cell adenomas in males (all doses tested) and in females (two highest doses tested) was also increased. Repeat dose studies in rats produced effects consistent with enzyme activation, which predisposes rats, but not humans, to thyroid neoplasms. In rats only there was an increase in interstitial cell hyperplasia at higher doses and an increase in uterine endometrial adenocarcinoma at the highest dose tested. The incidence of endometrial findings was slightly increased over concurrent controls but was within background range for female rats. Thus the relevance of the uterine endometrial adenocarcinomas is uncertain. Exposures in the carcinogenicity studies were 0.3- to 0.7-fold (mice) and 0.7- to 1.4-fold (rats) those in humans given 1,400 mg twice daily of fosamprenavir alone, and 0.2- to 0.3-fold (mice) and 0.3- to 0.7-fold (rats) those in humans given 1,400 mg once daily of fosamprenavir plus 200 mg ritonavir once daily or 0.1- to 0.3-fold (mice) and 0.3- to 0.6-fold (rats) those in humans given 700 mg of fosamprenavir plus 100 mg ritonavir twice daily.
- Reproduction/fertility
  No impairment of fertility or mating was seen in rats at doses providing 3 to 4 times the human exposure to fosamprenavir alone or exposure similar to that with fosamprenavir and ritonavir dosing in humans. No affect was seen on the development or maturation of sperm in rats at these doses.
- Teratogenicity/developmental toxicity
  Fosamprenavir was studied in rabbits at 0.8 and in rats at 2 times the exposure in humans to fosamprenavir alone and at 0.3 (rabbits) and 0.7 (rats) times the exposure in humans to the combination of fosamprenavir and ritonavir. In rabbits administered fosamprenavir (alone or in combination) the incidence of abortion was increased. In contrast, administration of amprenavir at a lower dose in rabbits was associated with abortions and an increased incidence of minor skeletal variations from deficient ossification of the femur, humerus, and trochlea. Fosamprenavir administered to pregnant rats (at 2 times human exposure) was associated with a reduction in pup survival and body weights in rats. F1 female rats had an increased time to successful mating, an increased length of gestation, a reduced number of uterine implantation sites per litter, and reduced gestational body weights compared to controls.
- Placental and breast milk passage
  It is unknown whether fosamprenavir crosses the placenta. Amprenavir is excreted in the milk of lactating rats; it is not known if it is excreted in human milk.

- Human studies in pregnancy
  There are very limited data on fosamprenavir in pregnant women. There is a pediatric liquid formulation approved for children older than 2 years of age, but there is no dosing information for neonates.

Indinavir (Crixivan, IDV) is classified as FDA pregnancy category C.

- Animal carcinogenicity studies
  There is no evidence that indinavir is mutagenic or clastogenic in both *in vitro* and *in vivo* assays. No increased incidence of any tumor types occurred in long-term studies in mice. At the highest dose studied in rats (640 mg/kg/day or 1.3-fold higher than systemic exposure at human therapeutic doses), thyroid adenomas were seen in male rats.
- Reproduction/fertility
  No effect of indinavir has been seen on reproductive performance, fertility, or embryo survival in rats.
- Teratogenicity/developmental toxicity
  There has been no evidence of teratogenicity or treatment-related effects on embryonic/fetal survival or fetal weights of indinavir in rats, rabbits, or dogs at exposures comparable to or slightly greater than therapeutic human exposure. In rats, developmental toxicity manifested by an increase in supernumerary and cervical ribs was observed at doses comparable to those administered to humans. No treatment-related external or visceral changes were observed in rats. No treatment-related external, visceral, or skeletal changes were seen in rabbits (fetal exposure limited, approximately 3% of maternal levels) or dogs (fetal exposure approximately 50% of maternal levels). Indinavir was administered to Rhesus monkeys during the third trimester of pregnancy (at doses up to 160 mg/kg twice daily) and to neonatal Rhesus monkeys (at doses up to 160 mg/kg twice daily). When administered to neonates, indinavir caused an exacerbation of the transient physiologic hyperbilirubinemia seen in this species after birth; serum bilirubin values were approximately 4-fold greater than controls at 160 mg/kg twice daily. A similar exacerbation did not occur in neonates after *in utero* exposure to indinavir during the third trimester of pregnancy. In Rhesus monkeys, fetal plasma drug levels were approximately 1% – 2% of maternal plasma drug levels approximately 1 hour after maternal dosing at 40, 80, or 160 mg/kg twice daily.

  In the Antiretroviral Pregnancy Registry, sufficient numbers of first-trimester exposure to indinavir in humans have been monitored to be able to detect at least a 2-fold increase in risk of overall birth defects. No such increase in birth defects has been observed with indinavir The prevalence of birth defects with first-trimester indinavir exposure was 2.2% (6/276, 95% CI: 0.8%–4.7%) compared to total prevalence of birth defects in the U.S. population based on CDC surveillance of 2.7% *[1]*.
- Placental and breast milk passage
  Significant placental passage of indinavir occurs in rats and dogs, but only limited placental transfer occurs in rabbits. In a Phase I study in pregnant women and their infants (PACTG 358, see below), transplacental passage of indinavir was minimal *[2]*. Additionally, in a study of cord blood samples from 21 women treated with indinavir during pregnancy, the cord blood concentration of indinavir was less than the assay limit of detection in samples from all women *[3]*. Indinavir is excreted in the milk of lactating rats at concentrations slightly greater than maternal levels (milk-to-plasma ratio 1.26 to 1.45); it is not known if indinavir is excreted in human milk.
- Human studies in pregnancy
  The optimal dosing regimen for use of indinavir in pregnant patients has not been established. A Phase I/II safety and pharmacokinetic study (PACTG 358) of indinavir (800 mg three times a day) in combination with zidovudine and lamivudine in pregnant HIV-infected women and their infants was conducted *[2]*. The mean indinavir plasma $AUC_{0\text{-}8hr}$ at weeks 30 to 32 of gestation (n =11) was 74% (95% CI: 50%–86%) lower than that observed 6 weeks postpartum. The pharmacokinetics of indinavir in these 11 patients at 6 weeks postpartum were generally similar to those observed in nonpregnant patients in another study. In another study, 2 pregnant HIV-infected women receiving combination therapy including indinavir (800 mg three

times a day) had significantly reduced AUC indinavir exposures in the third trimester compared to postpartum evaluations (52% and 86% respectively) *[4]*. Therefore, given the substantially lower antepartum exposures observed in these studies and the generally limited data in this patient population, use of indinavir as a sole PI is not recommended in HIV-infected pregnant patients.

Two studies have evaluated indinavir used in conjunction with low-dose ritonavir in twice-daily dosing. The first evaluated 2 women whose regimen included indinavir 800 mg twice daily with ritonavir 200 mg twice daily. Both women achieved third-trimester AUC indinavir levels greater than those for historical nonpregnant controls *[4]*. A more recent study evaluated use of combination therapy including indinavir 400 mg twice daily with ritonavir 100 mg twice daily. Data are available for 28 women, 23 (82%) of whom had C_{trough} values above the targeted cutoff of 120 ng/mL. Of the 5 women with low C_{trough} values, 3 had undetectable HIV RNA viral loads at delivery *[5]*. Based on these data, indinavir may be used in pregnancy with ritonavir boosting. Given the limited data on appropriate dosing, HIV RNA levels and, potentially, trough drug levels should be monitored during indinavir use in pregnancy.

References

1. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral pregnancy registry international interim report for 1 Jan 1989 – 31 July 2009. Wilmington, NC: Registry coordinating center; 2009.
2. Unadkat JD, Wara DW, Hughes MD, et al. Pharmacokinetics and safety of indinavir in human immunodeficiency virus-infected pregnant women. *Antimicrob Agents Chemother*, 2007. 51(2):783-6. http://www.ncbi.nlm.nih.gov/pubmed/17158945
3. Mirochnick M, Dorenbaum A, Holland D, et al. Concentrations of protease inhibitors in cord blood after in utero exposure. *Pediatr Infect Dis J*, 2002. 21(9):835-8. http://www.ncbi.nlm.nih.gov/pubmed/12352805
4. Kosel BW, Beckerman KP, Hayashi S, et al. Pharmacokinetics of nelfinavir and indinavir in HIV-1-infected pregnant women. *AIDS*, 2003. 17(8):1195-9. http://www.ncbi.nlm.nih.gov/pubmed/12819521
5. Ghosn J, De Montgolfier I, Cornélie C, et al. Antiretroviral therapy with a twice-daily regimen containing 400 milligrams of indinavir and 100 milligrams of ritonavir in human immunodeficiency virus type 1-infected women during pregnancy. *Antimicrob Agents Chemother*, 2008. 52(4):1542-4. http://www.ncbi.nlm.nih.gov/pubmed/18250187

Lopinavir + Ritonavir (Kaletra, LPV/r) is classified as FDA pregnancy category C.

- Animal carcinogenicity studies
  Neither lopinavir nor ritonavir was found to be mutagenic or clastogenic in a battery of *in vitro* and *in vivo* assays. Lopinavir/ritonavir combination was evaluated for carcinogenic potential by oral gavage administration to mice and rats for up to 104 weeks. Results showed an increase in the incidence of benign hepatocellular adenomas and an increase in the combined incidence of hepatocellular adenomas plus carcinoma in both males and females in mice and males in rats at doses that produced approximately 1.6 to 2.2 times (mice) and 0.5 times (rats) the human exposure at the recommended therapeutic dose of 400 mg/100 mg (based on AUC_{0-24hr} measurement). Administration of lopinavir/ritonavir did not cause a statistically significant increase in the incidence of any other benign or malignant neoplasm in mice or rats.
- Reproduction/fertility
  Lopinavir in combination with ritonavir at a 2:1 ratio produced no effects on fertility in male and female rats with exposures approximately 0.7-fold for lopinavir and 1.8-fold for ritonavir of the exposures in humans at the recommended therapeutic dose.
- Teratogenicity/developmental toxicity
  There has been no evidence of teratogenicity with administration of lopinavir + ritonavir to pregnant rats or rabbits. In rats treated with a maternally toxic dosage (100 mg lopinavir/50 mg ritonavir/kg/day), embryonic and fetal developmental toxicities (early resorption, decreased fetal viability, decreased fetal body weight,

increased incidence of skeletal variations, and skeletal ossification delays) were observed. Drug exposure in the pregnant rats was 0.7-fold for lopinavir and 1.8-fold for ritonavir of the exposures in humans at the recommended therapeutic dose. In a peri- and postnatal study in rats, a decrease in survival of pups between birth and postnatal Day 21 occurred with exposures of 40 mg lopinavir/20 mg ritonavir/kg/day or greater. In rabbits, no embryonic or fetal developmental toxicities were observed with a maternally toxic dosage, where drug exposure was 0.6-fold for lopinavir and 1-fold for ritonavir of the exposures in humans at the recommended therapeutic dose.

In the Antiretroviral Pregnancy Registry, sufficient numbers of first-trimester exposures to lopinavir + ritonavir have been monitored to be able to detect at least a 2-fold increase in risk of overall birth defects. No such increase in birth defects has been observed with lopinavir + ritonavir. The prevalence of birth defects with first-trimester lopinavir + ritonavir exposure was 1.7% (95% CI: 0.8%–3.2%) compared to total prevalence of birth defects in the U.S. population based on CDC surveillance of 2.7% *[1]*.

- Placental and breast milk passage
  Lopinavir crosses the human placenta; in a pharmacokinetic study, P1026s, the average ratio of lopinavir concentration in cord blood to maternal plasma at delivery was 0.20±0.13. For ritonavir, data in humans indicate only minimal transplacental passage (see ritonavir). Lopinavir and ritonavir are secreted in the breast milk of lactating rats; it is not known if either drug is excreted in human milk.

- Human studies in pregnancy
  The capsule formulation of lopinavir/ritonavir is no longer available; it has been replaced by a new tablet formulation of lopinavir 200 mg/ritonavir 50 mg that is heat stable and does not have a food requirement.

  In nonpregnant adults, plasma concentrations of lopinavir and ritonavir after administration of two 200/50 mg lopinavir/ritonavir tablets are similar to those achieved with three 133/33 mg lopinavir/ritonavir capsules given with food, although with less pharmacokinetic variability. In a study of 51 pregnant women, plasma trough lopinavir levels during the third trimester were compared among 28 women receiving the capsule and 23 women receiving the tablet formulations at standard dosing. No statistical difference was found between the groups, with a mean lopinavir trough level of 4.86 mg/L (capsule) and 4.57 mg/L (tablets) *[2]*. However, the inter-individual variability was lower with the tablets than the capsules. Five of 28 women (17.8%) in the capsule group and 4 of 23 women (17.4%) in the tablet group had trough levels less than the target (3 mg/L); 7 of the 9 women had HIV RNA levels less than detection at the time of their sampling, and 2 with subtherapuetic levels (0.7 and 2.44 mg/L) had plasma RNA of 83 and 56 copies/mL, respectively, at the time of their sampling.

  P1026s evaluated lopinavir pharmacokinetics following standard dosing with the new lopinavir/ritonavir tablet formulation (2 tablets twice daily) until 30 weeks gestation, followed by an increase to 3 tablets twice daily and return to standard dosing at postpartum hospital discharge. Median AUC was 72 µg*h/mL in 7 women receiving standard dosing during the second trimester, 97 µg*h/mL in 25 women receiving the increased dose during the third trimester, and 129 µg*h/mL in 19 women receiving standard dosing at 2 weeks postpartum. These data suggest that the higher lopinavir/ritonavir dose should be used in third-trimester pregnant women and that it should be considered in second-trimester pregnant women, especially those who are PI-experienced, and that lopinavir/ritonavir can be reduced to standard dosing shortly after delivery *[3]*.

  Once-daily dosing of lopinavir/ritonavir capsules or tablets is not recommended in pregnancy because there are no data to address whether drug levels are adequate with such administration.

References

1. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral pregnancy registry international interim report for 1 Jan 1989 – 31 July 2009. Wilmington, NC: Registry coordinating center; 2009.
2. Khuong-Josses MA, Azerad D, Boussaïri A, et al. Comparison of lopinavir level between the two formulations

(soft-gel capsule and tablet) in HIV-infected pregnant women. *HIV Clin Trials*, 2007. 8(4):254-5. http://www.ncbi.nlm.nih.gov/pubmed/17720666

3. Best B, Stek A, Hu C, et al. for the PACTG/IMPAACT P1026S team. High-dose lopinavir and standard-dose emtricitabine pharmacokinetics during pregnancy and postpartum. 15th Conference on Retroviruses and Opportunistic Infections, February 3-8, 2008; Boston, MA. Abstract 629. http://www.retroconference.org/2008/PDFs/629.pdf

Nelfinavir (Viracept, NFV) is classified as FDA pregnancy category B.

- Animal carcinogenicity studies
  Nelfinvair was neither mutagenic nor clastogenic in a series of *in vitro* and animal *in vivo* screening tests. However, thyroid follicular cell adenomas and carcinomas were increased over baseline in male rats receiving 300 mg/kg/day or higher (equal to a systemic exposure similar to that in humans at therapeutic doses) and female rats receiving 1,000 mg/kg/day (equal to a systemic exposure 3-fold higher than that in humans at therapeutic doses) of nelfinavir.

- Reproduction/fertility
  No effect of nelfinavir has been seen on reproductive performance, fertility, or embryo survival in rats at exposures comparable to human therapeutic exposure. Additional studies in rats indicated that exposure to nelfinavir in females from midpregnancy through lactation had no effect on the survival, growth, and development of the offspring to weaning. Subsequent reproductive performance of these offspring was also not affected by maternal exposure to nelfinavir.

- Teratogenicity/developmental toxicity
  No evidence of teratogenicity has been observed in pregnant rats at exposures comparable to human exposure and in rabbits with exposures significantly less than human exposure.

  In the Antiretroviral Pregnancy Registry, sufficient numbers of first-trimester exposures to nelfinavir have been monitored to be able to detect at least a 2-fold increase in risk of overall birth defects. No such increase in birth defects has been observed with nelfinavir. The prevalence of birth defects with first-trimester nelfinavir exposure was 3.4% (37/1,075, 95% CI: 2.4%–4.7%) compared to total prevalence of birth defects in the U.S. population based on CDC surveillance of 2.7% *[1]*.

- Placental and breast milk transfer
  In a Phase I study in pregnant women and their infants (PACTG 353, see below), transplacental passage of nelfinavir was minimal *[2]*. Additionally, in a study of cord blood samples from 38 women who were treated with nelfinavir during pregnancy, the cord blood nelfinavir concentration was less than the assay limit of detection in 24 (63%), and the cord blood concentration was low (median, 0.35 µg/mL) in the remaining 14 women *[3]*. Nelfinavir is excreted in the milk of lactating rats; it is not known if it is excreted in human milk.

- Human studies in pregnancy
  A Phase I/II safety and pharmacokinetic study (PACTG 353) of nelfinavir in combination with zidovudine and lamivudine was conducted in pregnant HIV-infected women and their infants *[2]*. Nelfinavir administered at a dose of 750 mg three times daily produced drug exposures in the first nine pregnant HIV-infected women enrolled in the study that were variable and generally lower than those reported in nonpregnant adults for both two and three times daily dosing. Therefore, the study was modified to evaluate an increased dose of nelfinavir given twice daily (1,250 mg twice daily), which resulted in adequate levels of nelfinavir in pregnancy. However, in another study of pregnant women in their second and third trimester dosed at 1,250 mg given twice daily, women in the third trimester had lower concentration of nelfinavir than women in their second trimester and lower concentration than in nonpregnant women *[4]*.

  In a pharmacokinetic study of combination therapy including the new nelfinavir 625-mg tablet formulation (given as 1,250 mg twice daily) in 25 women at 30 to 36 weeks gestation (and 12 also at 6 to 12 weeks

postpartum), peak levels and AUC were lower in the third trimester than postpartum *[5]*. Only 16% (4/25) of women during the third trimester and 8% (1/12) women postpartum had trough values greater that the suggested minimum trough of 800 ng/mL; however, viral load was <400 copies/mL in 96% of women in the third trimester and 86% postpartum.

In September 2007, the manufacturer of nelfinavir (Viracept) in the United States (Pfizer) sent a letter to providers regarding the presence of low levels of ethyl methane sulfonate (EMS), a process-related impurity, in nelfinavir. EMS is teratogenic, mutagenic, and carcinogenic in animals, although no data from humans exist and no increase in birth defects has been observed in the Antiretroviral Pregnancy Registry. Health care providers were advised not to initiate antiretroviral regimens containing Viracept (nelfinavir) in their pregnant female or new pediatric patients and to switch pregnant patients receiving Viracept (nelfinavir) to an alternative therapy unless no alternative was available. As of March 31, 2008, all Viracept (nelfinavir) manufactured and released by Pfizer now meets the new final EMS limits established by the FDA for prescribing to all patient populations, including pregnant women and pediatric patients. Viracept (nelfinavir) may now be prescribed for pregnant women as an alternate PI for women receiving antiretroviral therapy during pregnancy solely for prevention of mother-to-child transmission.

References

1. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral pregnancy registry international interim report for 1 Jan 1989 – 31 July 2009. Wilmington, NC: Registry coordinating center; 2009.
2. Bryson YJ, Mirochnick M, Stek A, et al. Pharmacokinetics and safety of nelfinavir when used in combination with zidovudine and lamivudine in HIV-infected pregnant women: Pediatric AIDS Clinical Trials Group (PACTG) Protocol 353. *HIV Clin Trials*, 2008. 9(2):115-25. http://www.ncbi.nlm.nih.gov/pubmed/18474496
3. Mirochnick M, Dorenbaum A, Holland D, et al. Concentrations of protease inhibitors in cord blood after in utero exposure. *Pediatr Infect Dis J*, 2002. 21(9):835-8. http://www.ncbi.nlm.nih.gov/pubmed/12352805
4. Villani P, Floridia M, Pirillo MF, et al. Pharmacokinetics of nelfinavir in HIV-1-infected pregnant and nonpregnant women. *Br J Clin Pharmacol*, 2006. 62(3):309-15. http://www.ncbi.nlm.nih.gov/pubmed/16934047
5. Read JS, Best BM, Stek AM, et al. Pharmacokinetics of new 625 mg nelfinavir formulation during pregnancy and postpartum. *HIV Med*, 2008. 9(10):875-82. http://www.ncbi.nlm.nih.gov/pubmed/18795962

Ritonavir (Norvir, RTV) is classified as FDA pregnancy category B.

- Animal carcinogenicity studies
  Ritonavir was neither mutagenic nor clastogenic in a series of *in vitro* and animal *in vivo* screening tests. Carcinogenicity studies in mice and rats have been completed. In male mice, at levels of 50, 100, or 200 mg/kg/day, a dose-dependent increase in adenomas of the liver and combined adenomas and carcinomas of the liver was observed; based on AUC, exposure in male mice at the highest dose was approximately 0.3-fold that in male humans at the recommended therapeutic dose. No carcinogenic effects were observed in female mice with exposures 0.6-fold that of female humans at the recommended therapeutic dose. No carcinogenic effects were observed in rats at exposures up to 6% of recommended therapeutic human exposure.
- Reproduction/fertility
  No effect of ritonavir has been seen on reproductive performance or fertility in rats at drug exposures 40% (male) and 60% (female) of that achieved with human therapeutic dosing; higher doses were not feasible due to hepatic toxicity in the rodents.
- Teratogenicity/developmental toxicity
  No ritonavir-related teratogenicity has been observed in rats or rabbits. Developmental toxicity was observed in rats, including early resorptions, decreased body weight, ossification delays, and developmental variations

such as wavy ribs and enlarged fontanelles; however, these effects occurred only at maternally toxic dosages (exposure equivalent to 30% of human therapeutic exposure). In addition, a slight increase in cryptorchidism was also noted in rats at exposures equivalent to 22% of the human therapeutic dose. In rabbits, developmental toxicity (resorptions, decreased litter size, and decreased fetal weight) was observed only at maternally toxic doses (1.8 times human therapeutic exposure based on body surface area).

In the Antiretroviral Pregnancy Registry, sufficient numbers of first-trimester exposures to ritonavir have been monitored to be able to detect at least a 2-fold increase in risk of overall birth defects. No such increase in birth defects has been observed with ritonavir. The prevalence of birth defects with first-trimester ritonavir exposure was 2.2% (22/1,000, 95% CI: 1.4%–3.3%) compared with total prevalence of birth defects in the U.S. population based on CDC surveillance of 2.7% *[1]*.

- Placental and breast milk transfer
  Transplacental passage of ritonavir has been observed in rats with fetal tissue to maternal serum ratios >1.0 at 24 hours post-dose in mid- and late-gestation fetuses. In a human placental perfusion model, the clearance index of ritonavir was very low, with little accumulation in the fetal compartment and no accumulation in placental tissue *[2]*. In a Phase I study in pregnant women and their infants (PACTG 354, see below), transplacental passage of ritonavir was minimal *[3]*. Additionally, in a study of cord blood samples from six women treated with ritonavir during pregnancy, the cord blood concentration was less than the assay limit of detection in 83%, and was only 0.38 µg/mL in the remaining woman *[4]*. Ritonavir is excreted in the milk of lactating rats; it is unknown if it is excreted in human milk.
- Human studies in pregnancy
  A Phase I/II safety and pharmacokinetic study (PACTG 354) of ritonavir in combination with zidovudine and lamivudine in pregnant HIV-infected women and their infants showed lower levels of ritonavir during pregnancy compared to postpartum *[3]*.

References

1. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral pregnancy registry international interim report for 1 Jan 1989 – 31 July 2009. Wilmington, NC: Registry coordinating center; 2009.
2. Casey BM, Bawdon RE. Placental transfer of ritonavir with zidovudine in the ex vivo placental perfusion model. *Am J Obstet Gynecol*, 1998. 179(3 Pt 1):758-61. http://www.ncbi.nlm.nih.gov/pubmed/9757985
3. Scott GB, Rodman JH, Scott WA, et al. Pharmacokinetic and virologic response to ritonavir (RTV) in combination with zidovudine (ZDV) and lamivudine (3TC) in HIV-10-infected pregnant women and their infants. 9th Conference on Retroviruses and Opportunistic Infections; February 24-28, 2002; Seattle, WA. Abstract 794-W. http://www.retroconference.org/2002/Abstract/13702.htm
4. Mirochnick M, Dorenbaum A, Holland D, et al. Concentrations of protease inhibitors in cord blood after in utero exposure. *Pediatr Infect Dis J*, 2002. 21(9):835-8. http://www.ncbi.nlm.nih.gov/pubmed/12352805

Saquinavir (Invirase [Hard Gel Capsule], SQV) is classified as FDA pregnancy category B.

- Animal carcinogenicity studies
  Saquinavir was neither mutagenic nor clastogenic in a series of *in vitro* and animal *in vivo* screening tests. Carcinogenicity studies found no indication of carcinogenic activity in rats and mice administered saquinavir for approximately 2 years, at plasma exposures approximately 60% of those obtained in humans at the recommended therapeutic dose (rats) and at exposures equivalent to those in humans at the recommended therapeutic dose (mice).
- Reproduction/fertility
  No effect of saquinavir has been seen on reproductive performance, fertility, or embryo survival in rats. Because of limited bioavailability of saquinavir in animals, the maximal plasma exposures achieved in rats were approximately 26% of those obtained in humans at the recommended clinical dose boosted with ritonavir.

- Teratogenicity/developmental toxicity
  No evidence of embryotoxicity or teratogenicity of saquinavir has been found in rabbits or rats. Because of limited bioavailability of saquinavir in animals and/or dosing limitations, the plasma exposures (AUC values) in the respective species were approximately 29% (using rat) and 21% (using rabbit) of those obtained in humans at the recommended clinical dose boosted with ritonavir.

- Placental and breast milk transfer
  Placental transfer of saquinavir in the rat and rabbit was minimal. In a Phase I study in pregnant women and their infants (PACTG 386, see below), transplacental passage of saquinavir was minimal *[1]*. Additionally, in a study of cord blood samples from eight women treated with saquinavir during pregnancy, the cord blood concentration of saquinavir was less than the assay limit of detection in samples from all women *[2]*. Saquinavir is excreted in the milk of lactating rats; it is not known if it is excreted in human milk.

- Human studies in pregnancy
  Three studies have evaluated the pharmacokinetics of saquinavir-hard gel capsules (HGC) combined with low-dose ritonavir (saquinavir-HGC 1,000 mg/ritonavir 100 mg given twice daily) in a total of 19 pregnant women; trough levels were greater than the target in all but 1 woman *[3,4]*. In a small study of 2 women who received saquinavir-HGC 1,200 mg/ritonavir 100 mg given once daily, trough levels were 285 and 684 ng/mL and the $AUC_{0\text{-}24}$ were 28,010 and 16,790 ng hour/mL, greater than the target AUC of 10,000 ng hour/mL *[5]*. Thus, the limited available data suggest that saquinavir-HGC 1,000 mg/ritonavir 100 mg given twice daily should achieve adequate trough levels in HIV-infected pregnant women. Data are too limited to recommend once-daily dosing at present. However, a recent analysis of saquinavir HGC administered once daily at 1,200mg/100mg ritonavir combined with various NRTIs during 46 pregnancies, demonstrated saquinavir levels greater than the target C_{min} in 46 (93.4%) of pregnancy episodes and undetectable viral load at delivery in 88% of episodes *[6]*. Target levels were achieved in the other 3 women with a dose of 1,600mg/100mg. The drug was well tolerated.

  The pharmacokinetics of the new 500-mg tablet formulation of saquinavir boosted with ritonavir in a dose of saquinavir 1,000 mg/ritonavir 100 mg given twice daily were studied in 14 HIV-infected pregnant women at 33 weeks gestation and parameters were comparable to those observed in nonpregnant individuals; none of the women had a subtherapeutic trough level *[7]*.

  One study of a saquinavir/ritonavir-based combination antiretroviral drug regimen in 42 women during pregnancy reported abnormal transaminase levels in 13 women (31%) within 2 to 4 weeks of treatment initiation, although the abnormalities were mild (toxicity grade 1–2 in most, grade 3 in 1 woman) *[8]*.

References

1. Zorrilla CD, Van Dyke R, Bardeguez A, et al. Clinical response and tolerability to and safety of saquinavir with low-dose ritonavir in human immunodeficiency virus type 1-infected mothers and their infants. *Antimicrob Agents Chemother*, 2007. 51(6):2208-10. http://www.ncbi.nlm.nih.gov/pubmed/17420209
2. Mirochnick M, Dorenbaum A, Holland D, et al. Concentrations of protease inhibitors in cord blood after in utero exposure. *Pediatr Infect Dis J*, 2002. 21(9):835-8. http://www.ncbi.nlm.nih.gov/pubmed/12352805
3. Hanlon M, O'Dea S, Woods S, et al. Evaluation of saquinavir/ritonavir based regimen for prevention of MTCT of HIV. 13th Conference on Retroviruses and Opportunistic Infections; February 5-8, 2006; Denver, CO. Abstract 721. http://www.retroconference.org/2006/PDFs/721.pdf
4. Khan W, Hawkins DA, Moyle G, et al. Pharmacokinetics (PK), safety, tolerability and efficacy of saquinavir hard-gel capsules/ritonavir (SQV/r) plus 2 nucleosides in HIV-infected pregnant women. XV International AIDS Conference; July 11-16, 2004; Bangkok, Thailand. Abstract ThPeB 7064.
5. Lopez-Cortes LF, Ruiz-Valderas R, Pascual R, et al. Once-daily saquinavir-hgc plus low-dose ritonavir (1200/100 mg) in HIV-infected pregnant women: pharmacokinetics and efficacy. *HIV Clin Trials*, 2003. 4(3):227-9. http://www.ncbi.nlm.nih.gov/pubmed/12815561

6. Lopez-Cortes LF, Ruiz-Valderas R, Rivero A, et al. Efficacy of low-dose boosted saquinavir once daily plus nucleoside reverse transcriptase inhibitors in pregnant HIV-1-infected women with a therapeutic drug monitoring strategy. *Ther Drug Monit*, 2007. 29(2):171-6. http://www.ncbi.nlm.nih.gov/pubmed/17417070
7. Burger D, Eggink A, van der ende I, et al. The pharmacokinetics of saquinavir in the new tablet formulation + ritonavir (1000/100 mg twice daily) in HIV-1-infected pregnant women. 14th Conference on Retoviruses and Opportunistic Infections; February 25-28, 2007; Los Angeles, CA. Abstract 741. http://www.retroconference.org/2007/PDFs/741.pdf
8. Hanlon M, O'Dea S, Clarke S, et al. Maternal hepatotoxicity with boosted saquinavir as part of combination ART in pregnancy. 14th Conference on Retoviruses and Opportunistic Infections; February 25-28, 2007; Los Angeles, CA. Abstract 753. http://www.retroconference.org/2007/PDFs/753.pdf

Tipranavir (Aptivus, TPV) is classified as FDA pregnancy category C.

- Animal carcinogenicity studies
  Tipranavir was neither mutagenic nor clastogenic in a battery of five *in vitro* and animal *in vivo* screening tests. Long-term carcinogenicity studies in mice and rats have been conducted with tipranavir. Mice were administered 30, 150, or 300 mg/kg/day tipranavir, 150/40 mg/kg/day tipranavir/ritonavir in combination, or 40 mg/kg/day ritonavir. The incidences of benign hepatocellular adenomas and combined adenomas/carcinomas were increased in females of all groups except in females given the low dose of tipranavir. These tumors were also increased in male mice at the high dose of tipranavir and in the tipranavir/ritonavir combination group. Hepatocellular carcinoma incidence was increased in female mice given the high dose of tipranavir and in both sexes receiving tipranavir/ritonavir. The combination of tipranavir and ritonavir caused an exposure-related increase in this same tumor type in both sexes. The clinical relevance of the carcinogenic findings in mice is unknown. Systemic exposures in mice (based on AUC or C_{max}) at all dose levels tested were below those in humans receiving the recommended dose level. Rats were administered 30, 100, or 300 mg/kg/day tipranavir, 100/26.7 mg/kg/day tipranavir/ritonavir in combination, or 10 mg/kg/day ritonavir. No drug-related findings in male rats were observed. At the highest dose of tipranavir, an increased incidence of benign follicular cell adenomas of the thyroid gland was observed in female rats. Based on AUC measurements, exposure to tipranavir at this dose level in rats is approximately equivalent to exposure in humans at the recommended therapeutic dose. This finding is probably not relevant to humans, because thyroid follicular cell adenomas are considered a rodent-specific effect secondary to enzyme induction.
- Reproduction/fertility
  Tipranavir had no effect on fertility or early embryonic development in rats at exposure levels similar to human exposures at the recommended clinical dose (500/200 mg per day of tipranavir/ritonavir).
- Teratogenicity/developmental toxicity
  No teratogenicity was detected in studies of pregnant rats and rabbits at exposure levels approximately 1.1-fold and 0.1-fold human exposure. In rats exposed to 400 mg/kg/day (~0.8-fold human exposure) and greater, fetal toxicity (decreased ossification and body weights) was observed. Fetal toxicity was not seen in rats and rabbits at levels of 0.2-fold and 0.1-fold exposures in humans. In rats, no adverse effects were seen on development at levels of 40 mg/kg/day (~0.2-fold human exposure), but growth inhibition in pups and maternal toxicity were seen at 400 mg/kg/day (~0.8-fold human exposure).
- Placental and breast milk transfer
  No animal studies of placental or breast milk passage of tipranavir have been reported. It is unknown if placental or breast milk passage of tipranavir occurs in humans.
- Human studies in pregnancy
  No studies of tipranavir have been conducted in pregnant women or neonates.

ENTRY INHIBITORS

Two drugs have been approved in this new class of antiretrovirals aimed at inhibiting viral binding or fusion of HIV to host target cells. Binding of the viral envelope glycoprotein gp120 to the CD4 receptor induces conformational changes that enable gp120 to interact with a chemokine receptor (e.g., CCR5 or CXCR4) on the host cell; binding of gp120 to the coreceptor causes subsequent conformational changes in the viral transmembrane glycoprotein gp41, exposing the "fusion peptide" of gp41, which inserts into the cell membrane. A helical region of gp41, called HR1, then interacts with a similar helical region, HR2, on gp41, resulting in a "zipping" together of the two helices and mediating the fusion of cellular and viral membranes. Enfuvirtide, which requires subcutaneous administration, is a synthetic 36 amino acid peptide derived from a naturally occurring motif within the HR2 domain of viral gp41, and the drug binds to the HR1 region, preventing the HR1-HR2 interaction and correct folding of gp41 into its secondary structure, thereby inhibiting virus-cell fusion. Enfuvirtide was approved for use in combination with other antiretroviral drugs to treat advanced HIV infection in adults and children aged 6 years or older. Maraviroc interferes with viral entry at the chemokine coreceptor level; it is a CCR5 coreceptor antagonist approved for combination therapy for HIV infection in adults infected with CCR5-tropic virus.

Enfuvirtide (Fuzeon, T-20) is classified as FDA pregnancy category B.

- Animal carcinogenicity studies
  Enfuvirtide was neither mutagenic or clastogenic in a series of *in vitro* and animal *in vivo* screening tests. Long-term animal carcinogenicity studies of enfuvirtide have not been conducted.
- Reproduction/fertility animal studies
  Reproductive toxicity has been evaluated in rats and rabbits. Enfuvirtide produced no adverse effects on fertility of male or female rats at doses up 30 mg/kg/day administered subcutaneously (1.6 times the maximum recommended adult human daily dose on a m^2 basis).
- Teratogenicity/developmental toxicity animal studies
  Studies in rats and rabbits revealed no evidence of harm to the fetus from enfuvirtide administered in doses up to 27 times and 3.2 times, respectively, the adult human daily dose on a m^2 basis.
- Placental and breast milk passage
  Studies of radio-labeled enfuvirtide administered to lactating rats indicated radioactivity was present in the milk; however, it is not known if this reflected radio-labeled enfuvirtide or radio-labeled metabolites (e.g., amino acid and peptide fragments) of enfuvirtide. It is not known if enfuvirtide crosses the human placenta or is excreted in human milk. A published case report of two peripartum pregnant patients and their neonates and data from an *ex vivo* human placental cotyledon perfusion model suggest that enfuvirtide does not cross the placenta *[1,2]*.
- Human studies in pregnancy
  Very limited data exist on the use of enfuvirtide in pregnant women *[1,3,4]*; no data exist in neonates.

References

1. Brennan-Benson P, Pakianathan M, Rice P, et al. Enfurvitide prevents vertical transmission of multidrug-resistant HIV-1 in pregnancy but does not cross the placenta. *AIDS*, 2006. 20(2):297-9. http://www.ncbi.nlm.nih.gov/pubmed/16511429
2. Ceccaldi PF, Ferreira C, Gavard L, et al. Placental transfer of enfuvirtide in the ex vivo human placenta perfusion model. *Am J Obstet Gynecol*, 2008. 198(4):433. e1-2. http://www.ncbi.nlm.nih.gov/pubmed/18241815
3. Cohan D, Feakins C, Wara D, et al. Perinatal transmission of multidrug-resistant HIV-1 despite viral suppression on an enfuvirtide-based treatment regimen. *AIDS*, 2005. 19(9):989-90. http://www.ncbi.nlm.nih.gov/pubmed/15905684

4. Meyohas MC, Lacombe K, Carbonne B, et al. Enfuvirtide prescription at the end of pregnancy to a multi-treated HIV-infected woman with virological breakthrough. *AIDS*, 2004. 18(14):1966-8. http://www.ncbi.nlm.nih.gov/pubmed/15353987

Maraviroc (Selzentry, MVC) is classified as FDA pregnancy category B.

- Animal carcinogenicity studies
  Maraviroc was neither mutagenic nor clastogenic in a series of *in vitro* and animal *in vivo* screening tests. Long-term animal carcinogenicity studies found no increase in tumor incidence in mice (transgenic rasH2 mice) and rats at exposures up to 11-fold higher than experienced with human therapeutic exposure at the recommended clinical dose (300 mg twice daily).
- Reproduction/fertility animal studies
  Reproductive toxicity has been evaluated in rats. Maraviroc produced no adverse effects on fertility of male or female rats or sperm of male rats at exposures up to 20-fold higher than experienced with human therapeutic exposure at the recommended clinical dose (300 mg twice daily).
- Teratogenicity/developmental toxicity animal studies
  Studies in rats and rabbits revealed no evidence of harm to the fetus from maraviroc administered in doses up to 20-fold higher in rats and 5-fold higher in rabbits than experienced with human therapeutic exposure at the recommended clinical dose (300 mg twice daily).
- Placental and breast milk passage
  It is unknown if maraviroc crosses the placenta in animals or humans. Studies in lactating rats indicate that maraviroc is extensively secreted into rat milk.
- Human studies in pregnancy
  No studies of maraviroc have been conducted in pregnant women or neonates.
- Additional concerns
  Although no increase in malignancy has been observed, maraviroc has a potential for an increased risk of malignancy due to the drug's mechanism of action and possible effects on immune surveillance.

INTEGRASE INHIBITORS

One drug has been approved in this new class of antiretrovirals aimed at inhibiting the viral enzyme integrase, the viral enzyme catalyzing the two-step process of insertion of HIV DNA into the genome of the host cell. Integrase catalyzes a preparatory step that excises two nucleotides from one strand at both ends of the HIV DNA and a final "strand transfer" step that inserts the viral DNA into the exposed regions of cellular DNA. This second step of the integration process is targeted by the integrase inhibitor drug class. Integration is required for the stable maintenance of the viral genome as well as for efficient viral gene expression and replication. Integrase also affects retrotranscription and viral assembly. Host cells lack the integrase enzyme. Because HIV integrase represents a distinct therapeutic target, integrase inhibitors would be expected to maintain activity against HIV resistant to other classes of antiretroviral drugs.

Raltegravir (Isentress) is classified as FDA pregnancy category C.

- Animal carcinogenicity studies
  Raltegravir was neither mutagenic nor clastogenic in a series of *in vitro* and animal *in vivo* screening tests. Long-term animal carcinogenicity studies of raltegravir are ongoing.

- Reproduction/fertility animal studies
  Raltegravir produced no adverse effects on fertility of male or female rats at doses up to 600 mg/kg/day (providing exposures 3-fold higher than the exposure at the recommended adult human dose).
- Teratogenicity/developmental toxicity animal studies
  Studies in rats and rabbits revealed no evidence of treatment-related effects on embryonic/fetal survival or fetal weights from raltegravir administered in doses producing systemic exposures approximately 3- to 4-fold higher than the exposure at the recommended adult human daily dose. In rabbits, no treatment-related external, visceral, or skeletal changes were observed. However, treatment-related increases in the incidence of supernumerary ribs were seen in rats given raltegravir at 600 mg/kg/day (providing exposures 3-fold higher than the exposure at the recommended human daily dose).
- Placental and breast milk passage
  Placental transfer of raltegravir was demonstrated in both rats and rabbits. In rats given a maternal dose of 600 mg/kg/day, mean fetal blood concentrations were approximately 1.5- to 2.5-fold higher than in maternal plasma at 1 and 24 hours post-dose, respectively. However, in rabbits, the mean drug concentrations in fetal plasma were approximately 2% of the mean maternal plasma concentration at both 1 and 24 hours following a maternal dose of 1,000 mg/kg/day. Raltegravir is secreted in the milk of lactating rats, with mean drug concentrations in milk about 3-fold higher than in maternal plasma at a maternal dose of 600 mg/kg/day. There were no effects in rat offspring attributable to raltegravir exposure through breast milk.
- Human studies in pregnancy
  No studies of raltegravir have been conducted in pregnant women or neonates. It is unknown if raltegravir is secreted in human milk.

ANTIRETROVIRAL PREGNANCY REGISTRY

The Antiretroviral Pregnancy Registry is an epidemiologic project to collect observational, nonexperimental data on antiretroviral exposure during pregnancy for the purpose of assessing the potential teratogenicity of these drugs. Registry data will be used to supplement animal toxicology studies and assist clinicians in weighing the potential risks and benefits of treatment for individual patients. The registry is a collaborative project of the pharmaceutical manufacturers with an advisory committee of obstetric and pediatric practitioners.

It is strongly recommended that health care providers who are treating HIV-infected pregnant women and their newborns report cases of prenatal exposure to antiretroviral drugs (either alone or in combination) to the Antiretroviral Pregnancy Registry. The registry does not use patient names, and birth outcome follow-up is obtained by registry staff from the reporting physician.

Referrals should be directed to:
Antiretroviral Pregnancy Registry
Research Park
1011 Ashes Drive
Wilmington, NC 28405
Telephone: 1–800–258–4263
Fax: 1–800–800–1052
www.APRegistry.com

UK National Guideline for the management of Pelvic Inflammatory Disease 2011

Clinical Effectiveness Group

British Association for Sexual Health and HIV

Guideline development group: Prof Jonathan Ross MB ChB MD FRCP (lead author) and Dr Gill McCarthy MB BS FRCP (lead editor on behalf of BASHH)

What is new in the 2011 guidelines?

- ceftriaxone has replaced cefoxitin to reflect the limited availability of cefoxitin in the UK and the equivalent efficacy of ceftriaxone
- use of ceftriaxone plus azithromycin as an alternative option for treating pelvic inflammatory disease
- moxifloxacin is an appropriate treatment for women with pelvic inflammatory disease at low risk of gonorrhoea where first line treatments have failed or cannot be tolerated
- greater clarity is provided on what issues should be discussed with women diagnosed with pelvic inflammatory disease
- the introduction of a patient information leaflet (appendix 1)

Introduction and methodology

Objectives

This guideline offers recommendations on the diagnostic tests, treatment regimens and health promotion principles needed for the effective management of pelvic inflammatory disease (PID) covering the management of the initial presentation, as well as how to reduce transmission and future infection.

It is aimed primarily at women aged 16 years or older (see specific guidelines for those under 16) presenting to health care professionals working in departments offering level 3 care in STI management within the United Kingdom. However, the principles of the recommendations should be adopted across all levels - level 1 and 2 providers may need to develop local care pathways where appropriate.

Included in the guideline is a patient information leaflet (appendix 1)

Search strategy

Five reference sources were used to provide a comprehensive basis for the guideline:

1. **Medline and Embase Search**

a.1987 – January 2010

The search strategy comprised the following terms in the title or abstract: 'pelvic inflammatory disease', 'adnexitis', 'oophoritis', 'parametritis', 'salpingitis', 'endometritis', 'PID' (excluding 'primary immune deficiency'), 'adnexal disease' or 'adnexal disease'. 10422 citations were identified.

b.1963 - 1986

The search strategy comprised the following terms in the title or abstract: 'pelvic inflammatory disease', 'adnexitis', 'oophoritis', 'parametritis', 'salpingitis' or 'adnexal disease'. The dataset was then limited to AIM journals and human subjects, identifying 2321 citations.

2. **2010 CDC STD Treatment Guidelines (www.cdc.gov/std/)**

3. **2009 RCOG Green Top Guidelines – Management of Acute Pelvic Inflammatory Disease (www.rcog.org.uk)**

4. **Royal College of Obstetrics and Gynaecology Working Group on PID Report 1996**[1]

5. **Cochrane Collaboration Databases (www.cochrane.org)**

Methods

Article titles and abstracts were reviewed and if relevant the full text article obtained. Priority was given to randomised controlled trial and systematic review evidence, and recommendations made and graded on the basis of best available evidence.

Piloting and feedback

The initial draft of the guideline including the patient information leaflet was piloted for validation by the Clinical Effectiveness Group (CEG) of BASHH using a sample of UK genitourinary medicine clinics. A standardised feed back form was completed by each pilot site and the guideline amended by the CEG editor. The final guideline was then reviewed by the CEG using the AGREE instrument before posting it on the BASHH website for external peer review for a 3 month period. Comments received were collated by the CEG editor and sent to the guideline chair for review and action. The final guideline was approved by the CEG and a review date agreed before publication on the BASHH website.

Aetiology

- PID is usually the result of infection ascending from the endocervix causing endometritis, salpingitis, parametritis, oophoritis, tuboovarian abcess and/or pelvic peritonitis.
- *Neisseria gonorrhoeae* and *Chlamydia trachomatis* have been identified as causative agents [1, 2] but account for only a quarter of cases in the UK, whilst *Gardnerella vaginalis*, anaerobes (including *Prevotella*, *Atopobium* and *Leptotrichia*) and other organisms commonly found in the vagina may also be implicated. *Mycoplasma genitalium* has also been associated with upper genital tract infection in women[3].

Clinical Features

Symptoms

The following features are suggestive of a diagnosis of PID[1, 2, 4, 5]:

- lower abdominal pain which is typically bilateral
- deep dyspareunia
- abnormal vaginal bleeding, including post coital, inter-menstrual bleeding and menorrhagia
- abnormal vaginal or cervical discharge which is often purulent

Signs

- lower abdominal tenderness which is usually bilateral
- adnexal tenderness on bimanual vaginal examination
- cervical motion tenderness on bimanual vaginal examination
- fever (>38°C)

A diagnosis of PID, and empirical antibiotic treatment, should be considered and usually offered in any young (under 25) sexually active woman who has recent onset, bilateral lower abdominal pain associated with local tenderness on bimanual vaginal examination, in whom pregnancy has been excluded.

Complications

- Women with HIV may have more severe symptoms associated with PID but respond well to standard antibiotic therapy[6]. No change in treatment recommendations compared to HIV uninfected patients is required[7-9]. (Grade B [III])
- The Fitz-Hugh-Curtis syndrome comprises right upper quadrant pain associated with perihepatitis which occurs in some women with PID. Although laparoscopic division of hepatic adhesions has been performed, there is insufficient clinical trial evidence to make specific recommendations for treatment beyond those for uncomplicated PID.
- The randomised controlled trial evidence for whether an intrauterine contraceptive device should be left in situ or removed in women presenting with PID is limited[10, 11]. Removal of the IUD should be considered and may be associated with better short term clinical outcomes[10]. The decision to remove the IUD needs to be balanced against the risk of pregnancy in those who have had otherwise unprotected intercourse in the preceding 7 days. Hormonal emergency contraception may be appropriate for some women in this situation.

Diagnosis

- PID may be symptomatic or asymptomatic. Even when present, clinical symptoms and signs lack sensitivity and specificity (the positive predictive value of a clinical diagnosis is 65-90% compared to laparoscopic diagnosis[2, 4, 5])
- Testing for gonorrhoea and Chlamydia in the lower genital tract is recommended since a positive result supports the diagnosis of PID. The absence of infection at this site does not exclude PID however[2, 4, 5]
- An elevated ESR or C reactive protein also supports the diagnosis but is non-specific [12].
- The **absence** of endocervical or vaginal pus cells has a good negative predictive value (95%) for a diagnosis of PID but their **presence** is non-specific (poor positive predictive value – 17%)[13].

The differential diagnosis of lower abdominal pain in a young woman includes:

- ectopic pregnancy – pregnancy should be excluded in all women suspected of having PID

- acute appendicitis – nausea and vomiting occurs in most patients with appendicitis but only 50% of those with PID. Cervical movement pain will occur in about a quarter of women with appendicitis [14, 15].
- endometriosis – the relationship between symptoms and the menstrual cycle may be helpful in establishing a diagnosis
- complications of an ovarian cyst e.g. torsion or rupture – often of sudden onset
- urinary tract infection – often associated with dysuria and/or urinary frequency
- functional pain – may be associated with longstanding symptoms

Management

It is likely that delaying treatment increases the risk of long term sequelae such as ectopic pregnancy, infertility and pelvic pain[16]. Because of this, and the lack of definitive diagnostic criteria, a low threshold for empiric treatment of PID is recommended. Broad spectrum antibiotic therapy is required to cover *N. gonorrhoeae*, *C. trachomatis* and a variety of aerobic and anaerobic bacteria commonly isolated from the upper genital tract in women with PID[1, 2].

Some of the best evidence for the effectiveness of antibiotic treatment in preventing the long term complications of PID comes from the PEACH study where women were treated with cefoxitin followed by doxycycline – pregnancy rates after 3 years were similar or higher than those in the general population [17, 18].

The choice of an appropriate treatment regimen may be influenced by:

- robust evidence on local antimicrobial sensitivity patterns
- robust evidence on the local epidemiology of specific infections in this setting
- cost
- patient preference and compliance
- severity of disease

General Advice

Rest is advised for those with severe disease. (Grade C [IV])

Appropriate analgesia should be provided. (Grade C [IV])

Intravenous therapy is recommended for patients with more severe clinical disease (Grade C [IV]) e.g. pyrexia > 38^{o}C, clinical signs of tubo-ovarian abcess, signs of pelvic peritonitis.

Patients should be advised to avoid unprotected intercourse until they, and their partner(s), have completed treatment and follow-up (Grade C [IV]).

- A detailed explanation of their condition with particular emphasis on the long term implications for the health of themselves and their partner(s) should be provided, reinforced with clear and accurate written information (Grade C [IV]). A patient information leaflet is included in appendix 1 of this guideline.

When giving information to patients, the clinician should consider the following:

- an explanation of what treatment is being given and its possible adverse effects
- that following treatment fertility is usually maintained but there remains a risk of future infertility, chronic pelvic pain or ectopic pregnancy
- clinically more severe disease is associated with a greater risk of sequelae
- repeat episodes of PID are associated with an exponential increase in the risk of infertility
- the earlier treatment is given the lower the risk of future fertility problems.
- future use of barrier contraception will significantly reduce the risk of PID
- the need to screen her sexual contacts for infection to prevent her becoming reinfected

Outpatient therapy is as effective as inpatient treatment for patients with clinically mild to moderate PID[17]. Admission for parenteral therapy, observation, further investigation and/or possible surgical intervention should be considered in the following situations[19]:

- a surgical emergency cannot be excluded
- lack of response to oral therapy
- clinically severe disease
- presence of a tuboovarian abcess
- intolerance to oral therapy
- pregnancy

Further Investigation

All sexually active patients should be offered:

- a pregnancy test
- screening for sexually transmitted infections including HIV[20]

Treatment

The following antibiotic regimens are evidence based.

Recommended Regimens

All the recommended regimens are of similar efficacy.

Outpatient Regimens

i.m. ceftriaxone* 250mg single dose followed by oral doxycycline 100mg twice daily *plus* metronidazole 400mg twice daily for 14 days

Grade A (Ib) [21-23]

*Clinical trial data support the use of cefoxitin for the treatment of PID but this agent is not easily available in the UK so ceftriaxone, which has a similar spectrum of activity, is recommended.

oral ofloxacin 400mg twice daily *plus* oral metronidazole 400mg twice daily for 14 days

Grade A (Ib) [23-27]

Metronidazole is included in some regimens to improve coverage for anaerobic bacteria. Anaerobes are of relatively greater importance in patients with severe PID and metronidazole may be discontinued in those patients with mild or moderate PID who are unable to tolerate it.

Ofloxacin and moxifloxacin should be avoided in patients who are at high risk of gonococcal PID because of increasing quinolone resistance in the UK (e.g. when the patient's partner has gonorrhoea, in clinically severe disease, following sexual contact abroad). Quinolones should also be avoided as first line empirical treatment for PID in areas where >5% of PID is caused by quinolone resistant *Neisseria gonorrhoeae*.

Levofloxacin is the L isomer of ofloxacin[28] and has the advantage of once daily dosing (500mg OD for 14 days). It may be used as a more convenient alternative to ofloxacin.[29]

Replacing intramuscular ceftriaxone with an oral cephalosporin (e.g. cefixime) is not recommended because there is no clinical trial evidence to support its use, and tissue levels are likely to be lower which might impact on efficacy. Reports of decreasing susceptibility of *Neisseria gonorrhoeae* to cephalosporins also supports the use of parenteral based regimens when gonococcal PID is suspected (to maximise tissue levels and overcome low level resistance).

Alternative Regimens

intramuscular ceftriaxone 250 mg immediately, followed by azithromycin 1 g/week for 2 weeks

Grade A (Ib)[30, 31]

Clinical trial evidence for this regimen is limited but it may be used when the treatments above are not appropriate e.g. allergy, intolerance:

oral moxifloxacin 400mg once daily for 14 days

Grade A (Ib)[29, 32, 33]

Three large RCTs support the efficacy of moxifloxacin for PID but because of evidence of an increased risk of liver reactions and other serious risks (such as QT interval prolongation), oral moxifloxacin should be used only when it is considered inappropriate to use the other antibacterial agents recommended for PID or when these have failed.

Inpatient Regimens

Intravenous therapy should be continued until 24 hours after clinical improvement and then switched to oral. Intravenous doxycycline is not currently licensed in the UK but is available from IDIS world medicines (01932 824100).

i.v. ceftriaxone 2g daily *plus* i.v. doxycycline 100mg twice daily (oral doxycycline may be used if tolerated) followed by oral doxycycline 100mg twice daily *plus* oral metronidazole 400mg twice daily for a total of 14 days

Grade A (Ib) [22, 23]

i.v. clindamycin 900mg 3 times daily *plus* i.v. gentamicin (2mg/kg loading dose) followed by 1.5mg/kg 3 times daily [a single daily dose of 7mg/kg may be substituted]) followed by either oral clindamycin 450mg 4 times daily or oral doxycycline 100mg twice daily plus oral metronidazole 400mg twice daily to complete 14 days

Grade A (Ib) [22]

Gentamicin levels need to be monitored if this regimen is used.

Alternative Regimens

Clinical trial evidence for the following regimens is more limited but they may be used when the treatments above are not appropriate e.g. allergy, intolerance:

i.v. ofloxacin 400mg BD *plus* i.v. metronidazole 500mg TID for 14 days

Grade B (III) [23-25, 34]

i.v. ciprofloxacin 200mg BD plus i.v. (or oral) doxycycline 100mg BD plus i.v. metronidazole 500mg TID for 14 days

Grade B (III) [24, 35]

Allergy

There is no clear evidence of the superiority of any one of the suggested regimens over the others. Therefore patients known to be allergic to one of the suggested regimens should be treated with an alternative.

Pregnancy and Breastfeeding

- PID in pregnancy is associated with an increase in both maternal and fetal morbidity, therefore parenteral therapy is advised although none of the suggested evidence based regimens are of proven safety in this situation.
- There are insufficient data from clinical trials to recommend a specific regimen and empirical therapy with agents effective against gonorrhoea, chlamydia and anaerobic infections should be considered taking into account local antibiotic sensitivity patterns (e.g. i.m. ceftriaxone plus oral or i.v. erythromycin, with the possible addition of oral or i.v. metronidazole 500mg 3 times daily in clinically severe disease) (Grade C [IV]).
- The risk of giving any of the recommended antibiotic regimens (listed above for non pregnant women) in very early pregnancy (prior to a pregnancy test becoming positive) is justified by the need to provide effective therapy and the low risk to the foetus (personal communication, UK National Teratology Information Service – 11.2.10).

Surgical Management

- Laparoscopy may help early resolution of the disease by dividing adhesions and draining pelvic abscesses[36] but ultrasound guided aspiration of pelvic fluid collections is less invasive and may be equally effective.[37, 38]
- It is also possible to perform adhesiolysis in cases of perihepatitis although there is no evidence whether this is superior to using only antibiotic therapy

Sexual Partners

- Current male partners of women with PID should be contacted and offered health advice and screening for gonorrhoea and chlamydia. Other recent sexual partners may also be offered screening - tracing of contacts within a 6 month period of onset of symptoms is recommended but this time period may be influenced by the sexual history (Grade C [IV]).
- Gonorrhoea or chlamydia diagnosed in the male partner should be treated appropriately and concurrently with the index patient. (Grade C [IV]).
- Because many cases of PID are not associated with gonorrhoea or chlamydia, broad spectrum empirical therapy should also be offered to male partners e.g. azithromycin 1g single dose (Grade C [IV]).
- If screening for gonorrhoea is not available additional specific antibiotics effective against *Neisseria gonorrhoeae* should be offered e.g. i.m. ceftriaxone 250mg single dose (see also UK National Guidelines for Gonorrhoea) (Grade C [IV]).
- Partners should be advised to avoid intercourse until they and the index patient have completed the treatment course (Grade C [IV]).

Follow Up

Review at 72 hours is recommended [5], particularly for those with a moderate or severe clinical presentation, and should show a substantial improvement in clinical symptoms and signs (Grade C [IV]). Failure to do so suggests the need for further investigation, parenteral therapy and/or surgical intervention.

Further review 2-4 weeks (Grade C [IV]) after therapy may be useful to ensure:

- adequate clinical response to treatment
- compliance with oral antibiotics
- screening and treatment of sexual contacts
- awareness of the significance of PID and its sequelae
- repeat pregnancy test, if clinically indicated

Repeat testing for gonorrhoea or chlamydia after 2 to 4 weeks is appropriate in those in whom persisting symptoms, antibiotic resistance pattern (gonorrhoea only), compliance with antibiotics and/or tracing of sexual contacts indicate the possibility of persisting or recurrent infection.

Auditable Outcome Measures

Appropriate short term audit outcomes include:

- proportion of women receiving treatment with a recommended regimen – target 95%
- number of named male contacts screened for infection and/or treated – target 0.4 (large urban centres) or 0.6 (other centres) per index case[39]

Qualifying statement

The recommendations in this guideline may not be appropriate for use in all clinical situations. Decisions to follow these recommendations must be based on the professional judgement of the clinician and consideration of individual patient circumstances and available resources.

All possible care has been undertaken to ensure the publication of the correct dosage of medication and route of administration. However, it remains the responsibility of the prescribing physician to ensure the accuracy and appropriateness of the medication they prescribe.

Editorial independence

This guideline was commissioned, edited and endorsed by the BASHH CEG without external funding being sought or obtained.

Declarations of interest

All members of the guideline writing committee completed the BASHH conflict of interest declaration detailed below at the time the guideline's final draft was submitted to the CEG. JR has received consultancy fees from Bayer pharma.

Author affiliation

- Prof Jonathan Ross, Professor of Sexual Health and HIV, Whittall Street Clinic Whittall Street B4 6DH
- Dr Gill McCarthy, Consultant Physician Sexual Health an HIV, The Wolverton Centre, Kingston Hospital NHS Trust, Galsworthy Road, Kingston upon Thames, KT2 7QB

Membership of the CEG

- Dr Keith Radcliffe (Chair); Consultant Physician in Genitourinary Medicine Whittall Street Clinic Whittall Street B4 6DH
- Dr David Daniels, West Midllesex University Hospitals NHS Trust, Sexual Health Clinic West Middlesex Hospital Twickenham Road, Isleworth, TW7 6AF
- Dr Mark FitzGerald Consultant Physician in Genitourinary Medicine, Musgrove Park Hospital, Taunton, TA1 5DA
- Dr Margaret Kingston, Consultant Physician in GU Medicine, Manchester Centre for Sexual Health, The Hathersage Centre, 280 Upper Brook Street, Manchester M13 0FH
- Dr Neil Lazaro, Associate Specialist in GU Medicine, Royal Preston Hospital, Preston PR2 9HT
- Dr Gill McCarthy, Consultant Physician in GU Medicine, Kingston Hospital NHS Trust, Wolverton Centre for Sexual Health Galsworthy Road, Kingston Upon Thames, KT2 7QB
- Dr Ann Sullivan, Consultant Physician in Genitourinary Medicine, Chelsea & Westminster Healthcare NHS Trust, John Hunter Clinic 2nd Floor St Stephen's Centre 369 Fulham Road SW10 9NH

Timescale for next revision : 2015

Acknowledgements : None

Reference List

1. Recommendations arising from the 31st Study Group: The Prevention of Pelvic Infection. In: Templeton A, editor. The Prevention of Pelvic Infection. London: RCOG Press; 1996:267-270.

2. Bevan CD, Johal BJ, Mumtaz G, Ridgway GL, Siddle NC. Clinical, laparoscopic and microbiological findings in acute salpingitis: report on a United Kingdom cohort. British Journal of Obstetrics & Gynaecology 1995;102(5):407-414.

3. Haggerty CL. Evidence for a role of Mycoplasma genitalium in pelvic inflammatory disease. Current Opinion in Infectious Diseases 2008;21(1):65-69.

4. Morcos R, Frost N, Hnat M, Petrunak A, Caldito G. Laparoscopic versus clinical diagnosis of acute pelvic inflammatory disease. J Reprod Med 1993;38(1):53-56.

5. Centers for Disease Control. Sexually Transmitted Diseases Treatment Guidelines 2006. MMWR - Morbidity & Mortality Weekly Report 2006;55(RR-11):56-60.

6. Kamenga MC, De Cock KM, St.Louis ME et al. The impact of human immunodeficiency virus infection on pelvic inflammatory disease: a case-control study in Abidjan, Ivory Coast. Am J Obstet Gynecol 1995;172(3):919-925.

7. Cohen CR, Sinei S, Reilly M et al. Effect of human immunodeficiency virus type 1 infection upon acute salpingitis: a laparoscopic study. J Infect Dis 1998;178(5):1352-1358.

8. Bukusi EA, Cohen CR, Stevens CE et al. Effects of human immunodeficiency virus 1 infection on microbial origins of pelvic inflammatory disease and on efficacy of ambulatory oral therapy. Am J Obstet Gynecol 1999;181(6):1374-1381.

9. Irwin KL, Moorman AC, O'Sullivan MJ et al. Influence of human immunodeficiency virus infection on pelvic inflammatory disease. Obstet Gynecol 2000;95(4):525-534.

10. Altunyurt S, Demir N, Posaci C. A randomized controlled trial of coil removal prior to treatment of pelvic inflammatory disease. European Journal of Obstetrics Gynecology and Reproductive Biology 2003;107:81-84.

11. Soderberg G, Lindgren S. Influence of an intrauterine device on the course of an acute salpingitis. Contraception 1981;24(2):137-143.

12. Miettinen AK, Heinonen PK, Laippala P, Paavonen J. Test performance of erythrocyte sedimentation rate and C- reactive protein in assessing the severity of acute pelvic inflammatory disease. Am J Obstet Gynecol 1993;169(5):1143-1149.

13. Yudin MH, Hillier SL, Wiesenfeld HC, Krohn MA, Amortegui AA, Sweet RL. Vaginal polymorphonuclear leukocytes and bacterial vaginosis as markers for histologic endometritis among women without symptoms of pelvic inflammatory disease. American Journal of Obstetrics and Gynecology 2003;188(2):318-323.

14. Bongard F, Landers DV, Lewis F. Differential diagnosis of appendicitis and pelvic inflammatory disease. A prospective analysis. American Journal of Surgery 1985;150(1):90-96.

15. Lewis FR, Holcroft JW, Boey J, Dunphy JE. Appendicitis: a critical review of diagnosis and treatment in 1000 cases. Archives of Surgery 1975;110:677-684.

16. Hillis SD, Joesoef R, Marchbanks PA et al. Delayed care of pelvic inflammatory disease as a risk factor for impaired fertility. Am J Obstet Gynecol 1993;168(5):1503-1509.

17. Ness RB, Soper DE, Holley RL et al. Effectiveness of inpatient and outpatient treatment strategies for women with pelvic inflammatory disease: results from the Pelvic Inflammatory Disease Evaluation and Clinical Health (PEACH) Randomized Trial. Am J Obstet Gynecol 2002;186(5):929-937.

18. Haggerty CL, Ness RB, Amortegui A et al. Endometritis does not predict reproductive morbidity after pelvic inflammatory disease. Am J Obstet Gynecol 2003;188(1):141-148.

19. Ross JDC, Stewart P. Management of Acute Pelvic Inflammatory Disease. http://www.rcog.org.uk/files/rcog-corp/uploaded-files/T32PelvicInflamatoryDisease2008MinorRevision.pdf . 2009.
Ref Type: Generic

20. Ross JD, Ison CA. UK National Screening and Testing Guidelines for STIs. Sex Transm Infect 2006;82:Suppl IV.

21. Arredondo JL, Diaz V, Gaitan H et al. Oral clindamycin and ciprofloxacin versus intramuscular ceftriaxone and oral doxycycline in the treatment of mild-to- moderate pelvic inflammatory disease in outpatients. Clin Infect Dis 1997;24(2):170-178.

22. Hemsell DL, Little BB, Faro S et al. Comparison of three regimens recommended by the Centers for Disease Control and Prevention for the treatment of women hospitalized with acute pelvic inflammatory disease. Clin Infect Dis 1994;19(4):720-727.

23. Martens MG, Gordon S, Yarborough DR, Faro S, Binder D, Berkeley A. Multicenter randomized trial of ofloxacin versus cefoxitin and doxycycline in outpatient treatment of pelvic inflammatory disease. Ambulatory PID Research Group. Southern Medical Journal 1993;86(6):604-610.

24. Walker CK, Kahn JG, Washington AE, Peterson HB, Sweet RL. Pelvic inflammatory disease: metaanalysis of antimicrobial regimen efficacy. J Infect Dis 1993;168(4):969-978.

25. Wendel GD, Jr., Cox SM, Bawdon RE, Theriot SK, Heard MC, Nobles BJ. A randomized trial of ofloxacin versus cefoxitin and doxycycline in the outpatient treatment of acute salpingitis. Am J Obstet Gynecol 1991;164(5 Pt 2):1390-1396.

26. Soper DE, Brockwell NJ, Dalton HP. Microbial etiology of urban emergency department acute salpingitis: treatment with ofloxacin. Am J Obstet Gynecol 1992;167(3):653-660.

27. Peipert JF, Sweet RL, Walker CK, Kahn J, Rielly-Gauvin K. Evaluation of ofloxacin in the treatment of laparoscopically documented acute pelvic inflammatory disease (salpingitis). Infectious Diseases in Obstetrics & Gynecology 1999;7(3):138-144.

28. Isaacson DM, Fernadez JA, Frosco M et al. Levofloxacin: A review of its antibacterial activity. Recent Res Devel in Antimicrob Agents & Chemotherapy 1996;1:391-439.

29. Judlin P, Liao Q, Liu Z, Reimnitz P, Hampel B, Arvis P. Efficacy and safety of moxifloxacin in uncomplicated pelvic inflammatory disease: the MONALISA study. BJOG: An International Journal of Obstetrics & Gynaecology 2010;117(12):1475-1484.

30. Savaris RF, Teixeira LM, Torres TG, Edelweiss MI, Moncada J, Schachter J. Comparing ceftriaxone plus azithromycin or doxycycline for pelvic inflammatory disease: a randomized controlled trial. Obstet Gynecol 2007;110(1):53-60.

31. Bevan CD, Ridgway GL, Rothermel CD. Efficacy and safety of azithromycin as monotherapy or combined with metronidazole compared with two standard multidrug regimens for the treatment

of acute pelvic inflammatory disease. Journal of International Medical Research 2003;31(1):45-54.

32. Heystek MJ, Ross JDC, PID Study Group. A randomised double-blind comparison of moxifloxacin and doxycycline/metronidazole/ciprofloxacin in the treatment of acute, uncomplicated pelvic inflammatory disease. Int J STD AIDS 2009;20:690-695.

33. Ross JDC, Cronje HS, Paszkowski T et al. Moxifloxacin versus ofloxacin plus metronidazole in uncomplicated pelvic inflammatory disease: results of a multicentre, double blind, randomised trial. Sex Transm Infect 2006;82:446-451.

34. Witte EH, Peters AA, Smit IB et al. A comparison of pefloxacin/metronidazole and doxycycline/metronidazole in the treatment of laparoscopically confirmed acute pelvic inflammatory disease. European Journal of Obstetrics, Gynecology, & Reproductive Biology 1993;50(2):153-158.

35. Heinonen PK, Teisala K, Miettinen A, Aine R, Punnonen R, Gronroos P. A comparison of ciprofloxacin with doxycycline plus metronidazole in the treatment of acute pelvic inflammatory disease. Scandinavian Journal of Infectious Diseases - Supplementum 1989;60:66-73.

36. Reich H, McGlynn F. Laparoscopic treatment of tuboovarian and pelvic abscess. J Reprod Med 1987;32(10):747-752.

37. Aboulghar MA, Mansour RT, Serour GI. Ultrasonographically guided transvaginal aspiration of tuboovarian abscesses and pyosalpinges: an optional treatment for acute pelvic inflammatory disease. Am J Obstet Gynecol 1995;172(5):1501-1503.

38. Corsi PJ, Johnson SC, Gonik B, Hendrix SL, McNeeley SG, Jr., Diamond MP. Transvaginal ultrasound-guided aspiration of pelvic abscesses. Infectious Disease in Obstetrics and Gynecology 1999;7(5):216-221.

39. Low N, Welch J, Radcliffe K. Developing national outcome standards for the management of gonorrhoea and genital chlamydia in genitourinary medicine clinics. Sex Transm Infect 2004;80(3):223-229.

Appendix 1: Patient information leaflet on PID

Currently in preparation – see BASHH website in due course for downloadable document.

UK National Guideline for the management of Pelvic Inflammatory Disease 2011

Clinical Effectiveness Group

British Association for Sexual Health and HIV

Guideline development group: Prof Jonathan Ross MB ChB MD FRCP (lead author) and Dr Gill McCarthy MB BS FRCP (lead editor on behalf of BASHH)

What is new in the 2011 guidelines?

- ceftriaxone has replaced cefoxitin to reflect the limited availability of cefoxitin in the UK and the equivalent efficacy of ceftriaxone
- use of ceftriaxone plus azithromycin as an alternative option for treating pelvic inflammatory disease
- moxifloxacin is an appropriate treatment for women with pelvic inflammatory disease at low risk of gonorrhoea where first line treatments have failed or cannot be tolerated
- greater clarity is provided on what issues should be discussed with women diagnosed with pelvic inflammatory disease
- the introduction of a patient information leaflet (appendix 1)

Introduction and methodology

Objectives

This guideline offers recommendations on the diagnostic tests, treatment regimens and health promotion principles needed for the effective management of pelvic inflammatory disease (PID) covering the management of the initial presentation, as well as how to reduce transmission and future infection.

It is aimed primarily at women aged 16 years or older (see specific guidelines for those under 16) presenting to health care professionals working in departments offering level 3 care in STI management within the United Kingdom. However, the principles of the recommendations should be adopted across all levels - level 1 and 2 providers may need to develop local care pathways where appropriate.

Included in the guideline is a patient information leaflet (appendix 1)

Search strategy

Five reference sources were used to provide a comprehensive basis for the guideline:

1. **Medline and Embase Search**

a.1987 – January 2010

The search strategy comprised the following terms in the title or abstract: 'pelvic inflammatory disease', 'adnexitis', 'oophoritis', 'parametritis', 'salpingitis', 'endometritis', 'PID' (excluding 'primary immune deficiency'), 'adnexal disease' or 'adnexal disease'. 10422 citations were identified.

b.1963 - 1986

The search strategy comprised the following terms in the title or abstract: 'pelvic inflammatory disease', 'adnexitis', 'oophoritis', 'parametritis', 'salpingitis' or 'adnexal disease'. The dataset was then limited to AIM journals and human subjects, identifying 2321 citations.

2. **2010 CDC STD Treatment Guidelines (www.cdc.gov/std/)**

3. **2009 RCOG Green Top Guidelines – Management of Acute Pelvic Inflammatory Disease (www.rcog.org.uk)**

4. **Royal College of Obstetrics and Gynaecology Working Group on PID Report 1996**[1]

5. **Cochrane Collaboration Databases (www.cochrane.org)**

Methods

Article titles and abstracts were reviewed and if relevant the full text article obtained. Priority was given to randomised controlled trial and systematic review evidence, and recommendations made and graded on the basis of best available evidence.

Piloting and feedback

The initial draft of the guideline including the patient information leaflet was piloted for validation by the Clinical Effectiveness Group (CEG) of BASHH using a sample of UK genitourinary medicine clinics. A standardised feed back form was completed by each pilot site and the guideline amended by the CEG editor. The final guideline was then reviewed by the CEG using the AGREE instrument before posting it on the BASHH website for external peer review for a 3 month period. Comments received were collated by the CEG editor and sent to the guideline chair for review and action. The final guideline was approved by the CEG and a review date agreed before publication on the BASHH website.

Aetiology

- PID is usually the result of infection ascending from the endocervix causing endometritis, salpingitis, parametritis, oophoritis, tuboovarian abcess and/or pelvic peritonitis.
- *Neisseria gonorrhoeae* and *Chlamydia trachomatis* have been identified as causative agents [1, 2] but account for only a quarter of cases in the UK, whilst *Gardnerella vaginalis*, anaerobes (including *Prevotella*, *Atopobium* and *Leptotrichia*) and other organisms commonly found in the vagina may also be implicated. *Mycoplasma genitalium* has also been associated with upper genital tract infection in women[3].

Clinical Features

Symptoms

The following features are suggestive of a diagnosis of PID[1, 2, 4, 5]:

- lower abdominal pain which is typically bilateral
- deep dyspareunia
- abnormal vaginal bleeding, including post coital, inter-menstrual bleeding and menorrhagia
- abnormal vaginal or cervical discharge which is often purulent

Signs

- lower abdominal tenderness which is usually bilateral
- adnexal tenderness on bimanual vaginal examination
- cervical motion tenderness on bimanual vaginal examination
- fever (>38°C)

A diagnosis of PID, and empirical antibiotic treatment, should be considered and usually offered in any young (under 25) sexually active woman who has recent onset, bilateral lower abdominal pain associated with local tenderness on bimanual vaginal examination, in whom pregnancy has been excluded.

Complications

- Women with HIV may have more severe symptoms associated with PID but respond well to standard antibiotic therapy[6]. No change in treatment recommendations compared to HIV uninfected patients is required[7-9]. (Grade B [III])
- The Fitz-Hugh-Curtis syndrome comprises right upper quadrant pain associated with perihepatitis which occurs in some women with PID. Although laparoscopic division of hepatic adhesions has been performed, there is insufficient clinical trial evidence to make specific recommendations for treatment beyond those for uncomplicated PID.
- The randomised controlled trial evidence for whether an intrauterine contraceptive device should be left in situ or removed in women presenting with PID is limited[10, 11]. Removal of the IUD should be considered and may be associated with better short term clinical outcomes[10]. The decision to remove the IUD needs to be balanced against the risk of pregnancy in those who have had otherwise unprotected intercourse in the preceding 7 days. Hormonal emergency contraception may be appropriate for some women in this situation.

Diagnosis

- PID may be symptomatic or asymptomatic. Even when present, clinical symptoms and signs lack sensitivity and specificity (the positive predictive value of a clinical diagnosis is 65-90% compared to laparoscopic diagnosis[2, 4, 5])
- Testing for gonorrhoea and Chlamydia in the lower genital tract is recommended since a positive result supports the diagnosis of PID. The absence of infection at this site does not exclude PID however[2, 4, 5]
- An elevated ESR or C reactive protein also supports the diagnosis but is non-specific [12].
- The **absence** of endocervical or vaginal pus cells has a good negative predictive value (95%) for a diagnosis of PID but their **presence** is non-specific (poor positive predictive value – 17%)[13].

The differential diagnosis of lower abdominal pain in a young woman includes:

- ectopic pregnancy – pregnancy should be excluded in all women suspected of having PID

- acute appendicitis – nausea and vomiting occurs in most patients with appendicitis but only 50% of those with PID. Cervical movement pain will occur in about a quarter of women with appendicitis [14, 15].
- endometriosis – the relationship between symptoms and the menstrual cycle may be helpful in establishing a diagnosis
- complications of an ovarian cyst e.g. torsion or rupture – often of sudden onset
- urinary tract infection – often associated with dysuria and/or urinary frequency
- functional pain – may be associated with longstanding symptoms

Management

It is likely that delaying treatment increases the risk of long term sequelae such as ectopic pregnancy, infertility and pelvic pain[16]. Because of this, and the lack of definitive diagnostic criteria, a low threshold for empiric treatment of PID is recommended. Broad spectrum antibiotic therapy is required to cover *N. gonorrhoeae*, *C. trachomatis* and a variety of aerobic and anaerobic bacteria commonly isolated from the upper genital tract in women with PID[1, 2].

Some of the best evidence for the effectiveness of antibiotic treatment in preventing the long term complications of PID comes from the PEACH study where women were treated with cefoxitin followed by doxycycline – pregnancy rates after 3 years were similar or higher than those in the general population [17, 18].

The choice of an appropriate treatment regimen may be influenced by:

- robust evidence on local antimicrobial sensitivity patterns
- robust evidence on the local epidemiology of specific infections in this setting
- cost
- patient preference and compliance
- severity of disease

General Advice

Rest is advised for those with severe disease. (Grade C [IV])

Appropriate analgesia should be provided. (Grade C [IV])

Intravenous therapy is recommended for patients with more severe clinical disease (Grade C [IV]) e.g. pyrexia > 38^{o}C, clinical signs of tubo-ovarian abcess, signs of pelvic peritonitis.

Patients should be advised to avoid unprotected intercourse until they, and their partner(s), have completed treatment and follow-up (Grade C [IV]).

- A detailed explanation of their condition with particular emphasis on the long term implications for the health of themselves and their partner(s) should be provided, reinforced with clear and accurate written information (Grade C [IV]). A patient information leaflet is included in appendix 1 of this guideline.

When giving information to patients, the clinician should consider the following:

- an explanation of what treatment is being given and its possible adverse effects
- that following treatment fertility is usually maintained but there remains a risk of future infertility, chronic pelvic pain or ectopic pregnancy
- clinically more severe disease is associated with a greater risk of sequelae
- repeat episodes of PID are associated with an exponential increase in the risk of infertility
- the earlier treatment is given the lower the risk of future fertility problems.
- future use of barrier contraception will significantly reduce the risk of PID
- the need to screen her sexual contacts for infection to prevent her becoming reinfected

Outpatient therapy is as effective as inpatient treatment for patients with clinically mild to moderate PID[17]. Admission for parenteral therapy, observation, further investigation and/or possible surgical intervention should be considered in the following situations[19]:

- a surgical emergency cannot be excluded
- lack of response to oral therapy
- clinically severe disease
- presence of a tuboovarian abcess
- intolerance to oral therapy
- pregnancy

Further Investigation

All sexually active patients should be offered:

- a pregnancy test
- screening for sexually transmitted infections including HIV[20]

Treatment

The following antibiotic regimens are evidence based.

Recommended Regimens

All the recommended regimens are of similar efficacy.

Outpatient Regimens

i.m. ceftriaxone* 250mg single dose followed by oral doxycycline 100mg twice daily *plus* metronidazole 400mg twice daily for 14 days

Grade A (Ib) [21-23]

*Clinical trial data support the use of cefoxitin for the treatment of PID but this agent is not easily available in the UK so ceftriaxone, which has a similar spectrum of activity, is recommended.

oral ofloxacin 400mg twice daily *plus* oral metronidazole 400mg twice daily for 14 days

Grade A (Ib) [23-27]

Metronidazole is included in some regimens to improve coverage for anaerobic bacteria. Anaerobes are of relatively greater importance in patients with severe PID and metronidazole may be discontinued in those patients with mild or moderate PID who are unable to tolerate it.

Ofloxacin and moxifloxacin should be avoided in patients who are at high risk of gonococcal PID because of increasing quinolone resistance in the UK (e.g. when the patient's partner has gonorrhoea, in clinically severe disease, following sexual contact abroad). Quinolones should also be avoided as first line empirical treatment for PID in areas where >5% of PID is caused by quinolone resistant *Neisseria gonorrhoeae*.

Levofloxacin is the L isomer of ofloxacin[28] and has the advantage of once daily dosing (500mg OD for 14 days). It may be used as a more convenient alternative to ofloxacin.[29]

Replacing intramuscular ceftriaxone with an oral cephalosporin (e.g. cefixime) is not recommended because there is no clinical trial evidence to support its use, and tissue levels are likely to be lower which might impact on efficacy. Reports of decreasing susceptibility of *Neisseria gonorrhoeae* to cephalosporins also supports the use of parenteral based regimens when gonococcal PID is suspected (to maximise tissue levels and overcome low level resistance).

Alternative Regimens

intramuscular ceftriaxone 250 mg immediately, followed by azithromycin 1 g/week for 2 weeks

Grade A (Ib)[30, 31]

Clinical trial evidence for this regimen is limited but it may be used when the treatments above are not appropriate e.g. allergy, intolerance:

oral moxifloxacin 400mg once daily for 14 days

Grade A (Ib)[29, 32, 33]

Three large RCTs support the efficacy of moxifloxacin for PID but because of evidence of an increased risk of liver reactions and other serious risks (such as QT interval prolongation), oral moxifloxacin should be used only when it is considered inappropriate to use the other antibacterial agents recommended for PID or when these have failed.

Inpatient Regimens

Intravenous therapy should be continued until 24 hours after clinical improvement and then switched to oral. Intravenous doxycycline is not currently licensed in the UK but is available from IDIS world medicines (01932 824100).

i.v. ceftriaxone 2g daily *plus* i.v. doxycycline 100mg twice daily (oral doxycycline may be used if tolerated) followed by oral doxycycline 100mg twice daily *plus* oral metronidazole 400mg twice daily for a total of 14 days

Grade A (Ib) [22, 23]

i.v. clindamycin 900mg 3 times daily *plus* i.v. gentamicin (2mg/kg loading dose) followed by 1.5mg/kg 3 times daily [a single daily dose of 7mg/kg may be substituted]) followed by either oral clindamycin 450mg 4 times daily or oral doxycycline 100mg twice daily plus oral metronidazole 400mg twice daily to complete 14 days

Grade A (Ib) [22]

Gentamicin levels need to be monitored if this regimen is used.

Alternative Regimens

Clinical trial evidence for the following regimens is more limited but they may be used when the treatments above are not appropriate e.g. allergy, intolerance:

i.v. ofloxacin 400mg BD *plus* i.v. metronidazole 500mg TID for 14 days

Grade B (III) [23-25, 34]

i.v. ciprofloxacin 200mg BD plus i.v. (or oral) doxycycline 100mg BD plus i.v. metronidazole 500mg TID for 14 days

Grade B (III) [24, 35]

Allergy

There is no clear evidence of the superiority of any one of the suggested regimens over the others. Therefore patients known to be allergic to one of the suggested regimens should be treated with an alternative.

Pregnancy and Breastfeeding

- PID in pregnancy is associated with an increase in both maternal and fetal morbidity, therefore parenteral therapy is advised although none of the suggested evidence based regimens are of proven safety in this situation.
- There are insufficient data from clinical trials to recommend a specific regimen and empirical therapy with agents effective against gonorrhoea, chlamydia and anaerobic infections should be considered taking into account local antibiotic sensitivity patterns (e.g. i.m. ceftriaxone plus oral or i.v. erythromycin, with the possible addition of oral or i.v. metronidazole 500mg 3 times daily in clinically severe disease) (Grade C [IV]).
- The risk of giving any of the recommended antibiotic regimens (listed above for non pregnant women) in very early pregnancy (prior to a pregnancy test becoming positive) is justified by the need to provide effective therapy and the low risk to the foetus (personal communication, UK National Teratology Information Service – 11.2.10).

Surgical Management

- Laparoscopy may help early resolution of the disease by dividing adhesions and draining pelvic abscesses[36] but ultrasound guided aspiration of pelvic fluid collections is less invasive and may be equally effective.[37, 38]
- It is also possible to perform adhesiolysis in cases of perihepatitis although there is no evidence whether this is superior to using only antibiotic therapy

Sexual Partners

- Current male partners of women with PID should be contacted and offered health advice and screening for gonorrhoea and chlamydia. Other recent sexual partners may also be offered screening - tracing of contacts within a 6 month period of onset of symptoms is recommended but this time period may be influenced by the sexual history (Grade C [IV]).
- Gonorrhoea or chlamydia diagnosed in the male partner should be treated appropriately and concurrently with the index patient. (Grade C [IV]).
- Because many cases of PID are not associated with gonorrhoea or chlamydia, broad spectrum empirical therapy should also be offered to male partners e.g. azithromycin 1g single dose (Grade C [IV]).
- If screening for gonorrhoea is not available additional specific antibiotics effective against *Neisseria gonorrhoeae* should be offered e.g. i.m. ceftriaxone 250mg single dose (see also UK National Guidelines for Gonorrhoea) (Grade C [IV]).
- Partners should be advised to avoid intercourse until they and the index patient have completed the treatment course (Grade C [IV]).

Follow Up

Review at 72 hours is recommended [5], particularly for those with a moderate or severe clinical presentation, and should show a substantial improvement in clinical symptoms and signs (Grade C [IV]). Failure to do so suggests the need for further investigation, parenteral therapy and/or surgical intervention.

Further review 2-4 weeks (Grade C [IV]) after therapy may be useful to ensure:

- adequate clinical response to treatment
- compliance with oral antibiotics
- screening and treatment of sexual contacts
- awareness of the significance of PID and its sequelae
- repeat pregnancy test, if clinically indicated

Repeat testing for gonorrhoea or chlamydia after 2 to 4 weeks is appropriate in those in whom persisting symptoms, antibiotic resistance pattern (gonorrhoea only), compliance with antibiotics and/or tracing of sexual contacts indicate the possibility of persisting or recurrent infection.

Auditable Outcome Measures

Appropriate short term audit outcomes include:

- proportion of women receiving treatment with a recommended regimen – target 95%
- number of named male contacts screened for infection and/or treated – target 0.4 (large urban centres) or 0.6 (other centres) per index case[39]

Qualifying statement

The recommendations in this guideline may not be appropriate for use in all clinical situations. Decisions to follow these recommendations must be based on the professional judgement of the clinician and consideration of individual patient circumstances and available resources.

All possible care has been undertaken to ensure the publication of the correct dosage of medication and route of administration. However, it remains the responsibility of the prescribing physician to ensure the accuracy and appropriateness of the medication they prescribe.

Editorial independence

This guideline was commissioned, edited and endorsed by the BASHH CEG without external funding being sought or obtained.

Declarations of interest

All members of the guideline writing committee completed the BASHH conflict of interest declaration detailed below at the time the guideline's final draft was submitted to the CEG. JR has received consultancy fees from Bayer pharma.

Author affiliation

- Prof Jonathan Ross, Professor of Sexual Health and HIV, Whittall Street Clinic Whittall Street B4 6DH
- Dr Gill McCarthy, Consultant Physician Sexual Health an HIV, The Wolverton Centre, Kingston Hospital NHS Trust, Galsworthy Road, Kingston upon Thames, KT2 7QB

Membership of the CEG

- Dr Keith Radcliffe (Chair); Consultant Physician in Genitourinary Medicine Whittall Street Clinic Whittall Street B4 6DH
- Dr David Daniels, West Midllesex University Hospitals NHS Trust, Sexual Health Clinic West Middlesex Hospital Twickenham Road, Isleworth, TW7 6AF
- Dr Mark FitzGerald Consultant Physician in Genitourinary Medicine, Musgrove Park Hospital, Taunton, TA1 5DA
- Dr Margaret Kingston, Consultant Physician in GU Medicine, Manchester Centre for Sexual Health, The Hathersage Centre, 280 Upper Brook Street, Manchester M13 0FH
- Dr Neil Lazaro, Associate Specialist in GU Medicine, Royal Preston Hospital, Preston PR2 9HT
- Dr Gill McCarthy, Consultant Physician in GU Medicine, Kingston Hospital NHS Trust, Wolverton Centre for Sexual Health Galsworthy Road, Kingston Upon Thames, KT2 7QB
- Dr Ann Sullivan, Consultant Physician in Genitourinary Medicine, Chelsea & Westminster Healthcare NHS Trust, John Hunter Clinic 2nd Floor St Stephen's Centre 369 Fulham Road SW10 9NH

Timescale for next revision : 2015

Acknowledgements : None

Reference List

1. Recommendations arising from the 31st Study Group: The Prevention of Pelvic Infection. In: Templeton A, editor. The Prevention of Pelvic Infection. London: RCOG Press; 1996:267-270.

2. Bevan CD, Johal BJ, Mumtaz G, Ridgway GL, Siddle NC. Clinical, laparoscopic and microbiological findings in acute salpingitis: report on a United Kingdom cohort. British Journal of Obstetrics & Gynaecology 1995;102(5):407-414.

3. Haggerty CL. Evidence for a role of Mycoplasma genitalium in pelvic inflammatory disease. Current Opinion in Infectious Diseases 2008;21(1):65-69.

4. Morcos R, Frost N, Hnat M, Petrunak A, Caldito G. Laparoscopic versus clinical diagnosis of acute pelvic inflammatory disease. J Reprod Med 1993;38(1):53-56.

5. Centers for Disease Control. Sexually Transmitted Diseases Treatment Guidelines 2006. MMWR - Morbidity & Mortality Weekly Report 2006;55(RR-11):56-60.

6. Kamenga MC, De Cock KM, St.Louis ME et al. The impact of human immunodeficiency virus infection on pelvic inflammatory disease: a case-control study in Abidjan, Ivory Coast. Am J Obstet Gynecol 1995;172(3):919-925.

7. Cohen CR, Sinei S, Reilly M et al. Effect of human immunodeficiency virus type 1 infection upon acute salpingitis: a laparoscopic study. J Infect Dis 1998;178(5):1352-1358.

8. Bukusi EA, Cohen CR, Stevens CE et al. Effects of human immunodeficiency virus 1 infection on microbial origins of pelvic inflammatory disease and on efficacy of ambulatory oral therapy. Am J Obstet Gynecol 1999;181(6):1374-1381.

9. Irwin KL, Moorman AC, O'Sullivan MJ et al. Influence of human immunodeficiency virus infection on pelvic inflammatory disease. Obstet Gynecol 2000;95(4):525-534.

10. Altunyurt S, Demir N, Posaci C. A randomized controlled trial of coil removal prior to treatment of pelvic inflammatory disease. European Journal of Obstetrics Gynecology and Reproductive Biology 2003;107:81-84.

11. Soderberg G, Lindgren S. Influence of an intrauterine device on the course of an acute salpingitis. Contraception 1981;24(2):137-143.

12. Miettinen AK, Heinonen PK, Laippala P, Paavonen J. Test performance of erythrocyte sedimentation rate and C- reactive protein in assessing the severity of acute pelvic inflammatory disease. Am J Obstet Gynecol 1993;169(5):1143-1149.

13. Yudin MH, Hillier SL, Wiesenfeld HC, Krohn MA, Amortegui AA, Sweet RL. Vaginal polymorphonuclear leukocytes and bacterial vaginosis as markers for histologic endometritis among women without symptoms of pelvic inflammatory disease. American Journal of Obstetrics and Gynecology 2003;188(2):318-323.

14. Bongard F, Landers DV, Lewis F. Differential diagnosis of appendicitis and pelvic inflammatory disease. A prospective analysis. American Journal of Surgery 1985;150(1):90-96.

15. Lewis FR, Holcroft JW, Boey J, Dunphy JE. Appendicitis: a critical review of diagnosis and treatment in 1000 cases. Archives of Surgery 1975;110:677-684.

16. Hillis SD, Joesoef R, Marchbanks PA et al. Delayed care of pelvic inflammatory disease as a risk factor for impaired fertility. Am J Obstet Gynecol 1993;168(5):1503-1509.

17. Ness RB, Soper DE, Holley RL et al. Effectiveness of inpatient and outpatient treatment strategies for women with pelvic inflammatory disease: results from the Pelvic Inflammatory Disease Evaluation and Clinical Health (PEACH) Randomized Trial. Am J Obstet Gynecol 2002;186(5):929-937.

18. Haggerty CL, Ness RB, Amortegui A et al. Endometritis does not predict reproductive morbidity after pelvic inflammatory disease. Am J Obstet Gynecol 2003;188(1):141-148.

19. Ross JDC, Stewart P. Management of Acute Pelvic Inflammatory Disease. http://www.rcog.org.uk/files/rcog-corp/uploaded-files/T32PelvicInflamatoryDisease2008MinorRevision.pdf . 2009.
Ref Type: Generic

20. Ross JD, Ison CA. UK National Screening and Testing Guidelines for STIs. Sex Transm Infect 2006;82:Suppl IV.

21. Arredondo JL, Diaz V, Gaitan H et al. Oral clindamycin and ciprofloxacin versus intramuscular ceftriaxone and oral doxycycline in the treatment of mild-to- moderate pelvic inflammatory disease in outpatients. Clin Infect Dis 1997;24(2):170-178.

22. Hemsell DL, Little BB, Faro S et al. Comparison of three regimens recommended by the Centers for Disease Control and Prevention for the treatment of women hospitalized with acute pelvic inflammatory disease. Clin Infect Dis 1994;19(4):720-727.

23. Martens MG, Gordon S, Yarborough DR, Faro S, Binder D, Berkeley A. Multicenter randomized trial of ofloxacin versus cefoxitin and doxycycline in outpatient treatment of pelvic inflammatory disease. Ambulatory PID Research Group. Southern Medical Journal 1993;86(6):604-610.

24. Walker CK, Kahn JG, Washington AE, Peterson HB, Sweet RL. Pelvic inflammatory disease: metaanalysis of antimicrobial regimen efficacy. J Infect Dis 1993;168(4):969-978.

25. Wendel GD, Jr., Cox SM, Bawdon RE, Theriot SK, Heard MC, Nobles BJ. A randomized trial of ofloxacin versus cefoxitin and doxycycline in the outpatient treatment of acute salpingitis. Am J Obstet Gynecol 1991;164(5 Pt 2):1390-1396.

26. Soper DE, Brockwell NJ, Dalton HP. Microbial etiology of urban emergency department acute salpingitis: treatment with ofloxacin. Am J Obstet Gynecol 1992;167(3):653-660.

27. Peipert JF, Sweet RL, Walker CK, Kahn J, Rielly-Gauvin K. Evaluation of ofloxacin in the treatment of laparoscopically documented acute pelvic inflammatory disease (salpingitis). Infectious Diseases in Obstetrics & Gynecology 1999;7(3):138-144.

28. Isaacson DM, Fernadez JA, Frosco M et al. Levofloxacin: A review of its antibacterial activity. Recent Res Devel in Antimicrob Agents & Chemotherapy 1996;1:391-439.

29. Judlin P, Liao Q, Liu Z, Reimnitz P, Hampel B, Arvis P. Efficacy and safety of moxifloxacin in uncomplicated pelvic inflammatory disease: the MONALISA study. BJOG: An International Journal of Obstetrics & Gynaecology 2010;117(12):1475-1484.

30. Savaris RF, Teixeira LM, Torres TG, Edelweiss MI, Moncada J, Schachter J. Comparing ceftriaxone plus azithromycin or doxycycline for pelvic inflammatory disease: a randomized controlled trial. Obstet Gynecol 2007;110(1):53-60.

31. Bevan CD, Ridgway GL, Rothermel CD. Efficacy and safety of azithromycin as monotherapy or combined with metronidazole compared with two standard multidrug regimens for the treatment

of acute pelvic inflammatory disease. Journal of International Medical Research 2003;31(1):45-54.

32. Heystek MJ, Ross JDC, PID Study Group. A randomised double-blind comparison of moxifloxacin and doxycycline/metronidazole/ciprofloxacin in the treatment of acute, uncomplicated pelvic inflammatory disease. Int J STD AIDS 2009;20:690-695.

33. Ross JDC, Cronje HS, Paszkowski T et al. Moxifloxacin versus ofloxacin plus metronidazole in uncomplicated pelvic inflammatory disease: results of a multicentre, double blind, randomised trial. Sex Transm Infect 2006;82:446-451.

34. Witte EH, Peters AA, Smit IB et al. A comparison of pefloxacin/metronidazole and doxycycline/metronidazole in the treatment of laparoscopically confirmed acute pelvic inflammatory disease. European Journal of Obstetrics, Gynecology, & Reproductive Biology 1993;50(2):153-158.

35. Heinonen PK, Teisala K, Miettinen A, Aine R, Punnonen R, Gronroos P. A comparison of ciprofloxacin with doxycycline plus metronidazole in the treatment of acute pelvic inflammatory disease. Scandinavian Journal of Infectious Diseases - Supplementum 1989;60:66-73.

36. Reich H, McGlynn F. Laparoscopic treatment of tuboovarian and pelvic abscess. J Reprod Med 1987;32(10):747-752.

37. Aboulghar MA, Mansour RT, Serour GI. Ultrasonographically guided transvaginal aspiration of tuboovarian abscesses and pyosalpinges: an optional treatment for acute pelvic inflammatory disease. Am J Obstet Gynecol 1995;172(5):1501-1503.

38. Corsi PJ, Johnson SC, Gonik B, Hendrix SL, McNeeley SG, Jr., Diamond MP. Transvaginal ultrasound-guided aspiration of pelvic abscesses. Infectious Disease in Obstetrics and Gynecology 1999;7(5):216-221.

39. Low N, Welch J, Radcliffe K. Developing national outcome standards for the management of gonorrhoea and genital chlamydia in genitourinary medicine clinics. Sex Transm Infect 2004;80(3):223-229.

Appendix 1: Patient information leaflet on PID

Currently in preparation – see BASHH website in due course for downloadable document.

SEARCH

United Kingdom National Guideline on the Management of Vulvovaginal Candidiasis (2007)

Clinical Effectiveness Group
British Association of Sexual Health and HIV

Introduction and Methodology

Scope and Purpose

The main objective is to assist practitioners in the management of uncomplicated and complicated Vulvovaginal Candidiasis.

This guideline offers recommendations on the diagnostic tests, treatment regimens and health promotion principles needed for the effective management of Vulvovaginal Candidiasis.

It is aimed primarily at people aged 16 years or older (see specific guidelines for those under 16) presenting to health care professionals, working in departments offering level 3 care in STI management (see national strategy[(2)]) within the United Kingdom. However, the principles of the recommendations should be adopted across all levels (levels 1 and 2 may need to develop, where appropriate, local care pathways).

Stakeholder Involvement

This guideline has been produced by physicians, including those with a specialist interest, with input from patients attending UK GUM clinics.
The draft guideline was placed on the BASHH website for a three month consultation period.
The process was overseen by the BASHH Clinical Effectiveness Group (CEG).
This is the second revision of the guideline first published in 1999.

Rigour of Development

An extensive literature review was performed using Medline for the years 1966-2007. MEDLINE search-keywords: vulvovaginal candidiasis, vaginal candidosis, vaginal candida. The resulting articles were handsearched and sorted. Further references were obtained from these articles.

The Cochrane Library was searched; search-keywords were vulvovaginal candidiasis, vaginal candidosis, vaginal candida (2007).

Aetiology

Causative Agents

Candida albicans 80-92%[1;2]
Non-*albicans* species e.g. *C. glabrata*, *C. tropicalis*, *C. krusei*, *C. parapsilosis*, and *Saccharomyces cerevisiae*

Clinical Features

Symptoms

Vulval itch
Vulval soreness
Vaginal discharge
Superficial dyspareunia
External dysuria

Signs

Erythema
Fissuring
Discharge, typically curdy but may be thin. Non-offensive
Oedema
Satellite lesions
Excoriation

None of these symptoms or signs are pathognomonic for vulvovaginal candidiasis; corroborative evidence of laboratory tests should be sought[3] as many women (more than half of self-diagnosed women in one study[4]) may have other conditions e.g. dermatitis, allergic reactions, lichen sclerosus. In addition, symptoms/signs are no guide to species.[3;5]

10-20% of women during reproductive years may be colonized with *Candida sp*.[6;7] but have no clinical signs or symptoms. These women do not require treatment.

Vulvo-vaginal candidiasis is mostly uncomplicated unless the following are present when it is regarded as complicated:

- Severe symptoms (a subjective assessment)

- Pregnancy
- Recurrent vulvovaginal candidiasis (more than 4 attacks per year)
- Non-albicans species
- Abnormal host (e.g. hyperoestrogenic state, diabetes mellitus, immunosuppression)

Diagnosis

In the context of comprehensive sexual health services, routine microscopy and culture is the standard of care for symptomatic women[3;9-13] (Evidence level III, grade C)

A vaginal swab should be taken from the anterior fornix[14] (Evidence level III, grade B) for the following:

- Gram or wet film examination[3;9-13] (Evidence level III, grade B)
- Directly plated to solid fungal media. Speciation to albicans/non-albicans is strongly preferred if uncomplicated disease, and essential if complicated disease suspected/present[15-18] (Evidence level III, grade B)

See British Association of Sexual Health and HIV Clinical Effectiveness Group guidelines 'Sexually Transmitted Infections: UK National Screening and Testing Guidelines', August 2006 for comprehensive guidance.
[www.bashh.org/guidelines/2006/sti_screening_guidelines_v14_0806.pdf]

Management

General Advice
Routine recommendation of use of vulval moisturisers as soap substitute and regular skin conditioner (permission may need to be given to the patient that this does not constitute "internal use").
Avoid tight fitting synthetic clothing[19;20]
Avoid local irritants e.g. perfumed products,
(Level of evidence: IV, grade C)

Treatment
Uncomplicated Vulvovaginal Candidiasis

robertc 28/8/07 11:05
Deleted:

Since all topical and oral azole therapies give a clinical and mycological cure rate of over 80% in uncomplicated acute vulvovaginal candidiasis, choice is a matter of personal preference, availability and affordability.[21;22]
Nystatin preparations give a 70-90% cure rate in this situation.[7]
See later section if severe symptoms/signs.
Topical azole therapies can cause vulvovaginal irritation and this should be considered if symptoms worsen or persist.

Topical Therapies

DRUG	FORMULATION	DOSAGE REGIMEN
Clotrimazole*	Pessary	500mg stat
Clotrimazole*	Pessary	200mg x 3 nights
Clotrimazole*	Pessary	100mg x 6 nights
Clotrimazole*	Vaginal cream (10%)	5g stat
Econazole**	Pessary (Ecostatin 1)	150mg stat
Econazole**	Pessary	150mg x 3 nights
Fenticonazole**	Pessary	600mg stat
Fenticonazole**	Pessary	200mg x 3 nights
Isoconazole*	Vaginal tablet	300mg x 2 stat
Miconazole**	Ovule	1.2g stat
Miconazole**	Pessary	100mg x 14 nights
Nystatin	Vaginal cream (100,000 units)	4g x 14 nights
Nystatin	Pessary (100,000 units)	1-2 x 14 nights

*Effect on latex condoms and diaphragms not known
**Product damages latex condoms and diaphragms

Oral Therapies

DRUG	FORMULATION	DOSAGE REGIMEN
Fluconazole*	Capsule	150mg stat
Itraconazole*	Capsule	200mg bd x 1 day

*Avoid in pregnancy/risk of pregnancy and breastfeeding

(Level of evidence: II, grade A[7;21;22])

Sexual Partners

There is no evidence to support the treatment of asymptomatic male sexual partners in either episodic or recurrent vulvovaginal candidiasis.[23;24]
(Level of evidence: I, grade A)

Follow-up

Unnecessary if symptoms resolve. Test of cure is unnecessary.

Complicated Vulvovaginal Candidiasis

Pregnancy

Asymptomatic colonization with *Candida species* is more common (30-40%)[25] and symptomatic candidosis is more prevalent throughout pregnancy.
Colonisation with *Candida species* is not associated with low birth weight or premature delivery.[26]

Treatment

Topical imidazoles should be used for symptomatic vulvovaginal candidiasis in pregnancy. There is no evidence to suggest asymptomatic women need to be treated.[27]
There is no evidence that any one topical imidazole is more effective than another.
Longer courses are recommended; a four day course will cure just over 50% whereas a seven day course cures over 90%.[27]
Oral therapy is contraindicated.
(Level of evidence: II, grade B[27])

Recurrent Vulvovaginal Candidiasis

Definition

- At least 4 documented episodes of symptomatic vulvovaginal candidiasis annually[8],with at least partial resolution of symptoms between episodes
- Positive microscopy or a moderate/heavy growth of *C albicans* should be documented on at least two occasions when symptomatic

(Level of evidence: IV, grade C)

Prevalence

Approximately 5% of women of reproductive age with a primary episode of vulvovaginal candidiasis will develop recurrent disease.[28;29]

Unknown
Field Code Changed

Pathogenesis

Caused by host factors rather than a more virulent strain or reintroduction of the organism to the genital tract.[30] It is usually due to *C albicans*.

Unknown
Field Code Changed

Host factors include persistence of Candida (as detected by PCR although culture-negative between attacks)[31], uncontrolled diabetes mellitus, immunosuppression, hyperoestrogenaemia (including HRT and the combined oral contraceptive pill),[19;25] disturbance of vaginal flora e.g. through use of broad-spectrum antibiotics,[19;32] and a link to allergy (in particular allergic rhinitis)[33] and pro-inflammatory genetic markers.

Unknown
Field Code Changed

There is no evidence that iron deficiency is implicated.[34]
One study[34] reported a statistically significantly lower serum level of zinc, magnesium and calcium in patients with recurrent vulvovaginal candidiasis, although all levels were within the normal range; other studies have refuted the link with serum zinc levels.[35]

Further Investigation

Speciated fungal culture

FBC, random blood glucose only if other indicators (Level of evidence: IV, grade C)

robertc 28/8/07 11:10
Deleted:

General Advice

- As per uncomplicated disease.
- Vulval emollients may give symptomatic relief as vulval dermatitis both secondary and primary is commonly present.
- Review contraception. Avoid high-oestrogen contraceptives. Low oestrogen pills do not highly predispose to vulvovaginal candidiasis but may possibly have a negative influence on relapsing episodes[36].
- Consider use of Depo-Provera[37].
  (Grade of evidence: III, grade B)
- Lack of evidence for desogestrel-only pill (Cerazette) but would be logical alternative. (Grade of evidence: IV, grade C)

Treatment

The principle of therapy involves an induction regimen to ensure clinical remission, followed immediately by a maintenance regimen.

Recommended Regimen

TREATMENT STAGE	DRUG	FORMULATION	DOSAGE REGIMEN
Induction	Fluconazole*	Capsule	150mg every 72 hours x 3 doses
Maintenance	Fluconazole*	Capsule	150mg once a week for 6 months

*Avoid in pregnancy/ risk of pregnancy and breastfeeding

Approximately 90% of women will remain disease-free at 6 months and 40% at 1 year.
(Level of evidence: Ib, grade A[38])

Alternative Regimens
Induction
Topical imidazole therapy can be increased to 10-14 days according to symptomatic response.
(Level of evidence: IV, grade C)

Maintenance

DRUG	FORMULATION	DOSAGE REGIMEN
Clotrimazole	Pessary	500mg once a week
Fluconazole*	Capsule	50mg daily
Itraconazole*	Capsule	50-100mg daily
Ketoconazole*	Capsule	100mg daily

*Avoid in pregnancy/risk of pregnancy and breastfeeding

Cautions:

- Risk (low) of idiosyncratic drug-induced hepatitis, particularly with itraconazole and ketoconazole.
- These regimens are unlicenced for the indication.
- Anecdotal reports of oral contraceptive failure with prolonged oral azole therapy.

Maintenance therapy should last six months; 90% of women should remain disease-free during treatment.
(Level of evidence: IIa, grade B[39-41])

If relapse between doses consider twice-weekly 150mg fluconazole or 50mg fluconazole daily.
(Level of evidence: IV, grade C)
Alternatively consider the addition of cetirizine 10mg od.[42]

There are no trials addressing the optimal duration of suppressive therapy. If recurrences after maintenance regimen are infrequent, each episode should be treated independently. If recurrent disease is re-established the induction and maintenance regimens should be repeated.
(Level of evidence: IV, grade C)

Alternative Treatments

Probiotics/Lactobacillus

Evidence does not support use of oral or vaginal lactobacillus for the prevention of vulvovaginal candidiasis.[43;44] Adverse effects from their use are extremely infrequent however and there are anecdotal reports of benefit. The mode of action might be via modulation of inflammatory processes[45] rather than due to a competitive effect with candida.

Diet

There is insufficient evidence to make any dietary recommendations, including on carbohydrate or yeast intake.[8;46]

Role of Allergy

Zafirlukast 20mg bd for 6 months[47] may induce remission. Zafirlukast may be considered as maintenance prophylaxis for recurrent vulvovaginal candidiasis, particularly in women with a history of atopy.[42] Cetirizine 10mg daily for 6 months[42] may

cause remission in women who fail to get complete resolution of symptoms with suppressive fluconazole.
(Level of evidence: IIb, grade B)

Tea tree oil (and other essential oils)
Are antifungal in vitro[48-50] but may cause hypersensitivity reactions.[51] Insufficient evidence to recommend use in recurrent vulvovaginal candidiasis.

Severe Vulvovaginal Candidiasis

Regardless of a history of recurrence, fluconazole 150mg should be repeated after three days as this improves symptomatic response but not recurrence.[52]
(Level of evidence: Ib, grade A).

David White 24/12/07 14:04
Deleted:

There is no benefit of 7 day local treatment over a single oral dose of fluconzole.[53] so if oral treatment is contra-indicated it is more logical to repeat a single dose pessary after three days.
(Level of evidence: IV, grade C)
Low-potency corticosteroids are also thought by some experts to improve symptomatic relief in conjunction with adequate antifungal therapy
(Level of evidence: IV, grade C)[8]

Diabetes Mellitus
Symptomatic vulvovaginal candidiasis is more prevalent in diabetics and most problematic in those with poor control.
Increased prevalence of species other than *C albicans*, in particular *C glabrata*.[54;55]
Glycaemic control should be optimized.
When C albicans is isolated, single-dose fluconazole (150mg) gives a similar response to non-diabetics.[55]
(Level of evidence: IIb, grade B)
Symptomatic women with C glabrata isolated: boric acid 600mg intravaginal suppository once a day for 14 days is as effective as fluconazole 150mgs stat[56]
(Level of evidence: Ib, grade A)

HIV Infection

Vulvovaginal candidiasis occurs more frequently and with greater persistence in HIV-infected women.[57]
Treat by conventional methods including use of suppressive antifungal regimens if necessary.[58]
(Level of evidence: III, grade B)

Non-*Albicans* Species
Majority are *Candida glabrata* and are still susceptible to available azoles[59] although most non-*albicans* species have higher MICs. *Candida krusei* is intrinsically resistant to fluconazole.[60]

In general for non-albicans infection longer courses may be needed although there is no data on optimum duration; two weeks is suggested. There no comparative evidence for different treatments. Suggested alternatives include:

Nystatin pessaries are the only licensed alternative to azole therapy and are therefore the usual first line treatment for non-albicans infection. Unfortunately there are ongoing problems with supply (June 2008) and in this case consider local pharmacy production of Amphotericin B vaginal suppositories 50mg once a day for 14 days which is has a 70% success rate.[61]
(Level of evidence: III, grade B)

Boric acid vaginal suppositories 600mg daily for 2-3 weeks.[59;62]
If mucosal irritation occurs the dose can be reduced to 300mg daily.[63] There is still limited evidence for this drug. There may be a teratogenic risk.[64]
(Level of evidence: III, grade B)

Intravaginal flucytosine (5g cream or 1g pessary) either separately[59;65] or with amphotericin[65] to reduce the chances of resistance (for which there is a low genetic barrier) can be used for two weeks.
(Level of evidence: III, grade B)

Qualifying statement

The recommendations in this guideline may not be appropriate for use in all clinical situations. Decisions to follow these recommendations

must be based on the professional judgment of the clinician and consideration of individual patient circumstances and available resources.

All possible care has been taken to ensure the publication of the correct dosage of medication and route of administration. However, it remains the responsibility of the prescribing physician to ensure the accuracy and appropriateness of the medication they prescribe.

Applicability

The diagnosis of VVC is syndromic. Diagnostic criteria may therefore vary with the clinical setting. It is acknowledged that some tests, e.g. for precise speciation of *Candida*, may not be available in all settings.

Some preparations e.g. flucytosine cream may not be available on local formularies. It is advised that such preparations are discussed with the unit pharmacist prior to prescribing.

Auditable Outcome Measures

- Cheapest acceptable topical/oral treatment option to be used in non-pregnant women. Target: 80%.
- All women with severe symptoms should receive fluconazole 150mg repeated after 3 days (unless contraindicated). Target: 100%
- All women with proven recurrent vulvovaginal candidiasis should be offered suppressive or alternative long term therapy. Target: 100%
- Asymptomatic male partners should not be treated. Target: 100%.

Acknowledgements

We wish to thank the following for their valuable contributions to this Guideline: David Daniels and Greta Forster who were the authors of the previous guidelines.

Authors and Centres

David White, Heart of England NHS Foundation Trust
Claire Robertson, Heart of England NHS Foundation Trust

Membership of the CEG

Clinical Effectiveness Group: Chairman Keith Radcliffe; Imtyaz Ahmed-Jushuf; David Daniels; Mark FitzGerald; Neil Lazaro; Gillian McCarthy; Guy Rooney

Conflict of Interest

David White: None
Claire Robertson: None

Evidence Base

MEDLINE search-keywords: vulvovaginal candidiasis, vaginal candidosis, vaginal candida (1966 – 2007)

COCHRANE LIBRARY search-keywords: vulvovaginal candidiasis, vaginal candidosis, vaginal candida (2007)

Reference List

robertc 28/8/07 15:03
Deleted:

(1) Holland J, Young ML, Lee O, Chen S. Vulvovaginal carriage of yeasts other than Candida albicans. Sexually transmitted infections 2003; 79(3):249-250.

(2) Sobel JD. Pathogenesis and epidemiology of vulvovaginal candidiasis. [Review] [60 refs]. Annals of the New York Academy of Sciences 1988; 544:547-557.

(3) Schaaf VM, Perez-Stable EJ, Borchardt K. The limited value of symptoms and signs in the diagnosis of vaginal infections. [see comments.]. Archives of Internal Medicine 1990; 150(9):1929-1933.

(4) Ferris DG, Dekle C, Litaker MS. Women's use of over-the-counter antifungal medications for gynecologic symptoms. Journal of Family Practice 1996; 42(6):595-600.

(5) Geiger AM, Foxman B, Sobel JD. Chronic vulvovaginal candidiasis: characteristics of women with Candida albicans, C glabrata and no candida. Genitourin-Med 1995; 71(5):304-307.

(6) Lindner JG, Plantema FH, Hoogkamp K. Quantitative studies of the vaginal flora of healthy women and of obstetric and gynaecological patients. J-Med-Microbiol 1978; 11(3):233-241.

(7) Odds FC. Candida and Candidosis; A review and bibliography. Second ed. London: Bailliere Tindall; 1988.

(8) Sobel JD, Faro S, Force RW, Foxman B, Ledger WJ, Nyirjesy PR et al. Vulvovaginal candidiasis: epidemiologic, diagnostic, and therapeutic considerations. [see comments.]. [Review] [29 refs]. American Journal of Obstetrics & Gynecology 1998; 178(2):203-211.

(9) Abbott J. Clinical and microscopic diagnosis of vaginal yeast infection: a prospective analysis. Annals of Emergency Medicine 1995; 25(5):587-591.

(10) Bergman JJ, Berg AO, Schneeweiss R, Heidrich FE. Clinical comparison of microscopic and culture techniques in the diagnosis of Candida vaginitis. Journal of Family Practice 1984; 18(4):549-552.

(11) Eckert LO, Hawes SE, Stevens CE, Koutsky LA, Eschenbach DA, Holmes KK. Vulvovaginal candidiasis: clinical manifestations, risk factors, management algorithm. Obstetrics & Gynecology 1998; 92(5):757-765.

(12) Sonnex C, Lefort W. Microscopic features of vaginal candidiasis and their relation to symptomatology. Sexually transmitted infections 1999; 75(6):417-419.

(13) Zdolsek B, Hellberg D, Froman G, Nilsson S, Mardh PA. Culture and wet smear microscopy in the diagnosis of low-symptomatic vulvovaginal candidosis. European Journal of Obstetrics, Gynecology, & Reproductive Biology 1995; 58(1):47-51.

(14) Emmerson J, Gunputrao A, Hawkswell J, Dexter A, Sykes R, Searle S et al. Sampling for vaginal candidosis: how good is it? International journal of STD & AIDS 1994; 5(5):356-358.

(15) Hopwood V, Crowley T, Horrocks CT, Milne JD, Taylor PK, Warnock DW. Vaginal candidosis: relation between yeast counts and symptoms and clinical signs in non-pregnant women. Genitourin-Med 1988; 64(5):331-334.

(16) Odds FC, Webster CE, Riley VC, Fisk PG. Epidemiology of vaginal Candida infection: significance of numbers of vaginal yeasts and their biotypes. European Journal of Obstetrics, Gynecology, & Reproductive Biology 1987; 25(1):53-66.

(17) Odds FC, Webster CE, Mayuranathan P, Simmons PD. Candida concentrations in the vagina and their association with signs and symptoms of vaginal candidosis. Journal of Medical & Veterinary Mycology 1988; 26(5):277-283.

(18) Priestley CJ, Jones BM, Dhar J, Goodwin L. What is normal vaginal flora? [see comments]. Genitourin-Med 1997; 73(1):23-28.

(19) Patel D, Gillespie B, Sobel J, Leaman D, Nyirjesy P, Weitz M, V et al. Risk factors for recurrent vulvovaginal candidiasis in women receiving maintenance antifungal therapy: results of a prospective cohort study. American journal of obstetrics and gynecology 2004; 190(3):644-653.

(20) Elegbe IA, Elegbe I. Quantitative relationships of Candida albicans infections and dressing patterns in Nigerian women. American Journal of Public Health 1983; 73(4):450-452.

(21) Watson MC, Grimshaw JM, Bond CM, Mollison J, Ludbrook A. Oral versus intra-vaginal imidazole and triazole anti-fungal agents for the treatment of uncomplicated vulvovaginal candidiasis (thrush): a systematic review. [Review] [27 refs]. BJOG: an International Journal of Obstetrics & Gynaecology 2002; 109(1):85-95.

(22) Watson MC, Grimshaw JM, Bond CM, Mollison J, Ludbrook A. Oral versus intra-vaginal imidazole and triazole anti-fungal treatment of uncomplicated vulvovaginal candidiasis (thrush). [update of Cochrane Database Syst Rev. 2001;(1):CD002845 ; 11279767.]. [Review] [37 refs]. Cochrane Database of Systematic Reviews 2001;(4):CD002845.

(23) Bisschop MP, Merkus JM, Scheygrond H, Van Cutsem J. Co-treatment of the male partner in vaginal candidosis: a double-blind randomized control study. British Journal of Obstetrics & Gynaecology 1986; 93(1):79-81.

(24) Fong IW. The value of treating the sexual partners of women with recurrent vaginal candidiasis with ketoconazole. Genitourin-Med 1992; 68(3):174-176.

(25) Bauters T, Dhont M, Temmerman M, I, Nelis H. Prevalence of vulvovaginal candidiasis and susceptibility to fluconazole in women. American journal of obstetrics and gynecology 2002; 187(3):569-574.

(26) Cotch MF, Hillier SL, Gibbs RS, Eschenbach DA. Epidemiology and outcomes associated with moderate to heavy Candida colonization during pregnancy. Vaginal Infections and Prematurity Study Group. American Journal of Obstetrics & Gynecology 1998; 178(2):374-380.

(27) Young GL, Jewell D. Topical treatment for vaginal candidiasis (thrush) in pregnancy. [update of Cochrane Database Syst Rev. 2000;(2):CD000225 ; 10796183.]. [Review] [33 refs]. Cochrane Database of Systematic Reviews 2001;(4):CD000225.

(28) Nyirjesy P. Chronic vulvovaginal candidiasis. Am-Fam-Physician 2001; 63(4):697-702.

(29) Hurley R. Recurrent Candida infection. Clinics in Obstetrics & Gynaecology - Supplement 1981; 8(1):209-214.

(30) Fidel PL, Jr., Sobel JD. Immunopathogenesis of recurrent vulvovaginal candidiasis. [Review] [117 refs]. Clinical Microbiology Reviews 1996; 9(3):335-348.

(31) El-Din SS, Reynolds MT, Ashbee HR, Barton RC, Evans EG. An investigation into the pathogenesis of vulvo-vaginal candidosis. Sexually transmitted infections 2001; 77(3):179-183.

(32) Pirotta MV, Garland SM. Genital Candida species detected in samples from women in Melbourne, Australia, before and after treatment with antibiotics. Journal of clinical microbiology 2006; 44(9).

(33) Moraes PS. Recurrent vaginal candidiasis and allergic rhinitis: a common association. Annals of Allergy, Asthma, & Immunology 1998; 81(2):165-169.

(34) Spacek J, Jilek P, Buchta V, Forstl M, Hronek M, Holeckova M. The serum levels of calcium, magnesium, iron and zinc in patients with recurrent vulvovaginal candidosis during attack, remission and in healthy controls. Mycoses 2005; 48(6):391-395.

(35) Bohler K, Meisinger V, Klade H, Reinthaller A. Zinc levels of serum and cervicovaginal secretion in recurrent vulvovaginal candidiasis. Genitourin-Med 1994; 70(5):308-310.

(36) Spinillo A, Pizzoli G, Colonna L, Nicola S, De Seta F, Guaschino S. Epidemiologic characteristics of women with idiopathic recurrent vulvovaginal candidiasis. Obstetrics & Gynecology 1993; 81(5 (Pt 1):721-727.

(37) Dennerstein GJ. Depo-Provera in the treatment of recurrent vulvovaginal candidiasis. Journal of Reproductive Medicine 1986; 31(9):801-803.

(38) Sobel J, Wiesenfeld H, Martens M, Danna P, Hooton T, Rompalo A et al. Maintenance fluconazole therapy for recurrent vulvovaginal candidiasis. The New England journal of medicine 2004; 351(9):876-883.

(39) Reef SE, Levine WC, McNeil MM, Fisher-Hoch S, Holmberg SD, Duerr A et al. Treatment options for vulvovaginal candidiasis, 1993. [Review] [97 refs]. Clinical Infectious Diseases 1995; 20 Suppl 1:S80-S90.

(40) Sobel JD. Recurrent vulvovaginal candidiasis. A prospective study of the efficacy of maintenance ketoconazole therapy. New England Journal of Medicine 1986; 315(23):1455-1458.

(41) Sobel JD. Treatment of recurrent vulvovaginal candidiasis with maintenance fluconazole. International Journal of Gynaecology & Obstetrics 1992; 37:17-34.

(42) Neves NA CLLACACE. Successful treatment of refractory recurrent vaginal candidiasis with cetirizine plus fluconazole. Journal of Lower Genital Tract Disease 9[3], 167-170. 2005.
Ref Type: Generic

(43) Falagas ME, Betsi GI, Athanasiou S. Probiotics for prevention of recurrent vulvovaginal candidiasis: a review. The Journal of antimicrobial chemotherapy 2006; 58(2).

(44) Pirotta M, Gunn J, Chondros P, Grover S, O'Malley P, Hurley S et al. Effect of lactobacillus in preventing post-antibiotic vulvovaginal candidiasis: a randomised controlled trial. BMJ (Clinical research ed) 2004; 329(7465).

(45) Kalliomaki M, Salminen S, Arvilommi H, Kero P, Koskinen P, Isolauri E. Probiotics in primary prevention of atopic disease: a randomised placebo-controlled trial. [see comments]. Lancet 2001; 357(9262):1076-1079.

(46) Mardh PA, Rodrigues AG, Genc M, Novikova N, Martinez-de-Oliveira J, Guaschino S. Facts and myths on recurrent vulvovaginal candidosis--a review on epidemiology, clinical manifestations, diagnosis, pathogenesis and therapy. [Review] [189 refs]. International journal of STD & AIDS 2002; 13(8):522-539.

(47) White DJ, Vanthuyne A, Wood PM, Ayres JG. Zafirlukast for severe recurrent vulvovaginal candidiasis: an open label pilot study. Sexually transmitted infections 2004; 80(3).

(48) Ergin A, Arikan S. Comparison of microdilution and disc diffusion methods in assessing the in vitro activity of fluconazole and Melaleuca alternifolia tea tree oil against vaginal Candida isolates. Journal of chemotherapy (Florence Italy) 2002; 14(5):465-472.

(49) Hammer KA, Carson CF, Riley TV. In-vitro activity of essential oils, in particular Melaleuca alternifolia (tea tree) oil and tea tree oil products, against Candida spp. J Antimicrob Chemother 1998; 42(5):591-595.

(50) Hammer KA, Carson CF, Riley TV. Antifungal effects of Melaleuca alternifolia (tea tree) oil and its components on Candida albicans, Candida glabrata and Saccharomyces cerevisiae. J Antimicrob Chemother 2004; 53(6):1081-1085.

(51) Crawford G, Sciacca J, James W. Tea tree oil: cutaneous effects of the extracted oil of Melaleuca alternifolia. Dermatitis : contact atopic occupational drug : official journal ofthe American Contact Dermatitis Society North American ContactDermatitis Group 2004; 15(2):59-66.

(52) Sobel JD, Kapernick PS, Zervos M, Reed BD, Hooton T, Soper D et al. Treatment of complicated Candida vaginitis: comparison of single and sequential doses of fluconazole. American Journal of Obstetrics & Gynecology 2001; 185(2):363-369.

(53) Sobel JD, Brooker D, Stein GE, Thomason JL, Wermeling DP, Bradley B et al. Single oral dose fluconazole compared with conventional clotrimazole topical therapy of Candida vaginitis. Fluconazole Vaginitis Study Group. American Journal of Obstetrics & Gynecology 1995; 172(4 Pt 1):1263-1268.

(54) Bohannon NJ. Treatment of vulvovaginal candidiasis in patients with diabetes. [Review] [62 refs]. Diabetes care 1998; 21(3):451-456.

(55) Goswami D, Goswami R, Banerjee U, Dadhwal V, Miglani S, Lattif AA et al. Pattern of Candida species isolated from patients with diabetes mellitus and vulvovaginal candidiasis and their response to single dose oral fluconazole therapy. The Journal of infection 2006; 52(2).

(56) Ray D, Goswami R, Banerjee U, Dadhwal V, Goswami D, Mandal P et al. Prevalence of Candida glabrata and Its Response to Boric Acid Vaginal Suppositories in Comparison With Oral Fluconazole in Patients With Diabetes and Vulvovaginal Candidiasis. Diabetes care 2007; 30(2).

(57) Duerr A, Heilig CM, Meikle SF, Cu US, Klein RS, Rompalo A et al. Incident and persistent vulvovaginal candidiasis among human immunodeficiency virus-infected women: Risk factors and severity. Obstetrics and gynecology 2003; 101(3).

(58) Sobel J. Vulvovaginal candidiasis: a comparison of HIV-positive and -negative women. International journal of STD & AIDS 2002; 13(6):358-362.

(59) Sobel J, Chaim W, Nagappan V, Leaman D. Treatment of vaginitis caused by Candida glabrata: use of topical boric acid and flucytosine. American journal of obstetrics and gynecology 2003; 189(5):1297-1300.

(60) Singh S, Sobel J, Bhargava P, Boikov D, Vazquez J. Vaginitis due to Candida krusei: epidemiology, clinical aspects, and therapy. Clinical infectious diseases : an official publication of theInfectious Diseases Society of America 2002; 35(9):1066-1070.

(61) Phillips A. Treatment of non-albicans Candida vaginitis with amphotericin B vaginal suppositories. American journal of obstetrics and gynecology 2005; 192(6):2009-2012.

(62) Sobel JD, Chaim W. Treatment of Torulopsis glabrata vaginitis: retrospective review of boric acid therapy. Clinical Infectious Diseases 1997; 24(4):649-652.

(63) Guaschino S, De Seta F, Sartore A, Ricci G, De Santo D, Piccoli M et al. Efficacy of maintenance therapy with topical boric acid in comparison with oral itraconazole in the treatment of recurrent vulvovaginal candidiasis. American Journal of Obstetrics & Gynecology 2001; 184(4):598-602.

(64) Acs N, Bβnhidy F, Puh≤ E, Czeizel AE. Teratogenic effects of vaginal boric acid treatment during pregnancy. International journal of gynaecology and obstetrics: the officialorgan of the International Federation of Gynaecology and Obstetrics 2006; 93(1):55-56.

(65) White DJ, Habib AR, Vanthuyne A, Langford S, Symonds M. Combined topical flucytosine and amphotericin B for refractory vaginal Candida glabrata infections. Sexually transmitted infections 2001; 77(3):212-213.

Question: 1 of 23

A 29-year-old junior doctor comes to the Emergency Department complaining of a severe headache and neck stiffness. He has had mild diarrhoea over the past few days, and some coryzal symptoms. On examination his BP is 155/82, his pulse is 85 and regular and his temperature is 37.8℃. He has signs consistent with severe meningism but there are no skin rashes or other signs of vasculitis.

Investigations:

Haemoglobin	13.8 g/dl	(13.5-17.7)
White cells	8.9 x 10^9/l	(4-11)
Platelet	183 x 10^9/l	(150-400)
Sodium	141 mmol/	(135-146)
Potassium	4.4 mmol/l	(3.5-5)
Creatinine	92 micromol/l	(79-118)

Lumbar puncture - lymphocytosis, slightly raised protein, normal glucose

Which of the following is the most likely diagnosis?

(Please select 1 option)

- **A** Cytomegalovirus meningitis
- **B** Enterovirus meningitis
- **C** Herpes simplex encephalitis
- **D** Meningococcal meningitis
- **E** Subarachnoid haemorrhage

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 23 mins 22 secs

Question: 10 of 23

A 17-year-old presents to the emergency department with facial and periorbital oedema. This is the third episode over the past two years, and on each of the previous two occasions the problem has been treated with oral corticosteroids.

On examination he has periorbital and bilateral lower limb pitting oedema. His BP is 125/72 mmHg, pulse is 72 and regular. He has no significant findings on auscultation of the chest.

Investigations show:

Haemoglobin	12.5 g/dl	(13.5-17.7)
White cell count	5.0 x 10^9/l	(4-11)
Platelets	260 x 10^9/l	(150-400)
Serum sodium	138 mmol/l	(135-146)
Serum potassium	4.2 mmol/l	(3.5-5)
Creatinine	110 µmol/l	(79-118)
Albumin	24 g/l	(35-50)
Urine	Protein +++	

Which of the following is the most appropriate initial way to treat him?

(Please select 1 option)

- ○ Admit for methylprednisolone and cyclophosphamide
- ○ Observe

two years, and on each of the previous two occasions the problem has been treated with oral corticosteroids.

On examination he has periorbital and bilateral lower limb pitting oedema. His BP is 125/72 mmHg, pulse is 72 and regular. He has no significant findings on auscultation of the chest.

Investigations show:

Haemoglobin	12.5 g/dl	(13.5-17.7)
White cell count	5.0 x 10^9/l	(4-11)
Platelets	260 x 10^9/l	(150-400)
Serum sodium	138 mmol/l	(135-146)
Serum potassium	4.2 mmol/l	(3.5-5)
Creatinine	110 µmol/l	(79-118)
Albumin	24 g/l	(35-50)
Urine	Protein +++	

Which of the following is the most appropriate initial way to treat him?

(Please select 1 option)

- ○ Admit for methylprednisolone and cyclophosphamide
- ○ Observe
- ○ Prednisolone 10 mg/day for six weeks
- ○ Prednisolone 60 mg/day for six weeks
- ○ Trial of ramipril

Serum sodium	138 mmol/l	(135-146)
Serum potassium	4.2 mmol/l	(3.5-5)
Creatinine	110 µmol/l	(79-118)
Albumin	24 g/l	(35-50)
Urine	Protein +++	

Which of the following is the most appropriate initial way to treat him?

(Please select 1 option)

- ○ Admit for methylprednisolone and cyclophosphamide
- ○ Observe
- ○ Prednisolone 10 mg/day for six weeks
- ◉ Prednisolone 60 mg/day for six weeks ✓ Correct
- ○ Trial of ramipril

The repeated cycles of corticosteroid responsive nephrotic syndrome suggest that this individual has minimal change disease. Therefore he is likely once again to respond to high dose prednisolone, with a tapering dose after the first six weeks of therapy.

In patients who fail to respond initially to corticosteroids, cyclophosphamide and chlorambucil are optional second line agents.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

A 52-year-old man has a history of hypertension, managed with amlodipine and indapamide. His GP recently tried to commence ramipril, but had to curtail this as his creatinine rose from 129 to 194 after one week of therapy.

He smokes 20 cigarettes per day and is a vasculopath having suffered a transient ischaemic attack (TIA) one year earlier.

On examination in the clinic his BP is 155/92 mmHg, pulse is regular at 80 and a left carotid bruit is audible.

Investigations:

Haemoglobin	12.0 g/dl	(13.5-17.7)
White cell count	6.0 x 10^9/l	(4-11)
Platelets	288 x 10^9/l	(150-400)
Serum sodium	140 mmol/l	(135-146)
Serum potassium	4.0 mmol/l	(3.5-5)
Creatinine	122 µmol/l	(79-118)
Ultrasound scan	Right kidney smaller than the left	
Renal MRA	Suggestive of 80% right renal artery stenosis	

Which of the following is the most appropriate next step in his management?

(Please select 1 option)

- **A** Add bisoprolol to his anti-hypertensive regimen
- **B** Re-introduce low dose ramipril to his regimen
- **C** Refer for urgent angioplasty and stenting
- **D** Refer for vascular surgery
- **E** Trial valsartan as an alternative to ACE inhibition

Creatinine	122 µmol/l	(79-118)
Ultrasound scan	Right kidney smaller than the left	
Renal MRA	Suggestive of 80% right renal artery stenosis	

Which of the following is the most appropriate next step in his management?

(Please select 1 option)

- **A** Add bisoprolol to his anti-hypertensive regimen ← This is the correct answer
- **B** Re-introduce low dose ramipril to his regimen
- **C** Refer for urgent angioplasty and stenting ✕ Incorrect answer selected
- **D** Refer for vascular surgery
- **E** Trial valsartan as an alternative to ACE inhibition

There is considerable debate about the success of angioplasty/stenting or vascular surgery in patients with atherosclerotic renal artery stenosis and difficult to manage hypertension. The most recent study by Bax et al showed no difference in outcomes between those patients managed with medical therapy versus stenting.

Other studies suggest that complications of stenting or angioplasty outweigh any benefits versus medical therapy.

There is no evidence to support re-introducing ACE inhibition or substituting an angiotensin receptor blocker (ARB) with respect to potential outcomes. As such, in the first instance, response to increased medical therapy for blood pressure should be assessed.

Reference:
Bax L, Woittiez AJ, Kouwenberg HJ et al. (2009) Stent placement in patients with atherosclerotic renal artery stenosis and impaired renal function: a randomized trial. Ann Intern Med. 150(12): 840-848

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Question: 12 of 23

A 17-year-old girl, who works at a petting zoo, presents with a headache and vomiting to the emergency department. Apparently she suffered a severe diarrhoeal illness which began a few days ago, and she is now passing diarrhoea mixed with blood and mucus.

She has no past history of note, and her only medication is the oral contraceptive pill.

On examination she looks unwell, her BP is 155/92 mmHg and she is pyrexial at 38.2°C. Her abdomen is soft and diffusely tender with very active bowel sounds.

Investigations reveal:

Haemoglobin	10.0 g/dl	(11.5-16.5)
White cell count	11.6 x 10^9/l	(4-11)
Platelets	50 x 10^9/l	(150-400)
Serum sodium	139 mmol/l	(135-146)
Serum potassium	6.0 mmol/l	(3.5-5)
Creatinine	295 µmol/l	(79-118)

What do expect to find on the blood film?

(Please select 1 option)

- **A** Decreased reticulocytes
- **B** Increased lymphocytes
- **C** Increased ghost cells
- **D** Increased schistocytes
- **E** Increased spherocytes

Haemoglobin	10.0 g/dl	(11.5-16.5)
White cell count	11.6 x 10^9/l	(4-11)
Platelets	50 x 10^9/l	(150-400)
Serum sodium	139 mmol/l	(135-146)
Serum potassium	6.0 mmol/l	(3.5-5)
Creatinine	295 µmol/l	(79-118)

What do expect to find on the blood film?

(Please select 1 option)

- A Decreased reticulocytes
- B Increased lymphocytes
- C Increased ghost cells
- **D** Increased schistocytes ✓ Correct
- E Increased spherocytes

This patient has a history consistent with *Escherichia coli* 157 infection, and a picture of haemolytic uraemic syndrome (HUS).

The hallmark of HUS is the appearance of schistocytes (fragmented, deformed, irregular, or helmet shaped red cells) on the blood film. Despite the low platelet count, petechiae and purpura are rarely seen, although GI bleeding is often noted.

Treatment is generally supportive. Non-steroidal anti-inflammatory drugs and anti-diarrhoeals should be avoided, and there is no evidence for the use of antibiotics in the condition.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Question: 13 of 23

A 67-year-old man with chronic renal failure, who uses peritoneal dialysis, presents to the renal ward with a cloudy bag. This is his first episode of continuous ambulatory peritoneal dialysis (CAPD) peritonitis in over two years of dialysing.

He has type 1 diabetes, which precipitated his renal impairment. On examination, he is pyrexial at 38.2°C. His abdomen is diffusely tender, although he has bowel sounds on auscultation.

Investigations showed:

Haemoglobin	10.2 g/dl	(13.5-17.7)
White cell count	13.6 x 10^9/l	(4-11)
Platelets	270 x 10^9/l	(150-400)
Serum sodium	138 mmol/l	(135-146)
Serum potassium	4.3 mmol/l	(3.5-5)
Creatinine	346 µmol/l	(79-118)
Dialysis fluid	>100 white cells per mm^3	

Which of the following is the most likely infecting organism?

(Please select 1 option)

- **A** *B. fragilis*
- **B** *Bacteroides spp*
- **C** *P. aeruginosa*
- **D** *S. aureus*
- **E** *S. pyogenes*

White cell count	13.6 x 10^9/l	(4-11)
Platelets	270 x 10^9/l	(150-400)
Serum sodium	138 mmol/l	(135-146)
Serum potassium	4.3 mmol/l	(3.5-5)
Creatinine	346 µmol/l	(79-118)
Dialysis fluid	>100 white cells per mm^3	

Which of the following is the most likely infecting organism?

(Please select 1 option)

- A *B. fragilis*
- B *Bacteroides spp*
- C *P. aeruginosa*
- D *S. aureus* ✓ Correct
- E *S. pyogenes*

S. aureus and *S. epidermidis* are the two commonest pathogens identified in cases of CAPD peritonitis.

Various treatment regimes exist, but the majority involve intraperitoneal vancomycin and an oral quinolone. Once culture results are received, the regime can then be tailored appropriately.

The key to avoiding long term complications of CAPD peritonitis is prompt intervention to avoid chronic colonisation of the CAPD catheter and adhesion formation, which prevents adequate fluid exchange.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Question: 14 of 23

A 50-year-old man is admitted to hospital with a third attack of renal stones in the last six months. He suffers from Crohn's disease and has previously had a limited small bowel resection, but his disease is now quiescent.

On examination his BP is 115/72 mmHg, his BMI is 19.5 kg/m^2, and he has a midline scar consistent with a previous laparotomy.

Investigations:

Haemoglobin	12.0 g/dl	(13.5-17.7)
White cell count	5.9 x 10^9/l	(4-11)
Platelets	172 x 10^9/l	(150-400)
Serum sodium	139 mmol/l	(135-146)
Serum potassium	3.9 mmol/l	(3.5-5)
Creatinine	133 µmol/l	(79-118)
24 hour urinary oxalate excretion	Increased	

Which of the following is likely to be the most effective and appropriate intervention?

(Please select 1 option)

- **A** Increase fluid intake
- **B** Reduce dietary calcium intake
- **C** Reduce intake of offal
- **D** Start bendroflumethiazide
- **E** Start furosemide

Haemoglobin	12.0 g/dl	(13.5-17.7)
White cell count	5.9 x 10^9/l	(4-11)
Platelets	172 x 10^9/l	(150-400)
Serum sodium	139 mmol/l	(135-146)
Serum potassium	3.9 mmol/l	(3.5-5)
Creatinine	133 µmol/l	(79-118)
24 hour urinary oxalate excretion	Increased	

Which of the following is likely to be the most effective and appropriate intervention?

(Please select 1 option)

- **A** Increase fluid intake ← This is the correct answer
- **B** Reduce dietary calcium intake
- **C** Reduce intake of offal
- **D** Start bendroflumethiazide ✗ Incorrect answer selected
- **E** Start furosemide

Reducing intake of offal is most helpful at reducing urate excretion; foods such as chocolate, rhubarb and nuts are high in oxalate. One contributor to this patient's increased oxalate excretion is undoubtedly his partial small bowel resection, and increasing dietary calcium intake decreases urinary oxalate excretion.

Therefore the most effective and appropriate intervention from those given is to increase his oral fluid intake significantly.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Question: 15 of 23

A 21-year-old woman presents to the clinic after her fifth episode of nephrolithiasis in the past three years. She tells you that both her brother and father also suffer from renal stones.

On examination her BP is 135/80 mmHg. General physical examination is entirely normal.

Investigations show:

Haemoglobin	12.0 g/dl	(11.5-16.5)
White cell count	6.4 x 10^9/l	(4-11)
Platelets	272 x 10^9/l	(150-400)
Serum sodium	138 mmol/l	(135-146)
Serum potassium	4.1 mmol/l	(3.5-5)
Creatinine	85 µmol/l	(79-118)
Calcium	2.89 mmol/l	(2.20-2.67)
PTH	Upper limit of normal range	

Which of the following is the most likely diagnosis?

(Please select 1 option)

- **A** Familial hypocalciuric hypercalcaemia
- **B** Primary hyperparathyroidism
- **C** PTHrP levels increased due to underlying malignancy
- **D** Secondary hyperparathyroidism
- **E** Tertiary hyperparathyroidism

Platelets	272 x 10^9/l	(150-400)
Serum sodium	138 mmol/l	(135-146)
Serum potassium	4.1 mmol/l	(3.5-5)
Creatinine	85 µmol/l	(79-118)
Calcium	2.89 mmol/l	(2.20-2.67)
PTH	Upper limit of normal range	

Which of the following is the most likely diagnosis?

(Please select 1 option)

- **A** Familial hypocalciuric hypercalcaemia ✓ Correct
- **B** Primary hyperparathyroidism
- **C** PTHrP levels increased due to underlying malignancy
- **D** Secondary hyperparathyroidism
- **E** Tertiary hyperparathyroidism

The strong family history points towards this autosomal dominant condition as being the most likely diagnosis. Most often it leads to asymptomatic elevated levels of serum calcium, although some patients with the condition may suffer recurrent episodes of renal stones.

The inherited condition is caused by a mutation in the calcium sensing receptor (CASR) gene, which encodes a calcium-sensing receptor expressed in the parathyroid gland and kidneys. The perceived lack of calcium levels by the parathyroid leads to normal to high levels of parathyroid hormone and therefore hypercalcaemia.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

A 62-year-old man attends a clinic complaining of progressive peripheral oedema, which has got to the stage where by the end of the day he is hardly able to wear his shoes. He has a past history of hypertension which is managed with amlodipine, but nil else of note.

On examination his BP is 155/85 mmHg. His pulse is 78 and regular. His heart sounds are normal and his chest is clear. He has gross pitting oedema to mid shin on both lower limbs.

Haemoglobin	13.9 g/dl	(13.5-17.7)
White cell count	7.6 x 10^9/L	(4-11)
Platelets	290 x 10^9/L	(150-400)
Serum sodium	140 mmol/l	(135-146)
Serum potassium	4.0 mmol/l	(3.5-5)
Creatinine	135 µmol/l	(79-118)
Albumin	24 g/l	(35-50)
Urinary protein	3.5 g/24 hr	

Renal biopsy: Thickened renal capillary walls seen on biopsy, but with patent lumina.

Which of the following treatments is most likely to affect this patient's prognosis?

(Please select 1 option)

- **A** Cyclophosphamide
- **B** Prednisolone
- **C** Ramipril
- **D** Rituximab
- **E** Simvastatin

Serum potassium	4.0 mmol/l	(3.5-5)
Creatinine	135 µmol/l	(79-118)
Albumin	24 g/l	(35-50)
Urinary protein	3.5 g/24 hr	

Renal biopsy: Thickened renal capillary walls seen on biopsy, but with patent lumina.

Which of the following treatments is most likely to affect this patient's prognosis?

(Please select 1 option)

- **A** Cyclophosphamide
- **B** Prednisolone ✕ Incorrect answer selected
- **C** Ramipril ← This is the correct answer
- **D** Rituximab
- **E** Simvastatin

Corticosteroids alone are ineffective in the treatment of membranous nephropathy. A study of alternating monthly treatment with chlorambucil and steroids did suggest some benefit but this is open to debate and has been disputed in a number of review articles.

Rituximab, a B-cell depleting anti-CD20 chimeric monoclonal antibody has shown some benefit in a small proof of concept study, although it is unlikely to be appropriate for widespread use.

In contrast, ramipril is proven to affect both proteinuria and hypertension in patients with a diagnosis of membranous nephropathy, and is therefore the backbone of therapy for this condition.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Question: 17 of 23

A 49-year-old owner of a pub is admitted in a confused and agitated state. He has recently tried to stop drinking and according to his wife it is 24 hours since his last drink.

When you see him his BP is elevated at 155/90 mmHg, pulse at 90, and he looks agitated. There are signs of chronic liver disease on physical examination. He is trying to pull the sheets over his head as he tells you he can see a large dog in the next bed.

Investigations show

Haemoglobin	10.9 g/dl	(13.5-18)
White cell count	8.2 x 10^9/l	(4-10)
Platelets	190 x 10^9/l	(150-400)
Sodium	139 mmol/l	(134-143)
Potassium	4.3 mmol/l	(3.5-5)
Creatinine	110 µmol/l	(60-120)
Glucose	4.5 mmol/l	(3.6-5.8)
ALT	190 IU/l	(5-60)

Which of the following is the most likely diagnosis?

(Please select 1 option)

- ○ Alcoholic hallucinosis
- ○ Delirium tremens
- ○ Hypomania
- ○ Schizophrenia
- ○ Wernicke's encephalopathy

Sodium	139 mmol/l	(134-143)
Potassium	4.3 mmol/l	(3.5-5)
Creatinine	110 µmol/l	(60-120)
Glucose	4.5 mmol/l	(3.6-5.8)
ALT	190 IU/l	(5-60)

Which of the following is the most likely diagnosis?

(Please select 1 option)

- Alcoholic hallucinosis ← This is the correct answer
- Delirium tremens ✕ Incorrect answer selected
- Hypomania
- Schizophrenia
- Wernicke's encephalopathy

As many as 25% of habitual alcohol drinkers may suffer from alcoholic hallucinosis when they withdraw from alcohol for 24 hours or longer. Hallucinations are usually visual or tactile, but may be auditory and persecutory.

Delirium tremens is associated with a much more profound disorientation and agitation, with severe autonomic dysfunction and cardiovascular collapse. It may well be preceded by alcohol withdrawal seizures.

Management of this patient involves B vitamin replacement with a preparation such as pabrinex, and the use of appropriate withdrawal medication.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 46 mins 59 secs

Question: 18 of 23

Which of the following are characteristic electrocardiogram (ECG) features of hypokalaemia?

(Please select 1 option)

- ○ Flattened p waves
- ○ ST elevation
- ○ U waves
- ○ Ventricular tachycardia
- ○ Wide QRS

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 47 mins 48 secs

Question: 18 of 23

Which of the following are characteristic electrocardiogram (ECG) features of hypokalaemia?

(Please select 1 option)

○	Flattened p waves
○	ST elevation
◉	U waves ✓ Correct
○	Ventricular tachycardia
○	Wide QRS

U waves are characteristic features of hypokalaemia.

Further ECG features of hypokalaemia include ST depression, low amplitude T waves and ventricular fibrillation.

Ventricular tachycardia is thought to be exceedingly rare in hypokalaemia.

The remaining answers are ECG findings typical of hyperkalaemia, together with absent P waves, tall tented t waves, asystole and ventricular fibrillation.

Next question

Tag Question
Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 47 mins 48 secs

Question: 19 of 23

A 32-year-old female smoker presents with acute severe asthma. The SaO2 are 80% on 15 L of oxygen and the pO2 is 8.2kPa (10.5-13).

There is widespread expiratory wheeze throughout the chest. She is given IV hydrocortisone, 100% oxygen and 5 mg of nebulised salbutamol.

What is the next step in your management?

(Please select 1 option)

- IV augmentin
- IV magnesium
- IV potassium
- IV theophylline
- Oral prednisolone

Submit answer | Skip question | Remove Tag | Remove question

Dashboard
Questions
Scores
Community
Help
Shop

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

(Please select 1 option)

○	IV augmentin
○	IV magnesium ← This is the correct answer
○	IV potassium
◉	IV theophylline ✕ Incorrect answer selected
○	Oral prednisolone

This question focuses on acute treatment of asthma.

Your initial approach should be SOS - salbutamol, oxygen and steroids intravenously (IV).

In the meantime a chest x-ray (CXR) should be organised to rule out pneumothorax.

You should then consider further efforts to treat bronchoconstriction - a silent chest, or a tiring patient should suggest ITU review.

The recommended dose of magnesium is 2 g over 30 minutes. The mechanism by which it has its effect is not fully understood, but it is thought that low magnesium levels in bronchial smooth muscle favour bronchoconstriction.

IV theophylline may be considered, but magnesium would be higher on the list.

IV antibiotic may be indicated, but your initial focus should be promoting bronchodilation.

IV potassium may be required as the beta agonists push down the potassium.

Oral prednisolone can wait, as you have already given IV hydrocortisone as part of your SOS approach.

Next question

Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Shop

Haemoglobin	13.8 g/dl	(13.5-17.7)
White cells	8.9 x 10^9/l	(4-11)
Platelet	183 x 10^9/l	(150-400)
Sodium	141 mmol/	(135-146)
Potassium	4.4 mmol/l	(3.5-5)
Creatinine	92 micromol/l	(79-118)

Lumbar puncture - lymphocytosis, slightly raised protein, normal glucose

Which of the following is the most likely diagnosis?

(Please select 1 option)

- A Cytomegalovirus meningitis
- **B** Enterovirus meningitis ✓ Correct
- C Herpes simplex encephalitis
- D Meningococcal meningitis
- E Subarachnoid haemorrhage

The answer is B), enterovirus meningitis. Enterovirus is the commonest cause of viral meningitis in the adult population. The corizal symptoms coupled with a mild diarrhoeal illness fit with this picture, as do the lumbar puncture findings. Management of viral meningitis is conservative, with adequate hydration and analgesia.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 4 mins 29 secs

Question: 2 of 23

A 42-year-old woman presents to the clinic with a chronic cough. Which of the following features would increase the suspicion that she is suffering from asthma?

(Please select 1 option)

- **A** Associated dizziness
- **B** Chronic cough without wheeze
- **C** Symptoms in response to exercise
- **D** Symptoms corresponding with a cold
- **E** Voice disturbance

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 49 mins 21 secs

Question: 20 of 23

A 27-year-old lady presents with generalised oedema of five months duration.

Investigations reveal proteinuria (5.5 g/day), hypoproteinaemia and hypercholesterolaemia, urea 10 mmol/L (2.5-7.5) and creatinine 200 mol/L (60-110). Renal biopsy confirms membranous glomerulonephritis.

What will be the most appropriate management to get remission?

(Please select 1 option)

- Azathiaprine
- Cyclophosphamide plus methylprednisolone
- Cyclosporin A
- Methylprednisolone
- Protein restriction

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

A 27-year-old lady presents with generalised oedema of five months duration.

Investigations reveal proteinuria (5.5 g/day), hypoproteinaemia and hypercholesterolaemia, urea 10 mmol/L (2.5-7.5) and creatinine 200 mol/L (60-110). Renal biopsy confirms membranous glomerulonephritis.

What will be the most appropriate management to get remission?

(Please select 1 option)

○	Azathiaprine
◉	Cyclophosphamide plus methylprednisolone ✓ Correct
○	Cyclosporin A
○	Methylprednisolone
○	Protein restriction

The twin aims of treating membranous nephropathy are

- First to induce a remission of the nephrotic syndrome and
- Second to prevent the development of end stage renal failure.

A meta-analysis of four randomised controlled studies comparing treatments of membranous nephropathy showed that regimes comprising chlorambucil or cyclophosphamide, either alone or with steroids, were more effective than symptomatic treatment or treatment with steroids alone in inducing remission of the nephrotic syndrome.

A small randomised controlled study of 17 patients with a persistent nephrotic syndrome and declining renal function suggested that ciclosporin A slowed the rate of decline of renal function: this requires confirmation in a larger trial.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 51 mins 22 secs

Question: 21 of 23

A 31-year-old female in her third pregnancy is receiving low molecular weight heparin (LMWH) at treatment doses due to a pulmonary embolism three months prior to conception. She is currently at 31 weeks gestation.

All fetal scans have been normal, and her blood pressure is 126/80 mmHg in the left lateral position.

Which of the following statements is correct?

(Please select 1 option)

- Breastfeeding is not advised
- Clexane treatment needs no monitoring in pregnancy
- It is safe for her to receive NSAIDs perinatally
- Prothrombin time is an indicator of anti-factor Xa activity
- The dose of Clexane should be increased in the third trimester

Submit answer | Skip question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Question: 21 of 23

A 31-year-old female in her third pregnancy is receiving low molecular weight heparin (LMWH) at treatment doses due to a pulmonary embolism three months prior to conception. She is currently at 31 weeks gestation.

All fetal scans have been normal, and her blood pressure is 126/80 mmHg in the left lateral position.

Which of the following statements is correct?

(Please select 1 option)

○	Breastfeeding is not advised ← This is the correct answer
○	Clexane treatment needs no monitoring in pregnancy
○	It is safe for her to receive NSAIDs perinatally
○	Prothrombin time is an indicator of anti-factor Xa activity
◉	The dose of Clexane should be increased in the third trimester ✕ Incorrect answer selected

There is no recommendation that the dose of LMWH should be increased in the third trimester.

Increases in prothrombin time and activated clotting time (ACT) are not linearly correlated with increasing LMWH anti-thrombotic activity and therefore are unsuitable and unreliable for monitoring LMWH activity.

Nonsteroidal antiinflammatory drug (NSAID) treatment increases the risk of haemorrhage in both mother and fetus.

It is not known whether unchanged enoxaparin sodium is excreted in human breast milk. The oral absorption of enoxaparin sodium is unlikely. However, as a precaution, lactating mothers receiving enoxaparin sodium should be advised to avoid breast feeding.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 53 mins 5 secs

Question: 22 of 23

A 40-year-old male presents to casualty with weakness and parasthesiae of the right arm and leg. The symptoms developed 12 hours after the onset of a piercing left sided headache. There is no neck stiffness, but there is a pain in the left side of the neck and occiput. Kernig's sign is negative. The patient is afebrile, and blood results are normal.

What is the investigation of choice?

(Please select 1 option)

- Contrast arteriography
- CT head
- Duplex scanning of the neck vessels
- Lumbar puncture
- MRI brain

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

A 40-year-old male presents to casualty with weakness and parasthesiae of the right arm and leg. The symptoms developed 12 hours after the onset of a piercing left sided headache. There is no neck stiffness, but there is a pain in the left side of the neck and occiput. Kernig's sign is negative. The patient is afebrile, and blood results are normal.

What is the investigation of choice?

(Please select 1 option)

○	Contrast arteriography ← This is the correct answer
◉	CT head ✕ Incorrect answer selected
○	Duplex scanning of the neck vessels
○	Lumbar puncture
○	MRI brain

Ischaemic neurological features (transient or completed strokes) are found in 30-80% of presenting patients presenting with carotid artery dissection. Pulsatile tinnitus is common, as well as syncope and amaurosis fugax. Headache is commonly ipsilateral to the side of the carotid dissection, and recurrence of the headache suggests extension or recurrence of the dissection. The most accurate study and the current gold standard for diagnosis of carotid artery dissection, contrast arteriography should be strongly considered if neurological findings are incompatible with the findings of CT head, there is mono or hemiparesis with normal mental state, signs or history of major cervical trauma with abnormal neurology, or basilar skull fracture in a patient with altered mental status. In the absence of arteriography, Duplex scanning or MRI with MRA may be considered the next best tests. Limitations of duplex scanning include difficulties of scanning the distal internal carotid artery, detecting emboli, and evaluating intracranial arteries. The combination of MRI and MRA is more reliable in detecting dissection than either modality alone. Lumbar puncture results may be misleading, as xanthochromia may occur when a haematoma propagates. This rare finding may lead to a diagnosis of subarachnoid hemorrhage and failure to perform further carotid workup.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 54 mins 35 secs

Question: 23 of 23

A patient is planning to travel through the southern states of America, but is worried about West Nile virus.

Which of the following statements regarding West Nile virus is correct?

(Please select 1 option)

- Infection is non-fatal
- Is a member of the arborvirus family
- May be associated with poliomyelitis-like paralysis
- Transplacental transmission does not occur
- Treatment with interferon is effective in West Nile virus encephalitis

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 55 mins 32 secs

Question: 23 of 23

A patient is planning to travel through the southern states of America, but is worried about West Nile virus.

Which of the following statements regarding West Nile virus is correct?

(Please select 1 option)

○	Infection is non-fatal
○	Is a member of the arborvirus family
◉	May be associated with poliomyelitis-like paralysis ✓ Correct
○	Transplacental transmission does not occur
○	Treatment with interferon is effective in West Nile virus encephalitis

Neurological manifestations of West Nile virus include

- A poliomyelitis-like paralysis
- Seizures
- A parkinsonian movement disorder.

West Nile virus is a *Flavivirus* of the Japanese encephalitis family and transplacental transmission has been reported.

In 2003 there were 276 deaths attributed to West Nile virus. Interestingly, West Nile Virus is endemic in the avian population. The deaths of large numbers of birds in an area may thus herald an imminent epidemic of West Nile virus.

Finish | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 5 mins 52 secs

Question: 2 of 23

A 42-year-old woman presents to the clinic with a chronic cough. Which of the following features would increase the suspicion that she is suffering from asthma?

(Please select 1 option)

- **A** Associated dizziness
- **B** Chronic cough without wheeze
- **C** Symptoms in response to exercise ← This is the correct answer
- **D** Symptoms corresponding with a cold
- **E** Voice disturbance ✕ Incorrect answer selected

The answer is C), symptoms in response to exercise. Guidelines from BTS/SIGN on the diagnosis of asthma suggest that the presence of wheeze, breathlessness, chest tightness or cough, particularly if symptoms are worse at night or in the early morning, after exercise, allergy exposure or cold air, are suggestive of the diagnosis. A family history of atopy or asthma, personal history of atopy, widespread wheeze, low FEV1 or PEFR also support the diagnosis. Dizziness, light headedness, voice disturbance and chronic cough without wheeze do not support a diagnosis of asthma.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 5 mins 52 secs

Question: 3 of 23

A 36-year-old single woman with a history of asthma comes to the clinic complaining of symptoms of indigestion.

She uses a steroid inhaler and on examination of her oropharynx you can see obvious evidence of candidiasis. You send her for an endoscopy, which unfortunately reveals extensive oesophageal candidiasis.

Which of the following tests would be most important to consider in this patient?

(Please select 1 option)

- **A** CD4 count
- **B** Complement testing
- **C** Fasting blood glucose
- **D** HIV antibody testing
- **E** Immunoglobulin testing

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 6 mins 47 secs

Question: 3 of 23

A 36-year-old single woman with a history of asthma comes to the clinic complaining of symptoms of indigestion.

She uses a steroid inhaler and on examination of her oropharynx you can see obvious evidence of candidiasis. You send her for an endoscopy, which unfortunately reveals extensive oesophageal candidiasis.

Which of the following tests would be most important to consider in this patient?

(Please select 1 option)

○	**A** CD4 count
○	**B** Complement testing
○	**C** Fasting blood glucose
◉	**D** HIV antibody testing ✓ Correct
○	**E** Immunoglobulin testing

The answer is D, HIV antibody testing.

Whilst candidiasis affecting the oropharynx may be a result of poor inhaler technique and deposition of steroid powder within the mouth, it does not usually result in oesophageal candidiasis. The other possible cause of recurrent oral and genital candida infection is diabetes mellitus, although again this would not normally lead to oesophageal disease.

In the case of this patient, immunocompromise should be suspected and HIV considered, with appropriate pre-test counselling.

Next question | Tag Question | Remove question

http://my.onexamination.com/Assessment/Questions.aspx

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 6 mins 47 secs

Question: 4 of 23

A 36-year-old single woman with a history of asthma comes to the clinic complaining of symptoms of indigestion. She uses a steroid inhaler and on examination of her oropharynx you can see obvious evidence of candidiasis. You send her for an endoscopy, which unfortunately reveals extensive oesophageal candidiasis.

Which of the following tests would be most important to consider in this patient?

(Please select 1 option)

- **A** CD4 count
- **B** Complement testing
- **C** Fasting blood glucose
- **D** HIV antibody testing
- **E** Immunoglobulin testing

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 7 mins 26 secs

Question: 4 of 23

A 36-year-old single woman with a history of asthma comes to the clinic complaining of symptoms of indigestion. She uses a steroid inhaler and on examination of her oropharynx you can see obvious evidence of candidiasis. You send her for an endoscopy, which unfortunately reveals extensive oesophageal candidiasis.

Which of the following tests would be most important to consider in this patient?

(Please select 1 option)

- A CD4 count
- B Complement testing
- C Fasting blood glucose
- **D** HIV antibody testing ✓ Correct
- E Immunoglobulin testing

The answer is D), HIV antibody testing. Whilst candidiasis affecting the oropharynx may be a result of poor inhaler technique and deposition of steroid powder within the mouth, it does not usually result in oesophageal candidiasis. The other possible cause of recurrent oral and genital candida infection is diabetes mellitus, although again this wouldn't normally lead to oesophageal disease. In the case of this patient, immunocompromise should be suspected and HIV considered, with appropriate pre-test counselling.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

A 20-year-old student comes to the clinic complaining of dysuria and minor scrotal swelling and pain. He has also noticed a purulent urethral discharge.

On examination his temperature is 37.5 C, his scrotum is mildly swollen and tender and you can express a mucopurulent discharge from his urethral meatus.

Investigations show:

Haemoglobin	13.9 g/dl	(13.5-17.7)
White cell count	8.8 x 10^9/l	(4-11)
Platelets	269 x 10^9/l	(150-400)
Serum sodium	141 mmol/l	(135-146)
Serum potassium	4.5 mmol/l	(3.5-5)
Creatinine	85 micromol/l	(79-118)
Urinary chlamydial antigen positive		

Which of the following is the most appropriate anti-microbial therapy for him?

(Please select 1 option)

- **A** Azithromycin 1 g as single dose
- **B** Ciprofloxacin 500 mg BD for 7 days
- **C** Minocycline 100 mg daily for 9 days
- **D** Norfloxacin 400 mg daily for 7 days
- **E** Penicillin V 500 mg BD for 7 days

Creatinine	85 micromol/l	(79-118)
Urinary chlamydial antigen positive		

Which of the following is the most appropriate anti-microbial therapy for him?

(Please select 1 option)

- **A** Azithromycin 1 g as single dose ✓ Correct
- **B** Ciprofloxacin 500 mg BD for 7 days
- **C** Minocycline 100 mg daily for 9 days
- **D** Norfloxacin 400 mg daily for 7 days
- **E** Penicillin V 500 mg BD for 7 days

The answer is A, azithromycin 1 g as a single dose.

In a student population where compliance may well be a problem, giving a single dose of antibiotics for the treatment of *Chlamydia* is the most sensible option.

Other options for treatment of *Chlamydia* include minocycline, although doxycycline causes less gastrointestinal disturbance. Ofloxacin 200 mg BD for seven days is also considered a potential option according to SIGN guidelines.

He should also be referred to the GUM clinic for screening for other sexually transmitted infections.

http://www.sign.ac.uk/guidelines/fulltext/42/section4.html

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

A 44-year-old man is brought to the hospital by his boyfriend.

Over the past few weeks he has complained of increasing headaches and nocturnal fevers. His boyfriend is now concerned that over the weekend he has taken to his bed and has become drowsy and confused.

On examination his temperature is 37.8°C and BP 150/90 mmHg. He has papilloedema and neck stiffness. He refuses to comply with most of the elements of neurological testing.

Investigations show:

Haemoglobin	11.9 g/dl	(13.5-17.7)
White cell count	9.7 x 10^9/l	(4-11)
Platelets	204 x 10^9/l	(150-400)
Serum Sodium	136 mmol/l	(135-146)
Serum Potassium	4.0 mmol/l	(3.5-5)
Creatinine	111 micromol/l	(79-118)
Glucose	6.7 mmol/l	(non fasting)
CSF	opening pressure 22cm water	turbid appearance
Glucose	6.5 mmol/l	india ink test positive
CT scan	Small ventricles but otherwise unremarkable	

Which of the following is the most likely diagnosis?

(Please select 1 option)

- **A** Cryptococcal meningitis
- **B** HIV dementia
- **C** HIV encephalopathy
- **D** Meningococcal meningitis
- **E** Tuberculous meningitis

CSF	opening pressure 22cm water	turbid appearance
Glucose	6.5 mmol/l	india ink test positive
CT scan	Small ventricles but otherwise unremarkable	

Which of the following is the most likely diagnosis?

(Please select 1 option)

- **A** Cryptococcal meningitis ← This is the correct answer
- **B** HIV dementia
- **C** HIV encephalopathy ✕ Incorrect answer selected
- **D** Meningococcal meningitis
- **E** Tuberculous meningitis

The answer is A, cryptococcal meningitis on a background of HIV infection.

The insidious onset seen here, coupled with signs of raised intracranial pressure, normal glucose on CSF sampling and positive india ink test are all strong pointers to the diagnosis of cryptococcal meningitis. India ink smears however are less sensitive and specific than CSF cryptococcal antigen test, which has a sensitivity of greater than 95%, but false negative tests can occur with a low organism burden.

MRI scanning is more sensitive than CT and may show low intensity lesions in the basal ganglia which enhance with gadolinium.

Treatment in this case would be with amphotericin B combined with flucytosine, although good results have also been seen with flucytosine and fluconazole combination therapy.

Despite aggressive intervention however, mortality is still high at around 6%.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd All rights reserved Terms and conditions Privacy policy

A 18-year-old student presents to the student health service with frank haematuria that begun some 48 hours after an upper respiratory tract infection.

On examination he is apyrexial, BP is 110/72 mmHg and pulse is 70. His chest is clear and his abdomen is soft and non-tender.

Investigations reveal:

Haemoglobin	14.0 g/dl	(13.5-17.7)
White cell count	8.0 x 10^9/l	(4-11)
Platelets	248 x 10^9/L	(150-400)
Serum sodium	138 mmol/l	(135-146)
Serum potassium	4.3 mmol/l	(3.5-5)
Creatinine	85 micromol/l	(79-118)
Urine blood +++		

Which of the following is the most appropriate way to manage him?

(Please select 1 option)

- **A** Methylprednisolone and cyclophosphamide
- **B** Observation
- **C** Prednisolone 60 mg/day
- **D** ACE inhibitor titrated to maximal tolerated dose
- **E** ACE inhibitor titrated to maximal tolerated dose and ARB in combination

Submit answer | Skip question | Tag Question | Remove question

Serum potassium	4.3 mmol/l	(3.5-5)
Creatinine	85 micromol/l	(79-118)
Urine blood +++		

Which of the following is the most appropriate way to manage him?

(Please select 1 option)

- **A** Methylprednisolone and cyclophosphamide
- **B** Observation ✓ Correct
- **C** Prednisolone 60 mg/day
- **D** ACE inhibitor titrated to maximal tolerated dose
- **E** ACE inhibitor titrated to maximal tolerated dose and ARB in combination

This patient almost certainly has IgA nephropathy, given his presentation with frank haematuria occurring in such close proximity to a recent upper respiratory tract infection.

The findings including normal blood pressure, normal creatinine and haematuria without proteinuria point towards a benign prognosis and for this reason he only requires regular monitoring rather than intervention with immunosuppressive agents.

Treatment with corticosteroids is usually reserved for those patients with hypertension and a rising creatinine.

Where there is significant hypertension +/- proteinuria, then ACE inhibitors are the first choice anti-hypertensive agent.

Post-streptococcus glomerulonephritis usually occurs one to three weeks after initial infection.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

A 50-year-old man is admitted to the hospital with a third attack of renal stones in the last six months.

He suffers from Crohn's disease and has previously had a limited small bowel resection, but his disease is now quiescent.

On examination his BP is 115/72 mmHg, his BMI is 19.5, he has a midline scar consistent with a previous laparotomy.

Investigations show:

Haemoglobin	12.0 g/dl	(11.5-16.5)
White cell count	6.4 x 10^9/l	(4-11)
Platelets	272 x 10^9/l	(150-400)
Serum sodium	138 mmol/l	(135-146)
Serum potassium	4.1 mmol/l	(3.5-5)
Creatinine	85 micromol/l	(79-118)
Calcium	2.89 mmol/l	(2.20-2.67)
PTH	Upper limit of normal range	

Which of the following is the most likely diagnosis?

(Please select 1 option)

- **A** Familial hypocalciuric hypercalcaemia
- **B** Primary hyperparathyroidism
- **C** PTHrP levels increased due to underlying malignancy
- **D** Secondary hyperparathyroidism
- **E** Tertiary hyperparathyroidism

Serum potassium	4.1 mmol/l	(3.5-5)
Creatinine	85 micromol/l	(79-118)
Calcium	2.89 mmol/l	(2.20-2.67)
PTH	Upper limit of normal range	

Which of the following is the most likely diagnosis?

(Please select 1 option)

- **A** Familial hypocalciuric hypercalcaemia ← This is the correct answer
- **B** Primary hyperparathyroidism ✕ Incorrect answer selected
- **C** PTHrP levels increased due to underlying malignancy
- **D** Secondary hyperparathyroidism
- **E** Tertiary hyperparathyroidism

There is no evidence of renal failure or malabsorption. Familial hypocalciuric hypercalcaemia is an autosomal dominant condition and this is the most likely diagnosis.

The disease most often leads to asymptomatic elevated levels of serum calcium, although some patients with the condition may suffer recurrent episodes of renal stones.

The inherited condition is caused by a mutation in the calcium sensing receptor (CASR) gene, which encodes a calcium sensing receptor expressed in the parathyroid gland and kidneys.

The perceived lack of calcium levels by the parathyroid leads to normal to high levels of parathyroid hormone and therefore hypercalcaemia.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

A 49-year-old woman comes to the clinic complaining of rapidly worsening lethargy and nausea. Over the past few days she has become increasingly unwell and is now barely able to get out of the house.

Other symptoms of note include progressive shortness of breath and a cough productive of blood stained sputum. Her only consultations with the doctor over the past six months have been about the shape of her nose; she has suffered some collapse of her nasal bridge and is considering plastic surgery.

On examination you notice collapse of the bridge of her nose, and nasal congestion when she speaks. Her BP is elevated at 155/95 mmHg. You can hear crepitations on auscultation of the chest.

Investigations show:

Haemoglobin	12.0 g/dl	(11.5-16.5)
White cell count	11.6 x 10^9/l	(4-11)
Platelets	202 x 10^9/l	(150-400)
Serum sodium	139 mmol/l	(135-146)
Serum potassium	5.8 mmol/l	(3.5-5)
Creatinine	285 micromol/l	(79-118)
CXR	Patchy interstitial shadowing	
C-ANCA	Positive	

Which of the following is the most appropriate treatment?

(Please select 1 option)

- **A** Infliximab
- **B** Methylprednisolone and azathioprine
- **C** Methylprednisolone and cyclophosphamide
- **D** Methylprednisolone and methotrexate
- **E** Prednisolone

CXR	Patchy interstitial shadowing
C-ANCA	Positive

Which of the following is the most appropriate treatment?

(Please select 1 option)

○	**A** Infliximab
○	**B** Methylprednisolone and azathioprine
○	**C** Methylprednisolone and cyclophosphamide ← This is the correct answer
○	**D** Methylprednisolone and methotrexate
◉	**E** Prednisolone ✕ Incorrect answer selected

Methylprednisolone and cyclophosphamide is the treatment of choice for induction of remission in Wegener's granulomatosis, the obvious diagnosis here.

Evidence from controlled trials suggests that once remission is achieved azathioprine or methotrexate may be reasonable alternatives to cyclophosphamide.

In refractory Wegener's, both infliximab and rituximab have shown some degree of promise.

Prognosis is dependent on prompt diagnosis and early intervention with immunosuppressive therapies, with evidence suggesting that time to diagnosis has shortened over the past few years.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken:

Question: 1 of 33

A 35-year-old Nigerian female was assessed in an antenatal clinic. She was clinical well.

Antenatal screening for syphilis revealed the following results:

Treponemal EIA total	Detected
Treponemal EIA IgM	Not detected
Treponemal TPPA	Detected 1:160
Treponemal RPR	Not detected

What is the likely diagnosis?

(Please select 1 option)

- **A** Acute syphilis infection
- **B** Early latent syphilis infection
- **C** Late latent syphilis infection
- **D** Non-specific reactivity
- **E** Yaws

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 26 mins 2 secs

Question: 10 of 33

A 70-year-old male with a preceding history of earache presents to hospital with clinical features consistent with meningitis.

What is the likeliest aetiology?

(Please select 1 option)

- **A** Influenza
- **B** Meningitides
- **C** Monocytogenes
- **D** Pneumoniae
- **E** Tuberculosis

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 29 mins 11 secs

Question: 10 of 33

A 70-year-old male with a preceding history of earache presents to hospital with clinical features consistent with meningitis.

What is the likeliest aetiology?

(Please select 1 option)

○	**A** Influenza
○	**B** Meningitides
○	**C** Monocytogenes
◉	**D** Pneumoniae ✓ Correct
○	**E** Tuberculosis

The preceding history of earache suggests that the meningitis is secondary to otitis media.

Although all the above organisms can cause meningitis, meningitis secondary to otitis media is most likely to be caused by *Streptococcus pneumoniae*.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 29 mins 11 secs

Question: 11 of 33

A patient with TB is receiving the following drugs as induction phase during treatment; rifampicin, isoniazid, pyrazinamide, ethambutol and pyridoxine. Which drug is most likely to cause peripheral neuropathy?

(Please select 1 option)

- **A** ethambutol
- **B** isoniazid
- **C** pyrazinamide
- **D** pyridoxine
- **E** rifampicin

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 29 mins 55 secs

Question: 11 of 33

A patient with TB is receiving the following drugs as induction phase during treatment; rifampicin, isoniazid, pyrazinamide, ethambutol and pyridoxine. Which drug is most likely to cause peripheral neuropathy?

(Please select 1 option)

○	**A** ethambutol
◉	**B** isoniazid ✓ Correct
○	**C** pyrazinamide
○	**D** pyridoxine
○	**E** rifampicin

Supplementation with pyridoxine, vitamin B6, reduces the risk.

Next question

Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 29 mins 55 secs

Question: 12 of 33

A patient with multiple drug resistant (MDR) TB is receiving prolonged treatment with moxifloxacin. Which side effect is likely to occur as a result of prolonged administration?

(Please select 1 option)

- **A** Achilles tendinitis
- **B** Hepatotoxicity
- **C** Nephrotoxicity
- **D** Peripheral neuropathy
- **E** Retinopathy

Submit answer | Skip question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 30 mins 46 secs

Question: 12 of 33

A patient with multiple drug resistant (MDR) TB is receiving prolonged treatment with moxifloxacin. Which side effect is likely to occur as a result of prolonged administration?

(Please select 1 option)

◉	**A** Achilles tendinitis ✓ Correct
○	**B** Hepatotoxicity
○	**C** Nephrotoxicity
○	**D** Peripheral neuropathy
○	**E** Retinopathy

This is an idiosyncratic reaction associated with prolonged use of quinolones.

Next question

Remove Tag
Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 30 mins 46 secs

Question: 13 of 33

Gentamicin, 7mg/kg once daily, is administered to an elderly patient with severe urosepsis. Twenty-four hours post administration gentamicin levels are > 2mg/l, Which of the following complications would you expect?

(Please select 1 option)

- **A** Hepatotoxicity
- **B** Nephrotoxicity
- **C** Ototoxicity
- **D** Peripheral neuropathy
- **E** Retinopathy

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 7 mins 25 secs

Question: 13 of 33

Gentamicin, 7mg/kg once daily, is administered to an elderly patient with severe urosepsis. Twenty-four hours post administration gentamicin levels are > 2mg/l, Which of the following complications would you expect?

(Please select 1 option)

○	**A** Hepatotoxicity
◉	**B** Nephrotoxicity ✓ Correct
○	**C** Ototoxicity
○	**D** Peripheral neuropathy
○	**E** Retinopathy

Prolonged exposure to gentamicin is likely to cause nephrotoxicity, particularly in elderly patients with renal impairment. Therefore the next dose of gentamicin should not be given if the gentamicin trough exceeds 2mg/l.

Next question

Tag Question
Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 7 mins 25 secs

Question: 14 of 33

A multiple drug resistant *Escherichia coli* was isolated from the urine of a patient with severe sepsis. What is the likely mechanism of resistance?

(Please select 1 option)

- **A** Alteration of drug target
- **B** Drug efflux
- **C** Drug impermeability
- **D** Extended spectrum beta-lactamase (ESBL) production
- **E** Penicillinase production

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 8 mins 48 secs

Question: 14 of 33

A multiple drug resistant *Escherichia coli* was isolated from the urine of a patient with severe sepsis. What is the likely mechanism of resistance?

(Please select 1 option)

◉	**A** Alteration of drug target ✕ Incorrect answer selected
○	**B** Drug efflux
○	**C** Drug impermeability
○	**D** Extended spectrum beta-lactamase (ESBL) production ← This is the correct answer
○	**E** Penicillinase production

Some *Escherichia coli* isolates produce an ESBL that inactivate second and third generation cephalosporins. The class of drugs that will most reliably treat these infections are the carbapenems.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 8 mins 48 secs

Question: 15 of 33

What is the mechanism of action of ciprofloxacin?

(Please select 1 option)

- **A** Cell wall inhibition
- **B** Inhibition of protein synthesis (translation)
- **C** Inhibition of protein synthesis (transcription)
- **D** Inhibition of folic acid metabolism
- **E** Interference with DNA replication

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 9 mins 17 secs

Question: 15 of 33

What is the mechanism of action of ciprofloxacin?

(Please select 1 option)

○	**A** Cell wall inhibition
○	**B** Inhibition of protein synthesis (translation)
○	**C** Inhibition of protein synthesis (transcription)
○	**D** Inhibition of folic acid metabolism
◉	**E** Interference with DNA replication ✓ Correct

Ciprofloxacin interferes with DNA synthesis by disrupting the function of DNA gyrase.

Next question

Tag Question

Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 9 mins 17 secs

Question: 16 of 33

What is the mechanism of action of trimethoprim?

(Please select 1 option)

- **A** Cell wall inhibition
- **B** Inhibition of protein synthesis (translation)
- **C** Inhibition of protein synthesis (transcription)
- **D** Inhibition of folic acid metabolism
- **E** Interference with DNA replication

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 9 mins 54 secs

Question: 16 of 33

What is the mechanism of action of trimethoprim?

(Please select 1 option)

- **A** Cell wall inhibition
- **B** Inhibition of protein synthesis (translation)
- **C** Inhibition of protein synthesis (transcription)
- **D** Inhibition of folic acid metabolism ✓ Correct
- **E** Interference with DNA replication

Trimethoprim interferes with the action of dihydrofolic reductase (DHFR), which is an enzyme that converts dihydrfolic to tetrahydrfolic acid, an essential stage in bacterial purine and, ultimately DNA synthesis.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 9 mins 54 secs

Question: 17 of 33

What is the mechanism of action of glycopeptides (e.g. vancomycin)?

(Please select 1 option)

- **A** Cell wall inhibition
- **B** Inhibition of protein synthesis (translation)
- **C** Inhibition of protein synthesis (transcription)
- **D** Inhibition of folic acid metabolism
- **E** Interference with DNA replication

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 10 mins 23 secs

Question: 17 of 33

What is the mechanism of action of glycopeptides (e.g. vancomycin)?

(Please select 1 option)

- **A** Cell wall inhibition ✓ Correct
- **B** Inhibition of protein synthesis (translation)
- **C** Inhibition of protein synthesis (transcription)
- **D** Inhibition of folic acid metabolism
- **E** Interference with DNA replication

Glycopeptides inhibit cell wall synthesis through steric hindrance of peptidoglycans, components of the bacterial cell wall.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 10 mins 23 secs

Question: 18 of 33

What is the mechanism of action of gentamicin, when used synergistically with benzylpenicillin to treat an infective endocarditis caused by *Viridans Streptococci*?

(Please select 1 option)

- **A** Cell wall inhibition
- **B** Inhibition of protein synthesis (translation)
- **C** Inhibition of protein synthesis (transcription)
- **D** Inhibition of folic acid metabolism
- **E** Interference with DNA replication

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 11 mins 11 secs

Question: 18 of 33

What is the mechanism of action of gentamicin, when used synergistically with benzylpenicillin to treat an infective endocarditis caused by *Viridans Streptococci*?

(Please select 1 option)

○	**A** Cell wall inhibition
○	**B** Inhibition of protein synthesis (translation) ← This is the correct answer
◉	**C** Inhibition of protein synthesis (transcription) ✕ Incorrect answer selected
○	**D** Inhibition of folic acid metabolism
○	**E** Interference with DNA replication

Gentamicin is synergistic to the action of benzylpenicillin. Benzylpenicillin is bactericidal, inhibiting cell wall synthesis, enabling gentamicin to enter the bacterial cell. It acts at the level of the ribosome, inhibiting protein synthesis.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 11 mins 11 secs

Question: 19 of 33

What is the mechanism of resistance for rifampicin resistant *Mycobacterium tuberculosis*?

(Please select 1 option)

- **A** Alteration in cell wall permeability
- **B** Alteration of the DNA dependent RNA transcriptase
- **C** Alteration of penicillin binding proteins (PBP's)
- **D** Efflux mechanism
- **E** Production of the inactivating enzyme, penicillinase

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 12 mins 18 secs

Question: 19 of 33

What is the mechanism of resistance for rifampicin resistant *Mycobacterium tuberculosis*?

(Please select 1 option)

◉	**A** Alteration in cell wall permeability ✕ Incorrect answer selected
○	**B** Alteration of the DNA dependent RNA transcriptase ← This is the correct answer
○	**C** Alteration of penicillin binding proteins (PBP's)
○	**D** Efflux mechanism
○	**E** Production of the inactivating enzyme, penicillinase

Rifampicin is a bacteriostatic antibiotic which acts by inhibiting protein synthesis. Mutations in *rpoB* gene cause alterations in the bacterial DNA dependent RNA transcriptase which prevents the binding of rifampicin.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Treponemal EIA total	Detected
Treponemal EIA IgM	Not detected
Treponemal TPPA	Detected 1:160
Treponemal RPR	Not detected

What is the likely diagnosis?

(Please select 1 option)

- **A** Acute syphilis infection
- **B** Early latent syphilis infection
- **C** Late latent syphilis infection ✓ Correct
- **D** Non-specific reactivity
- **E** Yaws

It is important that the serology is correctly interpreted and, during pregnancy, this lady is referred to a GU clinic for treatment with benzathine penicillin if not previously treated.

The detection of treponemal EIA total is confirmed by treponemal TPPA so this result is not a false positive. As treponemal IgM is not detected this is not consistent with acute infection.

In the absence of symptoms, late latent infection is more likely than early latent infection.

These results are unlikely to be cross reactivity secondary to yaws.

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 3 mins 30 secs

Question: 2 of 33

A 43-year-old Pakastani female presents with a two month history of weight loss, fever and night sweats.

Chest x ray reveals a large right sided pleural effusion.

What investigation is most likely to confirm a diagnosis of suspected TB?

(Please select 1 option)

- **A** CT scan of thorax
- **B** Interferon gamma releasing assay (IGRA)
- **C** Pleural aspirate
- **D** Pleural biopsy
- **E** Sputum analysis

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 12 mins 18 secs

Question: 20 of 33

What is the mechanism of resistance for penicillin resistant *Streptococcus pneumoniae*?

(Please select 1 option)

- **A** Alteration in cell wall permeability
- **B** Alteration of the DNA dependent RNA transcriptase
- **C** Alteration of penicillin binding proteins (PBP's)
- **D** Efflux
- **E** Production of the inactivating enzyme, penicillinase

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 13 mins

Question: 20 of 33

What is the mechanism of resistance for penicillin resistant *Streptococcus pneumoniae*?

(Please select 1 option)

○	**A** Alteration in cell wall permeability
○	**B** Alteration of the DNA dependent RNA transcriptase
○	**C** Alteration of penicillin binding proteins (PBP's) ← This is the correct answer
○	**D** Efflux
◉	**E** Production of the inactivating enzyme, penicillinase ✕ Incorrect answer selected

Penicillin is a bactericidal antibiotic which acts by inhibiting cell wall synthesis. Mutations in PBP's, enzymes required for cell wall synthesis, result in penicillin resistance.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 13 mins

Question: 21 of 33

A patient is diagnosed with an abnormality of oligopeptide disposal.

Which intracellular organelle is associated with the metabolism of oligopeptides?

(Please select 1 option)

- Golgi apparatus
- Lysosomes
- Peroxisomes
- Ribosomes
- Smooth endoplasmic reticulum

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

A patient is diagnosed with an abnormality of oligopeptide disposal.

Which intracellular organelle is associated with the metabolism of oligopeptides?

(Please select 1 option)

○	Golgi apparatus
○	Lysosomes ← This is the correct answer
◉	Peroxisomes ✕ Incorrect answer selected
○	Ribosomes
○	Smooth endoplasmic reticulum

Lysosomes (lysis- breakage, soma- body), carry hydrolases that degrade

- Nucleotides
- Proteins
- Lipids
- Phospholipids.

They also remove carbohydrate, sulfate, or phosphate groups from molecules.

Ribosomes are intimately associated with the rough endoplasmic reticulum and are responsible for protein translation.

Peroxisomes are responsible for the metabolism of fatty acids within cells.

Next question

Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 13 mins 50 secs

Question: 22 of 33

A patient is found to have an acquired syndrome associated with defective breakdown and disposal of intracellular fatty acids.

Which intracellular organelle is concerned with the breakdown of fatty acids?

(Please select 1 option)

- Golgi appartus
- Lysosomes
- Mitochondria
- Peroxisomes
- Smooth endoplasmic reticulum

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 14 mins 50 secs

Question: 22 of 33

A patient is found to have an acquired syndrome associated with defective breakdown and disposal of intracellular fatty acids.

Which intracellular organelle is concerned with the breakdown of fatty acids?

(Please select 1 option)

○	Golgi appartus
○	Lysosomes
○	Mitochondria
◉	Peroxisomes ✓ Correct
○	Smooth endoplasmic reticulum

Mitochondria are concerned with aerobic cell respiration and Golgi bodies are likely to be responsible for transporting products synthesised in the smooth endoplasmic reticulum.

Smooth endoplasmic reticulum is a site of lipid synthesis within the cell.

Lysosomes (lysis- breakage, soma- body) contain digestive enzymes which break down expendable cell organelles, engulfed viruses and other intracellular detritus.

Peroxisomes are responsible for the metabolism of fatty acids within cells.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Question: 23 of 33

A 16-year-old girl presented with fever, headache and photophobia.

Investigations revealed:

Cerebrospinal fluid examination

Opening pressure	260 mm H_20	(50-180)
Total protein	0.8 g/l	(0.15-0.45)
Glucose	4.2 mmol/l	(3.3-4.4)
White cell count	60 per ml	(<5)
Lymphocytes	90%	(60-70)
Plasma glucose	6.4 mmol/l	(3.0-6.0)

What is the most likely diagnosis?

(Please select 1 option)

- Bacterial meningitis
- Cryptococcal meningitis
- Tuberculosis meningitis
- Viral encephalitis
- Viral meningitis

Submit answer | Skip question | Tag Question | Remove question

Lymphocytes	90%	(60-70)
Plasma glucose	6.4 mmol/l	(3.0-6.0)

What is the most likely diagnosis?

(Please select 1 option)

- ○ Bacterial meningitis
- ○ Cryptococcal meningitis
- ○ Tuberculosis meningitis
- ○ Viral encephalitis
- ◉ Viral meningitis ✓ Correct

A normal cerbrospinal fluid (CSF) glucose together with

- A CSF lymphocytosis
- An increased opening pressure, and
- A raised CSF protein

are typical of a viral meningitis, which would be high on the list of differentials in patients of this age group (together with bacterial meningitis).

Further reading:
Cerebrospinal Fluid Analysis American Academy of Family Physicians

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 16 mins 36 secs

Question: 24 of 33

A 17-year-old girl underwent emergency splenectomy after a domestic accident.

Which one of the following organisms is most likely to cause life-threatening infection in the future?

(Please select 1 option)

- Actinomycosis
- *Haemophilus influenzae*
- *Pseudomonas aeruginosa*
- *Staphylococcus aureus*
- *Streptococcus pneumoniae*

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 18 mins 38 secs

Question: 24 of 33

A 17-year-old girl underwent emergency splenectomy after a domestic accident.

Which one of the following organisms is most likely to cause life-threatening infection in the future?

(Please select 1 option)

○	Actinomycosis
○	*Haemophilus influenzae*
○	*Pseudomonas aeruginosa*
○	*Staphylococcus aureus*
◉	*Streptococcus pneumoniae* ✓ Correct

Following splenectomy a person is at risk of *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Neisseria meningitidis*, *Escherichia coli* and *Pseudomonas aeruginosa*.

By far the most common is *Streptococcus pneumoniae,* which can cause life-threatening infection.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 18 mins 38 secs

Question: 25 of 33

A 45-year-old man presents with an ulcer on his right foot.

He has a twenty year history of type 1 diabetes and currently uses mixed insulin twice daily.

On examination he has a small ulcer of approximately 2 cm diameter on the outer aspect of his right big toe.

His peripheral pulses are all palpable but he has a peripheral neuropathy to the mid shins.

The ulcer has an erythematous margin and is covered by pus.

What is the most likely infective organism?

(Please select 1 option)

- ○ *Escherichia coli*
- ○ MRSA
- ○ *Pseudomonas aeruginosa*
- ○ *Staphylococcus aureus*
- ○ *Streptococcus pyogenes*

Submit answer | Skip question | Tag Question | Remove question

He has a twenty year history of type 1 diabetes and currently uses mixed insulin twice daily.

On examination he has a small ulcer of approximately 2 cm diameter on the outer aspect of his right big toe.

His peripheral pulses are all palpable but he has a peripheral neuropathy to the mid shins.

The ulcer has an erythematous margin and is covered by pus.

What is the most likely infective organism?

(Please select 1 option)

○	*Escherichia coli*
○	MRSA
○	*Pseudomonas aeruginosa*
◉	*Staphylococcus aureus* ✓ Correct
○	*Streptococcus pyogenes*

Although infection in diabetic foot ulcers is usually mixed, the most likely infective organism in this case is *Staph. aureus*.

Methicillin-resistant *Staphylococcus aureus* (MRSA) would be less likely but might be suspected if the patient developed an infection in hospital or had recurrent admissions.

The most appropriate antibiotic therapy is flucloxacillin, plus another broad spectrum agent with advice that the patient should not weight bear and should wear appropriate footwear.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 20 mins 13 secs

Question: 26 of 33

A 50-year-old female presents with dyspnoea, a new murmur and fever and is diagnosed with infective endocarditis.

Which of the following is associated with the best prognosis?

(Please select 1 option)

- Aortic valve infection
- Culture negative endocarditis
- Low complement levels
- *Staphylococcus aureus* infection
- *Streptococcus viridans* infection

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Question: 26 of 33

A 50-year-old female presents with dyspnoea, a new murmur and fever and is diagnosed with infective endocarditis.

Which of the following is associated with the best prognosis?

(Please select 1 option)

○	Aortic valve infection
○	Culture negative endocarditis
○	Low complement levels
○	*Staphylococcus aureus* infection
◉	*Streptococcus viridans* infection ✓ Correct

Features suggestive of a worse prognosis are:

- Acute endocarditis (*Staphylococcus aureus*)
- Heart failure
- Intravenous drug abuse (often left and right sided disease)
- Prosthetic valve infection
- Infection of the aortic rather than mitral valve
- Associated rhythm disturbance.

Subacute bacterial endocarditis (*Streptococcus viridans*) has a better prognosis.

Next question | Tag Question | Remove question

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 20 mins 52 secs

Question: 27 of 33

A 35-year-old woman presents with fever, rigors, malaise and weight loss.

She had undergone prosthetic valve replacement one month before. C3 level was reduced and echocardiography showed small vegetations.

Which micro-organism is most likely to be responsible for this?

(Please select 1 option)

- Candida
- *Coxiella burnetii*
- *Staphylococcus aureus*
- *Staphylococcus epidermidis*
- *Streptococcus viridans*

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Help
- Shop

(Please select 1 option)

○	Candida
○	*Coxiella burnetii*
○	*Staphylococcus aureus*
◉	*Staphylococcus epidermidis* ✓ Correct
○	*Streptococcus viridans*

Prosthetic valve endocarditis arising within two months of valve surgery is generally the result of intraoperative contamination of the prosthesis or a bacteraemia postoperative complication.

The nosocomial nature of these infections is reflected in their primary microbial causes:

- Coagulase-negative staphylococci (*Staphylococcus epidermidis*)
- *S. aureus*
- Facultative Gram-negative bacilli
- Diphtheroids
- Fungi.

The oral cavity, skin, and upper respiratory tract are the respective primary portals for the viridans streptococci, staphylococci, and HACEK organisms (*Haemophilus, Actinobacillus, Cardiobacterium, Eikenella*, and *Kingella*), causing community-acquired native valve endocarditis.

Streptococcus bovis originates from the gastrointestinal tract, where it is associated with polyps and colonic tumours, and enterococci enter the bloodstream from the genitourinary tract.

Next question | Tag Question | Remove question

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 22 mins 14 secs

Question: 28 of 33

A woman had lunch at a Chinese restaurant.

In the evening she presented with diarrhoea and vomiting. There was no fever.

Which of the following is the likely cause of food poisoning in her case?

(Please select 1 option)

- *Bacillus cereus*
- *Clostridium perfringens*
- *Escherichia coli*
- *Staphylococcus aureus*
- *Yersinia enterocolitica*

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

In the evening she presented with diarrhoea and vomiting. There was no fever.

Which of the following is the likely cause of food poisoning in her case?

(Please select 1 option)

◉	*Bacillus cereus* ✓ Correct
○	*Clostridium perfringens*
○	*Escherichia coli*
○	*Staphylococcus aureus*
○	*Yersinia enterocolitica*

Bacillus cereus food poisoning is the general description although two recognised types of illness are caused by two distinct metabolites. The diarrhoeal type of illness is caused by a large molecular weight protein, while the vomiting (emetic) type of illness is believed to be caused by a low molecular weight, heat-stable peptide.

The onset of watery diarrhoea, abdominal cramps, and pain occurs 6-15 hours after consumption of contaminated food. Symptoms usually persist for 24 hours. The emetic type of food poisoning is characterised by nausea and vomiting within 0.5 to 6 hours after consumption of contaminated foods. Occasionally, abdominal cramps and/or diarrhoea may also occur. Duration of symptoms is generally less than 24 hours.

A wide variety of foods including meats, milk, vegetables, and fish have been associated with the diarrhoeal type food poisoning. The vomiting-type outbreaks have generally been associated with rice products. *Staphylococcus aureus* and *Clostridium perfringens* are associated with meat and *Yersinia enterocolitica* with milk

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 24 mins 19 secs

Question: 29 of 33

A group of construction workers presented to the emergency department with diarrhoea, flushing, sweating and a hot mouth. They fell ill minutes after eating lunch in the staff canteen. They admitted that they had eaten tuna fish and wine.

What is the likely cause of food poisoning?

(Please select 1 option)

○	*Clostridium perfringens*
○	Heavy metal
○	Mushroom
○	Scrombotoxin
○	*Staphylococcus aureus*

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Question: 29 of 33

A group of construction workers presented to the emergency department with diarrhoea, flushing, sweating and a hot mouth. They fell ill minutes after eating lunch in the staff canteen. They admitted that they had eaten tuna fish and wine.

What is the likely cause of food poisoning?

(Please select 1 option)

○	*Clostridium perfringens*
○	Heavy metal
○	Mushroom
○	Scrombotoxin ← This is the correct answer
◉	*Staphylococcus aureus* ✕ Incorrect answer selected

Scrombotoxin food poisoning is caused by the ingestion of foods that contain high levels of histamine and possibly other vasoactive amines and compounds.

Histamine and other amines are formed by the growth of certain bacteria and the subsequent action of their decarboxylase enzymes on histidine and other amino acids in food, either during the production of a product such as Swiss cheese or by spoilage of foods such as fishery products, particularly tuna or mahi mahi.

Incubation period is 10-60 minutes.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 4 mins 52 secs

Question: 2 of 33

A 43-year-old Pakastani female presents with a two month history of weight loss, fever and night sweats.

Chest x ray reveals a large right sided pleural effusion.

What investigation is most likely to confirm a diagnosis of suspected TB?

(Please select 1 option)

○	**A** CT scan of thorax
○	**B** Interferon gamma releasing assay (IGRA)
○	**C** Pleural aspirate
◉	**D** Pleural biopsy ✓ Correct
○	**E** Sputum analysis

For suspected pleural TB, pleural biopsy sent in normal saline for AFB smear, mycobacterial culture and histology is the most sensitive method for laboratory confirmation.

In cases of suspected TB, every effort should be made to confirm a suspected diagnosis by culture. Susceptibility testing is important as detection of resistance alters the combination of drugs and duration of treatment.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 4 mins 52 secs

Question: 3 of 33

A 27-year-old Somali female presents with a two month history of weight loss, fever and night sweats.

Chest x ray reveals right upper lobe infiltrates. 3 x sputa are AFB smear.

What is the next most appropriate investigation?

(Please select 1 option)

- **A** Bronchoalveolar lavage (BAL)
- **B** CT scan of chest
- **C** HIV test
- **D** HIV test
- **E** Tuberculin skin test (TST)

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 26 mins 18 secs

Question: 30 of 33

A 41-year-old male has been diagnosed with infective endocarditis.

Which of the following is associated with the best prognosis?

(Please select 1 option)

- Aortic valve infection
- Intravenous drug abuse
- Prosthetic valve infection
- *Staphylococcus aureus* infection
- *Streptococcus viridans* infection

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Question: 30 of 33

A 41-year-old male has been diagnosed with infective endocarditis.

Which of the following is associated with the best prognosis?

(Please select 1 option)

○	Aortic valve infection
○	Intravenous drug abuse
○	Prosthetic valve infection
○	*Staphylococcus aureus* infection
◉	*Streptococcus viridans* infection ✓ Correct

Features suggestive of a worse prognosis are

- Acute endocarditis (*Staphylococcus aureus*)
- Heart failure
- IV drug abuse (often left and right sided disease)
- Prosthetic valve infection
- Infection of the aortic rather than mitral valve
- Associated rhythm disturbance.

Subacute bacterial endocarditis (*Streptococcus viridans*) has a better prognosis.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 26 mins 46 secs

Question: 31 of 33

Seventeen of twenty-four passengers on a Nile cruise develop bloody diarrhoea on the third day.

Which of the following organisms is the likely cause?

(Please select 1 option)

- *Entamoeba histolytica*
- *Giardia lamblia*
- *Schistosoma mansonii*
- *Shigella dysenteriae*
- *Vibrio cholerae*

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 27 mins 17 secs

Question: 31 of 33

Seventeen of twenty-four passengers on a Nile cruise develop bloody diarrhoea on the third day.

Which of the following organisms is the likely cause?

(Please select 1 option)

◉	*Entamoeba histolytica* ✕ Incorrect answer selected
○	*Giardia lamblia*
○	*Schistosoma mansonii*
○	*Shigella dysenteriae* ← This is the correct answer
○	*Vibrio cholerae*

Dysentery is characterised by the passing of frequent (sometimes very frequent) stools, that may contain blood, mucus or pus.

Shigella dysenteriae is responsible for bacillary dysentery, a disease most often associated with crowded, unsanitary conditions. Other species of *Shigella* may produce milder forms of diarrhoeal disease.

Dysentery is an oral infection transmitted via faecal contamination of water or food. During the one to four day incubation period, penetration of bacteria into the mucosal epithelial cells of the intestine causes an intense irritation of the intestinal wall, producing cramps and a watery, bloody diarrhoea.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 27 mins 17 secs

Question: 32 of 33

A 33-year-old male with type 1 diabetes presents with a two day history of pain, swelling and redness in his left middle finger. This began after he pricked his finger in the garden whilst pruning a bush.

His diabetic control has been quite reasonable with a HbA1c of 7.1% (3.8-6.4) on basal bolus insulin consisting of lispro tds and Humulin I in the evenings.

On examination he has a painful, red and swollen middle finger with the redness extending to the metacarpophalangeal joint. He is diagnosed with cellulitis.

What is the most appropriate treatment for this patient?

(Please select 1 option)

- Admit to hospital for IV antibiotics
- Oral flucloxacillin only
- Oral metronidazole only
- Oral penicillin V only
- Oral penicillin V and flucloxacillin

Submit answer | Skip question | Tag Question | Remove question

A 33-year-old male with type 1 diabetes presents with a two day history of pain, swelling and redness in his left middle finger. This began after he pricked his finger in the garden whilst pruning a bush.

His diabetic control has been quite reasonable with a HbA1c of 7.1% (3.8-6.4) on basal bolus insulin consisting of lispro tds and Humulin I in the evenings.

On examination he has a painful, red and swollen middle finger with the redness extending to the metacarpophalangeal joint. He is diagnosed with cellulitis.

What is the most appropriate treatment for this patient?

(Please select 1 option)

○	Admit to hospital for IV antibiotics
○	Oral flucloxacillin only
○	Oral metronidazole only
○	Oral penicillin V only
◉	Oral penicillin V and flucloxacillin ✓ Correct

The patient has digital cellulitis and the most likely organisms responsible are *Strep. pyogenes* or *Staph. aureus*.

The most appropriate treatment is penicillin V and flucloxacillin which should result in a rapid improvement.

If there is a deterioration then admission for IV antibiotics may be required but this should be unnecessary with appropriate antibiotic selection.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 30 mins 56 secs

Question: 33 of 33

A 16-year-old boy presented with fever, headache and neck stiffness for 24 hours. He had an identical illness requiring admission to hospital for one year previously.

Cerebrospinal fluid analysis shows white cells of 400/ml with a 90% neutrophilia and gram stain revealed scanty gram-negative diplococci.

Which component of the immune system is likely to be defective?

(Please select 1 option)

- B lymphocytes
- Complement pathway
- Immunoglobulin
- Neutrophils
- T lymphocytes

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 33 mins 4 secs

Question: 33 of 33

A 16-year-old boy presented with fever, headache and neck stiffness for 24 hours. He had an identical illness requiring admission to hospital for one year previously.

Cerebrospinal fluid analysis shows white cells of 400/ml with a 90% neutrophilia and gram stain revealed scanty gram-negative diplococci.

Which component of the immune system is likely to be defective?

(Please select 1 option)

○	B lymphocytes
◉	Complement pathway ✓ Correct
○	Immunoglobulin
○	Neutrophils
○	T lymphocytes

This young man has a recurrent meningococcal meningitis, and deficiencies of complement C5-9 predispose to *Neisseria* infections (complement deficiencies).

One must recognise that the diplococci seen on microscopy are those of *Neisseria meningitides*.

Finish | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 6 mins 21 secs

Question: 3 of 33

A 27-year-old Somali female presents with a two month history of weight loss, fever and night sweats.

Chest x ray reveals right upper lobe infiltrates. 3 x sputa are AFB smear.

What is the next most appropriate investigation?

(Please select 1 option)

○	**A** Bronchoalveolar lavage (BAL) ← This is the correct answer
○	**B** CT scan of chest
○	**C** HIV test
◉	**D** HIV test ✕ Incorrect answer selected
○	**E** Tuberculin skin test (TST)

The history, clinical presentation and radiological findings are highly suggestive of pulmonary TB.

BAL is more sensitive than sputum collection at detecting TB, either by smear or culture.

In cases of suspected TB every effort should be made to confirm a suspected diagnosis by culture. Susceptibility testing is important as detection of resistance alters the combination of drugs and duration of treatment.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 6 mins 21 secs

Question: 4 of 33

A 20-month-old baby is brought to the emergency department with a two day history of irritability, fever and non-blanching rash. BP was normal.

What is the likeliest diagnosis?

(Please select 1 option)

○	**A** *H. influenzae*
○	**B** *L. monocytogenes*
○	**C** *N. meningitidis*
○	**D** *S. aureus*
○	**E** *Streptococcus pneumoniae*

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 7 mins 50 secs

Question: 4 of 33

A 20-month-old baby is brought to the emergency department with a two day history of irritability, fever and non-blanching rash. BP was normal.

What is the likeliest diagnosis?

(Please select 1 option)

○	**A** *H. influenzae*
○	**B** *L. monocytogenes*
◉	**C** *N. meningitidis* ✓ Correct
○	**D** *S. aureus*
○	**E** *Streptococcus pneumoniae*

Meningococcal disease is an important cause of severe infection in young infants. Early recognition and treatment is essential for a favourable outcome.

Although other organisms can cause meningitis, *N. meningitidis* is the likeliest cause.

At 20 months, the infant should have been immunised against *H. influenzae* serotype B.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 7 mins 50 secs

Question: 5 of 33

A sexually active female presents to a GU clinic with multiple painful genital ulcers.

What is the likeliest cause?

(Please select 1 option)

- **A** *Chlamydia trachomatis*
- **B** Herpes simplex
- **C** *Haemophilus ducreyi*
- **D** Primary HIV infection
- **E** *Treponema pallidum*

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 8 mins 55 secs

Question: 5 of 33

A sexually active female presents to a GU clinic with multiple painful genital ulcers.

What is the likeliest cause?

(Please select 1 option)

○	**A** *Chlamydia trachomatis*
○	**B** Herpes simplex ← This is the correct answer
○	**C** *Haemophilus ducreyi*
○	**D** Primary HIV infection
◉	**E** *Treponema pallidum* ✕ Incorrect answer selected

Herpes simplex is a sexually transmitted disease and the commonest cause of multiple painful genital lesions.

C. trachomatis, *H. ducreyi* and *T. pallidum* do not normally cause painful genital ulceration.

Compared to herpes simplex, primary human immunodeficiency virus (HIV) infection is an unusual cause of genital ulceration.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 8 mins 55 secs

Question: 6 of 33

A 72-year-old female presents with a two month history of poor appetite, lethargy, intermittent fever and night sweats. She has poor dentition and over the last 12 months has required dental extraction.

On examination, a murmur consistent with mitral regurgitation is heard. A transthoracic echocardiogram reveals a vegetation on the mitral valve.

What is the likeliest cause of her endocarditis?

(Please select 1 option)

○	**A** *C. burnetii*
○	**B** *E. faecalis*
○	**C** MRSA
○	**D** *S. aureus*
○	**E** *S. mutans*

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 13 mins 18 secs

Question: 6 of 33

A 72-year-old female presents with a two month history of poor appetite, lethargy, intermittent fever and night sweats. She has poor dentition and over the last 12 months has required dental extraction.

On examination, a murmur consistent with mitral regurgitation is heard. A transthoracic echocardiogram reveals a vegetation on the mitral valve.

What is the likeliest cause of her endocarditis?

(Please select 1 option)

○	**A** *C. burnetii*
○	**B** *E. faecalis*
○	**C** MRSA
◉	**D** *S. aureus* ✕ Incorrect answer selected
○	**E** *S. mutans* ← This is the correct answer

S. mutans is a member of the viridans *Streptococcus* group and a common cause of bacterial endocarditis.

Poor dentition and procedures such as dental extraction are associated with transient viridans streptococcal bacteraemia.

In the presence of a pre-existing cardiac lesion this may have caused infective endocarditis.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 13 mins 18 secs

Question: 7 of 33

A 72-year-old male presents with a two month history of poor appetite, lethargy, intermittent fever and night sweats. Four months previously he had undergone TURP for benign prostatic hypertrophy.

On examination a murmur consistent with mitral regurgitation is heard. A transthoracic echocardiogram reveals a vegetation on the mitral valve.

What is the likeliest cause of his endocarditis?

(Please select 1 option)

- **A** *C. burnetii*
- **B** *E. faecalis*
- **C** MRSA
- **D** *S. aureus*
- **E** *S. mutans*

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 14 mins 42 secs

Question: 7 of 33

A 72-year-old male presents with a two month history of poor appetite, lethargy, intermittent fever and night sweats. Four months previously he had undergone TURP for benign prostatic hypertrophy.

On examination a murmur consistent with mitral regurgitation is heard. A transthoracic echocardiogram reveals a vegetation on the mitral valve.

What is the likeliest cause of his endocarditis?

(Please select 1 option)

○	**A** *C. burnetii*
○	**B** *E. faecalis* ← This is the correct answer
○	**C** MRSA
○	**D** *S. aureus*
◉	**E** *S. mutans* ✕ Incorrect answer selected

E. faecalis is a common cause of bacterial endocarditis following a urological procedure.

Urological procedures, such astransurethral resection of the prostate (TURP), may cause a transient *E. faecalis* bacteraemia.

In the presence of a pre-existing cardiac lesion this may have caused infective endocarditis.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 14 mins 42 secs

Question: 8 of 33

A 25-year-old female recently returned from Nigeria, presents to the emergency department with a two day history of fever and rigors.

Subsequently she develops a seizure.

What is the next most appropriate immediate investigation?

(Please select 1 option)

- **A** Blood culture
- **B** Blood film for malarial parasites
- **C** CT scan of head
- **D** Lumbar puncture
- **E** MR scan of head

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 15 mins 53 secs

Question: 8 of 33

A 25-year-old female recently returned from Nigeria, presents to the emergency department with a two day history of fever and rigors.

Subsequently she develops a seizure.

What is the next most appropriate immediate investigation?

(Please select 1 option)

○	**A** Blood culture
◉	**B** Blood film for malarial parasites ✓ Correct
○	**C** CT scan of head
○	**D** Lumbar puncture
○	**E** MR scan of head

With a recent history of travel to Nigeria, cerebral malaria caused by *P. falciparum* should be considered as a likely cause of her symptoms.

Therefore, a malaria blood film should be performed.

Other investigations may be required but investigations for malaria should be performed immediately.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 15 mins 53 secs

Question: 9 of 33

A 25-year-old male presents with fever malaise and lethargy two weeks after visiting family in India.

A blood film for malaria parasites is reported as negative.

What is the next most appropriate investigation?

(Please select 1 option)

- **A** Blood culture
- **B** Chest x ray
- **C** Interferon gamma releasing assay (IGRA)
- **D** Urine culture
- **E** Widal test

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 26 mins 2 secs

Question: 9 of 33

A 25-year-old male presents with fever malaise and lethargy two weeks after visiting family in India.

A blood film for malaria parasites is reported as negative.

What is the next most appropriate investigation?

(Please select 1 option)

◉	**A** Blood culture ✓ Correct
○	**B** Chest x ray
○	**C** Interferon gamma releasing assay (IGRA)
○	**D** Urine culture
○	**E** Widal test

After malaria, enteric fevers are important to exclude.

Blood cultures are the most important investigation for enteric fevers caused by *Salmonella typhi* or *S. paratyphi*.

The Widal test, a demonstration of agglutinating antibodies against somatic O and flagella H antigen of *Salmonella* species is non-specific and, therefore, less reliable.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

A 72-year-old man comes to the surgery with his wife.

She has witnessed two seizures at home, both of which have lasted for no longer than two minutes or so, accompanied by generalised limb jerking and incontinence of urine. He has been very embarrassed about the problem and did not want to come for review. She did not call an ambulance at the time as he seemed to be comfortable afterwards and she did not want the staff to see him "in a mess".

He has a history of cerebrovascular disease having suffered a minor stroke one year earlier, and suffered a myocardial infarction some three years ago. Medication includes ramipril, amlodipine, atorvastatin and aspirin.

On examination in the surgery he looks well. His BP is 142/79 mmHg, his pulse 75 and regular. Neurological examination is unremarkable apart from some very minor loss of co-ordination affecting his left hand. He wants you to arrange some investigations before bothering the hospital doctors.

Investigations show

Haemoglobin	12.1 g/dl	(13.5-18)
White cell count	8.2 x 10^9/l	(4-10)
Platelets	301 x 10^9/l	(150-400)
Sodium	141 mmol/l	(134-143)
Potassium	5.1 mmol/l	(3.5-5)
Creatinine	149 µ/l	(60-120)
ESR	12	(<20)
ECG	Sinus rhythm Inferior Q waves	

Which one of the following initial steps would be most appropriate in this case?

(Please select 1 option)

- ○ Carotid ultrasound scanning
- ○ EEG
- ○ Start low dose carbamazepine
- ○ Start low dose sodium valproate
- ○ Tilt table test

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 28 mins 20 secs

Question: 10 of 66

A 23-year-old female attends clinic for a routine appointment regarding a six month history of occasional fits.

She has seen the neurologists who have diagnosed idiopathic epilepsy and have prescribed lamotrigine. She informs you that she is doing well with this medication and has not had a fit for two months.

She has been told that she must stop driving but you have seen that she drove to attend the clinic. You discuss this with her and insist that she stops driving to which she informs you that she had stopped driving but since she is fit free she must continue to drive because of her employment.

Which of the following is the most appropriate action to take in these circumstances?

(Please select 1 option)

○	Inform patient that you will notify the DVLA
○	Inform patient that you will notify the police
○	Inform the epilepsy clinic that she is still driving and allow them to deal with this issue.
○	You cannot inform any external body due to patient confidentiality.
○	Your only action is to write in the notes that the patient has been repeatedly warned but chose to ignore advice as she presents no serious risk in view of her epilepsy control.

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

She has seen the neurologists who have diagnosed idiopathic epilepsy and have prescribed lamotrigine. She informs you that she is doing well with this medication and has not had a fit for two months.

She has been told that she must stop driving but you have seen that she drove to attend the clinic. You discuss this with her and insist that she stops driving to which she informs you that she had stopped driving but since she is fit free she must continue to drive because of her employment.

Which of the following is the most appropriate action to take in these circumstances?

(Please select 1 option)

◉	Inform patient that you will notify the DVLA ✓ Correct
○	Inform patient that you will notify the police
○	Inform the epilepsy clinic that she is still driving and allow them to deal with this issue.
○	You cannot inform any external body due to patient confidentiality.
○	Your only action is to write in the notes that the patient has been repeatedly warned but chose to ignore advice as she presents no serious risk in view of her epilepsy control.

The law is quite clear on such issues regarding epilepsy and the ability to drive. If the diagnosis is confirmed the patient must stop driving and inform the DVLA regarding the diagnosis.

If the patient continues to drive despite advice to the contrary then the doctor has a duty of care to society overriding confidentiality to the patient and may inform the DVLA.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 30 mins 34 secs

Question: 11 of 66

A 52-year-old female asks you for copies of her medical records. Within the records are several letters from hospital specialists, one of which refers to the patient in very unflattering terms. There is also a note in the records of a call that was made to the surgery by a neighbour of the patient who reported hearing noises through the wall and expressed concern that the patient may be suffering domestic violence.

Are the following statements true?

(Please select 1 option)

- Under the Data Protection Act 1998 you are allowed to withhold the note of the telephone call from the neighbour.
- Under the Data Protection Act 1998 you are obliged to disclose the record in its entirety
- You may withhold access to any references to third parties, including hospital specialists.
- You must seek the consent of the hospital specialists before disclosing their letters
- You must withhold access to any references to third parties, including hospital specialists

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Help
- Shop

(Please select 1 option)

○	Under the Data Protection Act 1998 you are allowed to withhold the note of the telephone call from the neighbour. ← This is the correct answer
○	Under the Data Protection Act 1998 you are obliged to disclose the record in its entirety
○	You may withhold access to any references to third parties, including hospital specialists.
◉	You must seek the consent of the hospital specialists before disclosing their letters ✕ Incorrect answer selected
○	You must withhold access to any references to third parties, including hospital specialists

Under data protection etc. The legislative framework for the disclosure of medical records is the Data Protection Act 1998. Under the Act, you may withhold access to any part of the record if you consider that disclosure would cause serious mental or physical harm to the patient or another person. You may also withhold access to part of the record that in effect discloses information about an identifiable third party, unless you have the consent of the third party to make the disclosure or it is reasonable in all the circumstances to make the disclosure without seeking consent. Information in a health record made by a healthcare professional involved in the care of the patient does not count as third party information for this purpose; where, as in this case, disclosure of a hospital letter is likely to generate a complaint, you may choose to inform the author that the disclosure has been made but are not obliged to do so. If information is likely to cause serious harm to the physical or mental health or condition of the data subject or any other person, then it can be withheld regardless of the author.

THE MDU Question supplied by the Medical Defence Union.

Next question

Rem

Work Smart Session - MRCP Part 1

Time taken: 32 mins 30 secs

Question: 12 of 66

A 56-year-old male with severe brain damage is apnoeic, unsedated, and temperature 36.9°C.

He is intubated and ventilated. His biochemistry is normal.

The combination of which of the following specialists would be able to confirm brain stem death?

(Please select 1 option)

○	Consultant/Associate specialist with three years experience
○	Consultant/Specialist registrar of two years experience
○	Staff grade with five years experience/ Consultant
○	Senior house officer of two years experience/Specialist registrar of five years experience
○	Specialist registrar with five years experience/Specialist registrar with five years experience

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 34 mins 19 secs

Question: 12 of 66

A 56-year-old male with severe brain damage is apnoeic, unsedated, and temperature 36.9°C.

He is intubated and ventilated. His biochemistry is normal.

The combination of which of the following specialists would be able to confirm brain stem death?

(Please select 1 option)

◉	Consultant/Associate specialist with three years experience ✗ Incorrect answer selected
○	Consultant/Specialist registrar of two years experience
○	Staff grade with five years experience/ Consultant ← This is the correct answer
○	Senior house officer of two years experience/Specialist registrar of five years experience
○	Specialist registrar with five years experience/Specialist registrar with five years experience

Criteria for the confirmation of brain stem death have to be tested by a consultant and confirmed by a doctor of at least five years post- registration who has experience in the testing of brain stem death.

Next question

Remove Tag
Remove question

© 2011 BMJ Publishing Group Ltd. All rights reserved. Terms and conditions Privacy policy

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 34 mins 19 secs

Question: 13 of 66

An 82-year-old lady with dementia presents from a nursing home with vaginal discharge.

High vaginal swabs have confirmed gonorrheal infection and she has been commenced on appropriate treatment.

What else would you like to do for this patient?

(Please select 1 option)

○	Contact tracing
○	Inform family
○	Inform police
○	None of the above
○	Non-official enquiry

Submit answer | Skip question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

What else would you like to do for this patient?

(Please select 1 option)

○	Contact tracing
◉	Inform family ✓ Correct
○	Inform police
○	None of the above
○	Non-official enquiry

This appears to be a case of elder sexual abuse.

For those who are legally competent voluntary referrals to social services, victims' services, the criminal justice system, or any other appropriate resource agency are encouraged.

Doctors should not report the incidence without the patient's permission.

Here this demented lady is not legally competent. In this case one should discuss this case with the next of kin first to establish if there truly is sexual abuse or whether in fact this patient has been having a relationship with a third party.

The facts should be established first before involving the police.

If in any doubt, contact your medical defence organisation.

Next question

Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 35 mins 5 secs

Question: 14 of 66

A 78-year-old male dies and is found by his children the following morning (after having seen him alive the night before). His GP attends to certify him dead.

The patient had a known history of ischaemic heart disease and was treated in the local hospital where angiography performed nine months previously for angina had revealed some insignificant coronary artery disease of two vessels for which medical therapy was deemed most appropriate. He had also been diagnosed eight years previously with diabetes mellitus for which he took metformin and gliclazide.

He had seen the practice nurse two weeks ago for review of his diabetes. One month ago he had seen the diabetologists for his annual review and had seen the cardiologists approximately six months ago. He had last seen a partner in the practice six weeks ago for advice concerning driving licence registration.

The family are keen to have a death certificate issued and proceed to cremation. They do not want any post mortem examination.

Which of the following is true concerning the issuing of a death certificate?

(Please select 1 option)

○	The certifying doctor may issue a death certificate
○	The death needs to be referred to the coroner
○	The diabetologist can certify the death.
○	The partner in the practice may issue a death certificate
○	The practice nurse can certify the death

weeks ago for advice concerning driving licence registration.

The family are keen to have a death certificate issued and proceed to cremation. They do not want any post mortem examination.

Which of the following is true concerning the issuing of a death certificate?

(Please select 1 option)

○	The certifying doctor may issue a death certificate
◉	The death needs to be referred to the coroner ✓ Correct
○	The diabetologist can certify the death.
○	The partner in the practice may issue a death certificate
○	The practice nurse can certify the death

Death certification is becoming a hot area post Shipman.

A death certificate may be completed if the practitioner has seen the deceased within 14 days of the death (28 days in NI). In this case the patient had been seen six weeks previously by the partner.

Consequently and in view of the sudden death the coroner should be informed although he may decide that in the circumstances reported the doctor may be able to issue a death certificate stating ischaemic heart disease if he deems appropriate and on the balance of advice given to him.

Next question

Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 37 mins 54 secs

Question: 15 of 66

Which one of the following deaths should be reported to the coroner?

(Please select 1 option)

○	A 73-year-old female who had undergone a hip replacement two months previously presents with severe chest pain and breathlessness. She is diagnosed with pulmonary embolism but dies.
○	A 72-year-old male is admitted with a myocardial infarction and dies 48 hours following admission.
○	A 69-year-old male with pneumoconiosis is admitted with fever and breathlessness. He dies two days later from pneumonia.
○	A 62-year-old male with a two year history of severe dementia is admitted from a nursing home with fever and breathlessness. He dies three days later with pneumonia.
○	A 52-year-old male with a long history of alcohol abuse is admitted with confusion. He dies two days later with hepatic failure.

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Community
- Help
- Shop

She is diagnosed with pulmonary embolism but dies.

A 72-year-old male is admitted with a myocardial infarction and dies 48 hours following admission.

A 69-year-old male with pneumoconiosis is admitted with fever and breathlessness. He dies two days later from pneumonia. ← This is the correct answer

A 62-year-old male with a two year history of severe dementia is admitted from a nursing home with fever and breathlessness. He dies three days later with pneumonia. ✗ Incorrect answer selected

A 52-year-old male with a long history of alcohol abuse is admitted with confusion. He dies two days later with hepatic failure.

Increasingly emphasis is placed on the appropriate reporting of deaths particularly from the enquiries into Shipman and the Coroners' Reform Bill. In fact, it is the duty of the Registrar of Births, Deaths and Marriages to report a death to the coroner but doctors need to be aware of the circumstances in which a death should be reported.

These include:

- The cause of death is unknown
- The deceased was not seen by the certifying doctor either after death or within 14 days before death
- The death was violent or unnatural
- The death may be due to an accident
- The death may be due to self neglect or neglect by others
- The death may be the result of industrial illness or due to the person's employment (as in D pneumoconiosis being an industrial disease)
- The death may be due to an abortion
- The death occurred during an operation or before recovery from anaesthesia
- The death may be suicide
- The death occurred during or shortly after being taken into police custody.

The MDU have published a guide to Coroners Inquiries which is free to members:

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 39 mins 51 secs

Question: 16 of 66

A 54-year-old male who is a HGV driver and has a 10 year history of type 2 diabetes is seen on annual review.

His glycaemic control is poor with a HBA1c of 10.5% on maximal oral hypoglycaemic therapy (3.8-6.4).

You suggest switching to insulin but he refuses to do this as he would lose his HGV licence. He also refuses to inform the DVLA himself.

What is the most appropriate action in this case?

(Please select 1 option)

- Continue to review patient in clinic and accept that he continues to drive
- Discharge him from clinic as there is nothing more that you can do
- Inform his employer that he must stop driving and suggest administrative work
- Inform the DVLA even if the patient withholds his consent
- Tell his next of kin that they should inform the DVLA that he is nol onger fit to drive

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Scores
- Community
- Help
- Shop

His glycaemic control is poor with a HBA1c of 10.5% on maximal oral hypoglycaemic therapy (3.8-6.4).

You suggest switching to insulin but he refuses to do this as he would lose his HGV licence. He also refuses to inform the DVLA himself.

What is the most appropriate action in this case?

(Please select 1 option)

◉	Continue to review patient in clinic and accept that he continues to drive ✓ Correct
○	Discharge him from clinic as there is nothing more that you can do
○	Inform his employer that he must stop driving and suggest administrative work
○	Inform the DVLA even if the patient withholds his consent
○	Tell his next of kin that they should inform the DVLA that he is nol onger fit to drive

In this particular case, the patient has poor glycaemic control, but otherwise has no features whatsoever that preclude him from driving such as retinopathy, neuropathy or hypoglycaemic episodes.

You cannot therefore force this patient to switch to insulin and neither can you stop him driving.

He will continue to need a regular medical every three years for his continued HGV licence.

Further reading:
Driver and Vehicle Licensing Agency

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 43 mins 24 secs

Question: 17 of 66

A 22-year-old female is admitted following severe injuries sustained in a road traffic accident. She is communicative but in shock with low blood pressure and tachycardia.

You realise that without a transfusion she will die but she informs you that she has recently become a Jehovah's Witness and that she adamantly refuses transfusion, despite knowledge that she could die.

Her distraught parents tell you that she has only recently joined the Jehovah's Witnesses and implore you to transfuse her, as they insist that she does not know her own mind.

Together with other intervention which she permits, what is the most appropriate action regarding possible transfusion?

(Please select 1 option)

- Declare her incompetent and transfuse
- Do not transfuse even if it means that she will die
- Get immediate psychiatric intervention to section her and then transfuse
- Transfuse immediately, irrespective of the patient's wishes
- Wait until she becomes unconscious and then get consent from her parents to transfuse

Submit answer | Skip question | Tag Question | Remove question

- Questions
- Scores
- Community
- Help
- Shop

shock with low blood pressure and tachycardia.

You realise that without a transfusion she will die but she informs you that she has recently become a Jehovah's Witness and that she adamantly refuses transfusion, despite knowledge that she could die.

Her distraught parents tell you that she has only recently joined the Jehovah's Witnesses and implore you to transfuse her, as they insist that she does not know her own mind.

Together with other intervention which she permits, what is the most appropriate action regarding possible transfusion?

(Please select 1 option)

○	Declare her incompetent and transfuse
○	Do not transfuse even if it means that she will die ← This is the correct answer
○	Get immediate psychiatric intervention to section her and then transfuse
○	Transfuse immediately, irrespective of the patient's wishes
◉	Wait until she becomes unconscious and then get consent from her parents to transfuse ✕ Incorrect answer selected

The patient appears competent and has elected to refuse the transfusion. Despite the parents' protestation you must respect the patient's wishes if, as seems likely here, she is making a reasoned judgement.

If the patient refuses the transfusion then even if she slips into unconsciousness you are not permitted to treat with transfusion even if it is in her best interests.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 45 mins 25 secs

Question: 18 of 66

A 30-year-old male is unconscious on admission following a road traffic accident. He was the driver of the car and there is the suspicion that he was responsible for the accident in which a passenger of another car died. In attendance with the patient is his wife who was uninjured in the accident.

The police are keen to obtain a blood sample for alcohol measurement but the patient is incapable of giving consent for this procedure.

What is the most appropriate action in these circumstances?

(Please select 1 option)

○	Draw a blood sample for later analysis when the patient is competent to consent.
○	Draw a blood sample which can be analysed immediately.
○	Inform the police that you may only take blood samples on medical grounds.
○	Obtain consent from his wife, as next of kin, to draw the blood sample.
○	Refuse to obtain a blood sample until the patient is competent to provide consent.

Submit answer | Skip question | Tag Question | Remove question

his wife who was uninjured in the accident.

The police are keen to obtain a blood sample for alcohol measurement but the patient is incapable of giving consent for this procedure.

What is the most appropriate action in these circumstances?

(Please select 1 option)

○	Draw a blood sample for later analysis when the patient is competent to consent. ← This is the correct answer
◉	Draw a blood sample which can be analysed immediately. ✕ Incorrect answer selected
○	Inform the police that you may only take blood samples on medical grounds.
○	Obtain consent from his wife, as next of kin, to draw the blood sample.
○	Refuse to obtain a blood sample until the patient is competent to provide consent.

There is clear guidance published on such a situation by the BMA.

Following the Police Reform Act, it is no longer necessary to obtain consent from unconscious or incapacitated drivers.

However, the sample is not tested until the person regains competence and gives valid consent to it being tested.

A competent person who refuses to allow his or her sample to be tested might be liable to prosecution.

Similarly, the new law recognises the duty to justice.

Next question

Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 46 mins 47 secs

Question: 19 of 66

Which of the following has been shown to increase the risk of prostate cancer?

(Please select 1 option)

- Caucasian race
- Exposure to cadmium
- Family history of colon cancer
- Low intake of animal fats
- Occupational exposure to dust

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 49 mins 11 secs

Question: 19 of 66

Which of the following has been shown to increase the risk of prostate cancer?

(Please select 1 option)

○	Caucasian race
◉	Exposure to cadmium ✓ Correct
○	Family history of colon cancer
○	Low intake of animal fats
○	Occupational exposure to dust

Black ethnicity is associated with a higher risk of prostate cancer than white.

A family history of breast cancer increases the risk of prostate cancer, as does a family history of prostate cancer.

An occupation in farming also seems to increase the risk of prostate cancer.

High intake of animal fats, and low selenium intake, as well as exposure to radiation and cadmium all increase the risk of prostate cancer.

Next question

Tag Question

Remove question

Potassium	5.1 mmol/l	(3.5-5)
Creatinine	149 µ/l	(60-120)
ESR	12	(<20)
ECG	Sinus rhythm Inferior Q waves	

Which one of the following initial steps would be most appropriate in this case?

(Please select 1 option)

- ◉ Carotid ultrasound scanning ✓ Correct
- ○ EEG
- ○ Start low dose carbamazepine
- ○ Start low dose sodium valproate
- ○ Tilt table test

EEG measurement is less useful in an elderly population, most likely because of structural changes related to age and pre-existing cerebrovascular disease. MRI however may be useful in detecting any structural abnormality such as a tumour, local vascular abnormality or old cerebral infarct.

In patients with a history of previous stroke foci of epileptic activity can occur in the penumbra around the previous infarct. In view of his previous stroke, carotid ultrasound scanning is also an important part of the initial assessment.

Finally, bearing in mind his previous infarct, he should be considered for 72 hour ECG monitoring, to exclude the possibility of a significant cardiac arrhythmia.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 5 mins 58 secs

Question: 2 of 66

A 72-year-old man with longstanding Parkinson's comes to the surgery.

He is maintained on high dose l-dopa therapy but is suffering significant on/off phenomena. This is really affecting his life and he feels unable to leave the house and go on excursions with his wife.

Other past history of note includes prostatism for which he takes an alpha-blocker and a 5-alpha reductase inhibitor. He has also suffered a myocardial infarction some five years earlier.

Which one of the following would be the most appropriate next therapeutic option for him?

(Please select 1 option)

○	Amitriptyline
○	Cabergoline
○	Change to soluble levodopa before meals
○	Entacapone
◉	Selegiline

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 49 mins 11 secs

Question: 20 of 66

You intend to undertake a study of patients who have undergone excision of minor lumps and bumps over the last five years.

Specifically you wish to compare post-operative infection rates and also whether there are any differences between the clinical diagnosis and the histological diagnosis between the differing grades of practitioner performing the procedure.

Which of the following statements is correct concerning this study?

(Please select 1 option)

- Approval for the study must be obtained from the local ethics committee.
- If a study had already published with exactly the same concept then this constitutes plagiarism.
- If such a study has already been published then the investigators must obtain consent from the original authors to replicate their work.
- The study is flawed in its design and should not be performed.
- This is an audit and does not require ethical committee approval.

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

You intend to undertake a study of patients who have undergone excision of minor lumps and bumps over the last five years.

Specifically you wish to compare post-operative infection rates and also whether there are any differences between the clinical diagnosis and the histological diagnosis between the differing grades of practitioner performing the procedure.

Which of the following statements is correct concerning this study?

(Please select 1 option)

◉	Approval for the study must be obtained from the local ethics committee. ✓ Correct
○	If a study had already published with exactly the same concept then this constitutes plagiarism.
○	If such a study has already been published then the investigators must obtain consent from the original authors to replicate their work.
○	The study is flawed in its design and should not be performed.
○	This is an audit and does not require ethical committee approval.

This is not an audit.

There is no information provided to indicate that there are either any local or national guidelines relating to such a study. Furthermore there is no information provided to indicate that there is a specific clinical problem to which an audit should be addressed.

Consequently this is a research study and is a retrospective study. As such it requires local ethical committee approval.

The study itself seems very reasonable and even if it were published elsewhere it would still be reasonable to perform in the investigator's practice as the outcomes may be completely different.

Using the same methods as another study is perfecly justifiable, if only to prove the veracity of the original publication. No consent is required from the original authors if a similar study has already been published.

EN
6:07 PM
2/24/2011

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 54 mins 7 secs

Question: 21 of 66

You are intending to publish a case report as a fascinoma of the month within a national medical journal. As part of the publication you provide an image from the MRI film of the abdomen.

Medical illustration have transferred the film to electronic format and have removed all patient identification markings. The case report itself is otherwise completely anonymous.

Which of the following concerning consent is correct?

(Please select 1 option)

○	Consent for publication may not be required depending on the journal to which the manuscript is submitted
○	Consent for publication of the image must be obtained from the radiologist
○	Consent for publication must be sought from the local ethics committee
○	Patient consent for publication is not required
○	Patient consent must be provided for publication

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Medical illustration have transferred the film to electronic format and have removed all patient identification markings. The case report itself is otherwise completely anonymous.

Which of the following concerning consent is correct?

(Please select 1 option)

○	Consent for publication may not be required depending on the journal to which the manuscript is submitted
○	Consent for publication of the image must be obtained from the radiologist
○	Consent for publication must be sought from the local ethics committee
○	Patient consent for publication is not required
◉	Patient consent must be provided for publication ✓ Correct

There is much controversy concerning case reports and consent, but without question, prior to publication, and particularly as you are using images, consent for publication must be obtained from the patient for use of both images and for the publication of the case report. This consent must also be appropriately informed.

All UK journals expect this prior to publication despite the anonymity of the subject matter. This is not an issue for which medical ethics committees are involved.

This is a complex area and there is flexibility around publication of images. However, there have been incidences of x rays being published which have been deemed to have been an invasion of privacy.

Further reading:
Law and Ethics Institute of Medical Illustrators

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 55 mins 59 secs

Question: 22 of 66

An 82-year-old female is reviewed after the staff of the nursing home in which she resides expressed concern regarding a vaginal discharge.

She has been in the nursing home for the last year and has profound Alzheimer's dementia.

Culture of the discharge reveals *Neisseria gonorrhoeae*.

Which is the most appropriate course of action for this patient?

(Please select 1 option)

- Contact the police
- Contact tracing of sexual partners
- Informal enquiry to the nursing home
- Seek advice from the MDU
- Treat the patient and discharge back to the nursing home

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Shop

(Please select 1 option)

○	Contact the police
○	Contact tracing of sexual partners
○	Informal enquiry to the nursing home
◉	Seek advice from the MDU ✓ Correct
○	Treat the patient and discharge back to the nursing home

These ethical questions can be quite tough to answer with accuracy.

This question specifically relates to elder abuse, in this case potential elder sexual abuse. The scenario is one that is often played out in the press, in which a care worker sexually abuses elderly patients in his or her care.

However, you are given very little information here and what you would do is undoubtedly treat the patient and establish how she contracted gonorrhoea.

The question states that she has a profound dementia, suggesting that abuse has occurred rather than consensual sex. Nonetheless, you need to establish the facts. You have a personal duty of care to the patient and next of kin to do this before contacting the police.

It is likely that the police will need to be called but first it would be worth talking things through and obtaining advice from the MDU. The advice may entail investigating the set-up at the nursing home, talking with the next of kin, (and social services if a social worker has been involved) and finely detailing any injuries that may be present on examination.

Only then should the decision to contact the police be made.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 57 mins 27 secs

Question: 23 of 66

A 76-year-old male presents with cognitive impairment and is diagnosed with dementia.

Which of the following is the most probable cause of the dementia?

(Please select 1 option)

- Alzheimer's disease
- Creutzfeldt-Jacob disease
- Lewy body dementia
- Pick's disease
- Vascular dementia

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

A 76-year-old male presents with cognitive impairment and is diagnosed with dementia.

Which of the following is the most probable cause of the dementia?

(Please select 1 option)

◉	Alzheimer's disease ✓ Correct
○	Creutzfeldt-Jacob disease
○	Lewy body dementia
○	Pick's disease
○	Vascular dementia

Dementia is a clinical state characterised by loss of function in multiple cognitive domains beyond what might be expected from normal aging.

Particularly affected areas may be memory, attention, language, and solving.

The most common form of dementia, Alzheimer's disease, accounts for 50-75% of all cases of dementia.

Another 20-30% is due to blood vessel disease (multi-infarct dementia).

The remaining cases result from a variety of less common disorders.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 58 mins 18 secs

Question: 24 of 66

A 47-year-old male presents with marked shortness of breath which has deteriorated over the last two weeks.

On examination he has a hard irregular thyroid mass and has some difficulty breathing. There appears to be no retrosternal extension and he appears clinically euthyroid.

What is the most likely diagnosis?

(Please select 1 option)

- Anaplastic carcinoma of thyroid
- Bleed into a thyroid nodule
- Follicular thyroid carcinoma
- Medullary thyroid carcinoma
- Multinodular goitre

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

A 47-year-old male presents with marked shortness of breath which has deteriorated over the last two weeks.

On examination he has a hard irregular thyroid mass and has some difficulty breathing. There appears to be no retrosternal extension and he appears clinically euthyroid.

What is the most likely diagnosis?

(Please select 1 option)

◉	Anaplastic carcinoma of thyroid ✓ Correct
○	Bleed into a thyroid nodule
○	Follicular thyroid carcinoma
○	Medullary thyroid carcinoma
○	Multinodular goitre

This patient is likely to have anaplastic carcinoma of the thyroid with compression/infiltration of the trachea.

This is unlikely to be a multinodular goitre as this would be unlikely to compress the trachea unless retrosternal and the description is more compatible with a thyroid malignancy.

Medullary thyroid cancer is associated most often with multiple endocrine neoplasia (MEN) II and would be particularly unusual.

Again follicular would be unlikely to produce such marked infiltrative features in such a short period of time. Typically patients with follicular disease would present with a nodule and/or LAP.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 37 secs

Question: 25 of 66

Does integrity refer to a virtue that requires the physician to do the following?

(Please select 1 option)

- Acknowledge and respond to the suffering of patients
- Ignore irrelevant differences between the physician and the patient
- Practise medicine according to intellectual and moral standards of excellence
- Risk health and life in the care of patients
- Treat in the best interests of the patient

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 5 mins 31 secs

Question: 25 of 66

Does integrity refer to a virtue that requires the physician to do the following?

(Please select 1 option)

○	Acknowledge and respond to the suffering of patients
○	Ignore irrelevant differences between the physician and the patient
◉	Practise medicine according to intellectual and moral standards of excellence ✓ Correct
○	Risk health and life in the care of patients
○	Treat in the best interests of the patient

Integrity refers to the practise of medicine according to appropriate ethical standards and excellence.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 5 mins 31 secs

Question: 26 of 66

Are ethics defined as the following?

(Please select 1 option)

- Codes and statements of professional organisations of physicians about appropriate conduct
- Obedience to the law
- Prescriptions found in Scripture
- The study of morality
- The study of the human conscience

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 6 mins 31 secs

Question: 26 of 66

Are ethics defined as the following?

(Please select 1 option)

◉	Codes and statements of professional organisations of physicians about appropriate conduct ✗ Incorrect answer selected
○	Obedience to the law
○	Prescriptions found in Scripture
○	The study of morality ← This is the correct answer
○	The study of the human conscience

Ethics are defined as the study of morality/the philosophical study of moral values and rules.

Next question

Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 6 mins 31 secs

Question: 27 of 66

By which of the following are most deaths determined?

(Please select 1 option)

- Absent pulse.
- Brain stem tests.
- Loss of pupilary reflex.
- The absence of vital signs.
- The coroner.

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 7 mins 23 secs

Question: 27 of 66

By which of the following are most deaths determined?

(Please select 1 option)

○	Absent pulse.
○	Brain stem tests.
◉	Loss of pupilary reflex. ✕ Incorrect answer selected
○	The absence of vital signs. ← This is the correct answer
○	The coroner.

The absence of vital signs is the commonest mode of diagnosing death and entails

- Absent pulse
- Absent heart sounds
- Respiratory arrest and
- Loss of pupillary light reflex.

Brain stem tests are generally reserved for ventilated cases where organ transplantation may be required.

Doctors most commonly diagnose death not the coroner who provides a verdict on the cause of death.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 7 mins 23 secs

Question: 28 of 66

Withholding the truth about a patient's illness is a violation of:

(Please select 1 option)

- Autonomy
- Beneficence
- Informed consent
- Infringement of the Human Rights Act
- The Bolam principle

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 8 mins 16 secs

Question: 28 of 66

Withholding the truth about a patient's illness is a violation of:

(Please select 1 option)

○	Autonomy ← This is the correct answer
○	Beneficence
○	Informed consent
◉	Infringement of the Human Rights Act ✕ Incorrect answer selected
○	The Bolam principle

By not informing the patient about all the aspects of their illness we are removing their ability to make decisions for themselves. In effect we, and their relatives, are making the decisions for them. This is the removal of their autonomy.

Informed consent relies upon the patient being provided with the information that is generated from the investigations to which he has consented. Justice implies going beyond one's own feelings, prejudices, and desires to find an appropriate balance among conflicting interests.

The Bolam principle is the basis upon which a doctors actions are judged such that they would be considered appropriate and reasonable to those actions that would be performed by a responsible body of their peers in similar circumstances.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 8 mins 16 secs

Question: 29 of 66

A placebo is defined as which of the following?

(Please select 1 option)

- A standard treatment against which a newer treatment is compared
- A substance given as a treatment for a disorder
- A way to deceive a patient into taking a medication
- An inert substance given as a medicine in an assessment of its suggestive effect
- The medication given to a patient for a specific type of ailment

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 9 mins 23 secs

Question: 29 of 66

A placebo is defined as which of the following?

(Please select 1 option)

- A standard treatment against which a newer treatment is compared
- A substance given as a treatment for a disorder
- A way to deceive a patient into taking a medication
- ◉ An inert substance given as a medicine in an assessment of its suggestive effect ✓ Correct
- The medication given to a patient for a specific type of ailment

A placebo typically produces mainly a psychological effect when administered to a patient or person involved in a trial.

Next question

Tag Question

Remove question

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 8 mins 26 secs

Question: 2 of 66

A 72-year-old man with longstanding Parkinson's comes to the surgery.

He is maintained on high dose l-dopa therapy but is suffering significant on/off phenomena. This is really affecting his life and he feels unable to leave the house and go on excursions with his wife.

Other past history of note includes prostatism for which he takes an alpha-blocker and a 5-alpha reductase inhibitor. He has also suffered a myocardial infarction some five years earlier.

Which one of the following would be the most appropriate next therapeutic option for him?

(Please select 1 option)

○	Amitriptyline
○	Cabergoline ← This is the correct answer
○	Change to soluble levodopa before meals
○	Entacapone
◉	Selegiline ✕ Incorrect answer selected

On/off phenomena may be considerably improved either by the addition of cabergoline (a dopamine agonist) or a subcutaneous infusion of apomorphine.

Liquid forms of l-dopa may also be helpful as they allow closer titration of dose, and splitting meals into smaller snacks and one larger evening meal also affects the pharmacokinetics (PK) of l-dopa positively.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd. All rights reserved. Terms and conditions Privacy policy

Work Smart Session - MRCP Part 1

Time taken: 8 mins 26 secs

Question: 3 of 66

A patient of yours suffers a myocardial infarction and dies in Spain. His relatives arrange for his body to be repatriated and plan for him to be cremated.

You last saw him alive seven days before his death.

Which of the following is true with respect to completion of cremation forms?

(Please select 1 option)

○	A colleague should complete form 4
○	A cremation may only take place if a coroner rules that no inquest or post mortem is needed
○	The Spanish doctor who originally treated him should complete form 4
○	You are allowed to complete form 5
○	You are allowed to complete forms 4 and 5

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 9 mins 23 secs

Question: 30 of 66

In which of the following cases is the individual's right to autonomy violated?

(Please select 1 option)

○	An athlete who seeks a second opinion
○	An infant whose parents elect for surgery to correct a congenital heart defect
○	An older man whose physician and family coerce him into having foot surgery
○	An older woman who refuses to undergo back surgery
○	A Jehovah's witness patient with symptomatic anaemia who refuses blood transfusion

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 10 mins 47 secs

Question: 30 of 66

In which of the following cases is the individual's right to autonomy violated?

(Please select 1 option)

- An athlete who seeks a second opinion
- An infant whose parents elect for surgery to correct a congenital heart defect
- An older man whose physician and family coerce him into having foot surgery ✓ Correct
- An older woman who refuses to undergo back surgery
- A Jehovah's witness patient with symptomatic anaemia who refuses blood transfusion

Autonomy refers to an individual's right to be self-governing. Although the procedures may be in the best interests of the patient, if the patient refuses and this refusal is informed, then the doctor or relatives cannot coerce that person into having the procedure.

Next question | Tag Question | Remove question

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 10 mins 47 secs

Question: 31 of 66

The need for new methods of defining and determining death was created by what medical procedure?

(Please select 1 option)

- Artificial resuscitation
- Brain surgery
- ITU ventilation
- Open heart surgery
- Organ transplantation

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 11 mins 36 secs

Question: 31 of 66

The need for new methods of defining and determining death was created by what medical procedure?

(Please select 1 option)

○	Artificial resuscitation
○	Brain surgery
◉	ITU ventilation ✗ Incorrect answer selected
○	Open heart surgery
○	Organ transplantation ← This is the correct answer

The conventional criteria previously established for clinical death were based upon cardiac standstill.

Due to the development of organ transplantation those criteria needed revision so that they are now based upon brain stem death.

Next question

Remove Tag

Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 11 mins 36 secs

Question: 32 of 66

Which of the following statements is the principal argument made by proponents of making commerce in human organs for legal use?

(Please select 1 option)

○	A person's heirs have the right to earn money by selling the deceased's organs.
○	Commercialisation is not ethically preferable to the gift model of organ donation.
○	It is an ethical trade in a capitalistic society
○	Shortages or surpluses would be eliminated.
○	There is already an active "black market" in transplantable organs.

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 13 mins 51 secs

Question: 32 of 66

Which of the following statements is the principal argument made by proponents of making commerce in human organs for legal use?

(Please select 1 option)

○	A person's heirs have the right to earn money by selling the deceased's organs.
○	Commercialisation is not ethically preferable to the gift model of organ donation.
○	It is an ethical trade in a capitalistic society
○	Shortages or surpluses would be eliminated. ← This is the correct answer
◉	There is already an active "black market" in transplantable organs. ✕ Incorrect answer selected

Although particularly controversial the arguments for commercial organ donation suggest that surpluses or deficits in organs would be eliminated and that the current black market in this resource associated with the inherent exploitation of the poor would be resolved.

However it is unethical to exploit live donors in impoverished countries as may happen currently.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Show tools

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 13 mins 51 secs

Question: 33 of 66

A 63-year-old smoker has been investigated for a cough and chest pain and a diagnosis of bronchial carcinoma is made on a plain chest x ray examination.

Before a tissue diagnosis can be made, he dies in hospital of a large and unexpected haemoptysis and a post mortem examination is carried out with the consent of the relatives. At this examination, the correct diagnosis is shown to be tuberculosis and there is no carcinoma.

In this circumstance, it is mandatory to make a report to a particular authority.

Which authority?

(Please select 1 option)

- ○ Consultant in Communicable Diseases Control
- ○ Coroner
- ○ General Medical Council
- ○ Health and Safety Executive
- ○ Strategic Health Authority

Submit answer | Skip question | Tag Question | Remove question

Before a tissue diagnosis can be made, he dies in hospital of a large and unexpected haemoptysis and a post mortem examination is carried out with the consent of the relatives. At this examination, the correct diagnosis is shown to be tuberculosis and there is no carcinoma.

In this circumstance, it is mandatory to make a report to a particular authority.

Which authority?

(Please select 1 option)

◉	Consultant in Communicable Diseases Control ✓ Correct
○	Coroner
○	General Medical Council
○	Health and Safety Executive
○	Strategic Health Authority

There are a number of notifiable infectious diseases that it is mandatory to report to the Consultant in Communicable Diseases Control. They include:

- tuberculosis
- malaria
- meningitis
- meningococcal sepsis.

Next question

Tag Question | Remove question

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 15 mins 20 secs

Question: 34 of 66

An 82-year-old male with longstanding Alzheimer's dementia presents as his carers are concerned about his increased episodes of aggression. Physically he is well.

Which is the most appropriate treatment for his aggressive outbursts?

(Please select 1 option)

- Diazepam
- Quetiapine
- Risperidone
- Temazepam
- Valproate

Submit answer | Skip question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

An 82-year-old male with longstanding Alzheimer's dementia presents as his carers are concerned about his increased episodes of aggression. Physically he is well.

Which is the most appropriate treatment for his aggressive outbursts?

(Please select 1 option)

○	Diazepam
◉	Quetiapine ✓ Correct
○	Risperidone
○	Temazepam
○	Valproate

Risperidone used to be a favourite treatment for aggression/agitation in dementia but recent studies indicate that it is associated with an increased mortality and a threefold increased risk of stroke.

Valproate is widely used for its calming effects in this situation but although widely used there is little evidence of the efficacy of valproate.

Valproic acid for agitation in dementia Cochrane Database Syst Rev. 2004;(2):CD003945

Haloperidol may be associated with cardiac arrhythmias, and its use is now discouraged for long term use.

The other options are associated with more prominent adverse effects.

Next question

Remove Tag | Remove question

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 16 mins 5 secs

Question: 35 of 66

An 85-year-old lady with advanced Alzheimer's dementia has inhaled her hearing aid. The respiratory rate is 35. A bronchoscopy is proposed.

Which of the following apply with regard to obtaining consent for the procedure?

(Please select 1 option)

○	If the mini mental score is above 20/30, consent can be taken from patient
○	Psychogeriatric opinion is needed before consent can be obtained
○	Relatives/next of kin will have to consent for the patient
○	The doctor will be able to consent for the patient
○	The procedure does not require a written consent

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Which of the following apply with regard to obtaining consent for the procedure?

(Please select 1 option)

○	If the mini mental score is above 20/30, consent can be taken from patient
○	Psychogeriatric opinion is needed before consent can be obtained
○	Relatives/next of kin will have to consent for the patient
○	The doctor will be able to consent for the patient
◉	The procedure does not require a written consent ✓ Correct

In this case, which is an emergency, informed written consent is not essential as the procedure is potentially life-saving and the doctor would be seen to be acting in the patient's best interest.

The process of consent for a procedure relies upon written and informed consent which the patient has to understand.

When a patient has impaired mental capacity, the doctor may be uncertain whether the patient is competent to give informed consent. Under English law no other person can consent to treatment on behalf of an adult, though it is desirable that next of kin are consulted before treating an adult without consent.

Recent legislation gives legal authority to people appointed by the patient, or by the state, or a relative or carer, to consent (or refuse) on behalf of the patient.

A mini-mental score may not adequately identify those unable to give consent.

Further reading:
Consent: key documents Department of Health

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 17 mins 13 secs

Question: 36 of 66

A patient attends for breast screening and asks you the following questions.

Which statement is correct?

(Please select 1 option)

○	Early diagnosis does not change the rate of death from breast cancer
○	In young patients with a BRCA mutation, mammographic screening has a low sensitivity for detecting tumours
○	Mammographic screening is more sensitive in patient groups with denser breast tissue
○	Mammographic screening is offered to all women aged 20-75 years
○	p53 mutation is a commonly identified in subjects with a strong family history of breast cancer

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

A patient attends for breast screening and asks you the following questions.

Which statement is correct?

(Please select 1 option)

○	Early diagnosis does not change the rate of death from breast cancer
○	In young patients with a BRCA mutation, mammographic screening has a low sensitivity for detecting tumours ← This is the correct answer
○	Mammographic screening is more sensitive in patient groups with denser breast tissue
○	Mammographic screening is offered to all women aged 20-75 years
◉	p53 mutation is a commonly identified in subjects with a strong family history of breast cancer ✕ Incorrect answer selected

In young patients MRI may help to delineate breast cancer in breast tissue which in younger patients is denser than the breast tissue of older patients. Mammography is more sensitive in older patient groups partly because in general the breast tissue is less dense.

Mammographic screening of all women between the ages of 50 and 70 years can reduce mortality from breast cancer by 25%. There is no consensus regarding the value of breast cancer screening among women who are 40- to 49-years-old.

The presence of a germ-line mutation of the BRCA1 or BRCA2 gene increases the risk of breast cancer considerably, and patients with these mutations should be offered the opportunity to receive screening at much younger than 50 years.

p53 mutations are rarely found in patients even with a family history of breast cancer.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd. All rights reserved. Terms and conditions Privacy policy

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 18 mins 12 secs

Question: 37 of 66

An 18-year-old male develops thirst, weight loss and polyuria. Investigations confirm that he has type 1 diabetes and he is treated with basal bolus insulin.

He is keen to know what limitations this diagnosis imposes on career opportunities.

Which of the following professions would he not be able to pursue?

(Please select 1 option)

- Ambulance control centre worker
- Civil engineer
- Milkman
- Physical education instructor
- Policeman

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 19 mins 4 secs

Question: 37 of 66

An 18-year-old male develops thirst, weight loss and polyuria. Investigations confirm that he has type 1 diabetes and he is treated with basal bolus insulin.

He is keen to know what limitations this diagnosis imposes on career opportunities.

Which of the following professions would he not be able to pursue?

(Please select 1 option)

○	Ambulance control centre worker
○	Civil engineer
○	Milkman
○	Physical education instructor
◉	Policeman ✓ Correct

The armed forces, working offshore or aboard ships, air pilot, HGV/PSV licence, police, fire or driving in the post office are career paths closed to subjects with insulin dependent diabetes .

Some local authorities do permit licences to taxi drivers with insulin treated diabetes whilst others do not.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 19 mins 4 secs

Question: 38 of 66

An 85-year-old woman with diabetes mellitus presented with sudden onset of wild flinging movements of the left arm which disappeared during sleep.

What is the most likely explanation?

(Please select 1 option)

- Contralateral subthalamic nucleus infarction
- Focal motor seizures
- Hypoglycaemia
- Ipsilateral caudate nucleus infarction
- Ipsilateral cerebellar infarction

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 19 mins 52 secs

Question: 38 of 66

An 85-year-old woman with diabetes mellitus presented with sudden onset of wild flinging movements of the left arm which disappeared during sleep.

What is the most likely explanation?

(Please select 1 option)

◉	Contralateral subthalamic nucleus infarction ✓ Correct
○	Focal motor seizures
○	Hypoglycaemia
○	Ipsilateral caudate nucleus infarction
○	Ipsilateral cerebellar infarction

This is hemiballismus, and in a diabetic patient is likely to be due to a vascular event in the contralateral subthalamic nucleus.

Next question

Tag Question

Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

A 75-year-old male presents with a two month history of dyspnoea, weight loss and generalised lethargy. Past medical history included a previous left-sided hemiparesis due to stroke for which he took aspirin and perindopril.

Examination revealed residual left sided hemiparesis together with a pale and slightly jaundiced appearance.

Investigations show:

Haemoglobin	5 g/dL (13.0-18.0)
MCV	109 fL (80-96)
White cell count	2 $x10^9$/L (4-11 $x10^9$)
Platelets	45 $x10^9$/L (150-400 $x10^9$)

- Urinalysis: Increased urobilinogen

What is the next most appropriate investigation?

(Please select 1 option)

- Bone marrow aspirate
- Direct antiglobulin test
- Endoscopy
- Serum haptoglobins
- Vitamin B_{12} concentration

Submit answer | Skip question | Remove Tag | Remove question

Avira
Update was finished successfully.
There were 9 new files installed.
Do not show this message again.
OK

- Urinalysis: increased urobilinogen

What is the next most appropriate investigation?

(Please select 1 option)

○	Bone marrow aspirate
○	Direct antiglobulin test
○	Endoscopy
○	Serum haptoglobins
◉	Vitamin B_{12} concentration ✓ Correct

In this situation, serum B_{12} estimation is the correct choice. With a pancytopenic picture and raised mean corpuscular volume (MCV), the most appropriate step is to check the B_{12} and folate.

The other choices are considered only after the basic assays.

Haemolysis does not explain the low WCC, nor the thrombocytopenia.

A haptoglobin only adds weight to a diagnosis of haemolysis, and a RBC-labelled scan would add greater sensitivity to the diagnosis of haemolysis.

The mild jaundice is typical of megaloblastic anaemia (vitamin B12 or folate deficiency) because of increased destruction of red cell precursors in the bone marrow.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 9 mins 51 secs

Question: 3 of 66

A patient of yours suffers a myocardial infarction and dies in Spain. His relatives arrange for his body to be repatriated and plan for him to be cremated.

You last saw him alive seven days before his death.

Which of the following is true with respect to completion of cremation forms?

(Please select 1 option)

◉	A colleague should complete form 4 ✕ Incorrect answer selected
○	A cremation may only take place if a coroner rules that no inquest or post mortem is needed ← This is the correct answer
○	The Spanish doctor who originally treated him should complete form 4
○	You are allowed to complete form 5
○	You are allowed to complete forms 4 and 5

Where deaths abroad are concerned, a cremation may only take place if the coroner is satisfied that a post mortem or inquest is not necessary.

It is highly unlikely that you will be in a position to complete forms 4 and 5, and it is not appropriate for form 4 to be completed by the Spanish doctor who originally treated the patient.

Ministry of Justice cremation guidelines

Next question

Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 9 mins 51 secs

Question: 4 of 66

You are completing a list of cremation form 5s for patients in the hospital where you work.

You examine one form where the junior doctor has completed the cause of death as stroke, but the patient appears to have fallen at home. The husband wants to arrange cremation as soon as possible.

Apparently the junior doctor is working nights and has gone home, so you cannot easily get hold of him to question him further.

Which of the following is true with respect to completion of the form?

(Please select 1 option)

- ○ Completion of form 5 to show that examination of the case has been "adequate" would be acceptable
- ○ It is acceptable in this case not to question the doctor
- ○ Medical referees will not mind if you have not contacted the doctor
- ○ When completing form 5 you must only be reasonably sure that the patient suffered a stroke
- ○ You should wait to complete the form until the doctor is available to answer questions

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 21 mins 22 secs

Question: 40 of 66

A 75-year-old man is awaiting transurethral resection of the prostate, but is brought into hospital in acute urinary retention.

Which of the following drugs might be responsible?

(Please select 1 option)

○	Ipatropium bromide inhaler
○	Montelukast
○	Serevent inhaler
○	Sodium chromoglycate
○	Theophylline

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Question: 40 of 66

A 75-year-old man is awaiting transurethral resection of the prostate, but is brought into hospital in acute urinary retention.

Which of the following drugs might be responsible?

(Please select 1 option)

◉	Ipatropium bromide inhaler ✓ Correct
○	Montelukast
○	Serevent inhaler
○	Sodium chromoglycate
○	Theophylline

Ipatropium bromide acts as an antimuscarinic bronchodilator and has traditionally been regarded as more effective in relieving bronchoconstriction associated with chronic bronchitis.

Side-effects are rare and it does not increase sputum viscosity or affect the mucociliary clearance of sputum.

Reported side-effects are dry mouth, blurred vision, constipation and urinary retention.

The nebulised drug has occasionally been reported to leak around the mask and precipitate acute angle closure glaucoma in susceptible patients.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 22 mins 21 secs

Question: 41 of 66

Which of the following statements is true regarding neck of femur fracture?

(Please select 1 option)

○	Extracapsular fractures have a higher incidence of avascular necrosis compared to intracapsular fractures
○	Internal rotation of the affected limb is a common clinical finding
○	In the young displaced fractures should be reduced and fixed urgently
○	Mortality for elderly patients is >80% at one year
○	Non-union is not a complication

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 23 mins 7 secs

Question: 41 of 66

Which of the following statements is true regarding neck of femur fracture?

(Please select 1 option)

○	Extracapsular fractures have a higher incidence of avascular necrosis compared to intracapsular fractures
○	Internal rotation of the affected limb is a common clinical finding
◉	In the young displaced fractures should be reduced and fixed urgently ✓ Correct
○	Mortality for elderly patients is >80% at one year
○	Non-union is not a complication

Intracapsular femoral fractures are at increased risk of avascular necrosis due to disruption of the capsular blood supply at the time of injury.

Patients more commonly present with a short, externally rotated limb.

In young patients the fracture should be reduced and fixed early to decrease the risks of avascular necrosis and non-union.

Mortality at one year is approximately 25%.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Question: 42 of 66

A 80-year-old man presents with deteriorating lumbar and bilateral hip pains. He has recently been seen by his GP with symptoms of prostatism.

Investigations revealed:

Full blood count	Normal	
Corrected calcium	2.3 mmol/l	(2.2-2.6)
ESR	22 mm/1st hr	(1-10)
Alkaline phosphatase	985 U/l	(60-110)
Gamma-GT	33 U/l	(<50)
Prostate specific antigen	6.6 pg/l	(0-6)

What is the most likely cause of this man's pain?

(Please select 1 option)

- Multiple myeloma
- Osteomalacia
- Paget's disease of the pelvis
- Polymyalgia rheumatica (PMR)
- Prostatic carcinoma with metastases

Alkaline phosphatase	985 U/l	(60-110)
Gamma-GT	33 U/l	(<50)
Prostate specific antigen	6.6 pg/l	(0-6)

What is the most likely cause of this man's pain?

(Please select 1 option)

- Multiple myeloma
- Osteomalacia
- Paget's disease of the pelvis ✓ Correct
- Polymyalgia rheumatica (PMR)
- Prostatic carcinoma with metastases

This elderly patient presenting with bone pains has elevated alkaline phosphatase with normal calcium concentrations suggesting a diagnosis of Paget's.

The slightly elevated PSA is in keeping with benign prostatic hypertrophy rather than prostatic malignancy where a PSA of above 10 would be expected.

The normal calcium and only slightly elevated erythrocyte sedimentation rate (ESR) argues against osteomalacia, myeloma and PMR.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 25 mins 54 secs

Question: 43 of 66

A 76-year-old male attends clinic with his wife who states that her husband has become disinterested and withdrawn.

Which of the following would favour a diagnosis of dementia rather than depression?

(Please select 1 option)

○	Agitation
○	Poor short term memory
○	Reduced libido
○	Self-reported concern of poor memory
○	Urinary incontinence

Submit answer | Skip question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 25 mins 54 secs

Question: 43 of 66

A 76-year-old male attends clinic with his wife who states that her husband has become disinterested and withdrawn.

Which of the following would favour a diagnosis of dementia rather than depression?

(Please select 1 option)

○	Agitation
○	Poor short term memory
○	Reduced libido
○	Self-reported concern of poor memory
○	Urinary incontinence

Submit answer | Skip question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

An 80-year-old woman with type 2 diabetes mellitus is referred with weakness.

She had been taking bendroflumethiazide, digoxin and tolbutamide.

On examination she had a temperature of 37.8ºC, a pulse of 98 bpm in atrial fibrillation, and a blood pressure of 118/72 mmHg.

Investigations show:

Sodium	121 mmol/L (137-144)
Potassium	3.3 mmol/L (3.5-4.9)
Urea	4.8 mmol/L (2.5-7.5)
Creatinine	83 µmol/L (60-110)
Glucose	15.2 mmol/L (3.0-6.0)
Chest X-ray	Normal

What is the most likely cause for the hyponatraemia?

(Please select 1 option)

- ○ Addison's disease
- ○ Bendroflumethiazide (bendroflumethiazide)
- ○ Hyperglycaemia
- ○ Syndrome of inappropriate secretion of antidiuretic hormone (SIADH)
- ○ Tolbutamide

Urea	4.8 mmol/L (2.5-7.5)
Creatinine	83 µmol/L (60-110)
Glucose	15.2 mmol/L (3.0-6.0)
Chest X-ray	Normal

What is the most likely cause for the hyponatraemia?

(Please select 1 option)

○	Addison's disease
○	Bendroflumethiazide (bendroflumethiazide) ← This is the correct answer
○	Hyperglycaemia
◉	Syndrome of inappropriate secretion of antidiuretic hormone (SIADH) ✕ Incorrect answer selected
○	Tolbutamide

This patient has hyponatraemia and hypokalaemia. This is probably due to the bendroflumethiazide which should be stopped.

It is unlikely to be SIADH, of which tolbutamide is a cause, as the hypokalaemia is not typically associated.

Her hyperglycaemia with an osmotic diuresis would cause dehydration.

Addison's disease would be associated with hyperkalaemia, hypotension and elevated urea.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 28 mins 59 secs

Question: 45 of 66

An 80-year-old male presented with acute right-sided weakness.

Examination revealed minimal right facial weakness, impaired elevation of the right shoulder, with relatively preserved right hand strength. There was global weakness in the right leg which appeared to be maximal in the foot.

Which of the following arteries is most likely to have been affected?

(Please select 1 option)

- Anterior cerebral artery
- Lenticulostriate artery
- Middle cerebral artery
- Posterior cerebral artery
- Posterior communicating artery

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

◉	Anterior cerebral artery ✓ Correct
○	Lenticulostriate artery
○	Middle cerebral artery
○	Posterior cerebral artery
○	Posterior communicating artery

It's a tricky question and it is purposely so.

The wording of the description could be due to middle or anterior artery circulation stroke but the challenge is to choose which is the more likely.

The case as described is the classic presentation of an anterior cerebral artery stroke as originally described in the literature. (Critchley M. The anterior cerebral artery and its syndromes. Brain 1930; 53:120-165.)

Unilateral occlusion (distal to ant. comm. origin) of **anterior cerebral artery** produces contralateral sensorimotor deficits mainly involving the lower extremity with relative sparing of face and hands (think of the humunculus).

The lateral lenticulostriate artery is a branch of the middle cerebral artery. Occlusion causes damage to the internal capsule resulting in contralateral hemiparesis and sensory deficit. Speech may be affected (medial temporal lobe) as well as visual function (Meyer's loop: optic radiations affected).

Middle cerebral artery: Occlusion at the stem (proximal segment) results in:

- Contralateral hemiplegia affecting face, arm, and leg (lesser)
- Homonymous hemianopia - ipsilateral head/eye deviation
- If on left: global aphasia

Posterior cerebral artery: A variety of neurological syndromes including:

- Pure hemisensory loss
- Visual field loss- a variety
- Visual agnosia
- Disorders of reading (alexia, dyslexia) and more ...

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 30 mins 14 secs

Question: 46 of 66

An 80-year-old male presented with palpitations of five hours duration.

One month previously he suffered weakness of the right arm and problems with his speech which resolved within four hours. He was taking no medication.

On examination, he was stable with a pulse of 135 beats per minute which was confirmed to be atrial fibrillation on ECG. He had a blood pressure of 112/80 mmHg and appeared clinically euthyroid.

Within one hour he reverted to sinus rhythm spontaneously.

Echocardiogram was normal but a 24 hour ECG revealed three episodes of atrial fibrillation each lasting around ten minutes.

Which one of the following is the most appropriate initial treatment for this patient?

(Please select 1 option)

- Amiodarone
- Aspirin
- Atenolol
- Digoxin
- Warfarin

Submit answer | Skip question | Tag Question | Remove question

taking no medication.

On examination, he was stable with a pulse of 135 beats per minute which was confirmed to be atrial fibrillation on ECG. He had a blood pressure of 112/80 mmHg and appeared clinically euthyroid.

Within one hour he reverted to sinus rhythm spontaneously.

Echocardiogram was normal but a 24 hour ECG revealed three episodes of atrial fibrillation each lasting around ten minutes.

Which one of the following is the most appropriate initial treatment for this patient?

(Please select 1 option)

○	Amiodarone
○	Aspirin
○	Atenolol
○	Digoxin
◉	Warfarin ✓ Correct

The most appropriate initial therapy for this patient who has a high risk of thrombo-embolic stroke is anticoagulation with warfarin maintaining an international normalised ratio (INR) between 2-3.

This should be the initial priority as he has already had one episode of transient ischaemic attack (TIA).

The maintenance of sinus rhythm would be the next step and amiodarone or sotalol are options.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 31 mins 49 secs

Question: 47 of 66

An 81-year-old frail man admitted with a stroke becomes increasingly drowsy after receiving nasogastric (NG) feeding for five days.

Which biochemical abnormality is the most likely cause of his drowsiness?

(Please select 1 option)

- Hyperglycaemia
- Hypermagnesaemia
- Hypernatraemia
- Hypocalcaemia
- Hypophosphataemia

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Question: 47 of 66

An 81-year-old frail man admitted with a stroke becomes increasingly drowsy after receiving nasogastric (NG) feeding for five days.

Which biochemical abnormality is the most likely cause of his drowsiness?

(Please select 1 option)

○	Hyperglycaemia
○	Hypermagnesaemia
○	Hypernatraemia
○	Hypocalcaemia
◉	Hypophosphataemia ✓ Correct

The chronology of his presentation five days after receiving NG feeds suggests hypophosphataemia associated with the re-feeding syndrome.

This is well described in elderly frail subjects who may have prior poor nutrition.

However, other electrolyte abnormalities are also described in association with NG feeds, for example, hypernatraemia.

But with this briefest of histories and the five days it is likely that the examiner is looking for hypophosphataemia.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 32 mins 32 secs

Question: 48 of 66

A 79-year-old male is admitted with acute confusion and is agitated and aggressive to staff.

His relatives who accompany him assert that he had been entirely self-caring, does not drink alcohol and was taking no previous medication. He was diagnosed with a urinary tract infection and commenced antibiotics but remained agitated and distressed.

Which one of the following treatments is the most appropriate for his agitation?

(Please select 1 option)

○	Chlorpromazine
○	Diazepam
○	Quetiapine
○	Temazepam
○	Trazodone

Submit answer | Skip question | Tag Question | Remove question

- Help
- Shop

Which one of the following treatments is the most appropriate for his agitation?

(Please select 1 option)

○	Chlorpromazine
○	Diazepam
◉	Quetiapine ✓ Correct
○	Temazepam
○	Trazodone

The best agent for acute agitation in this elderly patient would be quetiapine probably administered intramuscularly (IM).

Second line management would be lorazepam IM, or even IV.

Temazepam is too short-acting to be administered to this patient and may precipitate respiratory depression whilst diazepam oral has too long a duration of action to be of any use as an acute sedative in the elderly.

Trazodone, an anti-depressant, is useful orally as a chronic anxiolytic.

Reference:

Kim KY et al. Treatment of Delirium in Older Adults with Quetiapine Journal of Geriatric Psychiatry and Neurology, Vol. 16, No. 1, 29-31 (2003)

Next question | Tag Question | Remove question

http://my.onexamination.com/Assessment/Questions.aspx

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 33 mins 15 secs

Question: 49 of 66

A 70-year-old woman presented with a relatively short history of headaches and episodic impairment of consciousness.

What is the most likely cause?

(Please select 1 option)

○	Alzheimer-type dementia
○	Chronic subdural haematoma
○	Creutzfeldt-Jacob disease
○	Depressive stupor
○	Normal pressure hydocephalus

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

A 70-year-old woman presented with a relatively short history of headaches and episodic impairment of consciousness.

What is the most likely cause?

(Please select 1 option)

○	Alzheimer-type dementia
◉	Chronic subdural haematoma ✓ Correct
○	Creutzfeldt-Jacob disease
○	Depressive stupor
○	Normal pressure hydocephalus

This is the classical presentation of subdural haematoma.

Headache, drowsiness and confusion are common and often fluctuate.

Both dementia and depressive stupor (immobile, mute, unresponsive but fully conscious) are not associated with impaired consciousness.

Normal pressure hydocephalus is characterised by dementia, apraxia and urinary incontinence.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Question: 4 of 66

You are completing a list of cremation form 5s for patients in the hospital where you work.

You examine one form where the junior doctor has completed the cause of death as stroke, but the patient appears to have fallen at home. The husband wants to arrange cremation as soon as possible.

Apparently the junior doctor is working nights and has gone home, so you cannot easily get hold of him to question him further.

Which of the following is true with respect to completion of the form?

(Please select 1 option)

○	Completion of form 5 to show that examination of the case has been "adequate" would be acceptable
○	It is acceptable in this case not to question the doctor
○	Medical referees will not mind if you have not contacted the doctor
◉	When completing form 5 you must only be reasonably sure that the patient suffered a stroke ✕ Incorrect answer selected
○	You should wait to complete the form until the doctor is available to answer questions ← This is the correct answer

Doctors are now instructed that form 5 should always be completed after questioning the doctor who completed form 4 except under exceptional circumstances, that is, only if the doctor is seriously ill.

Unavailability of the doctor is not an appropriate excuse, so quite clearly in this case you should wait to complete the form.

The other major principle with respect to completion of form 5 is that you must be absolutely sure that the cause of death is correct.

Ministry of Justice cremation guidelines

Next question

Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 11 mins 41 secs

Question: 5 of 66

A female patient of yours unfortunately goes into premature labour at 23 weeks. The fetus is not viable. She wishes to have the fetal remains cremated.

Which of the following is true with respect to legal aspects of this case?

(Please select 1 option)

- Cremation of the remains is not subject to the Cremation Act
- Only a pathologist is allowed to complete form 4
- Only form 4 need be completed
- Only form 5 need be completed
- The case must be discussed with the coroner

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 33 mins 41 secs

Question: 50 of 66

A 60-year-old man presents with an episode of memory loss. Three days earlier he had become confused. His wife led him into the house - he apparently sat down at her request, and had a cup of tea. He then wandered around the house, confused, but remained conscious and able to have some conversation with his wife, though continuing to ask similar questions repeatedly.

After three hours, he abruptly returned to normal and had no recollection of the events.

What is the most likely diagnosis?

(Please select 1 option)

○	Alcohol related amnesia
○	Chronic subdural haematoma
○	Complex partial status epilepticus
○	Hysterical fugue state
◉	Transient global amnesia

Submit answer | Skip question | Tag Question | Remove question

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Question: 50 of 66

A 60-year-old man presents with an episode of memory loss. Three days earlier he had become confused. His wife led him into the house - he apparently sat down at her request, and had a cup of tea. He then wandered around the house, confused, but remained conscious and able to have some conversation with his wife, though continuing to ask similar questions repeatedly.

After three hours, he abruptly returned to normal and had no recollection of the events.

What is the most likely diagnosis?

(Please select 1 option)

○	Alcohol related amnesia
○	Chronic subdural haematoma
○	Complex partial status epilepticus
○	Hysterical fugue state
◉	Transient global amnesia ✓ Correct

This is the typical clinical description of transient global amnesia which represents a transient vascular insufficiency of both hippocampi.

Next question

Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 37 mins 8 secs

Question: 51 of 66

A 45-year-old woman noticed tinnitus in her left ear which progressed over some weeks to hearing loss in that ear.

On physical examination she is found to have a marked decrease in hearing on the left, with Rinne test indicating air conduction better than bone conduction. The other cranial nerves I - VII and IX - XII are intact.

A brain MRI scan revealed a solitary, fairly discreet, 3 cm mass located in the region of the left cerebellopontine angle.

Which of the following statements is most appropriate to tell the patient regarding these findings?

(Please select 1 option)

○	A test for HIV-1 is likely to be positive
○	Other family members should undergo MR imaging of the brain
○	Remissions and exacerbations are likely to occur in coming years
○	The lesion can be resected with a good prognosis
○	You are unlikely to survive for more than a year

Submit answer | Skip question | Tag Question | Remove question

Question: 51 of 66

A 45-year-old woman noticed tinnitus in her left ear which progressed over some weeks to hearing loss in that ear.

On physical examination she is found to have a marked decrease in hearing on the left, with Rinne test indicating air conduction better than bone conduction. The other cranial nerves I - VII and IX - XII are intact.

A brain MRI scan revealed a solitary, fairly discreet, 3 cm mass located in the region of the left cerebellopontine angle.

Which of the following statements is most appropriate to tell the patient regarding these findings?

(Please select 1 option)

○	A test for HIV-1 is likely to be positive
○	Other family members should undergo MR imaging of the brain
○	Remissions and exacerbations are likely to occur in coming years
◉	The lesion can be resected with a good prognosis ✓ Correct
○	You are unlikely to survive for more than a year

These acoustic neuromas are benign neoplasms.

A solitary mass is unlikely to be part of neurofibromatosis (which could be familial).

Next question

Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 38 mins 54 secs

Question: 52 of 66

A 72-year-old woman has a five year history of worsening mental functioning with trouble remembering things. She has no problems with movement.

She is noted on an MRI scan of the brain to have symmetrically increased size of the lateral ventricles along with cerebral cortical atrophy in a mainly frontal and parietal distribution.

A lumbar puncture reveals a normal opening pressure, and analysis of the clear, colorless cerebrospinal fluid reveals glucose and protein which are in normal ranges.

Cell count on the CSF shows 3 WBCs (all lymphocytes) and 1 RBC.

A fundoscopic examination is normal.

Which of the following findings is most likely associated with her underlying disease process?

(Please select 1 option)

○	Increased numbers of Lewy bodies
○	Loss of Betz cells
○	Loss of gamma aminobutyric acid (GABA)
○	Perivascular mononuclear inflammation
○	Presence of the e4 allele of apolipoprotein E

- Help
- Shop

A lumbar puncture reveals a normal opening pressure, and analysis of the clear, colorless cerebrospinal fluid reveals glucose and protein which are in normal ranges.

Cell count on the CSF shows 3 WBCs (all lymphocytes) and 1 RBC.

A fundoscopic examination is normal.

Which of the following findings is most likely associated with her underlying disease process?

(Please select 1 option)

○	Increased numbers of Lewy bodies
○	Loss of Betz cells
◉	Loss of gamma aminobutyric acid (GABA) ✕ Incorrect answer selected
○	Perivascular mononuclear inflammation
○	Presence of the e4 allele of apolipoprotein E ← This is the correct answer

She has findings characteristic for Alzheimer's disease.

Loss of GABA is seen in Parkinson's disease.

Perivascular mononuclear inflammation is seen in multiple sclerosis.

Loss of Betz cells is seen in motor neurone disease.

Next question

Remove Tag | Remove question

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 41 mins 51 secs

Question: 53 of 66

A 35-year-old healthy woman has a faint systolic murmur on physical examination. An echocardiogram is performed, and she is found to have a bicuspid aortic valve.

In explaining the meaning of this finding to her, which is the most appropriate statement?

(Please select 1 option)

○	An aortic valve replacement is eventually likely to be required
○	Other family members are likely to have the same condition
○	She should be treated with a cholesterol-lowering agent
○	The problem has resulted from past injection drug usage
○	This is one manifestation of an underlying autoimmune disease process

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

A 35-year-old healthy woman has a faint systolic murmur on physical examination. An echocardiogram is performed, and she is found to have a bicuspid aortic valve.

In explaining the meaning of this finding to her, which is the most appropriate statement?

(Please select 1 option)

◉	An aortic valve replacement is eventually likely to be required ✓ Correct
○	Other family members are likely to have the same condition
○	She should be treated with a cholesterol-lowering agent
○	The problem has resulted from past injection drug usage
○	This is one manifestation of an underlying autoimmune disease process

Bicuspid aortic valve (BAV) is perhaps the most common form of congenital heart disease in adults (1-2% of population).

Bicuspid valves have a propensity to wear out and calcify with ageing. Bicuspid aortic valve tends to be sporadic although there is a reported familial incidence of approximately 9%.

From a review of several sources in the literature, the Aeromedical Consultation Service (ACS) at Brooks AFB calculated a 1.2% per year incidence of aortic valve surgery in individuals with BAV, although the vast majority occur in the fifth and sixth decades of life.

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 43 mins 6 secs

Question: 54 of 66

A 74-year-old man has had increasingly severe, throbbing headaches for several months, centered on the right.

There is a palpable tender cord-like area over his right temple. His heart rate is regular with no murmurs, gallops, or rubs. Pulses are equal and full in all extremities, BP is 110/85 mmHg.

A biopsy of this lesion is obtained, and histologic examination reveals a muscular artery with lumenal narrowing and medial inflammation with lymphocytes, macrophages, and occasional giant cells.

He improves with a course of high-dose corticosteroid therapy.

Which of the following laboratory test findings is most likely to be present with this disease?

(Please select 1 option)

○	Anti-double stranded DNA titre of 1:1024
○	Erythrocyte sedimentation rate of 110 mm/hr
○	HDL cholesterol of 0.6 mmol/L
○	pANCA titre of 1:160
○	Rheumatoid factor titre of 80 IU/mL

Submit answer | Skip question | Tag Question | Remove question

Avira
Update was finished successfully.
There were 2 new files installed.
Do not show this message again.
OK

rubs. Pulses are equal and full in all extremities; BP is 110/65 mmHg.

A biopsy of this lesion is obtained, and histologic examination reveals a muscular artery with lumenal narrowing and medial inflammation with lymphocytes, macrophages, and occasional giant cells.

He improves with a course of high-dose corticosteroid therapy.

Which of the following laboratory test findings is most likely to be present with this disease?

(Please select 1 option)

○	Anti-double stranded DNA titre of 1:1024
◉	Erythrocyte sedimentation rate of 110 mm/hr ✓ Correct
○	HDL cholesterol of 0.6 mmol/L
○	pANCA titre of 1:160
○	Rheumatoid factor titre of 80 IU/mL

These are classic findings for temporal arteritis, the most typical involvement with giant cell arteritis.

Corticosteroid therapy typically produces a reduction of symptoms.

Not treating this condition puts the patient at risk for involvement of other branches of the external carotid artery, the worst of which would be the ophthalmic branch.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 44 mins 35 secs

Question: 55 of 66

A 70-year-old woman presented with episodic impairment of consciousness.

Which of the following is the most likely cause?

(Please select 1 option)

○	Alzheimer type dementia
○	Chronic subdural haematoma
○	Creutzfeldt-Jakob disease
○	Depressive stupor
○	Normal pressure hydrocephalus

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

A 70-year-old woman presented with episodic impairment of consciousness.

Which of the following is the most likely cause?

(Please select 1 option)

○	Alzheimer type dementia
◉	Chronic subdural haematoma ✓ Correct
○	Creutzfeldt-Jakob disease
○	Depressive stupor
○	Normal pressure hydrocephalus

This is quite a grey question. The clinical scenario is very brief with no mention of any neurological signs so a logical deduction must be made.

Alzheimer's disease would be expected to have a continous impairment of consciousness in its advanced stages but could be episodic if there were variation in drugs therapy or concurrent illnesses.

Similarly normal pressure hydrocephalus, Creutzfeldt-Jakob and depression would present with dementia (or apparent dementia) but not fluctuant.

Of all those listed, subdural haematoma is classically associated with fluctuating level of consciousness. This would make it the most likely.

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 45 mins 8 secs

Question: 56 of 66

A 72-year-old male presented with a quadrantic hemianopia.

Which of the following conditions is most likely to cause such a presentation?

(Please select 1 option)

- A lesion of the occipital cortex
- A lesion of the optic chiasma
- Bilateral diabetic retinopathy
- Chloroquine poisoning
- Tobacco amblyopia

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Question: 56 of 66

A 72-year-old male presented with a quadrantic hemianopia.

Which of the following conditions is most likely to cause such a presentation?

(Please select 1 option)

○	A lesion of the occipital cortex ← This is the correct answer
◉	A lesion of the optic chiasma ✕ Incorrect answer selected
○	Bilateral diabetic retinopathy
○	Chloroquine poisoning
○	Tobacco amblyopia

A lesion of the optic chiasm would cause a bitemporal hemianopia.

Diabetic retinopathy may cause an 'apparent quadrantic hemianopia' because the distribution of the retinal changes may just correspond to quadrantic hemianopia - but this is not the most likely.

Tobacco amblyopia causes symmetric central or centrocaecal scotomas.

Chloroquine poisoning causes symmetric bilateral scotomas.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 46 mins 33 secs

Question: 57 of 66

Which of the following features is characteristic of early Alzheimer's disease?

(Please select 1 option)

○	Ataxic gait
○	Impaired short term memory
○	Myoclonic jerks
○	Urinary incontinence
○	Visual hallucinations

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Question: 57 of 66

Which of the following features is characteristic of early Alzheimer's disease?

(Please select 1 option)

○	Ataxic gait
◉	Impaired short term memory ✓ Correct
○	Myoclonic jerks
○	Urinary incontinence
○	Visual hallucinations

Alzheimer's disease is characterised early in the disease by short term memory loss.

The other features listed here would suggest an alternative diagnosis such as:

- normal pressure hydrocephalus (gait ataxia and urinary incontinence),

- Creutzfeld-Jacob disease (myoclonic jerks) and

- delirium or vascular dementia (visual hallucinations).

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 46 mins 57 secs

Question: 58 of 66

Which one of the following is associated with parkinsonian features?

(Please select 1 option)

○	Chronic carbon dioxide retention
○	Kernicterus
○	Lead poisoning
○	Mercury poisoning
○	Wilson's disease

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

◉	Chronic carbon dioxide retention ✕ Incorrect answer selected
○	Kernicterus
○	Lead poisoning
○	Mercury poisoning
○	Wilson's disease ← This is the correct answer

Poisons that can cause parkinsonism include:

- manganese
- carbon monoxide
- carbon disulfide
- the cycad nut and
- the illicit drug MPTP (methyl-phenyl tetrahydropyridine).

There are also other diseases of the brain that combine parkinsonism.

These include:

- Wilson's disease
- Huntington's disease
- Shy-Drager syndrome
- striatonigral degeneration
- olivo-ponto-cerebellar degeneration
- cortical-basal ganglionic degeneration
- progressive supranuclear palsy
- diffuse Lewy body disease
- Creutzfeldt-Jacob disease and even
- Alzheimer's disease.

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 47 mins 48 secs

Question: 59 of 66

Which one of the following is a recognised feature of achondroplasia?

(Please select 1 option)

- Autosomal recessive inheritance
- May be diagnosed radiologically at birth
- Increased liability to pathological fractures
- Shortened spine
- Subfertility

Submit answer | Skip question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Which one of the following is a recognised feature of achondroplasia?

(Please select 1 option)

◉	Autosomal recessive inheritance ✗ Incorrect answer selected
○	May be diagnosed radiologically at birth ← This is the correct answer
○	Increased liability to pathological fractures
○	Shortened spine
○	Subfertility

Achondroplasia an autosomal dominant condition and one of the commonest forms of inherited dwarfism.

Epiphyseal dysplasia - thin zone of cartilage cells, diminished columnar arrangement short thick bones, spinal length almost always normal.

Features - short limbs, normal trunk, large head, saddle nose, exagerrated lumbar lordosis normal mental and sexual development, spinal problems.

Homozygotes - neonatal death.

(Harrisons)

Next question

Remove Tag

Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 14 mins 53 secs

Question: 5 of 66

A female patient of yours unfortunately goes into premature labour at 23 weeks. The fetus is not viable. She wishes to have the fetal remains cremated.

Which of the following is true with respect to legal aspects of this case?

(Please select 1 option)

○	Cremation of the remains is not subject to the Cremation Act ← This is the correct answer
○	Only a pathologist is allowed to complete form 4
○	Only form 4 need be completed
○	Only form 5 need be completed
◉	The case must be discussed with the coroner ✕ Incorrect answer selected

Cremation of fetal remains under 24 weeks is not subject to the Cremation Act.

As such, forms 4 and 5 should not be completed.

In spite of this, most crematoria are happy to make arrangements to cremate fetal remains.

Where body parts are removed at post mortem, arrangements for cremation of these are normally made by the pathology service.

Ministry of Justice cremation guidelines

Next question

Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 14 mins 53 secs

Question: 6 of 66

You are the general practitioner of a 76-year-old man who has been suffering from bronchial carcinoma for the past one and a half years. He is requiring increasing amounts of morphine to cope with his pain, and he dies in his sleep.

You certify the cause of death as bronchial carcinoma.

His wife who requests cremation asks to see form 4.

Which of the following is true with respect to her viewing the form?

(Please select 1 option)

- She is not allowed to view it under any circumstances
- The form should be typewritten if possible
- The name of the completing doctor must be obscured
- You can apply for certain information not to be disclosed by discussing this with the referee
- You cannot prevent her from reviewing all aspects of the form

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 48 mins 35 secs

Question: 60 of 66

Which of the following is a recognised feature of polymyalgia rheumatica?

(Please select 1 option)

- Weakness of distal muscle groups
- Elevated serum creatine phosphokinase activity
- An association with bronchial carcinoma
- Weight loss
- A peak incidence in the fourth decade of life

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 49 mins 18 secs

Question: 60 of 66

Which of the following is a recognised feature of polymyalgia rheumatica?

(Please select 1 option)

○	Weakness of distal muscle groups
○	Elevated serum creatine phosphokinase activity
○	An association with bronchial carcinoma
◉	Weight loss ✓ Correct
○	A peak incidence in the fourth decade of life

A. Stiffness and weakness is more typical of polymyositis.

B. This would suggest polymyositis.

C. This is typical.

E. It occcurs later in life.

Next question

Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 49 mins 18 secs

Question: 61 of 66

A 60-year-old man with a past history of controlled hypertension presents with acute onset weakness of his left arm, that resolved over 12 hours. He had suffered two similar episodes over the last three months.

Examination reveals a blood pressure of 132/82 mmHg and he is in atrial fibrillation with a ventricular rate of 85 per minute. CT brain scan is normal.

What is the most appropriate management?

(Please select 1 option)

- Amiodarone
- Aspirin
- Digoxin
- Dipyridamole
- Warfarin

Submit answer | Skip question | Tag Question | Remove question

Question: 61 of 66

A 60-year-old man with a past history of controlled hypertension presents with acute onset weakness of his left arm, that resolved over 12 hours. He had suffered two similar episodes over the last three months.

Examination reveals a blood pressure of 132/82 mmHg and he is in atrial fibrillation with a ventricular rate of 85 per minute. CT brain scan is normal.

What is the most appropriate management?

(Please select 1 option)

○	Amiodarone
○	Aspirin
○	Digoxin
○	Dipyridamole
◉	Warfarin ✓ Correct

This patient has had three transient ischaemic attacks due to atrial fibrillation.

The most appropriate therapeutic strategy for this patient would be warfarin. Studies reveal that warfarin would be therapeutically superior to aspirin in such a patient's case.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 50 mins 26 secs

Question: 62 of 66

A 19-year-old woman presents to the clinic having had five blackouts over the last year, all while she is standing up.

She gets warnings of blurred vision, nausea, and feeling hot. She has been witnessed twice to have jerking of all limbs while she is unconscious. The attacks last 30 to 60 seconds.

She recovers quickly after the attacks. She has never bitten her tongue or sustained any injuries.

Physical examination and an ECG are normal. Her grandmother and sister suffer from epilepsy.

Which of the following investigations is the most appropriate?

(Please select 1 option)

○	24 hour ECG recording
○	CT brain
○	ECHO
○	EEG
◉	Tilt table test

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Shop

Which of the following investigations is the most appropriate?

(Please select 1 option)

○	24 hour ECG recording
○	CT brain
○	ECHO
○	EEG
◉	Tilt table test ✓ Correct

The most likely diagnosis is vasovagal syncope.

The gradual onset of the attack is typical. It is common for patients with syncope to have jerking of their limbs while they are unconscious.

Warning symptoms of darkening/blurring of vision, dizziness, an feeling hot, are characteristic in syncope. Patients usually recover very quickly after the event.

Tilt table test is a useful test to support the diagnosis of vasovagal syncope.

Further reading:
Head-upright tilt t able testing Postgraduate Medicine

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 54 mins 1 secs

Question: 63 of 66

Temporal lobe lesions cause:

(Please select 1 option)

○	Apraxia
○	Astereognosis
○	Primitive reflexes
○	Visuospatial neglect
◉	Wernicke's (receptive) aphasia

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

○	Apraxia
○	Astereognosis
○	Primitive reflexes
○	Visuospatial neglect
◉	Wernicke's (receptive) aphasia ✓ Correct

Lesions of the frontal lobe include difficulties with task sequencing and executive skills.

Other symptoms include:

- expressive aphasia (receptive aphasias are due to a temporal lobe lesion)

- primitive reflexes

-perseveration (repeatedly asking the same question or performing the same task)

- anosmia and

- changes in personality.

Lesions of the parietal lobe include:

- apraxias

- neglect

- astereognosis (unable to recognise an object by feeling it) and

- visual field defects (typically homonymous inferior quadrantanopia).

They may also cause alcalculia (inability to perform mental arithmetic).

Lesions of the temporal lobe cause:

- changes in personality.

Lesions of the parietal lobe include:

- apraxias

- neglect

- astereognosis (unable to recognise an object by feeling it) and

- visual field defects (typically homonymous inferior quadrantanopia).

They may also cause alcalculia (inability to perform mental arithmetic).

Lesions of the temporal lobe cause:

- visual field defects (typically homonymous superior quadrantanopia)

- Wernicke's (receptive) aphasia

- auditory agnosia, and

- memory impairment.

Occipital lobe lesions include:

- cortical blindness (blindness due to damage to the visual cortex and may present as Anton syndrome where there is blindness but the patient is unaware or denies blindness)

- homonymous hemianopia and

- visual agnosia (seeing but not percieving objects - it is different to neglect since in agnosia the objects are seen and followed but cannot be named).

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 54 mins 45 secs

Question: 64 of 66

A 62-year-old lady is suffering from pain and stiffness of her shoulders and difficulty getting out of a chair.

Which of the following would support a diagnosis of polymyalgia rheumatica?

(Please select 1 option)

- Ankle stiffness
- Low grade fever
- Muscle tenderness
- Proximal muscle weakness
- Weight gain

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

(Please select 1 option)

○	Ankle stiffness
○	Low grade fever ← This is the correct answer
○	Muscle tenderness
◉	Proximal muscle weakness ✕ Incorrect answer selected
○	Weight gain

Polymyalgia rheumatica presents with early morning stiffness of the shoulder and pelvic girdles, fever, anorexia, weight loss and malaise.

There is no muscle tenderness or weakness and the feet are never affected.

Investigations may reveal:

- Normochromic / normocytic anaemia
- Raised erythrocyte sedimentation rate (ESR) often > 50 mm/hr
- Raised alkaline phosphatase (ALP) and
- Raised C-reactive protein (CRP).

Features of giant cell arteritis should be sought:

- Headache
- Visual disturbance
- Transient ischaemic attacks (TIAs)
- Jaw claudication and
- Thickened, tender, pulseless temporal arteries.

Diagnosis is by temporal artery biopsy and/or characteristic response to steroids.

EN
1:08 PM
2/26/2011

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 55 mins 47 secs

Question: 65 of 66

Osteomalacia may be expected in:

(Please select 1 option)

- Auto-immune adrenalitis
- Mercury poisoning
- Pernicious anaemia
- Pseudo-hypoparathyroidism
- Sarcoidosis

Submit answer | Skip question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 59 mins 44 secs

Question: 65 of 66

Osteomalacia may be expected in:

(Please select 1 option)

○	Auto-immune adrenalitis
◉	Mercury poisoning ✓ Correct
○	Pernicious anaemia
○	Pseudo-hypoparathyroidism
○	Sarcoidosis

Osteomalacia may occur with vitamin D deficiency.

Mercury poisoning or any heavy metal poisoning causes an acquired Fanconi syndrome with distal renal tubular acidosis.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 59 mins 44 secs

Question: 66 of 66

A 72-year-old lady has four months of memory loss, urinary incontinence and falls.

On examination she has mild memory loss and a broad-based, slow gait. Muscle tone is normal and both plantar reflexes are downgoing.

What is the likely diagnosis?

(Please select 1 option)

○	Alzheimer's disease
○	Frontal lobe dementia
○	Multi-infarct dementia
○	Normal-pressure hydrocephalus
○	Parkinson's disease

Submit answer | Skip question | Tag Question | Remove question

On examination she has mild memory loss and a broad-based, slow gait. Muscle tone is normal and both plantar reflexes are downgoing.

What is the likely diagnosis?

(Please select 1 option)

○	Alzheimer's disease
○	Frontal lobe dementia
○	Multi-infarct dementia
◉	Normal-pressure hydrocephalus ✓ Correct
○	Parkinson's disease

Normal-pressure hydrocephalus is characterised by abnormal gait, urinary incontinence, and dementia.

It is an important clinical diagnosis, because it is a potentially reversible cause of dementia.

It is important to distinguish it from Parkinson's disease.

The onset of gait disturbance and urinary symptoms is unusual so early in dementia.

Frontal lobe dementia is characterised by loss of 'executive' functions and multi-infarct state usually has a step-wise history.

Finish

Tag Question

Remove question

You are the general practitioner of a 76-year-old man who has been suffering from bronchial carcinoma for the past one and a half years. He is requiring increasing amounts of morphine to cope with his pain, and he dies in his sleep.

You certify the cause of death as bronchial carcinoma.

His wife who requests cremation asks to see form 4.

Which of the following is true with respect to her viewing the form?

(Please select 1 option)

○	She is not allowed to view it under any circumstances
○	The form should be typewritten if possible
○	The name of the completing doctor must be obscured
○	You can apply for certain information not to be disclosed by discussing this with the referee ← This is the correct answer
◉	You cannot prevent her from reviewing all aspects of the form ✕ Incorrect answer selected

The recent cremation regulations detail that the cremation applicant can view the form.

There may be circumstances though when you wish for certain information not to be disclosed, that the patient may have told you in confidence. In this case you can write to the cremation referee requesting that certain pieces of information are withheld.

When you complete the form it is important that you remember the information may be seen by a relative; also make sure that your handwriting is as legible as possible.

Ministry of Justice cremation guidelines

Next question

Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 19 mins 56 secs

Question: 7 of 66

You are working for the elderly care team in the hospital when an 82-year-old woman under your care is found dead by the nursing staff in the early hours of the morning.

She was not resuscitated due to a history of severe chronic obstructive pulmonary disease (COPD).

You have written the cause of death as old age and you complete cremation form 4.

Which of the following is true with respect to completion of the forms?

(Please select 1 option)

- Civil proceedings have been taken against doctors who have inappropriately completed form 5
- Old age is usually not an acceptable cause of death for cremation purposes when completing form 4
- The consultant who heads up the team may complete form 5
- The locum staff grade who qualified three years ago in India may sign form 5
- Your brother who is a house officer on another team at the hospital may sign form 5

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

the early hours of the morning.

She was not resuscitated due to a history of severe chronic obstructive pulmonary disease (COPD).

You have written the cause of death as old age and you complete cremation form 4.

Which of the following is true with respect to completion of the forms?

(Please select 1 option)

○	Civil proceedings have been taken against doctors who have inappropriately completed form 5
◉	Old age is usually not an acceptable cause of death for cremation purposes when completing form 4 ✓ Correct
○	The consultant who heads up the team may complete form 5
○	The locum staff grade who qualified three years ago in India may sign form 5
○	Your brother who is a house officer on another team at the hospital may sign form 5

A key point with respect to completing form 4 is that the cause of death must be accurately established.

Whilst old age may be acceptable when certifying for a burial, it is not accepted by cremation referees.

The latest guidelines for doctors include specific instructions that members of the same hospital team as the physician completing part 4 must not complete the form, nor may partners in the same GP practice complete the form either.

Additionally, relatives of the patient are forbidden from completing either form 4 or 5, and relatives of the doctor who completes form 4 cannot complete form 5.

Ministry of Justice cremation guidelines

Next question

Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 21 mins 37 secs

Question: 8 of 66

An 85-year-old patient presents with recurrent falls and a fracture of the distal ulna.

Which of the following statements is correct?

(Please select 1 option)

○	Bone fractures attributable to vitamin D deficiency are due to bone density
○	Low Vitamin D levels are not associated with muscle weakness
○	The toxic levels of Vitamin D occur at approximately twice the therapeutic dose
○	Vitamin D deficiency in the elderly is rare
○	Vitamin D replacement reduces the incidence of fractures in the elderly

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

○	Low Vitamin D levels are not associated with muscle weakness
○	The toxic levels of Vitamin D occur at approximately twice the therapeutic dose
○	Vitamin D deficiency in the elderly is rare
◉	Vitamin D replacement reduces the incidence of fractures in the elderly ✓ Correct

The clue is in the question!

Vitamin D deficiency in the elderly is common, especially in the housebound and those in residential and nursing homes, with an overall frequency of 17% in women aged 85 and over.

Vitamin D deficiency is associated with muscle weakness, as well as osteomalacia, and fractures among elderly people with vitamin D deficiency are often not attributable to reduced bone density.

Vitamin D replacement (800 IU daily) with calcium, has been shown to reduce falls and fractures by 47% compared with controls who received calcium only.

The correct dose of vitamin D replacement should be 800 IU.

Lowest doses at which adverse events have been observed with Vitamin D replacement are 200 nmol/l, which equates to a daily dose of 40,000 IU. See BMJ 2005;330:524-6.

Further reading:
Fracture prevention with vitamin D supplementation: a meta-analysis of randomized controlled trials JAMA 2005 May 11;293 (18):2257-64

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 23 mins 33 secs

Question: 9 of 66

You are asked to see a young man with a severe laceration to his arm.

Before you suture the wound, the patient tells you that he is HIV positive but asks you not to write it in his notes.

He tells you later in the conversation that he is a theatre nurse in a neighbouring hospital. He says that he has not told his employer about his HIV status as it does not impact on his work, and tells you that if you tell anybody he will "get you" for discrimination.

Which of the following is the most appropriate action that should be taken in this case?

(Please select 1 option)

○	Doctors should never inform a third party that a patient is HIV positive without the express consent of the patient.
○	You should arrange for the patient to have an HIV test and confirm the diagnosis before considering breaching his confidentiality.
○	You should discuss with your consultant and, if you feel the patient is practising in a way that places patients at risk, inform the occupational health department at his employing hospital, having informed the patient that you intend to do so.
○	You should tell the hospital infectious diseases consultant in order that the patient can be offered ongoing treatment for HIV
○	You should tell the patient that in your opinion he should inform his employer, but take no action yourself.

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

○	You should arrange for the patient to have an HIV test and confirm the diagnosis before considering breaching his confidentiality.
◉	You should discuss with your consultant and, if you feel the patient is practising in a way that places patients at risk, inform the occupational health department at his employing hospital, having informed the patient that you intend to do so. ✓ Correct
○	You should tell the hospital infectious diseases consultant in order that the patient can be offered ongoing treatment for HIV
○	You should tell the patient that in your opinion he should inform his employer, but take no action yourself.

You should discuss this with your consultant.

You have a duty as a doctor to protect all patients, not only your own, and this duty must be weighed against your duty of confidentiality to this patient.

The GMC expect doctors to breach confidentiality in certain circumstances where failing to do so may expose the patient or others to risk of death or serious harm, for example where a healthcare worker is practising in a way that places patients at risk.

As a doctor you may be called upon to justify your decision to disclose (or indeed to not disclose), and it would certainly be helpful to take senior advice.

If you decide to disclose information without consent, you should disclose the minimum necessary information to the minimum number of people for purpose.

In this case you may consider disclosing to the occupational health physician in the hospital where the patient works, although you may also consider disclosing the information to the nurses' regulatory body, the Nursing and Midwifery Council.

Business Link

Application for cremation of the body of a person who has died

Cremation 1
replacing Form A
01.09

This form can only be completed by a person who is at least 16 years of age.
Please complete this form in full, if a part does not apply enter 'N/A'.

Part 1 Details of the crematorium

Name of crematorium where cremation will take place

Name of funeral director

Telephone number

Part 2 Your details (the applicant)

Your full name

Address

Telephone number

Part 3 Details of the person who has died

Full name

Address

Occupation or last occupation if retired or not in work at date of death

continued over the page

Part 3 continued

Age at date of death

Sex

☐ Male ☐ Female

Status

☐ married/civil partnership ☐ widow/widower/surviving civil partner ☐ Single

Part 4 The application

1. Are you a near relative or an executor of the person who has died? ☐ Yes ☐ No

Near relative means the widow, widower or surviving civil partner of the person who has died, or a parent or child of the person who has died, or any other relative usually residing with the person who has died.

If No, please give the nature of your relationship and explain why you are making the application rather than a near relative or an executor.

2. Is there any near relative(s) or executor(s) who has not been informed of the proposed cremation? ☐ Yes ☐ No

If Yes, please give the name(s) and the reason(s) why they have not been contacted.

3. Has any near relative or executor expressed any objection to the proposed cremation? ☐ Yes ☐ No

If Yes, please give details.

4. What was the date and time of death of the person who has died?

Date ☐☐/☐☐/☐☐☐☐

Time

continued over the page

Part 4 continued

5. Please give the address where the person died.

Address

Please state whether it was the residence of the person who has died or a hotel, hospital, or nursing home etc.

- ☐ Their home
- ☐ Hospital
- ☐ Other (please specify)
- ☐ Hotel
- ☐ Nursing home

6. Do you know or suspect that the death of the person who has died was violent or unnatural? ☐ Yes ☐ No

7. Do you consider that there should be any further examination of the remains of the person who has died? ☐ Yes ☐ No

If you have answered Yes to questions **6** or **7**, please give reasons below.

8. What is the name, address and telephone number of the usual doctor of the person who has died?

Doctor's name

Address

Telephone number

continued over the page

9. Please give the name, address and telephone number of the doctor(s) who attended the person who has died during their last illness.

Doctor's name

Address

Telephone number

Doctor's name

Address

Telephone number

10. Was any implant placed in the body which may become hazardous when the body is cremated (e.g. a pacemaker, radioactive device or "Fixion" intramedullary nailing system)?

☐ Yes ☐ No

☐ I don't know

Implants may damage cremation equipment if not removed from the body of the deceased before cremation and some radioactive treatments may endanger the health of crematorium staff.

If Yes, please give details and state whether it has been removed.

Part 5 Inspection of certificates

You are entitled to inspect the certificates (if any) given by doctors under regulation 16(c)(i) of the Cremation Regulations 2008 (forms Cremation 4 and Cremation 5). If you do not wish to inspect any such certificates yourself you may nominate another person to inspect them instead of you.

Such certificates will only be available for inspection at the offices of the cremation authority for **48 hours** from the time that the cremation authority notifies you, or the person you have nominated, that the certificates are available to be inspected. You may take someone with you when you attend to inspect the certificates. If you, or the person nominated by you, do not attend to inspect the certificates at the time agreed with the cremation authority, the cremation may then proceed.

Please state if you would like to inspect the certificates given by the doctors or whether you would like to nominate someone else to do so instead and give a contact telephone number.

If certificates are given by medical practitioners:-

☐ I would like to inspect the certificates and

my contact telephone number is

☐ I nominate

to inspect the certificates and their contact telephone number is

---

Part 6 Statement of truth

I apply for the body of the person who has died to be cremated and I certify that I am at least 16 years of age.

I believe that the facts given in this application are true. I am aware that it is an offence to wilfully make a false statement with a view to obtaining the cremation of any human remains.

Print your full name

Signed

Dated

☐☐/☐☐/☐☐☐☐

Authorisation of cremation of deceased person by medical referee

Cremation 10
replacing Form F
01.09

Please complete this form in full, if a part does not apply enter 'N/A'.

Part 1 Details of the deceased

Full name

Address

Occupation or last occupation if retired or not in work at date of death

Part 2 Authorisation by medical referee

An application has been made for the cremation of the remains of the deceased.

I am satisfied that—

(a) the requirements of the Cremation (England and Wales) Regulations 2008 have been complied with;

(b) the inquiry/examination made by the persons who gave the relevant certificates has been adequate; and

(c) the fact and cause of death have been definitely ascertained or, if not ascertained, a coroner has opened an inquest.

Accordingly, I authorise the Registrar of the following crematorium to cremate the remains of the deceased within that crematorium—

Name of crematorium

Print your full name

Cremation authority

Signed

Dated / /

Regulation 23(1) of the Cremation (England and Wales) Regulations 2008

Certificate after post-mortem examination

Please complete this form in full, if a part does not apply enter 'N/A'.

Part 1 Details of the deceased

Full name

Address

Occupation or last occupation if retired or not in work at date of death

Part 2 Certification of person making post-mortem examination

I certify that I have made a post-mortem examination of the remains of the deceased under the authority of a licence granted under the Human Tissue Act 2004 for that purpose and the appropriate consents required by that Act having been obtained.

I am satisfied that the cause of death was

1. (a) Disease or condition directly leading to death (this does not mean the mode of dying, such as heart failure, asphyxia, asthenia, etc: it means the disease, injury, or complication which caused death)

(b) Other disease or condition, if any, leading to (a)

(c) Other disease or condition, if any, leading to (b)

continued over the page

Part 2 continued

2. Other significant conditions contributing to the death but not related to the disease or condition causing it.

☐ I am satisfied that there is no reason for making any toxicological analysis.

If a toxicology analysis has been made have the results been stated in this certificate or are they attached?

☐ stated in this certificate
☐ attached to this certificate

☐ I am satisfied that there is no reason for the holding of an inquest.

If the cause of death is such as to require that an inquest be held, the coroner should issue a certificate and meet the costs of the post-mortem examination by paying the fee prescribed by the Secretary of State.

I am aware that it is an offence to wilfully make a false statement with a view to obtaining the cremation of any human remains.

Your full name

Address

Registered qualifications

GMC reference number

Signed

Dated

Authorisation of cremation of body parts by medical referee

Cremation 12
replacing Form FF
01.09

Please complete this form in full, if a part does not apply enter 'N/A'.

Part 1 The deceased/stillborn child

In the case of a stillborn child who has not been given a name, insert a description sufficient to identify the body.

Full name

Address

Part 2 Authorisation by medical referee

An application has been made for the cremation of the body parts of the deceased/stillborn child.

I am satisfied that the requirements of the Cremation (England and Wales) Regulations 2008 have been complied with.

Accordingly, I authorise the Registrar of the following crematorium to cremate the remains of the deceased within that crematorium—

Name of crematorium

Print your full name

Cremation authority

Signed

Dated

Authorisation of cremation of stillborn child by medical referee

Cremation 13
introduced in 2009
01.09

Please complete this form in full, if a part does not apply enter 'N/A'.

Part 1 The stillborn child

Full name of child or description

Sex

☐ Male ☐ Female

Part 2 Authorisation by medical referee

An application has been made for the cremation of the stillborn child.

I am satisfied that—

(a) the requirements of the Cremation (England and Wales) Regulations 2008 have been complied with;

(b) the examination made by the person who gave the relevant certificate has been adequate; and

(c) there is no reason for further examination.

Accordingly, I authorise the Registrar of the following crematorium to cremate the stillborn child within that crematorium—

Name of crematorium

Print your full name

Cremation authority

Signed

Dated

☐☐/☐☐/☐☐☐☐

Application for cremation of body parts

Cremation 2
replacing Form AA
01.09

Body parts means material consisting of, or including, human cells from a deceased person or stillborn baby.

This form can only be completed by a person who is at least 16 years of age.
Please complete this form in full, if a part does not apply enter 'N/A'.

If your application is about a stillborn baby, replace the words 'person who has died' throughout this form with the words 'stillborn baby'.

Part 1 Details of the crematorium

Name of crematorium where cremation will take place

Name of funeral director

Telephone number

Part 2 Your details (the applicant)

Your full name

Address

Telephone number

Part 3 Details of the person who has died

In the case of a stillborn baby who has not been given a name, in place of the name and address insert a description sufficient to identify the baby.

Full name

Address

continued over the page

Part 3 continued

Age at date of death

Sex

☐ Male ☐ Female

Status

☐ married/civil partnership ☐ widow/widower/surviving civil partner ☐ Single

Part 4 The application

1. Are you a near relative or an executor of the person who has died? ☐ Yes ☐ No

Near relative means the widow, widower or surviving civil partner of the person who has died, or a parent or child of the person who has died, or any other relative usually residing with the person who has died, or a parent of a stillborn baby.

If No, please give the nature of your relationship and explain why you are making the application rather than a near relative or an executor.

2. Is there any near relative(s) or executor(s) who has not been informed of the proposed cremation? ☐ Yes ☐ No

If Yes, please give the name(s) and the reason(s) why they have not been contacted.

3. Has any near relative or executor expressed any objection to the proposed cremation? ☐ Yes ☐ No

If Yes, please give details.

continued over the page

Part 4 continued

4. What was the date and place of the death or stillbirth?

Date

Address

5. Please give the name and address of the cemetery, churchyard or crematorium where the body of the person who has died was buried or cremated.

Name of cemetery, churchyard or crematorium

Address

6. Please give the date that the burial or cremation took place.

Date

7. Please state whether the body parts were removed from the body of the person who has died at a:

☐ Coroner's post-mortem examination ☐ Hospital post-mortem examination

☐ Other (please specify)

continued over the page

Part 4 continued

8. Do you consider that there should be any further examination of the remains of the person who has died? ☐ Yes ☐ No

If Yes, please give reasons below.

Part 5 Statement of truth

I apply for the following body parts of the person who has died to be cremated and I certify that I am at least 16 years of age.

Specify body parts to be cremated.

I believe that the facts given in this application are true. I am aware that it is an offence to wilfully make a false statement with a view to obtaining the cremation of any human remains.

Print your full name

Signed

Dated ☐☐/☐☐/☐☐☐☐

Application for cremation of stillborn baby

Cremation 3
introduced in 2009
01.09

This form can only be completed by a person who is at least 16 years of age.
Please complete this form in full, if a part does not apply enter 'N/A'.

Part 1 Details of the crematorium

Name of crematorium where cremation will take place

Name of funeral director

Telephone number

Part 2 Your details (the applicant)

Your full name

Address

Telephone number

Part 3 Details of the stillborn baby

In the case of a stillborn baby who has not been given a name, in place of the name insert a description sufficient to identify the baby.

Full name of baby

Sex

☐ Male ☐ Female

Date of stillbirth

☐☐/☐☐/☐☐☐☐

continued over the page

Part 4 The application

1. Are you a parent of the stillborn baby? ☐ Yes ☐ No

If No, please give the nature of your relationship and explain why you are making the application.

2. Have both parents been informed of the proposed cremation? ☐ Yes ☐ No

If No, please give the name of the parent and the reason(s) why they have not been contacted.

3. Has a parent of the stillborn baby expressed any objection to the proposed cremation? ☐ Yes ☐ No

If Yes, please give details.

4. Please give the address where the baby was stillborn.

Address

Please state whether it was the applicant's own home, hospital etc.

continued over the page

Part 4 continued

5. Do you know or suspect that the baby was not stillborn? ☐ Yes ☐ No

6. Do you consider that there should be any further examination of the stillborn baby's remains? ☐ Yes ☐ No

If you have answered Yes to questions **5** or **6**, please give reasons below.

Part 5 Statement of truth

I apply for the stillborn baby to be cremated and I certify that I am at least 16 years of age.

I believe that the facts given in this application are true. I am aware that it is an offence to wilfully make a false statement with a view to obtaining the cremation of any human remains.

Print your full name

Signed

Dated ☐☐/☐☐/☐☐☐☐

Medical certificate

Cremation 4
replacing Form B
01.09

This form can only be completed by a registered medical practitioner.
Please complete this form in full, if a part does not apply enter 'N/A'.

Part 1 Details of the deceased

Full name

Address

Occupation or last occupation if retired or not in work at the date of death

Where a past occupation of the deceased person may suggest that the death was due to industrial disease, you should consider whether to refer the death to a coroner.

Part 2 The report on the deceased

1. What was the date and time of death of the deceased?

Date / /

Time

2. Please give the address where the deceased died.

Address

Please state whether it was the residence of the deceased or a hotel, hospital, or nursing home etc.

☐ Their home ☐ Hospital ☐ Other (please specify)

☐ Hotel ☐ Nursing home

continued over the page

Part 2 continued

3. Are you a relative of the deceased? ☐ Yes ☐ No

If Yes, please give the nature of your relationship.

4. Have you, so far as you are aware, any pecuniary interest in the death of the deceased? ☐ Yes ☐ No

If Yes, please give details.

5. Were you the deceased's usual medical practitioner? ☐ Yes ☐ No

If Yes, please state for how long.

If No, please give details of your medical role in relation to the deceased.

6. Please state for how long you attended the deceased during their last illness?

7. Please state the number of days and hours before the deceased's death that you last saw them alive?

Days

Hours

8. Please state the date and time that you saw the body of the deceased and the examination that you made of the body.

Date

☐☐/☐☐/☐☐☐☐

Time

Examination

continued over the page

9. From your medical notes, and the observations of yourself and others immediately before and at the time of the deceased's death, please describe the symptoms and other conditions which led to your conclusions about the cause of death.

10. If the deceased died in a hospital at which they were an in-patient, has a hospital post-mortem examination been made or supervised by a registered medical practitioner of at least five years' standing who is neither a relative of the deceased nor a relative of yours or a partner or colleague in the same practice or clinical team as you? ☐ Yes ☐ No

If Yes, are the results of that examination known to you? ☐ Yes ☐ No

Note: 'Five years' standing' means a medical practitioner who has been a fully registered person within the meaning of the Medical Act 1983 for at least five years and, if paragraph 10 of Schedule 1 to the Medical Act 1983 (Amendment) Order 2002 (S.I. 2002/3135) has come into force, has held a licence to practice for at least five years or since the coming into force of that paragraph.

continued over the page

Part 2 continued

11. Please give the cause of death

1. (a) Disease or condition directly leading to death (this does not mean the mode of dying, such as heart failure, asphyxia, asthenia, etc: it means the disease, injury, or complication which caused death)

(b) Other disease or condition, if any, leading to (a)

(c) Other disease or condition, if any, leading to (b)

2. Other significant conditions contributing to the death but not related to the disease or condition causing it.

12. Did the deceased undergo any operation in the year before their death? ☐ Yes ☐ No

If Yes, what was the date and nature of the operation and who performed it.

Date of operation

☐☐/☐☐/☐☐☐☐

Who performed it

Nature of operation

13. Do you have any reason to believe that the operation(s) shortened the life of the deceased? ☐ Yes ☐ No

If Yes, please give details.

continued over the page

Part 2 continued

14. Please give the full name and address details of any person who nursed the deceased during their last illness (Say whether professional nurse, relative, etc. If the illness was a long one, this question should be answered with reference to the period of four weeks before the death.)

15. Were there any persons present at the moment of death? ☐ Yes ☐ No

If Yes, please give the full name and address details of those persons and whether you have spoken to them about the death.

16. If there were persons present at the moment of death, did those persons have any concerns regarding the cause of death? ☐ Yes ☐ No

If Yes, please give details

17. In view of your knowledge of the deceased's habits and constitution do you have any doubts whatever about the character of the disease or condition which led to the death? ☐ Yes ☐ No

18. Have you any reason to suspect that the death of the deceased was

Violent ☐ Yes ☐ No

Unnatural ☐ Yes ☐ No

19. Have you any reason at all to suppose a further examination of the body is desirable? ☐ Yes ☐ No

If you have answered Yes to questions **17**, **18** or **19** please give details below:

continued over the page

20. Has a coroner been informed about the death? ☐ Yes ☐ No

If Yes, please state the outcome.

21. Has there been any discussion with a coroner's office about the death of the deceased? ☐ Yes ☐ No

If Yes, please state the coroner's office that was contacted and the outcome of the discussions.

22. Have you given the certificate required for registration of death? ☐ Yes ☐ No

If No, please give the full name and contact details of the medical practitioner who has

Full name

Address

Telephone number

23. Was any hazardous implant placed in the body (e.g. a pacemaker, radioactive device or 'Fixion' intramedullary nailing system)? ☐ Yes ☐ No

Implants may damage cremation equipment if not removed from the body of the deceased before cremation and some radioactive treatments may endanger the health of crematorium staff.

If Yes, has it been removed? ☐ Yes ☐ No

continued over the page

Part 3 Statement of truth

I certify that I am a registered medical practitioner.

I certify that the information I have given above is true and accurate to the best of my knowledge and belief and that I know of no reasonable cause to suspect that the deceased died either a violent or unnatural death or a sudden death of which the cause is unknown or in a place or circumstance which requires an inquest in pursuance of any Act.

I am aware that it is an offence to wilfully make a false statement with a view to procuring the cremation of any human remains.

Your full name

Address

Telephone number

Registered qualifications

GMC Reference number

Signed

Dated / /

Once completed, this certificate must be handed or sent in a closed envelope by, or on behalf of, the medical practitioner who signs it to the medical practitioner who is to give the confirmatory medical certificate except in a case where question 10 is answered in the affirmative, in which case the certificate must be so handed or sent to the medical referee at the cremation authority at which the cremation is to take place.

Confirmatory medical certificate

Cremation 5
replacing Form C
01.09

This form may only be completed by a registered medical practitioner of at least five years' standing who is not either a relative of the deceased, the medical practitioner who issued the medical certificate (form Cremation 4) or a relative or a partner or colleague in the same practice or clinical team as the medical practitioner who issued that certificate.

'Five years' standing' means a medical practitioner who has been a fully registered person within the meaning of the Medical Act 1983 for at least five years and, if paragraph 10 of Schedule 1 to the Medical Act 1983 (Amendment) Order 2002 (S.I. 2002/3135) has come into force, has held a licence to practice for at least five years or since the coming into force of that paragraph.

Please complete this form in full, if a part does not apply enter 'N/A'.

Part 1 Details of the deceased

Full name

Address

Occupation or last occupation if retired or not in work at the date of death

Part 2 The report on the deceased

1. Have you questioned the medical practitioner who gave the Medical Certificate (form Cremation 4)? ☐ Yes ☐ No

If No, please give reasons.

continued over the page

Part 2 continued

In answer to questions 2, 3, 4, and 5, please give names and addresses of persons questioned and say whether you spoke to them in person or by telephone. Any failure to answer one of these questions in the affirmative may be treated as inadequate enquiry.

2. Have you questioned any other medical practitioner who attended the deceased? ☐ Yes ☐ No

If Yes, please give the full name and address details of the medical practitioner(s).

3. Have you questioned any person who nursed the deceased during their last illness, or who was present at the death? ☐ Yes ☐ No

If Yes, please give the full name and address details.

4. Have you questioned any of the relatives of the deceased? ☐ Yes ☐ No

If Yes, please give the full name and address details.

5. Have you questioned any other person? ☐ Yes ☐ No

If Yes, please give the full name and address details.

continued over the page

6. Please state the date and time that you saw the body of the deceased and the examination that you made of the body.

Date

☐☐/☐☐/☐☐☐☐

Time

Examination

7. Do you agree with the cause of death given in question 11 of Part 2 of the Medical Certificate (form Cremation 4)? ☐ Yes ☐ No

If No, please give reasons and give the cause of death.

Reason(s) for disagreeing

1. (a) Disease or condition directly leading to death (this does not mean the mode of dying, such as heart failure, asphyxia, asthenia, etc: it means the disease, injury, or complication which caused death)

(b) Other disease or condition, if any, leading to (a)

(c) Other disease or condition, if any, leading to (b)

2. Other significant conditions contributing to the death but not related to the disease or condition causing it.

continued over the page

Part 3 Statement of truth

I certify that I am a registered medical practitioner of at least five years' standing and I am not a relative of the deceased, or a relative or a partner or colleague in the same practice or clinical team as the medical practitioner who has given the Medical Certificate (form Cremation 4).

I certify that the information I have given above is true and accurate to the best of my knowledge and belief and that I know of no reasonable cause to suspect that the deceased died either a violent or unnatural death or a sudden death of which the cause is unknown or in a place or circumstance which requires an inquest in pursuance of any Act.

I am aware that it is an offence to wilfully make a false statement with a view to procuring the cremation of any human remains.

Your full name

Address

Telephone number

Registered qualifications

GMC reference number

Signed

Dated

/ /

Once completed, this certificate and the Medical Certificate (form Cremation 4) must be handed or sent in a closed envelope by one of the medical practitioners giving the certificates to the medical referee at the cremation authority at which the cremation is to take place.

Certificate following anatomical examination

Cremation 7
replacing Form H
01.09

Please complete this form in full, if a part does not apply enter 'N/A'.

Part 1 Details of the deceased

Full name

Age at date of death

Sex
☐ Male ☐ Female

Date of death
☐☐/☐☐/☐☐☐☐

Part 2 Certification of anatomical examination

I certify that the body of the deceased has undergone an anatomical examination under the authority of a licence granted under the Human Tissue Act 2004[1] for that purpose.

The examination took place at

Your full name

Address

Registered qualifications

Signed

Dated
☐☐/☐☐/☐☐☐☐

[1] If the anatomical examination took place before the implementation of the Human Tissue Act 2004 on 1 September 2006, for the words 'Human Tissue Act 2004' substitute a reference to the relevant Anatomy Act under which the examination was authorised.

Certificate releasing body parts for cremation

Cremation 8
replacing Form DD
01.09

Please complete this form in full, if a part does not apply enter 'N/A'.

Part 1 Details of the deceased

Full name

Address

Age at date of death

Sex
☐ Male ☐ Female

Date of death
☐☐/☐☐/☐☐☐☐

Place of death

Part 2 Body parts for release

I confirm on behalf of (insert name and address of hospital trust or other authority lawfully holding the body parts)

that the following body parts are held in respect of the deceased—

☐ Heart ☐ Brain ☐ Chest ☐ Abdominal

☐ other Organs (please specify)

continued over the page

Part 2 continued

[1]delete if not applicable

I certify that there is no reason for any further inquiry or examination concerning the above body parts and that they are [with the consent of the coroner for the following district][1] now released for cremation in a suitably safe and prepared condition. I am aware that it is an offence to wilfully make a false statement with a view to procuring the cremation of any human remains .

Name of coroner's district (if applicable)

Your full name

Address

Registered qualifications

GMC reference number

Signed

Dated

/ /

Certificate of stillbirth

Cremation 9
introduced in 2009
01.09

Please complete this form in full, if a part does not apply enter 'N/A'.

Part 1 The stillborn child

Full name of child or description

Sex

☐ Male ☐ Female

Date of stillbirth

☐☐/☐☐/☐☐☐☐

Part 2 Certificate of stillbirth

I am a registered

☐ medical practitioner

☐ midwife

I certify that I have examined the body of the stillborn child and can certify that the child was stillborn.

I certify that the information I have given above is true and accurate to the best of my knowledge and belief. I am aware that it is an offence to wilfully make a false statement with a view to procuring a cremation.

Your full name

Address

☐☐☐☐ ☐☐☐☐

Registered qualifications

GMC reference number / Nursing and Midwifery Council Personal Indentification number (PIN)

Signed

Dated

☐☐/☐☐/☐☐☐☐

Regulation 20(1)(c)(i) of the Cremation (England and Wales) Regulations 2008

Ministry of JUSTICE

Cremation Regulations 2008

Your right to inspect the medical certificates

7 November 2008

Cremation Regulations 2008

Your right to inspect the medical certificates

You have applied for cremation and that means that you have the right to inspect the medical forms about the death of the deceased. Inspection of the forms will take place before the cremation is authorised by the medical referee (that is the doctor attached to the crematorium).

Part 5 of the application form deals with this right. Please read it carefully. The funeral director will have explained this right to you, but you might find it helpful to have something in writing as well.

There are two medical forms. One is completed by the doctor who treated the deceased during his or her last illness, the other by a doctor who did not and who is independent of the first doctor. The second doctor has to examine the deceased, and discuss the death with the first doctor and at least one other person.

If you know the cause of death and have no problems with that cause you may decide that there is very little reason why you need to inspect these forms. However, if you do have doubts or were surprised that the death happened when it did, you may decide that you would like to inspect them.

You can nominate someone else to inspect the forms on your behalf. You might want to do this, for example, if you think someone else would be in a better position to go through the forms (perhaps because that person was present at the death and you were not).

If you already have serious concerns about the death and believe the case should be investigated by a coroner, you should contact the coroner’s office right away. Your funeral director will be able to provide contact details and other assistance. Where the death is unnatural or violent, it should have already been referred to a coroner by a doctor or by the police.

The forms will be available for inspection at the crematorium office for up to 48 hours after you are informed that they have been received there. It is important that you can be contacted during this period.

The medical referee may be able to give you advice on the cause of death, but he or she may charge a fee for this service. As the referee is often also a working doctor, you will need to take account of this when arranging the meeting.

If you want the funeral to be held within the next two or three days, it could be difficult to do this and also inspect the medical forms.

© Crown copyright
Produced by the Ministry of Justice

Alternative format versions of this report are available on request from brian.patterson@justice.gsi.gov.uk or 020 3334 6404

Ministry of JUSTICE

Cremation Regulations 2008

Guidance for cremation authorities and crematorium managers

3 November 2008

Contents

The new regulations	2
Cremation of non-viable foetal remains	2
The forms	3
Annex A	4
Further information	9
Annex B	10

The new regulations

1. The Cremation Regulations 2008 come into effect on 1 January 2009. They modernise and consolidate all previous regulations, replacing the Cremation Regulations 1930 as amended. A copy of the regulations is attached to this guidance. The previous forms may be used for a transitional period of one month, that is until 31 January 2009.

2. All cremation managers should familiarise themselves with the text of the new regulations. There are very few policy changes which require different procedures. The only significant one is that applicants now have the right to inspect the medical forms (forms Cremation 4 and Cremation 5) before the medical referee authorises the cremation. We expect the numbers of applicants wishing to exercise this right to be relatively low but we will keep the position under close review. Where a post-mortem examination is requested by the medical referee, we also consider that the applicant should, on request, be able to have a copy of the post mortem examination report.

3. A more minor change is that the countersignature on the application form is no longer required.

4. The forms make it clear that it is a criminal offence under the Cremation Act 1902 to wilfully make a false statement in order to procure a cremation.

Cremation of non-viable foetal remains

5. Foetal remains under 24 weeks gestation are not subject to the provisions of the Cremation Act or regulations. Further information about the disposal of such remains is published by the Human Tissue Authority and the Stillbirth and Neonatal Death Society (SANDS).

(See the Human Tissue Authority Code of Practice, ‘The removal, storage and disposal of human organs and tissue (Code 5), published July 2006; and the SANDS ‘Pregnancy Loss and Death of Baby – Guidelines for Professionals’, chapters 16 and 17 (hard copies are available from SANDS Head Office 020 7436 7940.)

The forms

6. It is important that you fully adhere to the statutory wording on the forms. The only adaptations which you may make are to add the name and address of the crematorium together with contact details. You should not add marginal notes or explanations. Medical referees have been instructed to reject forms which do not follow the statutory wording.

7. There are 13 forms which are explained at **Annex A**.

Annex A

Form Cremation 1 – Application for Cremation of Remains of Deceased Person (replacing form A)

1. Cremation managers should ensure that all parts of the form have been completed before the form is passed to your medical referee. However, a form should not be rejected solely because, for example, the applicant does not know the postcode of the place of death or deceased person's medical practitioner. We are encouraging funeral directors to assist applicants in providing such information.

2. Question 10 asks about hazardous implants. The medical referee will need to check the information provided carefully and compare it with that provided by the certifying doctor. The funeral director may also be able to provide information or confirm that the implant has been removed.

3. Part 5 of the form deals with applicants' **right to inspect** the medical forms (forms Cremation 4 and Cremation 5) before the medical referee authorises cremation. We expect funeral directors to advise the applicant of the right in neutral terms and neither to encourage nor deter applicants from exercising it (we have suggested a form of wording). Clearly if the death needs to be referred to the coroner after form Cremation 1 has been completed, and it then requires a post-mortem examination to be held or an inquest to be opened, the right of inspection will no longer apply as there will be no forms Cremation 4 and Cremation 5 to inspect.

4. To avoid any delay to the funeral by the applicant inspecting the forms, you should encourage funeral directors and medical practitioners to ensure that the forms Cremation 1, Cremation 4 and Cremation 5 are received as soon before the date of the funeral as possible. The applicant may delegate inspection to a nominee or be accompanied by someone. You should make every effort to ensure that the applicant can inspect the forms in private although we appreciate that it may not always be easy to find a suitable place.

5. The applicant should not be charged a fee to inspect the forms. However, if he or she wants a medical explanation for the cause of death they should be advised that the medical referee may charge a fee for this (that is entirely a matter for the medical referee).

On the other hand, if the applicant wishes to draw the medical referee's attention to an (alleged) inconsistency or inaccuracy within the medical forms then there should be no charge for so doing. Cases where the cause of death is not considered by the medical referee to be natural need to be referred to the local coroner for further consideration.

6. The inspection should take place at least 24 hours before the funeral is due to take place in order that any further investigation or clarification is carried out by the medical referee or others. The family may wish that the funeral service go ahead but that the cremation is deferred in case the coroner wishes the body to be examined. In such cases it will be necessary for the body to be returned to the funeral directors pending any final decision by the coroner. We anticipate that cases like these will be extremely rare.

7. We do not expect there will be great demand for inspection, given that the more 'difficult' cases will have already been referred to the coroner for investigation, and that the vast majority of families have no concerns with the death. Regulation 32 requires the registrar of each cremation authority to keep a register of cremations and one of the particulars that is required to be kept is the name and address of any person who exercises the new right to inspect the medical certificates. As we shall be reviewing the operation of the new right it would also be very helpful if you would send us details of the cases where the forms have been inspected.

Form Cremation 2 – Application for Cremation of Body Parts (replacing form AA)

8. There is no right to inspect the associated certificate releasing body parts for cremation (form Cremation 8) because it provides no information about the cause of death and the body will have already been cremated or buried.

Form Cremation 3 – Application for Cremation of Stillborn Baby

9. You should ensure that the form Cremation 3 is either accompanied by a form Cremation 9 (certificate of stillbirth) or by a declaration given by a person who can give information concerning the birth (see regulation 20(2)). Where the stillbirth took place outside England and Wales, a broadly equivalent form to form Cremation 9 can be given (please refer to regulation 14(4)). There is no right to inspect the certificate of stillbirth as there is no cause of death.

Form Cremation 4 – Medical Certificate (replacing form B)

10. You should ensure that all questions have been answered before passing the forms to the medical referee. All doctors must be fully registered with the General Medical Council (GMC).

Form Cremation 5 – Confirmatory Medical Certificate (replacing form C)

11. Medical referees have been given information about the eligibility of doctors from the European Economic Area (EEA) whose periods of qualification before full registration with the GMC may count towards the five-year period and is attached at **Annex B**. It is very important that doctors from outside the EEA and with less than five years' full registration do not sign form Cremation 5. You should reject forms completed by such doctors and advise the funeral director so that any fees paid can be refunded or transferred to a suitably qualified doctor.

Form Cremation 6 – Certificate of Coroner (replacing form E)

12. The space for the cause of death to be recorded should not be left blank (even if the cause is unascertained).

Form Cremation 7 – Certificate following Anatomical Examination (replacing form H)

13. The form refers to licences granted under the Human Tissue Act 2004 but it can be adapted to deal with older anatomical remains where disposal of the body has been delayed.

Form Cremation 8 – Certificate releasing Body Parts for Cremation (replacing form DD)

14. The body parts must belong to a named person. Anonymous material should be incinerated.

Form Cremation 9 – Certificate of Stillbirth

15. This form should be linked with form Cremation 3 and the appropriate registration document. If the medical referee if satisfied that cremation can take place, he or she will authorise it on form Cremation 13. The form may be completed by a registered midwife as well as by a fully registered medical practitioner.

Form Cremation 10 – Authorisation of Cremation of Deceased Person by Medical Referee (replacing form F)

16. The medical referee will authorise cremation of a deceased person after he or she is satisfied by the information on form Cremation 1, form Cremation 4, form Cremation 5, form Cremation 6 or form Cremation 7 as well as the registration document where registration is required before cremation can take place (this will not be necessary in cases involving the coroner).

17. If the applicant or the applicant's nominee has asked to inspect the medical forms you may wish to advise the medical referee. However, if the applicant or nominee has no concerns to raise with the medical referee or does not wish to seek advice from the referee there is no overwhelming need to do so. If the applicant or nominee has made it clear to staff at the crematorium that they wish to raise matters of concern with a coroner authorisation of the cremation should not take place until these have been resolved. You will need to be in close liaison with the funeral directors and the coroner's office while the situation remains unresolved.

Form Cremation 12 – Authorisation of Cremation of Body Parts by Medical Referee (replacing form FF)

18. The medical referee will only authorise cremation after consideration of a form Cremation 2 and form Cremation 8 and the appropriate registration documentation.

Form Cremation 13 – Authorisation of Cremation of Remains of Stillborn Child by Medical Referee

19. The medical referee will only authorise cremation of a stillborn baby after having considered forms Cremation 3 and either Cremation 9 (or the overseas equivalent) or a declaration given by a person who can give information concerning the birth and the appropriate registration document.

Form Cremation 11 – Certificate after Post-Mortem Examination

20. You will need to decide whether you or the family will pay for any post-mortem examination ordered by the medical referee and that all the relevant provisions of the Human Tissue Act 2004 are met. These include any necessary consent from the applicant or other family member for the post-mortem examination to take place, that the pathologist is duly licensed by the Human Tissue Authority 2004 and that the place where the post-mortem is to take place is also duly licensed.

Further information

21. This guidance is not exhaustive. If you have any further queries or need further information about the new regulations please contact Brian Patterson on 020 3334 6404 (brian.patterson@justice.gsi.gov.uk).

Annex B

European Economic Area

European Union Members: Universities where Primary European Qualifications can be obtained within each state

Austria – Graz, Innsbruck, Salzburg, Salzburg (Paracelsus), Vienna (Wien)

Belgium – Antwerp, Brussels, Diepenbeek (Limburg), Gent, Louvain (Leuven), Liege, Mons, Namur

Bulgaria – Pleven, Plovdiv, Sofia, Trakia (Thrace), Varna

Cyprus – Medical Council of Cyprus (equivalent to General Medical Council)

Czech Republic – Brno (Masaryk Univ.), Hradec Kralove, Pilsen, Prague (Charles University), Olomouc

Denmark – Aarhus, Copenhagen, Syddansk (Odense)

Estonia – Tartu

Finland – Helsinki, Kuopio, Oulu, Tampere, Turku

France – Aix-Marseille, Amiens (Jules Verne), Angers, Besançon (Franche-Comté), Bordeaux (Victor Segalen), Brest (Bretagne), Caen, Clermont-Ferrand (Auvergne), Dijon, Grenoble, Univ Scientifique et Medicale Grenoble, Lille, Henri Warembourg de Lille, Limoges, Lyon-Sud, Lyon (Univ Claude-Bernard), Lyon (Alexis-Carrel), Montpellier-Nimes, Nancy, Nantes, Nice, Paris (Denis Diderot), Paris (Pierre et Marie Curie), Paris (René Descartes), Paris-Sud, Paris Val de Marne (Creteil), Poitiers, Reims, Rennes, Rouen,St Etienne, Strasbourg, Toulouse, Tours

Germany – Aachen, Berlin (Freiuniversität), Berlin (Humboldt), Bochum, Bonn, Dresden, Düsseldorf, Erlangen-Nürnberg, Essen, Frankfurt-am-Main, Freiburg im Breisgau, Giessen, Göttingen, Greifswald, Halle/Wittenberg, Hamburg, Hannover, Heidelberg, Homburg, Jena, Kiel, Köln (Cologne), Leipzig, Lübeck, Magdeburg, Mainz, Mannheim, Marburg, München (Ludwig-Maximilians), München (Technische), Münster, Regensburg, Rostock, Ulm, Witten-Herdecke, Tübingen, Würzburg

Greece – Alexandroupolis (Thrace), Athens (National), Crete, Ioannina, Patras, Larissa (Thessaly) Thessaloniki

Hungary – Semmelweis/Budapest, Debrecen, Pécs, Szeged

Iceland – Reykjavik

Ireland – Cork, Dublin (RCS), University College Dublin, Galway,

Italy – Ancona, Bari, Bologna, Brescia, Cagliari, Catania, Catanzaro (Reggio-Calabria), Chieti (D'Annunzio), Ferrara, Firenze, Genova, Messina, Milano, Modena, Napoli, Napoli (Federico II), Padova, Palermo, Parma, Pavia, Perugia, Pisa, Roma, Rome (Campus Bio-Medico), Sassari, Siena, Torino, Trieste, Udine, Varese, Verona

Latvia – Riga (Stradins), University of Latvia (Riga)

Liechtenstein – Nil

Lithuania – Kaunas, Vilnius

Luxembourg – Nil

Malta – Univ of Malta (Msida)

Netherlands – Amsterdam, Amsterdam (Vrije) Groningen, Leiden, Maastricht, Nijmegen, Rotterdam (Erasmus), Utrecht

Norway – Bergen, Oslo, Tromsø, Trondheim

Poland – Bialystok, Bydgoszcz, Gdansk, Krakow (Jagiellonian), Lodz (Military), Lublin, Poznan, Szczecin, Warsaw (Academy and Postgraduate), Wroclaw

Portugal – Beira, Coimbra, Lisbon, Porto (Abel Salazar) Porto

Romania – Arad, Brasov, Bucharest, Cluj-Napoca, Constanta, Craiova, Iasi, Muras, Oradea, Sibiu, Targu Timisoara

Slovakia – Bratislava, Kosice

Slovenia – Ljubljana

Spain – Albacete (Castillo la Mancha), Alcalá, Alicante, Badajoz (Extremadura), Barcelona, Barcelona (Autonoma), Barcelona (Pompeu Fabra), Cádiz, Córdoba, Granada, La Laguna Las Palmas de Gran Canaria, Lleida, Madrid (San Pablo), Madrid (Autonoma), Madrid (Complutense), Málaga Murcia, Pamplona (Navarra), Oviedo, Reus (Tarragona/Rovira Virgili) Salamanca, San Sebastian (Pais Vasco), Santa Cruz de Tenerife, Santander (Cantabria), Sevilla, Tenerife, Valencia, Valladolid, Zaragosa

Sweden – Göteborg, Linköping, Lund, Stockholm (Karolinska), Umeä, Uppsala

Switzerland* – Basel, Bern, Genève, Lausanne, Zürich

United Kingdom – five years' registration required wherever qualified

*Swiss nationals benefit from EC freedom of movement legislation.

© Crown copyright
Produced by the Ministry of Justice

Alternative format versions of this report are available on request from brian.patterson@justice.gsi.gov.uk or 020 3334 6404.

Ministry of JUSTICE

Cremation Regulations 2008

Guidance for doctors

3 November 2008

Contents

Summary of guidance	2
Introduction	4
Those who can sign forms Cremation 4 and Cremation 5 – Overseas Doctors	4
Corroboration of cause of death – deaths in hospital	6
Dentists	7
Completion of forms Cremation 4 and 5	7
Right of inspection	8
Form Cremation 4 – Medical Certificate	8
Form Cremation 5 – Confirmatory Medical Certificate	10
Requirement for form Cremation 5	10
Causes of death – old age	11
Deaths abroad	12
Body parts	12
Unidentified remains	12
Cremation of non-viable foetal remains	12
Annex A: European Economic Area and locations of institutions awarding primary medical qualifications	13

Summary – please read the full guidance carefully

- You must answer **all the questions** on the forms.
- The form Cremation 5 doctor should always properly check Form Cremation 4 – it is your responsibility to check thoroughly both forms and to query any inconsistencies.
- The medical referee is likely to reject **illegible forms**.
- We expect the doctor signing form Cremation 4 to have treated the deceased during the last illness and to have normally seen the deceased within 14 days of death.
- **Modes of death**, e.g. 'multi organ failure' or 'heart attack' are unacceptable as a cause of death; the medical referee is likely to reject forms without a proper cause of death.
- **'Old age'** as a standalone cause of death for over 80s is acceptable for registration purposes, but medical referees have been advised to exercise caution if 'old age' is given as a cause of death and may well make further enquiries.
- You should complete the **forms as soon as possible**: delays to funerals are unfair to bereaved families.
- **Form Cremation 5 doctors** must be registered medical practitioners for at least five years and, if paragraph 10 of Schedule 1 to the Medical Act 1983 (Amendment) Order 2002 (S.I. 2002/3135) is in force, hold a licence to practise.
- Up-to-date information about the qualifications of European doctors is on the General Medical Council's website – see also **Annex A** of this guidance.
- The form Cremation 5 doctor cannot be a partner or work colleague of the form Cremation 4 doctor or a relative of the deceased; the two doctors must be truly independent of one another, i.e. not on the same team in hospital or a locum at the same surgery.
- It is expected that at least one of questions 2 to 5 of form Cremation 5 will be answered in the affirmative.

General

- Medical referees are unable to authorise a cremation **unless the relevant forms have been properly completed in accordance with the regulations.**

- Medical referees have the statutory power to reject incompletely completed forms and may refuse to authorise cremation until the forms are completed to their satisfaction.

- Medical referees also have the power to make any enquiry they may consider necessary about an application or certificate.

- You should assist medical referees in the discharge of their duties by completing the cremation certificates fully and accurately, and by responding to any further enquiries as helpfully as possible.

- Forms Cremation 4 and Cremation 5 do not need to be completed where the application relates to the cremation of body parts, to a stillborn child or to the exhumed remains of a deceased person who has already been buried for a period of one year or more.

Introduction

1. This guidance provides advice to doctors who complete certificates in connection with applications for cremation. It complements advice provided to crematoria medical referees. The main aim is to ensure that medical practitioners are aware of and meet the requirements of the regulations and avoid unnecessary delay to funerals.

2. Forms Cremation 4 and Cremation 5 are available on our website www.justice.gov.uk. You may be asked to complete forms which have been 'personalised' for each crematorium, including marginal explanatory notes. Forms which do not comply with the statutory requirements are not valid. If you have any doubts about the forms you should check with the crematorium manager. The forms made under the previous 1930 regulations may be used until 31 January 2009.

Those who can sign forms Cremation 4 and Cremation 5 – overseas doctors

3. Regulation 17 of the Cremation Regulations 2008 requires the confirmatory medical certificate (form Cremation 5) to be completed by a registered medical practitioner of at least five years' standing. This means a registered medical practitioner who has been fully registered under the Medical Act 1983 for at least five years and, if paragraph 10 of Schedule 1 to the Medical Act 1983 (Amendment) Order 2002 has come into force, who has held a licence to practice under that Act for at least five years or since that paragraph came into force.

4. So far as overseas doctors are concerned, European Economic Area (EEA) member states must recognise one another's diplomas in medicine, subject to certain standards being fulfilled. A list of 'primary European qualifications' which are recognised in the UK in accordance with EC Directive 2005/36/EC is set out in Schedule 1 to the European Primary Medical Qualification Regulations 1996. Schedule 1 to these regulations contains a list of amendments to Schedule 2 to the Medical Act 1983. At that time this Schedule to the Act contained a list of primary European qualifications.

Primary European qualifications are no longer described in this way and Schedule 2 to the Medical Act 1983 was revoked on 3 December 2007 by the European Qualifications (Health and Social Care Professions) Regulations 2007 (Regulation 31).

5. Unlike previous Directives, the current Directive extends the principle of mutual recognition of professional qualifications to those awarded outside the EEA if the holder of a 'third country' qualification is an exempt person (i.e. a national of a relevant European state or entitled to be treated as such) and has three years' professional experience in the profession concerned on the territory of the relevant European state that initially recognised the qualification. A list of the EEA member states and the places where primary medical qualifications are granted is given at **Annex A**. It follows that a **national of any EEA member state** holding a primary European qualification is entitled to be registered in the UK as a fully registered medical practitioner and experience acquired under the primary European qualification outside the UK should be treated as if acquired within the UK. Accordingly, an overseas doctor who has a primary European qualification in an EEA member state will be eligible to sign a cremation form Cremation 5 provided he or she has been registered for five years and holds a licence to practise. The medical register is made up of three lists (as specified in section 30(1) of the Medical Act). Doctors will only be added to the visiting practitioners lists if they obtain registration under the sections of the Act specified (sections 27A, 27B and Schedule 2a).

Corroboration of cause of death – deaths in hospital

6. Regulation 17 also requires that the registered medical practitioner who completes the confirmatory medical certificate should not be a relative of the deceased, or a relative or partner or colleague in the same practice or clinical team of the doctor who has given the cremation certificate in form Cremation 4.

7. The reason for this is to provide corroboration of the medical circumstances in which death took place. Medical referees will need to be satisfied that the doctors who complete forms Cremation 4 and Cremation 5 are sufficiently independent of each other in all cases.

8. Similarly, where a junior hospital doctor has completed the certificate in form Cremation 4, the doctor who signs the form Cremation 5 should not have been in charge of the case, nor directly concerned in the patient's treatment. The deceased's GP should not complete form Cremation 5 (this includes where the deceased has been resident in a care home if the GP had treated the deceased at some stage).

You should be aware that criminal and General Medical Council proceedings have been successfully brought against doctors who have falsely completed the forms.

Dentists

9. Dentists are not qualified to sign cremation certificates.

Completion of forms Cremation 4 (Medical Certificate) and Cremation 5 (Confirmatory Medical Certificate) (replacing forms B and C)

10. The most frequently occurring errors in completion these forms are:

(a) failure to complete **all** questions in full

(b) deletion of questions

(c) incorrect completion of forms

(d) illegible handwriting

(e) discrepancies between the forms as to the date and time of death.

11. Abbreviations for causes of death are unacceptable where the abbreviation is unclear, unusual or ambiguous; in such cases, the medical referee is likely to make further enquiries of you. You should sign the form. The signatures cannot be an abbreviation or a stamp.

12. You must complete the form yourself. It must not be completed by another person on your behalf. The form Cremation 5 doctor should not amend form Cremation 4, but instead record any differences (e.g. as to the cause of death) on his or her own form.

13. Medical referees will expect that the evidence offered on the certificates demonstrates sound clinical grounds for the cause of death given, and you should complete form Cremation 4 with this in mind.

Right of inspection

14. When you complete form Cremation 4 or Cremation 5 you should be aware that the applicant for cremation has a new right to inspect these forms. **Some of the information which is requested by the forms (in particular, questions 9 and 12 on form Cremation 4) may have been given to you by the deceased in confidence. If it is included in the form it may be disclosed to the applicant for cremation if they chose to inspect the form. If this would be a breach of confidence you may give the information to the medical referee on a separate sheet of paper attached to the form explaining your reasons for this and that the information should not be disclosed.** It is therefore important that you bear this in mind when you complete the forms. You should also ensure that your handwriting is legible.

15. The following paragraphs address some other common issues.

Form Cremation 4 – Medical Certificate

Question 5: 'usual medical attendant'

16. The usual medical attendant is normally taken to be the deceased's GP. Where the deceased has been an in-patient in hospital for a short period of time, that is less than 24 hours, it may be better to regard the patient's GP as the usual medical attendant, rather than the hospital doctor who attended him or her. (See also paragraph 8 above.) It is appreciated that many patients in hospital are treated by a number of doctors.

Question 6: 'how long you attended the deceased during their last illness?'

17. To complete form Cremation 4 you should have attended the deceased during their last illness. In the primary care setting, a demonstrable prior period of care or the presence of the certifying doctor at the death will usually be enough. In exceptional circumstances, a general practitioner partner may be acceptable if he or she had seen the deceased outside the normally acceptable

period (14 days) and the attending partner is unavailable although in such cases there will usually have been consultation with a coroner.

18. The minimum period of hospital care sufficient to meet the requirement should normally be 24 hours. When the period is less than 24 hours you must inform a coroner.

Question 7: 'the number of days and hours before the deceased's death that you saw them alive'

19. The normal expectation is that you will have seen the deceased during the course of the last illness within 14 days before death; otherwise you should refer the death to a coroner.

Question 9: symptoms and other conditions

20. You should complete this box with your observations of the deceased's symptoms etc. in the period leading up to death.

Question 10: hospital post-mortem examination

21. If a non-coronial hospital post-mortem examination, i.e. one requiring consent, has been carried out or supervised either by you or by someone with the necessary five years' period of full registration, you should indicate this here and the cause of death in Question 11 should be the findings of the examination. In these cases form Cremation 5 (the Confirmatory Medical Certificate) is not required.

Question 11: cause of death

22. The cause of death should normally be that set out on the medical certificate of the cause of death sent to the Registrar of Deaths. Your answer should indicate when this has been informed by other sources, e.g. patient history, operative procedures or medical or lay witnesses.

Questions 12 and 13: operations

23. You should refer any operation which may have shortened the life of the deceased to a coroner for consideration and possible investigation.

Questions 14, 15 and 16: those nursing the deceased or present at death

24. The doctor completing form Cremation 5 must be able to contact the people you name. Therefore you must give full names and contact details.

Questions 20 and 21: referral to coroner/coroner's office

25. You are asked to ensure that a coroner is notified if any suspicious circumstances come to your attention. In cases where either of the form Cremation 4 or form Cremation 5 doctors has consulted a coroner but the coroner does not consider that his or her involvement is necessary, this should be recorded by the medical practitioner concerned.

Question 23: implants

26. Some implants cause a serious health and safety risk at the crematorium and must be removed.

Form Cremation 5 – Confirmatory Medical Certificate

Requirement for form Cremation 5

27. Form Cremation 5 is not required where the death occurred in hospital, the deceased was an in-patient there, and a post-mortem has been carried out or supervised by a registered medical practitioner of at least five years' standing who is not a relative of the deceased, or a relative, partner or colleague in the same practice or clinical team of the medical practitioner giving form Cremation 4, and the medical attendant giving form Cremation 4 knows the results of the examination.

28. If form Cremation 5 has been completed where there is no need to do so, any fee paid should be refunded to the applicant.

29. The cause of death on the form Cremation 5 does not need to be the same as the one given on the form Cremation 4, but you should explain any discrepancy.

30. We consider that, with the exception of Questions 6 and 7, you should answer in the **affirmative** all the questions in Part 2 in all but the most extreme circumstances (e.g. if the form Cremation 4 doctor is taken seriously ill, for example). Nevertheless, Question 2 should be answered in the affirmative **only if** you have seen and questioned a medical practitioner **other than** the form Cremation doctor.

Question 1: 'have you questioned the medical practitioner?'

31. If you have not seen or spoken to the form Cremation 4 doctor, you should only complete form Cremation 5 to show that the enquiries have been 'adequate'. This should only be necessary in the most exceptional circumstances, for example when the form Cremation 4 doctor has fallen seriously ill.

32. Medical referees will expect that the evidence offered on the certificates demonstrates sound clinical grounds for the cause of death given, and you should complete form Cremation 5 with this in mind.

Causes of death – old age

33. The General Register Office advises that in certain circumstances and if the deceased is older than 80 years of age 'old age' may be an acceptable cause of death on medical certificates. 'Old age' alone, however, is unlikely to be an acceptable cause of death for cremation purposes, as the medical referee must be satisfied that the cause of death has been definitely ascertained. 'Old age' is commonly given as a cause of death where the deceased has been suffering from a number of conditions leading to death but it has not been possible to decide which particular condition led to the death. We cannot offer substantive guidance on a matter which must ultimately be a clinical decision for you. However, medical referees must be satisfied that 'old age' is an appropriate cause of death in all the circumstances. It cannot be used where the cause of death is properly 'unascertained' and which should on that account be referred to a coroner.

Deaths abroad

34. Where someone dies abroad and the body is repatriated to England or Wales for cremation, it is unlikely that you will be in a position to complete forms Cremation 4 or Cremation 5. An application for cremation may be made if a coroner certifies that no post-mortem examination or inquest is necessary. Enquiries about such cases should be directed to us or to a coroner.

Body parts

35. The cremation of body parts removed following a post-mortem examination will normally only require involvement by pathologists.

Unidentified remains

36. It is highly unlikely that applications for the cremation of unidentified remains will arise without the involvement of a coroner.

Cremation of non-viable foetal remains

37. Foetal remains under 24 weeks of age are not subject to the provisions of the Cremation Act or Regulations, although most crematoria will be prepared to cremate such remains at their discretion. Clearly forms Cremation 4 and Cremation 5 should not be completed.

Annex A

European Economic Area

European Union Members: Universities where Primary European Qualifications can be obtained within each state

Austria – Graz, Innsbruck, Salzburg, Salzburg (Paracelsus), Vienna (Wien)

Belgium – Antwerp, Brussels, Diepenbeek (Limburg), Gent, Louvain (Leuven), Liege, Mons, Namur

Bulgaria – Pleven, Plovdiv, Sofia, Trakia (Thrace), Varna

Cyprus – Medical Council of Cyprus (equivalent to General Medical Council)

Czech Republic – Brno (Masaryk Univ.), Hradec Kralove, Pilsen, Prague (Charles University), Olomouc

Denmark – Aarhus, Copenhagen, Syddansk (Odense)

Estonia – Tartu

Finland – Helsinki, Kuopio, Oulu, Tampere, Turku

France – Aix-Marseille, Amiens (Jules Verne), Angers, Besançon (Franche-Comté), Bordeaux (Victor Segalen), Brest (Bretagne), Caen, Clermont-Ferrand (Auvergne), Dijon, Grenoble, Univ Scientifique et Medicale Grenoble, Lille, Henri Warembourg de Lille, Limoges, Lyon-Sud, Lyon (Univ Claude-Bernard), Lyon (Alexis-Carrel), Montpellier-Nimes, Nancy, Nantes, Nice, Paris (Denis Diderot), Paris (Pierre et Marie Curie), Paris (René Descartes), Paris-Sud, Paris Val de Marne (Creteil), Poitiers, Reims, Rennes, Rouen,St Etienne, Strasbourg, Toulouse, Tours

Germany – Aachen, Berlin (Freiuniversität), Berlin (Humboldt), Bochum, Bonn, Dresden, Düsseldorf, Erlangen-Nürnberg, Essen, Frankfurt-am-Main, Freiburg im Breisgau, Giessen, Göttingen, Greifswald, Halle/Wittenberg, Hamburg, Hannover, Heidelberg, Homburg, Jena, Kiel, Köln (Cologne), Leipzig, Lübeck, Magdeburg, Mainz, Mannheim, Marburg, München (Ludwig-Maximilians), München (Technische), Münster, Regensburg, Rostock, Ulm, Witten-Herdecke, Tübingen, Würzburg

Greece – Alexandroupolis (Thrace), Athens (National), Crete, Ioannina, Patras, Larissa (Thessaly) Thessaloniki

Hungary – Semmelweis/Budapest, Debrecen, Pécs, Szeged

Iceland – Reykjavik

Ireland – Cork, Dublin (RCS), University College Dublin, Galway,

Italy – Ancona, Bari, Bologna, Brescia, Cagliari, Catania, Catanzaro (Reggio-Calabria), Chieti (D'Annunzio), Ferrara, Firenze, Genova, Messina, Milano, Modena, Napoli, Napoli (Federico II), Padova, Palermo, Parma, Pavia, Perugia, Pisa, Roma, Rome (Campus Bio-Medico), Sassari, Siena, Torino, Trieste, Udine, Varese, Verona

Latvia – Riga (Stradins), University of Latvia (Riga)

Liechtenstein – Nil

Lithuania – Kaunas, Vilnius

Luxembourg – Nil

Malta – Univ of Malta (Msida)

Netherlands – Amsterdam, Amsterdam (Vrije) Groningen, Leiden, Maastricht, Nijmegen, Rotterdam (Erasmus), Utrecht

Norway – Bergen, Oslo, Tromsø, Trondheim

Poland – Bialystok, Bydgoszcz, Gdansk, Krakow (Jagiellonian), Lodz (Military), Lublin, Poznan, Szczecin, Warsaw (Academy and Postgraduate), Wroclaw

Portugal – Beira, Coimbra, Lisbon, Porto (Abel Salazar) Porto

Romania – Arad, Brasov, Bucharest, Cluj-Napoca, Constanta, Craiova, Iasi, Muras, Oradea, Sibiu, Targu Timisoara

Slovakia – Bratislava, Kosice

Slovenia – Ljubljana

Spain – Albacete (Castillo la Mancha), Alcalá, Alicante, Badajoz (Extremadura), Barcelona, Barcelona (Autonoma), Barcelona (Pompeu Fabra), Cádiz, Córdoba, Granada, La Laguna Las Palmas de Gran Canaria, Lleida, Madrid (San Pablo), Madrid (Autonoma), Madrid (Complutense), Málaga Murcia, Pamplona (Navarra), Oviedo, Reus (Tarragona/Rovira Virgili) Salamanca, San Sebastian (Pais Vasco), Santa Cruz de Tenerife, Santander (Cantabria), Sevilla, Tenerife, Valencia, Valladolid, Zaragosa

Sweden – Göteborg, Linköping, Lund, Stockholm (Karolinska), Umeä, Uppsala

Switzerland* – Basel, Bern, Genève, Lausanne, Zürich

United Kingdom – five years' registration required wherever qualified

*Swiss nationals benefit from EC freedom of movement legislation.

© Crown copyright
Produced by the Ministry of Justice

Alternative format versions of this report are available on request from brian.patterson@justice.gsi.gov.uk or 020 3334 6404.

Ministry of JUSTICE

Cremation Regulations 2008

Guidance for funeral directors

3 November 2008

Contents

The new regulations 2
The forms 2
Annex A 3
Further information 8
Annex B 9
Annex C 11

The new regulations

1. The Cremation Regulations 2008 come into effect on 1 January 2009. They modernise and consolidate all previous regulations, replacing the Cremation Regulations 1930 as amended. A copy of the regulations is attached to this guidance. The forms can be downloaded from our website at www.justice.gov.uk. The forms made under the 1930 Regulations may also be used until 31 January 2009.

2. You should familiarise yourself with the text of the new regulations although there are very few policy changes requiring different procedures. The only significant new provision is that giving the applicant for cremation a right to inspect the medical forms (forms Cremation 4 and Cremation 5) before the medical referee authorises cremation. We expect the numbers of applicants wishing to exercise this right to be relatively low, but we will keep the position under close review.

The forms

3. It is important that the statutory wording is fully adhered to. Medical referees have been instructed to reject forms that do not follow the statutory wording.

4. A minor change to the application form is that the countersignature is no longer required.

5. The forms make it clear that it is a criminal offence under the Cremation Act 1902 wilfully to make a false statement in order to procure a cremation.

6. There are 13 forms which are explained in **Annex A**.

Annex A

Form Cremation 1 - Application for cremation of remains of deceased person (replacing form A)

1. This form is to be completed by the applicant for cremation. This should usually be a near relative or an executor. If the applicant is not a near relative or an executor reasons should be given on the form explaining why that person is making the application rather than a near relative or an executor. All questions will need to be answered. All parts of the form have to be completed before it is passed to the medical referee. You should assist applicants in providing the information which is required.

2. Question 10 asks about hazardous implants. The medical referee will need to check the information provided with that given by the certifying doctor. After discussion with the applicant, you may also be able to provide information or confirm that the implant has been removed.

3. Part 5 of the form deals with the applicant's **right to inspect** the medical forms (forms Cremation 4 and Cremation 5) before the medical referee authorises cremation. We expect you to advise the applicant in neutral terms of the right and neither to encourage nor deter applicants from exercising it (a suggested form of words is set out at **Annex B**). In certain circumstances, the death may need to be referred to a coroner. The coroner may then require a post-mortem examination to be held or an inquest to be opened. In these circumstances there is no right of inspection, as there are no medical forms to inspect and the death is being fully investigated.

4. You should ensure that forms Cremation 1, 4 and 5 are sent to the crematorium as soon as possible before the date of the funeral. This is to ensure that the funeral is not delayed in the event that the applicant wants to inspect the forms. The applicant may not, however, want to inspect the forms if he or she would like the funeral to take place as soon after death as possible.

5. There is no easy solution to reconciling the applicant's right of inspection with a timely funeral. Your main role is to ensure that the forms are completed as quickly as possible, to facilitate inspection, and - importantly - to keep in contact with all the parties concerned in the process. If the applicant says that they want to see the forms you will need to advise them that they may delegate inspection to a nominee or that they may be accompanied. Space at crematorium offices is sometimes short and we appreciate that it may not always be easy to identify a suitable place for the applicant to inspect the forms. [It may be acceptable for the applicant to inspect the forms at your office, but that should only be with the agreement of the cremation authority.]

6. We have advised cremation authorities that we do not expect the applicant to be charged a separate fee for inspecting the forms. However, if the applicant wants a medical explanation for the cause of death you should advise him or her that the medical referee may charge a fee for doing this (that is entirely a matter for the medical referee). On the other hand, if the applicant wishes to draw the medical referee's attention to a possible inconsistency or inaccuracy within the medical forms, we do not think that there should be a charge for so doing.

7. If the applicant's inspection of the forms raises a possibility that the cause of death was not natural, the medical referee may consider that the case should be referred to a coroner for further consideration. Any assistance that you can provide in ensuring that the referral takes place as smoothly and speedily as possible will be welcomed.

8. The forms must be inspected at least 24 hours before the funeral is due to take place, to enable any further investigation or clarification to be carried out by the medical referee or others. The family may want the funeral to go ahead but cremation to be deferred, in case the coroner wants the body to be examined. In such cases it will be necessary for the body to be returned to your premises pending any final decision by the coroner. We anticipate that cases like these will be extremely rare.

9. We do not expect there will be great demand for inspection, given that the more 'difficult' cases will have already been referred to the coroner for investigation and most applicants do not have concerns about the circumstances surrounding the death.

Form Cremation 2 - Application for cremation of body parts (replacing form AA)

10. This form should also be completed by a near relative or an executor. If it is more appropriate for the form to be completed by someone acting on behalf of the next of kin (perhaps the bereavement officer at the hospital) then an explanation for this should be given on the form. There is no right to inspect the associated certificate releasing body parts for cremation (form Cremation 8), because it provides no information about the cause of death and the body will have already been cremated or buried. Applications for the cremation of body parts are likely to remain as infrequent as under the previous regulations.

Form Cremation 3 - Application for cremation of stillborn baby

11. This form may be completed by one of the parents of the stillborn baby but may also be completed by the bereavement officer at the hospital. There is no right to inspect the associated certificate of stillbirth (form Cremation 9), as there is no cause of death. You should ensure that form Cremation 3 is either accompanied by form Cremation 9 or by a declaration given by a person who can give information concerning the birth (see regulation 20(2)). Where the stillbirth took place outside England and Wales, a broadly equivalent form to form Cremation 9 can be given (please refer to regulation 14(4)).

Form Cremation 4 - Medical certificate (replacing form B)

12. This form will need to be completed by a doctor who can certify the cause of death. It contains the most detailed information about the circumstances surrounding the death. All questions should be answered. The doctor completing the form will need to give information as to whether any hazardous implant has been removed and whether the death has been discussed with a coroner.

Form Cremation 5 - Confirmatory medical certificate (replacing form C)

13. Medical referees have been given information about the eligibility of doctors from the European Economic Area (EEA) whose periods of qualification before full registration with the General Medical Council may count towards the five-year period. It is attached at **Annex C**. It is very important that doctors from outside the EEA and with less than five years full registration do not sign form Cremation 5. Medical referees should inform you that they have rejected such forms, so that you can refund any fee the doctor concerned may have been paid.

Form Cremation 6 - Certificate of coroner (replacing form E)

14. Please note that there is a space for the cause of death to be recorded. This should not be left blank (even if the cause is unascertained).

Form Cremation 7 - Certificate following anatomical examination (replacing form H)

Form Cremation 8 - Certificate releasing body parts for cremation (replacing form DD)

Form Cremation 9 - Certificate of stillbirth

15. This form should be linked with form Cremation 3 and the appropriate registration document. If the medical referee is satisfied that cremation can take place, he or she will authorise it with form Cremation 13. The form may be completed by a registered midwife as well as by a fully registered medical practitioner.

Form Cremation 10 - Authorisation of cremation of deceased person by medical referee (replacing form F)

Form Cremation 11 - Certificate after post-mortem examination (replacing form D)

16. Cremation authorities will need to decide who should pay for any post-mortem examination ordered by the medical referee and that all the relevant provisions of the Human Tissue Act 2004 are met. These include any necessary consent from the applicant or other family member for the post-mortem examination to take place, that the post-mortem is made by a pathologist under the authority of a licence issued for that purpose by the Human Tissue Authority, and that the place where the post-mortem is to take place is also duly licensed. You may be asked to assist in obtaining the necessary consent.

Form Cremation 12 - Authorisation of cremation of body parts by medical referee (replacing form FF)

Form Cremation 13 - Authorisation of cremation of remains of stillborn child by medical referee

17. The medical referee will only authorise cremation of a stillborn baby after having considered form Cremation 3 and either form Cremation 9 (or the overseas equivalent) or a declaration given by a person who can give information concerning the birth and the appropriate registration document.

Further information

18. This guidance is not exhaustive. If you have any further queries or need more information about the new regulations please contact Brian Patterson on 020 3334 6404 (brian.patterson@justice.gsi.gov.uk).

Annex B

Suggested form of words to use to explain the right of inspection to applicants

It is essential that you present the right to the applicant in the correct terms. We suggest the following words are used – but only when the death has not been referred to a coroner:

You have the right to inspect the medical forms which doctors complete before cremation is authorised. Cremation is authorised by a medical referee, that is, a doctor whose role it is to check the medical forms.

If you are satisfied that you know the cause of death and have no problems with that cause then you may decide that there is little reason why you need to inspect the forms.

However, if you do have doubts about the cause of death or were surprised that the death happened when it did, you may wish to inspect the forms.

You can inspect the forms yourself or you can nominate someone else to inspect on your behalf. You might want to do this, for example, if you think someone else would be in a better position to go through the forms (perhaps because that person was present at the death and you were not).

You do not have to make up your mind now.

If you already have serious concerns about the death and believe the case should be investigated by a coroner, you need to contact the coroner's office [at this point you should provide contact details and other assistance].

The forms will be available for you to inspect at the crematorium office for no longer than 48 hours after you are informed that they have arrived there.

If you wish, the medical referee can give you advice about the cause of death, but he or she may charge a fee for this service. More information is set out in this leaflet [you should then hand over the leaflet].

If you want the funeral to be held within the next two or three days, it may well be difficult for that to happen and for you also to be able to inspect the medical forms. However, that is your decision.

Annex C

European Economic Area

European Union Members: Universities where Primary European Qualifications can be obtained within each state

Austria – Graz, Innsbruck, Salzburg, Salzburg (Paracelsus), Vienna (Wien)

Belgium – Antwerp, Brussels, Diepenbeek (Limburg), Gent, Louvain (Leuven), Liege, Mons, Namur

Bulgaria – Pleven, Plovdiv, Sofia, Trakia (Thrace), Varna

Cyprus – Medical Council of Cyprus (equivalent to General Medical Council)

Czech Republic – Brno (Masaryk Univ.), Hradec Kralove, Pilsen, Prague (Charles University), Olomouc

Denmark – Aarhus, Copenhagen, Syddansk (Odense)

Estonia – Tartu

Finland – Helsinki, Kuopio, Oulu, Tampere, Turku

France – Aix-Marseille, Amiens (Jules Verne), Angers, Besançon (Franche-Comté), Bordeaux (Victor Segalen), Brest (Bretagne), Caen, Clermont-Ferrand (Auvergne), Dijon, Grenoble, Univ Scientifique et Medicale Grenoble, Lille, Henri Warembourg de Lille, Limoges, Lyon-Sud, Lyon (Univ Claude-Bernard), Lyon (Alexis-Carrel), Montpellier-Nimes, Nancy, Nantes, Nice, Paris (Denis Diderot), Paris (Pierre et Marie Curie), Paris (René Descartes), Paris-Sud, Paris Val de Marne (Creteil), Poitiers, Reims, Rennes, Rouen,St Etienne, Strasbourg, Toulouse, Tours

Germany – Aachen, Berlin (Freiuniversität), Berlin (Humboldt), Bochum, Bonn, Dresden, Düsseldorf, Erlangen-Nürnberg, Essen, Frankfurt-am-Main, Freiburg im Breisgau, Giessen, Göttingen, Greifswald, Halle/Wittenberg, Hamburg, Hannover, Heidelberg, Homburg, Jena, Kiel, Köln (Cologne), Leipzig, Lübeck, Magdeburg, Mainz, Mannheim, Marburg, München (Ludwig-Maximilians), München (Technische), Münster, Regensburg, Rostock, Ulm, Witten-Herdecke, Tübingen, Würzburg

Greece – Alexandroupolis (Thrace), Athens (National), Crete, Ioannina, Patras, Larissa (Thessaly) Thessaloniki

Hungary – Semmelweis/Budapest, Debrecen, Pécs, Szeged

Iceland – Reykjavik

Ireland – Cork, Dublin (RCS), University College Dublin, Galway,

Italy – Ancona, Bari, Bologna, Brescia, Cagliari, Catania, Catanzaro (Reggio-Calabria), Chieti (D'Annunzio), Ferrara, Firenze, Genova, Messina, Milano, Modena, Napoli, Napoli (Federico II), Padova, Palermo, Parma, Pavia, Perugia, Pisa, Roma, Rome (Campus Bio-Medico), Sassari, Siena, Torino, Trieste, Udine, Varese, Verona

Latvia – Riga (Stradins), University of Latvia (Riga)

Liechtenstein – Nil

Lithuania – Kaunas, Vilnius

Luxembourg – Nil

Malta – Univ of Malta (Msida)

Netherlands – Amsterdam, Amsterdam (Vrije) Groningen, Leiden, Maastricht, Nijmegen, Rotterdam (Erasmus), Utrecht

Norway – Bergen, Oslo, Tromsø, Trondheim

Poland – Bialystok, Bydgoszcz, Gdansk, Krakow (Jagiellonian), Lodz (Military), Lublin, Poznan, Szczecin, Warsaw (Academy and Postgraduate), Wroclaw

Portugal – Beira, Coimbra, Lisbon, Porto (Abel Salazar) Porto

Romania – Arad, Brasov, Bucharest, Cluj-Napoca, Constanta, Craiova, Iasi, Muras, Oradea, Sibiu, Targu Timisoara

Slovakia – Bratislava, Kosice

Slovenia – Ljubljana

Spain – Albacete (Castillo la Mancha), Alcalá, Alicante, Badajoz (Extremadura), Barcelona, Barcelona (Autonoma), Barcelona (Pompeu Fabra), Cádiz, Córdoba, Granada, La Laguna Las Palmas de Gran Canaria, Lleida, Madrid (San Pablo), Madrid (Autonoma), Madrid (Complutense), Málaga Murcia, Pamplona (Navarra), Oviedo, Reus (Tarragona/Rovira Virgili) Salamanca, San Sebastian (Pais Vasco), Santa Cruz de Tenerife, Santander (Cantabria), Sevilla, Tenerife, Valencia, Valladolid, Zaragosa

Sweden – Göteborg, Linköping, Lund, Stockholm (Karolinska), Umeä, Uppsala

Switzerland* – Basel, Bern, Genève, Lausanne, Zürich

United Kingdom – five years' registration required wherever qualified

*Swiss nationals benefit from EC freedom of movement legislation under the terms of bilateral agreement, signed on 1 June 2002

© Crown copyright
Produced by the Ministry of Justice

Alternative format versions of this report are available on request from brian.patterson@justice.gsi.gov.uk or 020 3334 6404

Good practice in consent implementation guide:

consent to examination or treatment

Good practice in consent implementation guide:

consent to examination or treatment

Contents

Page

Introduction to this Implementation Guide 3

Model policy for consent to examination or treatment 7

I Introduction 9

II Documentation.....11

III When should consent be sought? 14

IV Provision of information 17

V Who is responsible for seeking consent? 20

VI Refusal of treatment.....22

VII Tissue 23

VIII Clinical photography and conventional or digital video recordings 24

IX Training 26

Appendix A 12 key points on consent: the law in England 27

Appendix B Current forms in use in this organisation 29

Appendix C Useful contact details 30

Appendix D How to seek a court declaration.....31

Appendix E Seeking consent: remembering the patient's perspective 32

Model consent form 1.....33 – 36

Model consent form 2.....37 – 40

Model consent form 3.....41 – 42

Model consent form 4.....43 – 46

About the consent form.....47

Introduction to this Implementation Guide

This *Good practice in consent implementation guide* contains a model consent policy and four consent forms, together with an accompanying information leaflet *About the consent form*. This model documentation has been developed as part of the Department of Health's 'good practice in consent' initiative, as promised in the *NHS Plan,* with the aim of assisting NHS organisations to promote good practice in the way patients are asked to give their consent to treatment, care or research. An electronic version of this documentation can be downloaded from www.doh.gov.uk/consent.

The four forms are designed to meet the needs of different groups of patients at different times:

- consent form 1 for patients able to consent for themselves
- consent form 2 for those with parental responsibility, consenting on behalf of a child/young person
- consent form 3 both for patients able to consent for themselves and for those with parental responsibility consenting on behalf of a child/young person, where the procedure does not involve any impairment of consciousness. This form is shorter than the others, as the fact that the patient is expected to remain alert during the procedure makes some of the information covered in forms 1 and 2 unnecessary. The use of this form is optional.
- consent form 4 for adults who lack capacity to consent to a particular treatment. As no-one else can give consent on behalf of such a patient, they may only be treated if that treatment is believed to be in their 'best interests'. This form requires health professionals to document both how they have come to the conclusion that the patient lacks the capacity to make this particular healthcare decision, and why the proposed treatment would be in the patient's best interests. It also allows the involvement of those close to the patient in making this healthcare decision to be documented.

The development of these forms does not change the current position on *when* written, as opposed to oral, consent to treatment is necessary. It is a matter of local determination what form of consent is appropriate for individual procedures, within the broad guidelines set out in the model consent policy.

Further forms relating to post-mortems and the removal, retention and use of human organs and tissue following post-mortem will be added to this set in due course. A guide to their implementation will be published at the same time.

Customisation of model documentation

Circular HSC 2001/023 makes clear that both consent forms and consent policy should be recognisable across the NHS and that the text included in this implementation guide should not be amended or removed. However, it may be appropriate to customise the documentation to reflect local needs, and the extent to which customisation is acceptable is set out below.

Consent forms

Additional material relevant to local circumstances may be included in consent forms, as long as this does not result in forms becoming too unwieldy or in the font size being reduced inappropriately. NHS trusts who have developed the practice of documenting anaesthetic consent on the main consent form (as opposed to on the anaesthetic record) should feel free to include such a section within their new forms.

Relevant sections of the forms (such as those dealing with benefits and risks) may be pre-printed where high through-put specialties make this feasible and desirable. If this is done, it will, of course, always be necessary for health professionals to consider whether additional risk/benefit information should be added by hand, to reflect the particular needs of the individual patient. It is essential, however, to ensure that this does not lead to a 'conveyor belt' approach to consent in these circumstances.

While consent forms 1 and 2 have been designed in the form of 4 page booklets with the crucial information for patients on the facing inside pages, they may if desired be reduced to 2 sides of a single sheet by making the guidance notes on the back available to health professionals in another way. There must, however, be clear reference on the forms to the availability of those guidance notes, which must be readily accessible. As the guidance notes on consent form 2 (which explain the relatively complicated legal position regarding who may give consent on behalf of a child) may be less familiar to health professionals, it may generally be more appropriate to take this approach for consent form 1 than for consent form 2.

Whatever the format used, a copy of the page documenting the details of the treatment should be offered to the patient, for example through the use of 'no carbon required' (NCR) copies.

The text for patients 'About the consent form' should be made available to patients in advance of their being asked to sign a consent form, and may be published in any appropriate format. Text should only be omitted if it will never be relevant (for example the section on anaesthesia could be omitted if the organisation involved would never be seeking consent for anaesthesia).

Consent policy

The model policy has been designed to encourage the addition of local information where indicated. If it is felt to be helpful to extend the scope of the model policy, this should be done by means of a separate schedule so that it does not affect the existing layout of the rest of the policy. This will enable staff moving between NHS organisations to know exactly where to look for particular information in their new organisation's policy.

Implementation

The required time-scales for implementing the model consent documentation are set out in circular HSC 2001/023. The Clinical Negligence Scheme for Trusts will be revising its consent to treatment standard to reflect the new requirements from the Department of Health and will ensure that Trusts are aware of when they will be assessed against that new standard.

Guidance on consent

The Department has published a range of guidance documents on consent, which are freely available from the NHS Response Line (08701 555 455) or from www.doh.gov.uk/consent. These are listed below:

- *Reference guide to consent for examination or treatment*, March 2001
- *12 key points on consent: the law in England*, March 2001
- *Consent – what you have a right to expect*, July 2001 (leaflet for patients, with versions for adults, children/young people, people with learning disabilities, parents and relatives/carers)

- *Seeking consent: working with children*, November 2001
- *Seeking consent: working with older people*, November 2001
- *Seeking consent: working with people with learning disabilities*, November 2001

Model policy for consent to examination or treatment

1 Introduction

Why consent is crucial

1. Patients have a fundamental legal and ethical right to determine what happens to their own bodies. Valid consent to treatment is therefore absolutely central in all forms of healthcare, from providing personal care to undertaking major surgery. Seeking consent is also a matter of common courtesy between health professionals and patients.

This policy

2. The Department of Health has issued a range of guidance documents on consent (see overleaf), and these should be consulted for details of the law and good practice requirements on consent. This policy sets out the standards and procedures in this [Trust/PCT/PCG/practice] which aim to ensure that health professionals are able to comply with the guidance. While this document is primarily concerned with healthcare, social care colleagues should also be aware of their obligations to obtain consent before providing certain forms of social care, such as those that involve touching the patient or client.

What consent is – and isn't

3. "Consent" is a patient's agreement for a health professional to provide care. Patients may indicate consent non-verbally (for example by presenting their arm for their pulse to be taken), orally, or in writing. For the consent to be valid, the patient must:

    - be competent to take the particular decision;
    - have received sufficient information to take it; and
    - not be acting under duress.

4. The context of consent can take many different forms, ranging from the active request by a patient of a particular treatment (which may or may not be appropriate or available) to the passive acceptance of a health professional's advice. In some cases, the health professional will suggest a particular form of treatment or investigation and after discussion the

patient may agree to accept it. In others, there may be a number of ways of treating a condition, and the health professional will help the patient to decide between them. Some patients, especially those with chronic conditions, become very well informed about their illness and may actively request particular treatments. In many cases, 'seeking consent' is better described as 'joint decision-making': the patient and health professional need to come to an agreement on the best way forward, based on the patient's values and preferences and the health professional's clinical knowledge.

5. Where an adult patient lacks the mental capacity (either temporarily or permanently) to give or withhold consent for themselves, **no-one else can give consent on their behalf**. However, treatment may be given if it is in their best interests, as long as it has not been refused in advance in a valid and applicable advance directive. For further details on advance directives see the Department of Health's *Reference guide to consent for examination or treatment* (chapter 1, paragraph 19).

Guidance on consent

6. The Department of Health has issued a number of guidance documents on consent, and these should be consulted for advice on the current law and good practice requirements in seeking consent. Health professionals must also be aware of any guidance on consent issued by their own regulatory bodies.

    - *Reference guide to consent for examination or treatment* provides a comprehensive summary of the current law on consent, and includes requirements of regulatory bodies such as the General Medical Council where these are more stringent. Copies are available [insert local access details] and may also be accessed on the internet at www.doh.gov.uk/consent.

    - *12 key points on consent: the law in England* has been distributed widely to health professionals working in England. This one-page document summarises those aspects of the law on consent which arise on a daily basis and is attached at Appendix A. Further copies are available from www.doh.gov.uk/consent.

    - Specific guidance, incorporating both the law and good practice advice, is available for health professionals working with children, with people with learning disabilities and with older people. Copies of these booklets are available [insert local details] and on the internet at www.doh.gov.uk/consent.

II Documentation

1. For significant procedures, it is essential for health professionals to document clearly both a patient's agreement to the intervention and the discussions which led up to that agreement. This may be done either through the use of a consent form (with further detail in the patient's notes if necessary), or through documenting in the patient's notes that they have given oral consent.

Written consent

2. Consent is often wrongly equated with a patient's signature on a consent form. A signature on a form is *evidence* that the patient has given consent, but is not *proof* of valid consent. If a patient is rushed into signing a form, on the basis of too little information, the consent may not be valid, despite the signature. Similarly, if a patient has given valid verbal consent, the fact that they are physically unable to sign the form is no bar to treatment. Patients may, if they wish, withdraw consent after they have signed a form: the signature is evidence of the process of consent-giving, not a binding contract.

3. It is rarely a legal requirement to seek written consent,[1] but it is good practice to do so if any of the following circumstances apply:

   - the treatment or procedure is complex, or involves significant risks (the term 'risk' is used throughout to refer to any adverse outcome, including those which some health professionals would describe as 'side-effects' or 'complications')
   - the procedure involves general/regional anaesthesia or sedation
   - providing clinical care is not the primary purpose of the procedure
   - there may be significant consequences for the patient's employment, social or personal life

[1.] The Mental Health Act 1983 and the Human Fertilisation and Embryology Act 1990 require written consent in certain circumstances.

- the treatment is part of a project or programme of research approved by this [Trust/PCT/PCG]

[Individual Trusts/PCTs/PCGs may choose to list in an Annex whether written/oral/non-verbal consent is appropriate for specified procedures.]

4. Completed forms should be kept with the patient's notes. Any changes to a form, made after the form has been signed by the patient, should be initialled and dated by both patient and health professional.

5. It will not usually be necessary to document a patient's consent to routine and low-risk procedures, such as providing personal care or taking a blood sample. However, if you have any reason to believe that the consent may be disputed later or if the procedure is of particular concern to the patient (for example if they have declined, or become very distressed about, similar care in the past), it would be helpful to do so.

Procedures to follow when patients lack capacity to give or withhold consent

6. Where an adult patient does not have the capacity to give or withhold consent to a significant intervention, this fact should be documented in form 4 (form for adults who are unable to consent to investigation or treatment), along with the assessment of the patient's capacity, why the health professional believes the treatment to be in the patient's best interests, and the involvement of people close to the patient. The standard consent forms should never be used for adult patients unable to consent for themselves. For more minor interventions, this information should be entered in the patient's notes.

7. An apparent lack of capacity to give or withhold consent may in fact be the result of communication difficulties rather than genuine incapacity. You should involve appropriate colleagues in making such assessments of incapacity, such as specialist learning disability teams and speech and language therapists, unless the urgency of the patient's situation prevents this. If at all possible, the patient should be assisted to make and communicate their own decision, for example by providing information in non-verbal ways where appropriate.

8. Occasionally, there will not be a consensus on whether a particular treatment is in an incapacitated adult's best interests. Where the consequences of having, or not having, the treatment are potentially serious, a court declaration may be sought. See Appendix D for details of how to do this.

Availability of forms

9. Standard consent forms and forms for adults who are unable to consent for themselves are reproduced in Appendix B and are available from [local details]. There are three versions of the standard consent form: **form 1** for adults or competent children, **form 2** for parental consent for a child or young person and **form 3** for cases where it is envisaged that the patient will remain alert throughout the procedure and no anaesthetist will be involved in their care. The use of form 3 is optional but may be thought more appropriate than form 1 in situations where patients do not need to be made aware of issues surrounding general or regional anaesthesia and do not need to make any advance decisions about additional procedures because they will be in a position to make any such decisions at the time if necessary.

III When should consent be sought?

1. When a patient formally gives their consent to a particular intervention, this is only the *endpoint* of the consent process. It is helpful to see the whole process of information provision, discussion and decision-making as part of 'seeking consent'. This process may take place at one time, or over a series of meetings and discussions, depending on the seriousness of what is proposed and the urgency of the patient's condition.

Single stage process

2. In many cases, it will be appropriate for a health professional to initiate a procedure immediately after discussing it with the patient. For example, during an ongoing episode of care a physiotherapist may suggest a particular manipulative technique and explain how it might help the patient's condition and whether there are any significant risks. If the patient is willing for the technique to be used, they will then give their consent and the procedure can go ahead immediately. In many such cases, consent will be given orally.

3. If a proposed procedure carries significant risks, it will be appropriate to seek written consent, and health professionals must take into consideration whether the patient has had sufficient chance to absorb the information necessary for them to make their decision. As long as it is clear that the patient understands and consents, the health professional may then proceed.

Two or more stage process

4. In most cases where *written* consent is being sought, treatment options will generally be discussed well in advance of the actual procedure being carried out. This may be on just one occasion (either within primary care or in a hospital out-patient clinic), or it might be over a whole series of consultations with a number of different health professionals. The consent process will therefore have at least two stages: the first being the provision of information, discussion of options and initial (oral) decision, and the second being confirmation that the patient still wants to go ahead. The consent form should be used as a means of documenting the information stage(s), as well as the confirmation stage.

5. Patients receiving elective treatment or investigations for which written consent is appropriate should be familiar with the contents of their consent form before they arrive for the actual procedure, and should have received a copy of the page documenting the decision-making process. They may be invited to sign the form, confirming that they wish treatment to go ahead, at any appropriate point before the procedure: in out-patients, at a pre-admission clinic, or when they arrive for treatment. If a form is signed before patients arrive for treatment, however, a member of the healthcare team **must** check with the patient at this point whether they have any further concerns and whether their condition has changed. This is particularly important where there has been a significant lapse of time between the form being signed and the procedure. When confirming the patient's consent and understanding, it is advisable to use a form of words which requires more than a yes/no answer from the patient: for example beginning with "tell me what you're expecting to happen", rather than "is everything all right?"

6. While administrative arrangements will vary, it should always be remembered that for consent to be valid, the patient must feel that it would have been possible for them to refuse, or change their mind. It will rarely be appropriate to ask a patient to sign a consent form after they have begun to be prepared for treatment (for example, by changing into a hospital gown), unless this is unavoidable because of the urgency of the patient's condition.

Seeking consent for anaesthesia

7. Where an anaesthetist is involved in a patient's care, it is their responsibility (not that of a surgeon) to seek consent for anaesthesia, having discussed the benefits and risks. However, in elective treatment it is not acceptable for the patient to receive no information about anaesthesia until their pre-operative visit from the anaesthetist: at such a late stage the patient will not be in a position genuinely to make a decision about whether or not to undergo anaesthesia. Patients should therefore either receive a general leaflet about anaesthesia in out-patients, or have the opportunity to discuss anaesthesia in a pre-assessment clinic. The anaesthetist should ensure that the discussion with the patient and their consent is documented in the anaesthetic record, in the patient's notes or on the consent form. Where the clinician providing the care is personally responsible for anaesthesia (eg where local anaesthesia or sedation is being used), then he or she will also be responsible for ensuring that the patient has given consent to that form of anaesthesia.

8. In addition, where general anaesthesia or sedation is being provided as part of dental treatment, the General Dental Council currently holds dentists responsible for ensuring that the patient has all the necessary information. In such cases, the anaesthetist and dentist will therefore share that responsibility.

Emergencies

9. Clearly in emergencies, the two stages (discussion of options and confirmation that the patient wishes to go ahead) will follow straight on from each other, and it may often be appropriate to use the patient's notes to document any discussion and the patient's consent, rather than using a form. The urgency of the patient's situation may limit the quantity of information that they can be given, but should not affect its quality.

Treatment of young children

10. When babies or young children are being cared for in hospital, it will not usually seem practicable to seek their parents' consent on every occasion for every routine intervention such as blood or urine tests or X-rays. However, you should remember that, in law, such consent is required. Where a child is admitted, you should therefore discuss with their parent(s) what routine procedures will be necessary, and ensure that you have their consent for these interventions in advance. If parents specify that they wish to be asked before particular procedures are initiated, you must do so, unless the delay involved in contacting them would put the child's health at risk.

11. Only people with 'parental responsibility' are entitled to give consent on behalf of their children. You must be aware that not all parents have parental responsibility for their children (for example, unmarried fathers do not automatically have such responsibility although they can acquire it). If you are in any doubt about whether the person with the child has parental responsibility for that child, you must check.

IV Provision of information

1. The provision of information is central to the consent process. Before patients can come to a decision about treatment, they need comprehensible information about their condition and about possible treatments/investigations and their risks and benefits (including the risks/benefits of doing nothing). They also need to know whether additional procedures are likely to be necessary as part of the procedure, for example a blood transfusion, or the removal of particular tissue. Once a decision to have a particular treatment/investigation has been made, patients need information about what will happen: where to go, how long they will be in hospital, how they will feel afterwards and so on.

2. Patients and those close to them will vary in how much information they want: from those who want as much detail as possible, including details of rare risks, to those who ask health professionals to make decisions for them. There will always be an element of clinical judgement in determining what information should be given. However, the *presumption* must be that the patient wishes to be well informed about the risks and benefits of the various options. Where the patient makes clear (verbally or non-verbally) that they do not wish to be given this level of information, this should be documented.

3. The following sources of patient information are available in this [Trust/PCT/PCG]:

    - [Insert local details, including advice on accessibility/readability for those developing such materials. Also include what specific provision is made for those who, for reasons of disability or otherwise, would not find printed information particularly accessible (tapes, pictorial materials etc) together with details of local independent advocacy groups where these exist. Some Trusts have developed 'patient passports' determining what information is needed at which points in a patient's 'journey' through healthcare. Others have made provision for patients to receive tape-recordings of consultations so that they have a permanent record of what was discussed.]

Provision for patients whose first language is not English

4. This [Trust/PCT/PCG] is committed to ensuring that patients whose first language is not English receive the information they need and are able to communicate appropriately with healthcare staff. It is not appropriate to use children to interpret for family members who do not speak English.

    - [Insert local details of how to access translation and interpreting service, what materials are available in which languages etc. Reference other relevant local policies or guidance eg on use of interpreting. Helpful guidance is found in the toolkit *Bridging the Gap* produced by Sheffield Health Authority and the Commission for Racial Equality.[2]]

Access to more detailed or specialist information

5. Patients may sometimes request more detailed information about their condition or about a proposed treatment than that provided in general leaflets. This [Trust/PCT/PCG] has made the following arrangements to assist patients to obtain such information:

    - [Insert local details eg help via PALS, access on site to NHS Direct Online and the National Electronic Library for Health, links with local medical libraries. In hospitals, this policy can be adapted at Directorate level to include more specific information here.]

Access to health professionals between formal appointments

6. After an appointment with a health professional in primary care or in out-patients, patients will often think of further questions which they would like answered before they take their decision. Where possible, it will be much quicker and easier for the patient to contact the healthcare team by phone than to make another appointment or to wait until the date of an elective procedure (by which time it is too late for the information genuinely to affect the patient's choice). [Insert local details of what systems are in place at GP practice/ Directorate level eg GP surgeries which have a defined hour in the day for phone calls, space in consent form for contact number of appropriate health professional, such as specialist nurse.]

---

2. Contact David Codner (Senior Manager Black and Minority Ethnic Health Issues) at Sheffield Health Authority for details

Open access clinics

7. Where patients access clinics directly, it should not be assumed that their presence at the clinic implies consent to particular treatment. You should ensure that they have the information they need before proceeding with an investigation or treatment. [Insert local details of relevant arrangements, such as provision of information through primary care.]

V Who is responsible for seeking consent?

1. The health professional carrying out the procedure is ultimately responsible for ensuring that the patient is genuinely consenting to what is being done: it is they who will be held responsible in law if this is challenged later.

2. Where oral or non-verbal consent is being sought at the point the procedure will be carried out, this will naturally be done by the health professional responsible. However, team work is a crucial part of the way the NHS operates, and where written consent is being sought it may be appropriate for other members of the team to participate in the process of seeking consent.

Completing consent forms

3. The standard consent form provides space for a health professional to provide information to patients and to sign confirming that they have done so. The health professional providing the information must be competent to do so: either because they themselves carry out the procedure, or because they have received specialist training in advising patients about this procedure, have been assessed, are aware of their own knowledge limitations and are subject to audit.

4. If the patient signs the form in advance of the procedure (for example in out-patients or at a pre-assessment clinic), a health professional involved in their care on the day should sign the form to confirm that the patient still wishes to go ahead and has had any further questions answered. It will be appropriate for any member of the healthcare team (for example a nurse admitting the patient for an elective procedure) to provide the second signature, as long as they have access to appropriate colleagues to answer questions they cannot handle themselves.

   [Insert local details, where appropriate at Directorate level, covering:

   - what training is available for health professionals who do not themselves carry out specific procedures, but could potentially provide the information patients need in coming to a decision.

- what procedures are in place to ensure that the health professionals 'confirming' the patient's consent have genuine access to appropriate colleagues where they are personally not able to answer any remaining questions.]

Responsibility of health professionals

5. It is a health professional's own responsibility:

   - to ensure that when they require colleagues to seek consent on their behalf they are confident that the colleague is competent to do so; and

   - to work within their own competence and not to agree to perform tasks which exceed that competence.

   If you feel that you are being pressurised to seek consent when you do not feel competent to do so [insert local details of whom to contact, such as clinical governance lead.]

VI Refusal of treatment

1. If the process of seeking consent is to be a meaningful one, refusal must be one of the patient's options. A competent adult patient is entitled to refuse any treatment, except in circumstances governed by the *Mental Health Act 1983*. The situation for children is more complex: see the Department of Health's *Seeking consent: working with children* for more detail. The following paragraphs apply primarily to adults.

2. If, after discussion of possible treatment options, a patient refuses all treatment, this fact should be clearly documented in their notes. If the patient has already signed a consent form, but then changes their mind, you (and where possible the patient) should note this on the form.

3. Where a patient has refused a particular intervention, you must ensure that you continue to provide any other appropriate care to which they have consented. You should also ensure that the patient realises they are free to change their mind and accept treatment if they later wish to do so. Where delay may affect their treatment choices, they should be advised accordingly.

4. If a patient consents to a particular procedure but refuses certain aspects of the intervention, you must explain to the patient the possible consequences of their partial refusal. If you genuinely believe that the procedure cannot be safely carried out under the patient's stipulated conditions, you are not obliged to perform it. You must, however, continue to provide any other appropriate care. Where another health professional believes that the treatment can be safely carried out under the conditions specified by the patient, you must on request be prepared to transfer the patient's care to that health professional.

VII Tissue

1. The legal position regarding the use of human tissue (including blood samples and other bodily fluids provided for testing) raises some difficult issues and is currently under review. Such tissue can be very valuable in education and research, and its use may lead to developments in medical knowledge and hence improvements in healthcare for all. At present, this [Trust/PCT/PCG] requires that patients should be given the opportunity to refuse permission for tissue taken from them during surgery or other procedure to be used for education or research purposes. [Insert local details of how this should be done. The system must be well-publicised and transparent, making provision for patients to record their consent or objection to the use of such tissue and for this to be notified to the laboratory. Patients must also be able to record any objections to particular uses or use of particular tissues.]

2. Explicit consent is not necessary for public health surveillance using the unlinked anonymous method, but a well-publicised opt-out policy must apply. [Insert local details.]

3. Pending the outcome of the review of the law governing the use of human organs and tissue, the Department of Health believes that tissue samples may be used for quality assurance purposes without requiring specific patient consent *provided* there is an active policy of informing patients of such use. This is essential to ensure the high quality of service which all patients have the right to expect. Wherever possible, samples of tissue used in this way should be anonymised or pseudonymised. [Insert local details of policy.]

VIII Clinical photography and conventional or digital video recordings

1. Photographic and video recordings made for clinical purposes form part of a patient's record. Although consent to certain recordings, such as X-rays, is implicit in the patient's consent to the procedure, health professionals should always ensure that they make clear in advance if any photographic or video recording will result from that procedure.

2. Photographic and video recordings which are made for treating or assessing a patient must not be used for any purpose other than the patient's care or the audit of that care, without the express consent of the patient or a person with parental responsibility for the patient. The one exception to this principle is set out in paragraph 3 below. If you wish to use such a recording for education, publication or research purposes, you must seek consent in writing, ensuring that the person giving consent is fully aware of the possible uses of the material. In particular, the person must be made aware that you may not be able to control future use of the material once it has been placed in the public domain. If a child is not willing for a recording to be used, you must not use it, even if a person with parental responsibility consents.

3. Photographic and video recordings, made for treating or assessing a patient and from which there is no possibility that the patient might be recognised, may be used within the clinical setting for education or research purposes without express consent from the patient, as long as this policy is well publicised. However, express consent must be sought for any form of publication.

4. If you wish to make a photographic or video recording of a patient specifically for education, publication or research purposes, you must first seek their written consent (or where appropriate that of a person with parental responsibility) to make the recording, and then seek their consent to use it. Patients must know that they are free to stop the recording at any time and that they are entitled to view it if they wish, before deciding whether to give consent to its use. If the patient decides that they are not happy for any recording to be used, it must be destroyed. As with recordings made with therapeutic intent, patients must receive full information on the possible future uses of the recording, including the fact that it may not be possible to withdraw it once it is in the public domain.

5. The situation may sometimes arise where you wish to make a recording specifically for education, publication or research purposes, but the patient is temporarily unable to give or withhold consent because, for example, they are unconscious. In such cases, you may make such a recording, but you must seek consent as soon as the patient regains capacity. You must not use the recording until you have received consent for its use, and if the patient does not consent to any form of use, the recording must be destroyed.

6. If the patient is likely to be permanently unable to give or withhold consent for a recording to be made, you should seek the agreement of some-one close to the patient. You must not make any use of the recording which might be against the interests of the patient. You should also not make, or use, any such recording if the purpose of the recording could equally well be met by recording patients who are able to give or withhold consent.

IX Training

[Insert details of training available on consent in this organisation, covering both basic training on the law of consent, and training on any specific procedures used in this organisation.]

Dated:
Person responsible for policy:
Policy approved by:
Policy to be reviewed by [date]:

Appendix A

12 key points on consent: the law in England

When do health professionals need consent from patients?

1. Before you examine, treat or care for competent adult patients you must obtain their consent.

2. Adults are always assumed to be competent unless demonstrated otherwise. If you have doubts about their competence, the question to ask is: "can this patient understand and weigh up the information needed to make this decision?" Unexpected decisions do not prove the patient is incompetent, but may indicate a need for further information or explanation.

3. Patients may be competent to make some health care decisions, even if they are not competent to make others.

4. Giving and obtaining consent is usually a process, not a one-off event. Patients can change their minds and withdraw consent at any time. If there is any doubt, you should always check that the patient still consents to your caring for or treating them.

Can children give consent for themselves?

5. Before examining, treating or caring for a child, you must also seek consent. Young people aged 16 and 17 are presumed to have the competence to give consent for themselves. Younger children who understand fully what is involved in the proposed procedure can also give consent (although their parents will ideally be involved). In other cases, some-one with parental responsibility must give consent on the child's behalf, unless they cannot be reached in an emergency. If a competent child consents to treatment, a parent **cannot** over-ride that consent. Legally, a parent can consent if a competent child refuses, but it is likely that taking such a serious step will be rare.

Who is the right person to seek consent?

6. It is always best for the person actually treating the patient to seek the patient's consent. However, you may seek consent on behalf of colleagues if you are capable of performing the procedure in question, or if you have been specially trained to seek consent for that procedure.

What information should be provided?

7. Patients need sufficient information before they can decide whether to give their consent: for example information about the benefits and risks of the proposed treatment, and alternative treatments. If the patient is not offered as much information as they reasonably need to make their decision, and in a form they can understand, their consent may not be valid.

8. Consent must be given voluntarily: not under any form of duress or undue influence from health professionals, family or friends.

Does it matter how the patient gives consent?

9. No: consent can be written, oral or non-verbal. A signature on a consent form does not itself prove the consent is valid – the point of the form is to record the patient's decision, and also increasingly the discussions that have taken place. Your Trust or organisation may have a policy setting out when you need to obtain written consent.

Refusal of treatment

10. Competent adult patients are entitled to refuse treatment, even when it would clearly benefit their health. The only exception to this rule is where the treatment is for a mental disorder and the patient is detained under the Mental Health Act 1983. A competent pregnant woman may refuse any treatment, even if this would be detrimental to the fetus.

Adults who are not competent to give consent

11. **No-one** can give consent on behalf of an incompetent adult. However, you may still treat such a patient if the treatment would be in their best interests. 'Best interests' go wider than best medical interests, to include factors such as the wishes and beliefs of the patient when competent, their current wishes, their general well-being and their spiritual and religious welfare. People close to the patient may be able to give you information on some of these factors. Where the patient has never been competent, relatives, carers and friends may be best placed to advise on the patient's needs and preferences.

12. If an incompetent patient has clearly indicated in the past, while competent, that they would refuse treatment in certain circumstances (an 'advance refusal'), and those circumstances arise, you must abide by that refusal.

This summary cannot cover all situations. For more detail, consult the *Reference guide to consent for examination or treatment*, available from the NHS Response Line 08701 555 455 and at www.doh.gov.uk/consent.

Appendix B

Current forms in use in this organisation

Appendix C

Useful contact details

[eg risk managers, training managers, clinical governance leads, clinical ethics committees]

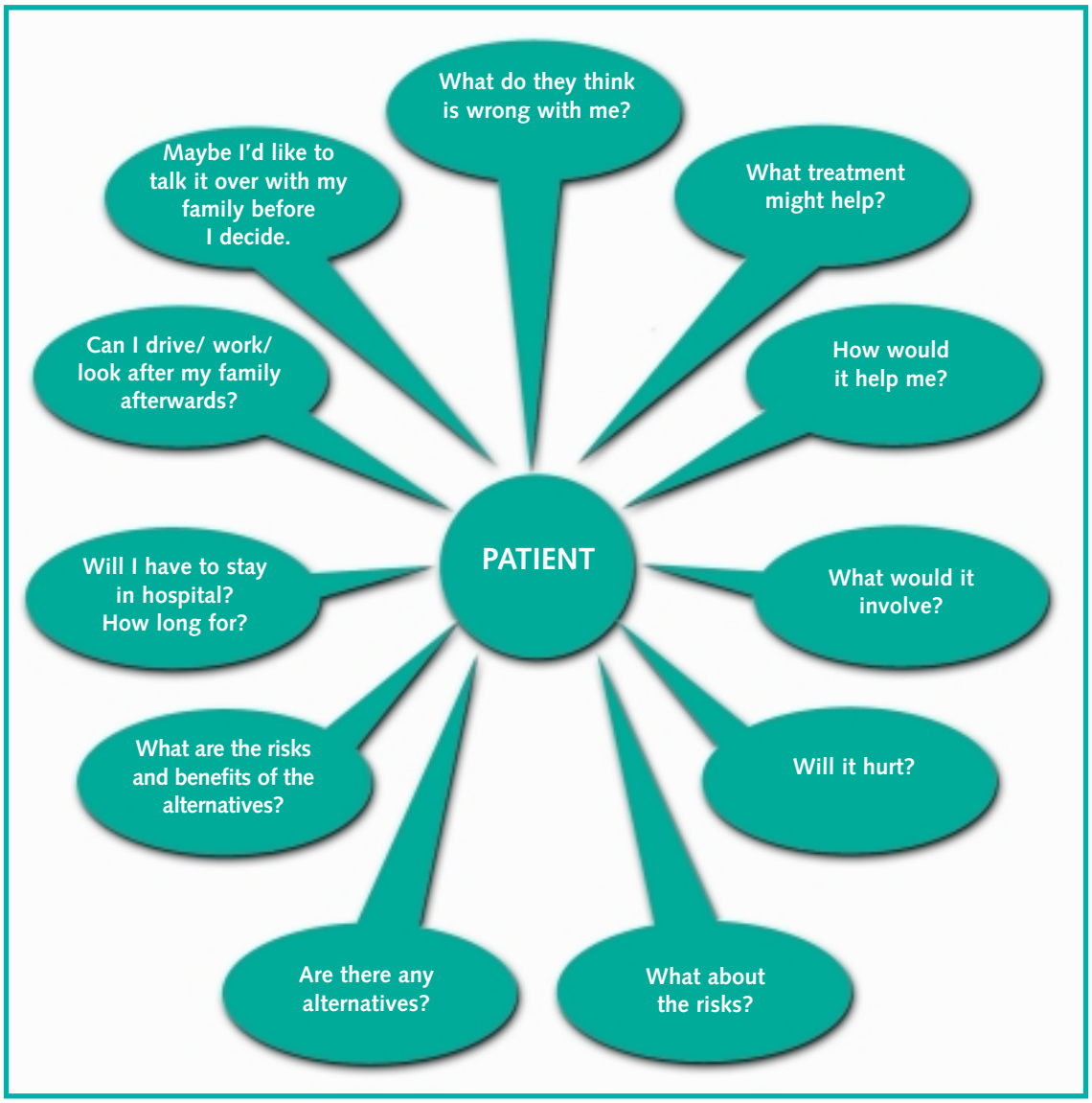
Appendix D

How to seek a court declaration

[eg details of how to contact the organisation's legal services, what information they will require etc]

Appendix E

Seeking consent: remembering the patient's perspective



[NHS organisation name]

consent form 1

Patient agreement to investigation or treatment

Patient details (or pre-printed label)

Patient's surname/family name _____

Patient's first names _____

Date of birth _____

Responsible health professional _____

Job title _____

NHS number (or other identifier) _____

☐ Male ☐ Female

Special requirements _____
(eg other language/other communication method)

To be retained in patient's notes

Patient identifier/label

Name of proposed procedure or course of treatment

(include brief explanation if medical term not clear) _____

_____

_____

Statement of health professional (to be filled in by health professional with appropriate knowledge of proposed procedure, as specified in consent policy)

I have explained the procedure to the patient. In particular, I have explained:

The intended benefits _____

_____

_____

Serious or frequently occurring risks _____

_____

_____

Any extra procedures which may become necessary during the procedure

☐ blood transfusion _____

☐ other procedure (please specify) _____

_____

I have also discussed what the procedure is likely to involve, the benefits and risks of any available alternative treatments (including no treatment) and any particular concerns of this patient.

☐ The following leaflet/tape has been provided _____

This procedure will involve:

☐ general and/or regional anaesthesia ☐ local anaesthesia ☐ sedation

Signed _____ Date _____

Name (PRINT) _____ Job title _____

Contact details (if patient wishes to discuss options later) _____

Statement of interpreter (where appropriate)

I have interpreted the information above to the best of my ability and in a way in which I believe s/he can understand.

Signed _____ Date _____

Name (PRINT) _____

Top copy accepted by patient: yes/no (please ring)

Patient identifier/label

Statement of patient

Please read this form carefully. If your treatment has been planned in advance, you should already have your own copy of page 2 which describes the benefits and risks of the proposed treatment. If not, you will be offered a copy now. If you have any further questions, do ask – we are here to help you. You have the right to change your mind at any time, including after you have signed this form.

I agree to the procedure or course of treatment described on this form.

I understand that you cannot give me a guarantee that a particular person will perform the procedure. The person will, however, have appropriate experience.

I understand that I will have the opportunity to discuss the details of anaesthesia with an anaesthetist before the procedure, unless the urgency of my situation prevents this. (This only applies to patients having general or regional anaesthesia.)

I understand that any procedure in addition to those described on this form will only be carried out if it is necessary to save my life or to prevent serious harm to my health.

I have been told about additional procedures which may become necessary during my treatment. I have listed below any procedures **which I do not wish to be carried out** without further discussion.

_____

_____

_____

Patient's signature _____ Date _____

Name (PRINT) _____

A witness should sign below if the patient is unable to sign but has indicated his or her consent. Young people/children may also like a parent to sign here (see notes).

Signed _____ Date _____

Name (PRINT) _____

Confirmation of consent (to be completed by a health professional when the patient is admitted for the procedure, if the patient has signed the form in advance)

On behalf of the team treating the patient, I have confirmed with the patient that s/he has no further questions and wishes the procedure to go ahead.

Signed _____ Date _____

Name (PRINT) _____ Job title _____

Important notes: (tick if applicable)

☐ See also advance directive/living will (eg Jehovah's Witness form)

☐ Patient has withdrawn consent (ask patient to sign/date here) _____

Guidance to health professionals (to be read in conjunction with consent policy)

What a consent form is for

This form documents the patient's agreement to go ahead with the investigation or treatment you have proposed. It is not a legal waiver – if patients, for example, do not receive enough information on which to base their decision, then the consent may not be valid, even though the form has been signed. Patients are also entitled to change their mind after signing the form, if they retain capacity to do so. The form should act as an aide-memoire to health professionals and patients, by providing a check-list of the kind of information patients should be offered, and by enabling the patient to have a written record of the main points discussed. In no way, however, should the written information provided for the patient be regarded as a substitute for face-to-face discussions with the patient.

The law on consent

See the Department of Health's *Reference guide to consent for examination or treatment* for a comprehensive summary of the law on consent (also available at www.doh.gov.uk/consent).

Who can give consent

Everyone aged 16 or more is presumed to be competent to give consent for themselves, unless the opposite is demonstrated. If a child under the age of 16 has "sufficient understanding and intelligence to enable him or her to understand fully what is proposed", then he or she will be competent to give consent for himself or herself. Young people aged 16 and 17, and legally 'competent' younger children, may therefore sign this form for themselves, but may like a parent to countersign as well. If the child is not able to give consent for himself or herself, some-one with parental responsibility may do so on their behalf and a separate form is available for this purpose. Even where a child is able to give consent for himself or herself, you should always involve those with parental responsibility in the child's care, unless the child specifically asks you not to do so. If a patient is mentally competent to give consent but is physically unable to sign a form, you should complete this form as usual, and ask an independent witness to confirm that the patient has given consent orally or non-verbally.

When NOT to use this form

If the patient is 18 or over and is not legally competent to give consent, you should use form 4 (form for adults who are unable to consent to investigation or treatment) instead of this form. A patient will not be legally competent to give consent if:

- they are unable to comprehend and retain information material to the decision and/or
- they are unable to weigh and use this information in coming to a decision.

You should always take all reasonable steps (for example involving more specialist colleagues) to support a patient in making their own decision, before concluding that they are unable to do so. Relatives **cannot** be asked to sign this form on behalf of an adult who is not legally competent to consent for himself or herself.

Information

Information about what the treatment will involve, its benefits and risks (including side-effects and complications) and the alternatives to the particular procedure proposed, is crucial for patients when making up their minds. The courts have stated that patients should be told about 'significant risks which would affect the judgement of a reasonable patient'. 'Significant' has not been legally defined, but the GMC requires doctors to tell patients about 'serious or frequently occurring' risks. In addition if patients make clear they have particular concerns about certain kinds of risk, you should make sure they are informed about these risks, even if they are very small or rare. You should always answer questions honestly. Sometimes, patients may make it clear that they do not want to have any information about the options, but want you to decide on their behalf. In such circumstances, you should do your best to ensure that the patient receives at least very basic information about what is proposed. Where information is refused, you should document this on page 2 of the form or in the patient's notes.

[NHS organisation name]

consent form 2

Parental agreement to investigation or treatment for a child or young person

Patient details (or pre-printed label)

Patient's surname/family name _____

Patient's first names _____

Date of birth _____

Age _____

Responsible health professional _____

Job title _____

NHS number (or other identifier) _____

☐ Male ☐ Female

Special requirements _____
(eg other language/other communication method)

To be retained in patient's notes

Patient identifier/label

Name of proposed procedure or course of treatment

(include brief explanation if medical term not clear) _____

_____

_____

Statement of health professional (to be filled in by health professional with appropriate knowledge of proposed procedure, as specified in consent policy)

I have explained the procedure to the child and his or her parent(s). In particular, I have explained:

The intended benefits _____

_____

_____

Serious or frequently occurring risks _____

_____

_____

Any extra procedures which may become necessary during the procedure

☐ blood transfusion _____

☐ other procedure (please specify) _____

_____

I have also discussed what the procedure is likely to involve, the benefits and risks of any available alternative treatments (including no treatment) and any particular concerns of this patient and his or her parents.

☐ The following leaflet/tape has been provided _____

This procedure will involve:

☐ general and/or regional anaesthesia ☐ local anaesthesia ☐ sedation

Signed _____ Date _____

Name (PRINT) _____ Job title _____

Contact details (if child/parent wish to discuss options later) _____

Statement of interpreter (where appropriate)

I have interpreted the information above to the child and his or her parents to the best of my ability and in a way in which I believe they can understand.

Signed _____ Date _____

Name (PRINT) _____

Top copy accepted by patient/parent: yes/no (please ring)

Patient identifier/label

Statement of parent

Please read this form carefully. If the procedure has been planned in advance, you should already have your own copy of page 2 which describes the benefits and risks of the proposed treatment. If not, you will be offered a copy now. If you have any further questions, do ask – we are here to help you and your child. You have the right to change your mind at any time, including after you have signed this form.

I agree to the procedure or course of treatment described on this form and **I confirm** that I have 'parental responsibility' for this child.

I understand that you cannot give me a guarantee that a particular person will perform the procedure. The person will, however, have appropriate experience.

I understand that my child and I will have the opportunity to discuss the details of anaesthesia with an anaesthetist before the procedure, unless the urgency of the situation prevents this. (This only applies to children having general or regional anaesthesia.)

I understand that any procedure in addition to those described on this form will only be carried out if it is necessary to save the life of my child or to prevent serious harm to his or her health.

I have been told about additional procedures which may become necessary during my child's treatment. I have listed below any procedures **which I do not wish to be carried out** without further discussion.

_____

_____

_____

Signature _____ Date _____

Name (PRINT) _____ Relationship to child _____

Child's agreement to treatment (if child wishes to sign)

I agree to have the treatment I have been told about.

Name _____ Signature _____

Date _____

Confirmation of consent (to be completed by a health professional when the child is admitted for the procedure, if the parent/child have signed the form in advance)

On behalf of the team treating the patient, I have confirmed with the child and his or her parent(s) that they have no further questions and wish the procedure to go ahead.

Signed _____ Date _____

Name (PRINT) _____ Job title _____

Important notes: (tick if applicable)

☐ See also advance directive/living will (eg Jehovah's Witness form)

☐ Parent has withdrawn consent (ask parent to sign/date here) _____

Guidance to health professionals (to be read in conjunction with consent policy)

This form

This form should be used to document consent to a child's treatment, where that consent is being given by a person with parental responsibility for the child. The term 'parent' has been used in this form as a shorthand for 'person with parental responsibility'. Where children are legally competent to consent for themselves (see below), they may sign the standard 'adult' consent form (form 1). There is space on that form for a parent to countersign if a competent child wishes them to do so.

Who can give consent?

Everyone aged 16 or more is presumed to be competent to give consent for themselves, unless the opposite is demonstrated. The courts have stated that if a child under the age of 16 has "sufficient understanding and intelligence to enable him or her to understand fully what is proposed", then he or she will be competent to give consent for himself or herself. If children are not able to give consent for themselves, some-one with parental responsibility may do so on their behalf.

Although children acquire rights to give consent for themselves as they grow older, people with 'parental responsibility' for a child retain the right to give consent on the child's behalf until the child reaches the age of 18. Therefore, for a number of years, both the child and a person with parental responsibility have the right to give consent to the child's treatment. In law, health professionals only need the consent of one appropriate person before providing treatment. This means that in theory it is lawful to provide treatment to a child under 18 which a person with parental responsibility has authorised, even if the child refuses. As a matter of good practice, however, you should always seek a competent child's consent before providing treatment unless any delay involved in doing so would put the child's life or health at risk. Younger children should also be as involved as possible in decisions about their healthcare. Further advice is given in the Department's guidance *Seeking consent: working with children*. Any differences of opinion between the child and their parents, or between parents, should be clearly documented in the patient's notes.

Parental responsibility

The person(s) with parental responsibility will usually, but not invariably, be the child's birth parents. People with parental responsibility for a child include: the child's mother; the child's father if married to the mother at the child's conception, birth or later; a legally appointed guardian; the local authority if the child is on a care order; or a person named in a residence order in respect of the child. Fathers who have never been married to the child's mother will only have parental responsibility if they have acquired it through a court order or parental responsibility agreement (although this may change in the future).

Information

Information about what the treatment will involve, its benefits and risks (including side-effects and complications) and the alternatives to the particular procedure proposed, is crucial for children and their parents when making up their minds about treatment. The courts have stated that patients should be told about 'significant risks which would affect the judgement of a reasonable patient'. 'Significant' has not been legally defined, but the GMC requires doctors to tell patients about 'serious or frequently occurring' risks. In addition if patients make clear they have particular concerns about certain kinds of risk, you should make sure they are informed about these risks, even if they are very small or rare. You should always answer questions honestly.

Guidance on the law on consent

See the Department of Health publications *Reference guide to consent for examination or treatment* and *Seeking consent: working with children* for a comprehensive summary of the law on consent (also available at www.doh.gov.uk/consent).

Patient identifier/label

[NHS organisation name] consent form 3

Patient/parental agreement to investigation or treatment

(procedures where consciousness not impaired)

Name of procedure

(include brief explanation if medical term not clear) _____

_____

_____

Statement of health professional (to be filled in by health professional with appropriate knowledge of proposed procedure, as specified in consent policy)

I have explained the procedure to the patient/parent. In particular, I have explained:
The intended benefits _____

_____

_____

Serious or frequently occurring risks _____

_____

_____

I have also discussed what the procedure is likely to involve, the benefits and risks of any available alternative treatments (including no treatment) and any particular concerns of those involved.

☐ The following leaflet/tape has been provided _____

Signed _____ Date _____

Name (PRINT) _____ Job title _____

Statement of interpreter (where appropriate)

I have interpreted the information above to the patient/parent to the best of my ability and in a way in which I believe s/he/they can understand.

Signed _____ Date _____ Name (PRINT) _____

Statement of patient/person with parental responsibility for patient

I agree to the procedure described above.

I understand that you cannot give me a guarantee that a particular person will perform the procedure. The person will, however, have appropriate experience.

I understand that the procedure will/will not involve local anaesthesia.

Signature _____ Date _____

Name (PRINT) _____ Relationship to patient _____

Confirmation of consent (to be completed by a health professional when the patient is admitted for the procedure, if the patient/parent has signed the form in advance)

I have confirmed that the patient/parent has no further questions and wishes the procedure to go ahead.

Signature _____ Date _____

Name (PRINT) _____ Job title _____

Top copy accepted by patient/parent: yes/no (please ring)

Guidance to health professionals (to be read in conjunction with consent policy)

This form

This form documents the patient's agreement (or that of a person with parental responsibility for the patient) to go ahead with the investigation or treatment you have proposed. **It is only designed for procedures where the patient is expected to remain alert throughout and where an anaesthetist is not involved in their care: for example for drug therapy where written consent is deemed appropriate.** In other circumstances you should use either form 1 (for adults/competent children) or form 2 (parental consent for children/young people) as appropriate.

Consent forms are not legal waivers – if patients, for example, do not receive enough information on which to base their decision, then the consent may not be valid, even though the form has been signed. Patients also have every right to change their mind after signing the form.

Who can give consent

Everyone aged 16 or more is presumed to be competent to give consent for themselves, unless the opposite is demonstrated. If a child under the age of 16 has "sufficient understanding and intelligence to enable him or her to understand fully what is proposed", then he or she will be competent to give consent for himself or herself. Young people aged 16 and 17, and legally 'competent' younger children, may therefore sign this form for themselves, if they wish. If the child is not able to give consent for himself or herself, some-one with parental responsibility may do so on their behalf. Even where a child is able to give consent for himself or herself, you should always involve those with parental responsibility in the child's care, unless the child specifically asks you not to do so. If a patient is mentally competent to give consent but is physically unable to sign a form, you should complete this form as usual, and ask an independent witness to confirm that the patient has given consent orally or non-verbally.

When NOT to use this form (see also 'This form' above)

If the patient is 18 or over and is not legally competent to give consent, you should use form 4 (form for adults who are unable to consent to investigation or treatment) instead of this form. A patient will not be legally competent to give consent if:

- they are unable to comprehend and retain information material to the decision and/or
- they are unable to weigh and use this information in coming to a decision.

You should always take all reasonable steps (for example involving more specialist colleagues) to support a patient in making their own decision, before concluding that they are unable to do so. Relatives **cannot** be asked to sign this form on behalf of an adult who is not legally competent to consent for himself or herself.

Information

Information about what the treatment will involve, its benefits and risks (including side-effects and complications) and the alternatives to the particular procedure proposed, is crucial for patients when making up their minds about treatment. The courts have stated that patients should be told about 'significant risks which would affect the judgement of a reasonable patient'. 'Significant' has not been legally defined, but the GMC requires doctors to tell patients about 'serious or frequently occurring' risks. In addition if patients make clear they have particular concerns about certain kinds of risk, you should make sure they are informed about these risks, even if they are very small or rare. You should always answer questions honestly. Sometimes, patients may make it clear that they do not want to have any information about the options, but want you to decide on their behalf. In such circumstances, you should do your best to ensure that the patient receives at least very basic information about what is proposed. Where information is refused, you should document this overleaf or in the patient's notes.

The law on consent

See the Department of Health's *Reference guide to consent for examination or treatment* for a comprehensive summary of the law on consent (also available at www.doh.gov.uk/consent).

[NHS organisation name]

consent form 4

Form for adults who are unable to consent to investigation or treatment

Patient details (or pre-printed label)

Patient's surname/family name _____

Patient's first names _____

Date of birth _____

Responsible health professional _____

Job title _____

NHS number (or other identifier) _____

☐ Male ☐ Female

Special requirements _____
(eg other language/other communication method)

To be retained in patient's notes

Patient identifier/label

All sections to be completed by health professional proposing the procedure

A Details of procedure or course of treatment proposed

(NB see guidance to health professionals overleaf for details of situations where court approval must first be sought)

B Assessment of patient's capacity

I confirm that the patient lacks capacity to give or withhold consent to this procedure or course of treatment because:

☐ the patient is unable to comprehend and retain information material to the decision; and/or
☐ the patient is unable to use and weigh this information in the decision-making process; or
☐ the patient is unconscious

Further details (excluding where patient unconscious): for example how above judgements reached; which colleagues consulted; what attempts made to assist the patient make his or her own decision and why these were not successful.

C Assessment of patient's best interests

To the best of my knowledge, the patient has not refused this procedure in a valid advance directive. Where possible and appropriate, I have consulted with colleagues and those close to the patient, and I believe the procedure to be in the patient's best interests because:

(Where incapacity is likely to be temporary, for example if patient unconscious, or where patient has fluctuating capacity)

The treatment cannot wait until the patient recovers capacity because:

D Involvement of the patient's family and others close to the patient

The final responsibility for determining whether a procedure is in an incapacitated patient's best interests lies with the health professional performing the procedure. However, it is good practice to consult with those close to the patient (eg spouse/partner, family and friends, carer, supporter or advocate) unless you have good reason to believe that the patient would not have wished particular individuals to be consulted, or unless the urgency of their situation prevents this. "Best interests" go far wider than "best medical interests", and include factors such as the patient's wishes and beliefs when competent, their current wishes, their general well-being and their spiritual and religious welfare.

(to be signed by a person or persons close to the patient, if they wish)

I/We have been involved in a discussion with the relevant health professionals over the treatment of (patient's name). I/We understand that he/she is unable to give his/her own consent, based on the criteria set out in this form. I/We also understand that treatment can lawfully be provided if it is in his/her best interests to receive it.

Any other comments (including any concerns about decision)

Name _____ Relationship to patient _____

Address (if not the same as patient) _____

_____

_____

Signature _____ Date _____

If a person close to the patient was not available in person, has this matter been discussed in any other way (eg over the telephone?)

☐ Yes ☐ No

Details:

Signature of health professional proposing treatment

The above procedure is, in my clinical judgement, in the best interests of the patient, who lacks capacity to consent for himself or herself. Where possible and appropriate I have discussed the patient's condition with those close to him or her, and taken their knowledge of the patient's views and beliefs into account in determining his or her best interests.

I have/have not sought a second opinion.

Signature _____ Date _____

Name (PRINT) _____ Job title _____

Where second opinion sought, s/he should sign below to confirm agreement:

Signature _____ Date _____

Name (PRINT) _____ Job title _____

Guidance to health professionals (to be read in conjunction with consent policy)

This form should only be used where it would be usual to seek written consent but an adult patient (18 or over) lacks capacity to give or withhold consent to treatment. If an adult **has** capacity to accept or refuse treatment, you should use the standard consent form and respect any refusal. Where treatment is very urgent (for example if the patient is critically ill), it may not be feasible to fill in a form at the time, but you should document your clinical decisions appropriately afterwards. If treatment is being provided under the authority of Part IV of the *Mental Health Act 1983,* different legal provisions apply and you are required to fill in more specialised forms (although in some circumstances you may find it helpful to use this form as well). If the adult now lacks capacity, but has clearly refused particular treatment in advance of their loss of capacity (for example in an advance directive or 'living will'), then you must abide by that refusal if it was validly made and is applicable to the circumstances. For further information on the law on consent, see the Department of Health's *Reference guide to consent for examination or treatment* (www.doh.gov.uk/consent).

When treatment can be given to a patient who is unable to consent

For treatment to be given to a patient who is unable to consent, the following **must** apply:

- the patient must lack the capacity ('competence') to give or withhold consent to this procedure AND
- the procedure must be in the patient's best interests.

Capacity

A patient will lack capacity to consent to a particular intervention if he or she is:

- unable to comprehend and retain information material to the decision, especially as to the consequences of having, or not having, the intervention in question; and/or
- unable to use and weigh this information in the decision-making process.

Before making a judgement that a patient lacks capacity you must take all steps reasonable in the circumstances to assist the patient in taking their own decisions (this will clearly not apply if the patient is unconscious). This may involve explaining what is involved in very simple language, using pictures and communication and decision-aids as appropriate. People close to the patient (spouse/partner, family, friends and carers) may often be able to help, as may specialist colleagues such as speech and language therapists or learning disability teams, and independent advocates or supporters.

Capacity is 'decision-specific': a patient may lack capacity to take a particular complex decision, but be quite able to take other more straight-forward decisions or parts of decisions.

Best interests

A patient's best interests are not limited to their best medical interests. Other factors which form part of the best interests decision include:

- the wishes and beliefs of the patient when competent
- their current wishes
- their general well-being
- their spiritual and religious welfare

Two incapacitated patients, whose *physical* condition is identical, may therefore have different best interests.

Unless the patient has clearly indicated that particular individuals should not be involved in their care, or unless the urgency of their situation prevents it, you should attempt to involve people close to the patient (spouse/partner, family and friends, carer, supporter or advocate) in the decision-making process. Those close to the patient cannot require you to provide particular treatment which you do not believe to be clinically appropriate. However they will know the patient much better than you do, and therefore are likely to be able to provide valuable information about the patient's wishes and values.

Second opinions and court involvement

Where treatment is complex and/or people close to the patient express doubts about the proposed treatment, a second opinion should be sought, unless the urgency of the patient's condition prevents this. Donation of regenerative tissue such as bone marrow, sterilisation for contraceptive purposes and withdrawal of artificial nutrition or hydration from a patient in PVS must never be undertaken without prior High Court approval. High Court approval can also be sought where there are doubts about the patient's capacity or best interests.

About the consent form

About the consent form

Before a doctor or other health professional examines or treats you, they need your consent. Sometimes you can simply tell them whether you agree with their suggestions. However, sometimes a written record of your decision is helpful – for example if your treatment involves sedation or general anaesthesia. You'll then be asked to sign a consent form. If you later change your mind, you're entitled to withdraw consent – even after signing.

What should I know before deciding?

Health professionals must ensure you know enough to enable you to decide about treatment. They'll write information on the consent form and offer you a copy to keep as well as discussing the choices of treatment with you. Although they may well recommend a particular option, you're free to choose another. People's attitudes vary on things like the amount of risk or pain they're prepared to accept. That goes for the amount of information, too. If you'd rather not know about certain aspects, discuss your worries with whoever is treating you.

Should I ask questions?

Always ask anything you want. As a reminder, you can write your questions in the space over the page. The person you ask should do his or her best to answer, but if they don't know they should find some-one else who is able to discuss your concerns. To support you and prompt questions, you might like to bring a friend or relative. Ask if you'd like someone independent to speak up for you.

Is there anything I should tell people?

If there's any procedure you **don't** want to happen, you should tell the people treating you. It's also important for them to know about any illnesses or allergies which you may have or have suffered from in the past.

Can I find out more about giving consent?

The Department of Health leaflet *Consent – what you have a right to expect* is a detailed guide on consent in versions for adults, children, parents, carers/relatives and people with learning disabilities. Ask for one from your clinic or hospital, order one from the NHS Responseline (08701 555 455) or read it on the web site www.doh.gov.uk/consent.

Who is treating me?

Amongst the health professionals treating you may be a "doctor in training" – medically qualified, but now doing more specialist training. They range from recently qualified doctors to doctors almost ready to be consultants. They will only carry out procedures for which they have been appropriately trained. Someone senior will supervise – either in person accompanying a less experienced doctor in training or available to advise someone more experienced.

What about anaesthesia?

If your treatment involves general or regional anaesthesia (where more than a small part of your body is being anaesthetised), you'll be given general information about it in advance. You'll also have an opportunity to talk with the anaesthetist when he or she assesses your state of health shortly before treatment. Hospitals sometimes have pre-assessment clinics which provide patients with the chance to discuss things a few weeks earlier.

Will samples be taken?

Some kinds of operation involve removing a part of the body (such as a gall bladder or a tooth). You would always be told about this in advance. Other operations may mean taking samples as part of your care. These samples may be of blood or small sections of tissue, for example of an unexplained lump. Such samples may be further checked by other health professionals to ensure the best possible standards. Again, you should be told in advance if samples are likely to be taken.

Sometimes samples taken during operations may also be used for teaching, research or public health monitoring in the future interests of all NHS patients. The NHS trust treating you will have a local system for checking whether you're willing for this to happen.

Photographs and videos

As part of your treatment some kind of photographic record may be made – for example X-rays, clinical photographs or sometimes a video. You will always be told if this is going to happen. The photograph or recording will be kept with your notes and will be held in confidence as part of your medical record. This means that it will normally be seen only by those involved in providing you with care or those who need to check the quality of care you have received. The use of photographs and recordings is also extremely important for other NHS work, such as teaching or medical research. However, we will not use yours in a way that might allow you to be identified or recognised without your express permission.

What if things don't go as expected?

Amongst the 25,000 operations taking place every day, sometimes things don't go as they should. Although the doctor involved should inform you and your family, often the patient is the first to notice something amiss. If you're worried – for example about the after-effects of an operation continuing much longer than you were told to expect – tell a health professional right away. Speak to your GP, or contact your clinic - the phone number should be on your appointment card, letter or consent form copy.

What are the key things to remember?

It's your decision! It's up to you to choose whether or not to consent to what's being proposed. Ask as many questions as you like, and remember to tell the team about anything that concerns you or about any medication, allergies or past history which might affect your general health.

Questions to ask health professionals

As well as giving you information health professionals must listen and do their best to answer your questions. Before your next appointment, you can write some down in the space below.

Questions may be about the **treatment itself**, for example:

- What are the main treatment options?
- What are the benefits of each of the options?
- What are the risks, if any, of each option?
- What are the success rates for different options – nationally, for this unit or for you (the surgeon)?
- Why do you think an operation (if suggested) is necessary?
- What are the risks if I decide to do nothing for the time being?
- How can I expect to feel after the procedure?
- When am I likely to be able to get back to work?

Questions may also be about how the treatment might affect your future state of health or style of life, for example:

- Will I need long-term care?
- Will my mobility be affected?
- Will I still be able to drive?
- Will it affect the kind of work I do?
- Will it affect my personal/sexual relationships?
- Will I be able to take part in my favourite sport/exercises?
- Will I be able to follow my usual diet?

Health care professionals should welcome your views and discuss any issues so they can work in partnership with you for the best outcome.

If you require further FREE copies of this publication
please contact:

Department of Health Publications
PO Box 777
London SE1 6XH
Fax: 01623 724524
E-mail doh@prolog.uk.com

Please quote reference 25751 when ordering.

It is also available on our website at:
www.doh.gov.uk/consent

This publication can also be made available in braille, by email, or in large print, on request.

The text of this document may be reproduced without formal permission or charge for personal or in-house use.

First Published: November 2001

© Crown Copyright
Produced by the Department of Health
25751 1p 10k Nov 01 (BEL)
CHLORINE FREE PAPER

Directgov

Ministry of JUSTICE

Cremation Regulations 2008

Guidance for crematorium medical referees

20 September 2010

Contents

Summary of guidance	2
Introduction	4
Act and Regulations	5
Functions	6
Cremation forms – general	8
Those who can sign Forms Cremation 4 and Cremation 5	9
Completion of Forms Cremation 1, Cremation 4 and Cremation 5	11
Other matters	20
Annex A – European Economic Area	22

Summary of guidance

- All questions on Forms Cremation 1, 4 and 5 should be answered.
- You must be satisfied that the applicant is entitled to sign and complete Form Cremation 1.
- It is your responsibility to check forms Cremation 4 and Cremation 5 thoroughly and to query any inconsistencies. Do not assume that the Form Cremation 5 doctor has properly checked Form Cremation 4.
- You should reject illegible forms.
- We consider that Form Cremation 4 should only be completed by a doctor who treated the deceased during the last illness and who had seen him or her within 14 days of death – and not by anyone else on that doctor's behalf. There may be more than one doctor treating a person on a hospital ward – or elsewhere during the last illness. If the main treating doctor has gone on leave or fallen ill it may be possible for another doctor to complete Form Cremation 4.
- Modes of death, e.g. "multi-organ failure" or "heart attack", are unacceptable as a cause of death; you should reject forms which do not have a proper cause of death.
- "Old age" as a stand-alone cause of death for over 80s is acceptable for registration purposes, but you should explore the recent history with the Form Cremation 4 doctor and exercise caution.
- You should not be pressurised into accepting last minute applications; you should, however, be prepared to make yourself available at some stage during each working day.
- If a coroner has completed Form Cremation 6, you still need to check Form Cremation 1 to ensure that the proper person has applied for the cremation.
- If a coroner's office has been made aware of the case but has decided not to issue Form Cremation 6, you must make your own decision on whether to authorise the cremation, liaising with the coroner's office as necessary.
- You may order a post-mortem examination. You will, however, need the permission of the appropriate adult, and it should be made clear who will pay for the post-mortem before you issue instructions.

- You must give written reasons to the applicant if you reject an application.

- You must be satisfied that either a coroner has issued Form Cremation 6, or the death has been registered, or is not required to be registered.

- Form Cremation 5 doctors must be registered medical practitioners for at least 5 years and, if paragraph 10 of Schedule 1 to the Medical Act 1983 (Amendment) Order 2002 (S.I. 2002/3135) is in force, hold a licence to practice.

- Up-to-date information about the qualifications of European doctors is on the General Medical Council's website – see also Annex A.

- The Form Cremation 5 doctor cannot be a partner or colleague in the same practice or clinical team of the Form Cremation 4 doctor, or a relative of the deceased; the two doctors must be truly independent of one another, i.e. not on the same team in hospital or a locum at the same surgery.

Introduction

You should familiarise yourself with the legislation under which you perform your duties. The Cremation Regulations 2008 come into effect on 1 January 2009. Forms 1 to 13 replace and add to forms A to H under previous Regulations. The old forms may still be used for a transitional period of one month, that is until 31 January 2009.

Act and Regulations

The 2008 Regulations ("the Regulations") can be found at www.legislation.gov.uk/uksi/2008/2841/contents/made

Functions

Your functions as medical referee are set out in regulations 23 to 28 of the Cremation Regulations 2008, as follows:

- Not to allow a cremation unless you are satisfied that the death has been properly registered, or is not required to be registered, or that a coroner has issued a certificate as set out in Form Cremation 6;
- To be satisfied that the application and certificates are as required by the Regulations;
- To be satisfied that adequate enquiries have been made by the doctors giving the certificates;
- To be satisfied either that the application has been made by an executor or a near relative of the deceased, or that there is sufficient explanation why the application has not been made by an executor or near relative;
- Not to allow the cremation unless you are satisfied that the fact and cause of death have been definitely ascertained, or if not so ascertained that the Coroner has investigated the death and no longer requires the body for further examination;
- Power to request a pathologist to carry out a post-mortem examination if the cause of death has not been definitely ascertained or, in particular, the cause of death given on either Form Cremation 4 or Cremation 5 suggests that it might be due to poison, violence, an illegal operation, privation or neglect (in practice, these cases would normally be referred to the Coroner), subject to the consent of the appropriate person (as set out in Part 1 of the Human Tissue Act 2004) being obtained;
- Not to allow the cremation if such a post-mortem examination fails to reveal the cause of death, unless an inquest has been opened and a coroner has issued Form Cremation 6;
- Not to allow the cremation if there are other suspicious circumstances connected to the death of the deceased, whether revealed in the medical certificates or otherwise, unless an inquest has been opened and a coroner has given form Cremation 6;

- Not to allow the cremation until an inquest has been opened, if a coroner has given notice of his intention to open an inquest;

- To make such reports to the Secretary of State as may from time to time be required;

- To consider any representations from the applicant for cremation following his or her inspection of the medical certificates, and to refer the case to a coroner as necessary.

You should avoid any unnecessary delay to cremations but it is essential that you ensure that no cremation takes place unless all the relevant forms have been properly completed in accordance with the Regulations. You have the statutory power to reject inadequately completed forms, and you may refuse to authorise cremation until the forms have been completed satisfactorily. However, you must give your reasons if you refuse to authorise a cremation, and you should be aware that your decisions can be reviewed by the courts.

Cremation forms – general

All the cremation forms can be downloaded from our website at www.justice.gov.uk/cremation. Non-statutory versions of these forms should not be used. Crematoria must not change in any way the wording of the form, and you should not authorise any cremation which uses such a form.

Those who can sign Forms Cremation 4 and Cremation 5

Regulation 17 of the Cremation Regulations requires the confirmatory medical certificate (Form Cremation 5) to be completed by a registered medical practitioner of at least 5 years' standing. This means a registered medical practitioner who has been fully registered under the Medical Act 1983 for at least 5 years and, if paragraph 10 of Schedule 1 to the Medical Act 1983 (Amendment) Order 2002 has come into force, who has held a licence to practice for at least 5 years or since that paragraph came into force. All doctors signing these forms must be registered with the General Medical Council. In cases of doubt advice from the GMC's Contact Centre should be sought (Tel: 0161 923 6602).

Overseas doctors

Overseas doctors who are fully registered in the UK may sign Form Cremation 4 or, if fully registered in the UK for 5 years or more, may sign Form Cremation 5. Otherwise, it will depend on whether the doctor comes from and qualified outside the European Economic Area (EEA) or within it.

EC Directive 2005/36/EC (recognition of medical qualifications) have replaced earlier directives. Unlike previous Directives, the current Directive extends the principle of mutual recognition of professional qualifications to those awarded outside the EEA if the holder of a 'third country' qualification is an exempt person (i.e. a national of a relevant European State or entitled to be treated as such) and has three years' professional experience in the profession concerned on the territory of the relevant European State that initially recognised the qualification. (a list of the EEA member states and the places where primary European qualifications are obtained is at Annex A). Details of qualifications gained outside the EEA will need to be checked with the GMC.

A national of any EEA member state holding a primary European qualification is entitled to be registered in the UK as a fully registered medical practitioner. Experience acquired under the primary European qualification outside the UK should count towards any period of registration. Accordingly, an overseas doctor who has a primary European qualification in an EEA member state may sign a Form Cremation 5, provided he or she has held the qualification for five years and is registered in the UK. It may occasionally be necessary to ascertain the date and place of the qualification with the doctor concerned. If you have any doubt, you should check with the General Medical Council. Details of a doctor's qualification are published in the List of Registered Medical Practitioners which can be accessed through the GMC website.

[Information about EEA medical schools can be found at http://www.iime.org/database/europe.]

Corroboration of cause of death

Regulation 17 also requires that the registered medical practitioner who completes the confirmatory medical certificate (Form Cremation 5) must not be a relative of the deceased, or a relative, colleague or partner in the same practice or clinical team of the doctor who has completed the cremation certificate in Form Cremation 4. The same medical practitioner may not issue both Forms Cremation 4 and Cremation 5. Nor should the medical referee sign Form Cremation 5 except in an emergency.

The purpose of requiring two independent doctors to complete separate Forms Cremation 4 and Cremation 5 is to provide corroboration of the medical circumstances in which death took place. Accordingly, the doctors must be truly independent of one another. You must be satisfied that the doctors who complete Forms Cremation 4 and Cremation 5 are sufficiently independent of each other in all cases. The fact that it may sometimes be difficult to find an independent doctor is never a sufficient reason for failing to do so. Furthermore, outside the hospital setting, and particularly within the care-home setting, the patient's GP should not sign Form Cremation 5.

Similarly, where a junior hospital doctor has completed the certificate in Form Cremation 4, the doctor who completes the Form Cremation 5 should not have been in charge of the case, nor directly involved in the patient's treatment. Criminal and General Medical Council proceedings have been successfully brought against doctors who have falsely completed the forms.

Dentists

Dentists are not qualified to complete cremation certificates.

Completion of Forms Cremation 1, Cremation 4 and Cremation 5

General

It is essential that:

- All forms are completed in full
- All questions are answered
- No questions are deleted
- The forms are written in legible handwriting
- Any discrepancies between the forms as to the date and time of death are resolved.

Discrepancies as to date and time of death give particular cause for concern and you should always challenge them. It may, for example, be explained that the doctor saw the deceased, and only verified death, many hours after the family believe death occurred. This explanation should not be accepted without confirmation from all parties

Abbreviations for causes of death are unacceptable where they are unclear, unusual or ambiguous; in such cases, you should make further enquiries of the doctor concerned. There must be a hand-written signature, not an abbreviation or a stamp. It is for the doctor concerned to complete the certificate and not for another person to do so on his or her behalf. The doctor completing the confirmatory certificate should not seek to amend the certificate of the attending doctor, but should instead record any differences (e.g. as to the cause of death) on his or her own certificate, with an explanation of any differences.

It is for you to decide whether the information provided on the certificate allows you to authorise the cremation, with or without further enquiry. If there has been insufficient enquiry or there is an unclear cause of death, you are likely to need to make further enquiries of one or both doctors and in some cases the applicant.

Form Cremation 1: Application for cremation: the right of inspection (replacing form A)

There is no need for a counter-signature.

The application should be made by an executor or a near relative of the deceased. Where it is not, enquiries should be made to ascertain either that efforts to identify any executor or near relative have failed, or that the executor or near relative do not oppose the application, or wish to make the application themselves. In some cases, the next of kin will be described as being too upset to make the application personally and will have delegated this responsibility to another member of the family. This is understandable, but you may still need to make further enquiries to establish the true position.

The main additional question on Form Cremation 1 relates to the new right of inspection of forms Cremation 4 and Cremation 5. This is an important Shipman-related reform: the families of Shipman's victims believed that if they had had seen the cremation forms he had completed about their relative they would have recognised that the information was wrong, and he would have been exposed much sooner. You will not necessarily be involved in the process, but you may sometimes be asked to explain to applicants the answers on the Form. You may also need to take account of any concerns the applicant may have about the accuracy of the information on the forms, in case you have to refer the case to a coroner or for other investigation. The main purpose of the applicant’s right of inspection is to identify areas of concern which might require further investigation. The applicant’s right to inspect the forms should not depend upon whether he or she is willing to pay a fee to the referee for a medical explanation of the cause of death.

Form Cremation 2: Application for disposal of body parts (replacing form AA)

Broadly similar considerations apply to Form Cremation 2 as to Form Cremation 1 (see paragraphs 18 to 20 above). There is no right of inspection of any of the forms relating to body parts.

Form Cremation 3: Application for cremation of remains of stillborn baby

The 1930 Regulations had no statutory application forms in respect of a stillborn baby and we are aware that cremations took place solely on the basis of a registration document. The cremation of a stillborn baby will now require an application form, as well as either a form completed by a medical practitioner or midwife (see paragraph 46 below) or a declaration given by a person who can give information about the birth. It is expected that either one of the parents will complete this form, or a hospital bereavement officer will do so.

As there is no cause of death to investigate, the applicant has no right to inspect the medical form (Form Cremation 9). You need to be satisfied, as with Form Cremation 1, that the applicant is entitled to make the application and also that there is nothing contained within the information on the forms provided to suggest that the infant was not live-born.

Form Cremation 4: Medical certificate (replacing form B)

QUESTION 5: “USUAL MEDICAL PRACTITIONER”

With a few exceptions, the usual medical practitioner is taken to be the deceased’s general practitioner. Where the deceased has been an in-patient in hospital for a short period of time, in our view under 24 hours, the patient’s GP, rather than the hospital doctor who attended him or her for a majority of this period, should be regarded as the usual medical practitioner.

QUESTION 6: “PLEASE STATE FOR HOW LONG YOU ATTENDED THE DECEASED DURING THEIR LAST ILLNESS?”

The certifying doctor should have attended the deceased during his or her last illness. In the primary care setting, the deceased should have been treated by the certifying doctor during the days before the death. A general practitioner colleague may certify if he or she had seen the deceased outside the normally acceptable period (14 days) and the attending partner is unavailable although it is likely that such cases will have been discussed with a coroner. It should never be acceptable for the certifying doctor to have seen the body only after death and not treated the deceased during the last illness.

The minimum period of hospital care sufficient to meet the attendance requirement is normally 24 hours before death, unless it is a readmission, or a coroner has been informed. You may need to make enquiries to ascertain that the coroner's position has been established.

QUESTION 7: "PLEASE STATE THE NUMBER OF DAYS AND HOURS BEFORE THE DECEASED'S DEATH THAT YOU LAST SAW THEM ALIVE?"

The normal expectation is that the deceased will have been seen within 14 days before death; otherwise you should be satisfied that a coroner is aware of the case and is satisfied that no further investigation is necessary. You may accept a more extended period in a hospice or palliative care setting, if named nurses are available for consultation.

QUESTION 8: "PLEASE STATE THE DATE AND TIME THAT YOU SAW THE BODY OF THE DECEASED AND THE EXAMINATION YOU MADE OF THE BODY

Where there has been a non-coronial consented (or hospital) post-mortem examination carried out by the certifying medical attendant this should be indicated here and the cause of death in Question 10 will then be the findings of the examination. If there has been such a post-mortem examination performed by a registered medical practitioner of at least 5 years' standing (or, if not, was supervised by such a medical practitioner) the confirmatory medical certificate (Form Cremation 5) need not be completed.

QUESTION 9: DESCRIPTION OF SYMPTOMS AND OTHER CONDITIONS

This is a new section in free-text form, which gives the doctor an opportunity to explain how he or she arrived at the cause of death. The doctor should always refer to his or her medical notes, as well as his or her own observations as to the condition of the deceased. You should make further enquiries of the treating doctor if satisfactory explanations are not provided in this section.

QUESTION 11: CAUSE OF DEATH

You must ensure that all sections of this question have been answered. A mode of death on its own is never acceptable. The failure of an organ needs to explain the cause of that failure.

QUESTION 12 AND 13: OPERATIONS

The answers to these questions are intended both to identify possible surgical mishaps (although such deaths should have been referred to a coroner to investigate), and to indicate diagnostic procedures which contributed to the cause of death. If surgical procedures of potential significance are not included, this may call into question the reliability of the certificate.

QUESTIONS 14, 15 AND 16: THOSE NURSING THE DECEASED OR PRESENT AT THE DEATH

These questions are intended to help in gathering confirmatory information. Specific names (and contact details) should be given, as they will assist both the confirmatory doctor and you. Indeed, an unnamed nurse or family member with no contact details is unlikely to be of any value.

QUESTIONS 17, 18 AND 19: BACKGROUND AND CIRCUMSTANCES

These questions are likely to be answered in the negative, but if not they will invariably prompt further investigation and, in many cases, reference to a coroner.

QUESTIONS 20 AND 21 – REFERRAL TO A CORONER/CORONER'S OFFICE

If you are wholly satisfied as to the cause of death, you do not need to pursue any coronial investigation further. However, in cases of doubt you may wish to discuss the case further with a coroner or his or her staff. It is for you to be quite satisfied as to the cause of death before authorising cremation.

QUESTION 22 – REGISTRATION OF DEATH

In the majority of cases where the doctor registering the death has also completed Form Cremation 4, you are unlikely to need to make further enquiries about the registration. However, if the answer is "no", the confirmatory doctor (or you) should enquire of the doctor who has signed the medical certificate of the cause of death, in order to ensure that any possible discrepancies or uncertainties are resolved.

QUESTION 23 – REMOVAL OF IMPLANTS

Some implants may cause damage to the cremator, and may even be a serious health and safety risk if they explode. Fixion nail implants, inserted under pressure into bones, are of particular concern on health and safety grounds. You must be satisfied that any implant remaining within the body of the deceased is safe – otherwise it must be removed. Plastic hip joints, for example, are understood to cause no problem.

PART 3 – STATEMENT OF TRUTH

In cases of doubt (particularly where the form has been poorly completed), you should check the registered qualifications and the General Medical Council reference number on the General Medical Council's web-site. All signatories must be registered medical practitioners, although the date of registration is immaterial.

Form Cremation 5: Confirmatory Medical Certificate (replacing form C)

Form Cremation 5 must be completed, unless the categories in Regulations 16(c)(iii), 17(3), 18 or 24(2) apply, i.e. when a coroner has issued Form Cremation 6, there has been an anatomical examination of the body or there has been a consented post-mortem examination as described above (see paragraph 28). If Form Cremation 5 has been completed where there was no need for it, you should draw this to the attention of the doctor concerned, so that any fee paid may be refunded. You should also ask the funeral director to ensure that the applicant is not charged a fee for this unnecessary service.

The cause of death on Form Cremation 5 does not need to be the same as the one given on Form Cremation 4, but you should make enquiries about any discrepancy.

There should also be an affirmative answer to at least one of questions 2 to 5. This should not introduce significant delay to the completion of Form Cremation 5 or to the funeral arrangements. Nevertheless, Question 2 should be answered in the affirmative only if the signatory of Form Cremation 5 has questioned a medical practitioner other than the signatory of Form Cremation 4. It should be clear in response to each question whether the Form Cremation 5 doctor has spoken face-to-face to the other person or on the telephone.

Form Cremation 6: Certificate of Coroner (replacing form E)

A coroner must be notified if any suspicious circumstances come to your attention. Where a coroner has been consulted by the signatories of either Form Cremation 4 or Form Cremation 5, or by you, and the coroner considers that his/her involvement is unnecessary, the medical practitioner concerned or you, as appropriate, should record this next to Question 21 of Form Cremation 4, or after Question 7 of Form Cremation 5, or on a blank space on Form Cremation 8.

Coroners and medical referees sometimes take a different view about what is an acceptable or appropriate cause of death. You are not bound to accept the view of the coroner and may refuse to authorise cremation if you do not consider that you can. In such cases, you should advise the coroner of your decision and consider whether a post- mortem examination is necessary (see paragraphs 49 and 50).

Form Cremation 7: Anatomical Examination (replacing form H)

The relatives or executors of the deceased may apply for the cremation of a body which has been subject to anatomical examination in accordance with the Human Tissue Act 2004 or the previous Anatomy Acts, using Form Cremation 1 accompanied by Form Cremation.7. Alternatively, the authorities of the School of Anatomy or other such licensed institution may make the application. In these cases, you should be satisfied that the appropriate person has signed the application and that there is a satisfactory reason why the executor or near relative has not made the application. Where there is any doubt, you should make enquiries to ascertain whether efforts to identify any executor or near relative have failed, or whether the executor or near relative do not oppose the application, but do not wish to make the application themselves.

Application may occasionally be made for the cremation of parts remaining from a body donated under the provisions of the Human Tissue Act 2004 (or the legislation which that Act superseded) and which has already been separately cremated. Provided the retained body parts were removed in the course of the examination of the donated body, we take the view that it is reasonable to cremate on the authority of the existing Form Cremation 7.

Form Cremation 8: Certificate releasing body parts for cremation (replacing form DD)

Regulation 19 deals with the cremation of body parts removed following a post-mortem examination. Body parts may also be incinerated as desired and the medical referee will have no involvement in such cases. You will need to examine this form, together with the application form (Form Cremation 2) and to be satisfied that registration of the deceased has taken place [or a coroner has issued Form Cremation 6 in relation to this death].

Form Cremation 9: Certificate of stillbirth

You should be satisfied that the information on this form matches that on the application form for stillbirth (Form Cremation 3). Form Cremation 9 may be completed by either a registered medical practitioner or a registered midwife. In cases of doubt, you may wish to check registration with the appropriate governing body, either the General Medical Council or the Nursing and Midwifery Council.

Forms Cremation 10 (replacing form F), Cremation 12 (replacing form FF) and Cremation13: Medical referee's authority to cremate

When completing these forms, you should check the details of the name, address and occupation of the deceased against those on the other forms and registration document, if any, and query any discrepancies before you authorise cremation. The occupation of the deceased, combined with the apparent cause of death, may indicate that the person had died from an industrial disease. If you are concerned that this has been overlooked it may be helpful to discuss the matter with a coroner, as any failure accurately to record this information may have an impact on any outstanding industrial disease compensation claims. You should have some local knowledge of the industrial processes which take place, or have taken place, in your area. The Reporting of Injuries, Diseases and Dangerous Occurrences Regulations 1995 (1995 No 3163) lists industrial diseases which have to be reported. An electronic copy of these regulations is at www.opsi.gov.uk/SI/si1995/Uksi_19953163_en_1.htm.

You must always complete Part 2 of Form Cremation 10, 12 or 13.

Form Cremation 11: Certificate after Post-Mortem Examination (replacing form D)

On very rare occasions, the information on the forms (usually Cremation 4 and Cremation 5 if completed) may remain unsatisfactory and a coroner may be unwilling either to open an inquest or order a post-mortem examination. You may then refuse to authorise the cremation, giving your reasons. However, the family may still wish to have the body cremated. The only available option would then be for you to arrange for a post-mortem examination performed by a pathologist of your own or the cremation authority's choice, under Regulation 24(2). Any post-mortem must be carried out under the authority of a licence issued under the Human Tissue Act 2004.

In all cases of this kind, the consent of the family must be obtained as set out in the Human Tissue Act 2004. Although the Act provides for the deceased to have given consent for a post-mortem examination whilst still alive, this is likely to be uncommon. It will otherwise be necessary for the pathologist to be satisfied that an appropriate adult has a "qualifying relationship" with the deceased person, which is defined by section 54 of the 2004 Act as meaning a spouse, civil partner, parent, child, brother, sister, grandparent, grandchild, child of a brother or sister, stepfather, stepmother, half-brother, half-sister and friend of long standing. Any decision about any fee for the post-mortem examination will need to be agreed between the appropriate adult and other family members and the cremation authority. Subject to the number of tests required the fee may be quite substantial

Other matters

Causes of death – old age

The General Register Office advises that in certain circumstances, and if the deceased is over 80 years of age, ”old age” may be an acceptable cause of death on medical certificates. “Old age” alone, however, is unlikely to be an acceptable cause for cremation purposes, as you must be satisfied that the cause of death has been definitely ascertained. ”Old age” is commonly given as a cause of death where the deceased has been suffering from a number of conditions leading to death, but where it has not been possible to decide which particular condition led to the death. We cannot offer substantive guidance on a matter which is ultimately a clinical decision by the certifying doctor or doctors. However, you should be satisfied that that “old age” is an appropriate cause of death in all the circumstances. It cannot be used where the cause of death is properly “unascertained” and which should on that account be referred to a coroner.

Deaths Abroad

Where someone dies abroad and the body is repatriated to England or Wales for cremation, special arrangements apply, as set out under Regulation 14 of the Regulations.

Where someone dies in Scotland, you may accept the equivalent of the cremation application forms and those forms issued under the regulations applicable in Scotland. At present, these forms are those made under the Cremation (Scotland) Regulations 1935, as amended.

Where someone dies outside England, Wales or Scotland (but not Northern Ireland, the Isle of Man or the Channel Islands – see paragraph 55 below), you may accept an application form containing the particulars requested in Form Cremation 1, if this is accompanied by a declaration by the applicant that all particulars are true to the best of his or her knowledge and belief.

Where someone dies in Northern Ireland, the Isle of Man or the Channel Islands, you may accept certificates if they are substantially similar to Forms Cremation 4, 5, 6 and 7 and given in accordance with the law relating to cremation in force in Northern Ireland (i.e. the Cremation (Belfast) Regulations (Northern Ireland) 1961); the Isle of Man (Cremation Regulations 2000), the Bailiwick of Jersey or the Bailiwick of Guernsey, as the case may be.

In practice, most applications for cremation in relation to deaths outside the United Kingdom will require a Form Cremation 6 from a coroner, who will examine the relevant foreign documents including the death certificate. The coroner will need to be satisfied that the cause of death has been ascertained or it will be necessary to hold an inquest. You are not expected to investigate deaths of this kind.

Stillbirths outside England and Wales

In the case of stillbirths outside England and Wales, you may accept under Regulation 14(4) a medical certificate of stillbirth given by a registered medical practitioner or registered midwife (or a person entitled to practice as a medical practitioner or midwife) in the place where the stillbirth occurred. You would do this after making such enquiries as you consider necessary, provided you are satisfied that the baby was stillborn and that there is no reason for further examination. In the case of stillbirths in Scotland, if cremation is authorised on presentation of a certificate of registration under the hand to the Registrar of Births, Deaths and Marriages in the form of Schedule 8 appended to the Registration of Births, Still-births, Deaths and Marriages (Prescription of Forms) (Scotland) Regulations 1965, the General Register Office for Scotland should be notified (at New Register House, Edinburgh EH1 3YT) to ensure that the stillbirth is registered in Scotland.

Unidentified Remains

You should not consider applications for the cremation of unidentified remains unless a coroner's Form Cremation 6 has been produced. The circumstances which make it impossible to identify the remains will also require the death to be reported to a coroner and adequate enquiry will then have taken place.

Cremation of non-viable foetal remains

Foetal remains under 24 weeks gestation are not subject to the provisions of the Cremation Act or Regulations, although most crematoria will be prepared to cremate such remains at their discretion. You should not complete a Form Cremation 9 to authorise their cremation. If you are asked by crematoria managers and staff for professional advice on an application to cremate pre-viable foetuses, it is entirely a matter for you whether you provide such advice.

Annex A – European Economic Area

European Union Members: Universities where Primary European Qualifications can be obtained within each state

- Austria – Graz, Innsbruck, Salzburg, Salzburg (Paracelsus), Vienna (Wien)
- Belgium – Antwerp, Brussels, Diepenbeek (Limburg), Gent, Louvain (Leuven), Liege, Mons, Namur
- Bulgaria – Pleven, Plovdiv, Sofia, Trakia (Thrace), Varna
- Cyprus – Medical Council of Cyprus (equivalent to General Medical Council)
- Czech Republic – Brno (Masaryk Univ.), Hradec Kralove, Pilsen, Prague (Charles University), Olomouc
- Denmark – Aarhus, Copenhagen, Syddansk (Odense),
- Estonia – Tartu
- Finland – Helsinki, Kuopio, Oulu, Tampere, Turku
- France –Aix-Marseille, Amiens (Jules Verne), Angers, Besançon (Franche-Comté), Bordeaux (Victor Segalen), Brest (Bretagne), Caen, Clermont-Ferrand (Auvergne), Dijon, Grenoble, Univ Scientifique et Medicale Grenoble, Lille, Henri Warembourg de Lille, Limoges, Lyon-Sud, Lyon (Univ Claude-Bernard), Lyon (Alexis-Carrel), Montpellier-Nimes, Nancy, Nantes,Nice, Paris (Denis Diderot), Paris (Pierre et Marie Curie), Paris (René Descartes), Paris-Sud, Paris Val de Marne (Creteil), Poitiers, Reims, Rennes, Rouen,St Etienne, Strasbourg, Toulouse, Tours,
- Germany – Aachen, Berlin (Freiuniversität), Berlin (Humboldt), Bochum, Bonn, Dresden, Düsseldorf, Erlangen-Nürnberg, Essen, Frankfurt-am-Main, Freiburg im Breisgau, Giessen, Göttingen, Greifswald, Halle/Wittenberg, Hamburg, Hannover, Heidelberg, Homburg, Jena, Kiel, Köln (Cologne), Leipzig, Lübeck, Magdeburg, Mainz, Mannheim,Marburg, München (Ludwig-Maximilians), München (Technische), Münster, Regensburg, Rostock, Ulm, Witten-Herdecke, Tübingen, Würzburg
- Greece – Alexandroupolis (Thrace), Athens (National), Crete, Ioannina, Patras, Larissa (Thessaly) Thessaloniki,

- Hungary – Semmelweis/Budapest, Debrecen, Pécs, Szeged
- Iceland – Reykjavik
- Ireland – Cork, Dublin (RCS), University College Dublin, Galway, Trinity College, Dublin
- Italy – Ancona, Bari, Bologna, Brescia, Cagliari, Catania, Catanzaro (Reggio-Calabria), Chieti (D'Annunzio), Ferrara, Firenze, Genova, Messina, Milano, Modena, Napoli, Napoli (Federico II), Padova, Palermo, Parma, Pavia, Perugia, Pisa, Roma, Rome (Campus Bio-Medico), Sassari, Siena, Torino, Trieste, Udine, Varese, Verona
- Latvia – Riga (Stradins), Univ of Latvia (Riga)
- Liechtenstein – Nil
- Lithuania – Kaunas, Vilnius
- Luxembourg – Nil
- Malta – Univ of Malta (Msida)
- Netherlands – Amsterdam, Amsterdam (Vrije) Groningen, Leiden, Maastricht, Nijmegen, Rotterdam (Erasmus), Utrecht,
- Norway – Bergen, Oslo, Tromsø, Trondheim
- Poland – Bialystok, Bydgoszcz, Gdansk, Krakow (Jagiellonian), Lodz (Military), Lublin, Poznan, Szczecin,,Warsaw (Academy and Postgraduate), Wroclaw
- Portugal – Beira, Coimbra, Lisbon, Porto (Abel Salazar) Porto
- Romania – Arad, Brasov, Bucharest, Cluj-Napoca, Constanta, Craiova, Iasi, Muras, Oradea, Sibiu, Targu Timisoara,
- Slovakia –Bratislava, Kosice,
- Slovenia – Ljubljana
- Spain – Albacete (Castillo la Mancha),Alcalá, Alicante, Badajoz (Extremadura), Barcelona, Barcelona (Autonoma), Barcelona (Pompeu Fabra), Cádiz, Córdoba, Granada, La Laguna Las Palmas de Gran Canaria, Lleida,-–Madrid (San Pablo), Madrid (Autonoma), Madrid (Complutense), Málaga Murcia, Pamplona (Navarra), Oviedo, Reus (Tarragona/Rovira Virgili) Salamanca, San Sebastian (Pais Vasco), Santa Cruz de Tenerife, Santander (Cantabria), Sevilla, Tenerife, Valencia, Valladolid, Zaragosa,

- Sweden – Göteborg, Linköping, Lund, Stockholm (Karolinska), Umeä, Uppsala
- Switzerland* – Basel, Bern, Genève, Lausanne, Zürich
- United Kingdom – 5 years' registration required wherever qualified

*Swiss nationals benefit from EC freedom of movement legislation under the terms of bilateral agreement, signed on 1 June 2002

Alternative format versions of this report are available on request from Coroners and Burials Division: joanne.noble@justice.gsi.gov.uk or 020 3334 2272

© Crown copyright

Produced by the Ministry of Justice

Ministry of
JUSTICE

```
//print page var gAutoPrint = true; // Flag for whether or not to automatically call the print function function printSpecial() { if (document.getElementById != null) { var html = '\n\n'; if (document.getElementsByTagName != null) { var headTags = document.getElementsByTagName("head"); if (headTags.length > 0) html += headTags[0].innerHTML; } html += '\n\n\n'; var printReadyElem = document.getElementById("printReady"); if (printReadyElem != null) { html += printReadyElem.innerHTML; } else { alert("Could not find the printReady section in the HTML"); return; } html += '\n\n'; var printWin = window.open("","printSpecial"); printWin.document.open(); printWin.document.write(html); printWin.document.close(); if (gAutoPrint) printWin.print(); } else { alert("Sorry, the print ready feature is only available in modern browsers."); } }
```

Ministry of JUSTICE

Work Smart Session - MRCP Part 1

Time taken:

Question: 1 of 3

A 36-year-old alcoholic has an endoscopy some 16 hours after his admission with a variceal haemorrhage. This is his second admission in 6 months with an upper GI bleed and he has required a 4 unit blood transfusion. Endoscopy reveals a number of large varices, including one with adherent clot.

Which of the following is the therapy with the best evidence with respect to reducing the risk of a variceal bleed over the next few months?

(Please select 1 option)

○	**A** High dose omeprazole
○	**B** Propanolol
○	**C** Sclerotherapy
○	**D** Variceal banding
○	**E** Vasopressin

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

A 36-year-old alcoholic has an endoscopy some 16 hours after his admission with a variceal haemorrhage. This is his second admission in 6 months with an upper GI bleed and he has required a 4 unit blood transfusion. Endoscopy reveals a number of large varices, including one with adherent clot.

Which of the following is the therapy with the best evidence with respect to reducing the risk of a variceal bleed over the next few months?

(Please select 1 option)

○	**A** High dose omeprazole
○	**B** Propanolol
○	**C** Sclerotherapy
◉	**D** Variceal banding ✓ Correct
○	**E** Vasopressin

The answer is D), variceal banding. Banding is proven to eliminate varices with fewer procedures and complications than injection sclerotherapy. A recent trial has demonstrated that beta blockade and sclerotherapy is better than beta blockade alone in prophylaxis against bleeding. The vasopressin analogue, terlipressin is used to control bleeding acutely, along with somatostatin analogues.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 2 mins 32 secs

Question: 2 of 3

A 34-year-old skier comes to the Emergency Department with pain and swelling over the first metacarpophalangeal joint (MCP joint) after a fall whilst practicing on the dry ski slope. On examination there is extensive swelling and bruising over the ulnar aspect of the joint.

What is he most likely to have injured?

(Please select 1 option)

- **A** Accessory collateral ligament
- **B** Proximal phalanx
- **C** Radial collateral ligament
- **D** Scaphoid bone
- **E** Ulnar collateral ligament

Submit answer | Skip question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Question: 2 of 3

A 34-year-old skier comes to the Emergency Department with pain and swelling over the first metacarpophalangeal joint (MCP joint) after a fall whilst practicing on the dry ski slope. On examination there is extensive swelling and bruising over the ulnar aspect of the joint.

What is he most likely to have injured?

(Please select 1 option)

○	**A** Accessory collateral ligament
◉	**B** Proximal phalanx ✕ Incorrect answer selected
○	**C** Radial collateral ligament
○	**D** Scaphoid bone
○	**E** Ulnar collateral ligament ← This is the correct answer

The answer is E), ulnar collateral ligament. Skier's thumb was formerly known as gamekeeper's thumb, and it relates to injury to the base of the thumb, resulting in damage/ rupture of the ulnar collateral ligament. Once acute swelling has subsided, then gross instability of the thumb may result. Where a complete tear of the ligament is suspected, MRI may be valuable in confirming the diagnosis, as surgical repair is required. In cases of a partial rupture, immobilisation in a thumb spica is the standard therapy.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

A 24-year-old woman who is known to suffer from mitral valve prolapse comes to the emergency department complaining of sudden, terrible, tearing pain between her shoulder blades. She notes that her mother died suddenly when she was aged 38.

On examination her BP is 166/94 mmHg, her pulse is 95 and regular. Her chest is clear. Her skin seems rather thin and pale white, you can see extensive bruising over her shins, and her blood vessels are easily visible as you look at her arms.

She has a number of keloid scars, which appear to have occurred after relatively minor skin injuries. She is given oxygen and diamorphine for pain relief.

Investigations show

Haemoglobin	12.0 g/dl	(11.5-16.5)
White cells	6.8 x 10^9/L	(4-11)
Platelets	180 x 10^9/L	(150-400)
Sodium	140 mmol/l	(135-146)
Potassium	4.2 mmol/l	(3.5-5)
Creatinine	90 µmol/l	(79-118)
AP chest x ray	Mediastinum width 9.5 cm	
ECG	3 mm inferior ST elevation	

Which of the following is the most appropriate initial therapy?

(Please select 1 option)

- ○ Alteplase

Haemoglobin	12.0 g/dl	(11.5-16.5)
White cells	6.8 x 10^9/L	(4-11)
Platelets	180 x 10^9/L	(150-400)
Sodium	140 mmol/l	(135-146)
Potassium	4.2 mmol/l	(3.5-5)
Creatinine	90 µmol/l	(79-118)
AP chest x ray	Mediastinum width 9.5 cm	
ECG	3 mm inferior ST elevation	

Which of the following is the most appropriate initial therapy?

(Please select 1 option)

- Alteplase
- Angioplasty
- Heparin and IV nitrate
- IV beta-blockade
- Streptokinase

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

AP chest x ray	Mediastinum width 9.5 cm
ECG	3 mm inferior ST elevation

Which of the following is the most appropriate initial therapy?

(Please select 1 option)

○	Alteplase
○	Angioplasty
○	Heparin and IV nitrate
◉	IV beta-blockade ✓ Correct
○	Streptokinase

The history is highly suspicious of aortic dissection, with involvement of the right coronary artery suggesting a type A dissection.

This patient needs beta-blockade to reduce her BP and myocardial oxygen demand and investigation to confirm the diagnosis. Most emergency departments have rapid access to CT pulmonary angiogram and this is the investigation of choice.

Regarding type A dissection, progression to surgery is inevitable.

The underlying clinical features are suggestive of Ehlers-Danlos syndrome which puts her at high risk of vascular rupture/dissections.

Finish

Tag Question | Remove question

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Work Smart Session - MRCP Part 1

Time taken:

Question: 1 of 100

A patient who was recently admitted to the medical receiving unit with general malaise has been found to have deranged renal function. Your registrar asks you to arrange "an urgent scan" to exclude obstruction of the kidneys.

Which of the following is most appropriate?

(Please select 1 option)

- Ultrasound renal tract
- CT KUB (Kidneys, Ureters and Bladder)
- MRI kidneys
- MR angiography of renal tract
- Plain abdominal x ray

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Question: 10 of 100

A 59-year-old man with chronic renal failure comes to the surgery complaining of tiredness and lethargy. He has a longstanding history of type 1 diabetes and takes a range of medications.

On examination his BP is 145/84 mmHg.

Investigations show

Haemoglobin	9.4 g/dl	(13.5-18)
White cell count	6.4 x 10^9/l	(4-10)
Platelets	162 x 10^9/l	(150-400)
Sodium	140 mmol/l	(134-143)
Potassium	5.0 mmol/l	(3.5-5)
Creatinine	219 µmol/l	(60-120)
Ferritin	10 Microgram/l	(20-60)
Faecal occult blood	Negative	
Urine	Protein ++	

Which of the following is the most appropriate next step?

(Please select 1 option)

- ○ Erythropoietin
- ○ IV iron transfusion
- ○ Oral ferrous sulphate
- ○ Referral for lower GI endoscopy
- ○ Referral for upper GI endoscopy

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 5 hrs 40 mins 46 secs

Work Smart Session - MRCP Part 1

Question: 100 of 100

A 65-year-old male patient is admitted with renal failure and is diagnosed with acute tubular necrosis (ATN).

Which of the following is least likely to be the cause of acute tubular necrosis?

(Please select 1 option)

- Corticosteroid therapy
- Hypertension
- Hypovolaemia
- Paracetamol poisoning
- Rhabdomyolysis

Submit answer | Skip question | Tag Question | Remove question

A 65-year-old male patient is admitted with renal failure and is diagnosed with acute tubular necrosis (ATN).

Which of the following is least likely to be the cause of acute tubular necrosis?

(Please select 1 option)

◉	Corticosteroid therapy ✓ Correct
○	Hypertension
○	Hypovolaemia
○	Paracetamol poisoning
○	Rhabdomyolysis

Renal failure from ATN occurs in 25% patients with severe hepatic damage.

Accelerated hypertension can cause small vessel obstruction with proliferative endarteritis of intralobular arteries and fibrinoid necrosis of afferent arterioles and glomerular capillary tuft.

Corticosteroid therapy has not been associated with ATN.

Other causes of ATN include

- Hypotension
- Hepatic failure
- Eclampsia and
- Drugs such as aminoglycosides, cephalosporins, cisplatin, amphotericin.

Sodium	140 mmol/l	(134-143)
Potassium	5.0 mmol/l	(3.5-5)
Creatinine	219 µmol/l	(60-120)
Ferritin	10 Microgram/l	(20-60)
Faecal occult blood	Negative	
Urine	Protein ++	

Which of the following is the most appropriate next step?

(Please select 1 option)

- ○ Erythropoietin
- ○ IV iron transfusion ← This is the correct answer
- ○ Oral ferrous sulphate
- ◉ Referral for lower GI endoscopy ✕ Incorrect answer selected
- ○ Referral for upper GI endoscopy

This patient has a low serum ferritin, a common occurrence in patients with chronic renal failure. Often patients with chronic renal failure struggle with their eating, and have deficient iron absorption. As such IV iron transfusion is the therapy of choice.

Once iron stores are restored and ferritin is in the normal range, if the patient is still anaemic then erythropoietin would be the next appropriate option.

Given the FOB is negative, GI blood loss is less likely as a cause of his anaemia.

Next question

Remove Tag | Remove question

Rate this question

☆☆☆☆☆

Time taken: 1 hrs 39 mins 14 secs

Work Smart Session - MRCP Part 1

Question: 11 of 100

A 63-year-old man, with chronic renal failure and type 2 diabetes, presents to the surgery complaining of generalised aching. He takes twice daily mixed insulin for his diabetes, and ramipril for vascular risk modification.

On examination his BP is 155/92 mmHg, pulse is 75 and regular. Physical examination is otherwise unremarkable.

Haemoglobin	10.9 g/dl	(13.5-18)
White cell count	6.1 x 10^9/l	(4-10)
Platelets	191 x 10^9/l	(150-400)
Sodium	140 mmol/l	(134-143)
Potassium	5.3 mmol/l	(3.5-5)
Creatinine	320 µmol/l	(60-120)
Calcium	2.05 Mmol/l	(2.2-2.67)
Urine	Protein +	

Which of the following is the most likely underlying diagnosis?

(Please select 1 option)

- Hypoparathyroidism
- Primary hyperparathyroidism
- Secondary hyperparathyroidism
- Tertiary hyperparathyroidism
- Vitamin D intoxication

Calcium	2.05 Mmol/l	(2.2-2.67)
Urine	Protein +	

Which of the following is the most likely underlying diagnosis?

(Please select 1 option)

- ○ Hypoparathyroidism
- ○ Primary hyperparathyroidism
- ◉ Secondary hyperparathyroidism ✓ Correct
- ○ Tertiary hyperparathyroidism
- ○ Vitamin D intoxication

Chronic renal failure leads to low levels of hydroxylated vitamin D, and hence to hypocalcaemia. This leads to a secondary increase in parathyroid hormone levels.

The second, fourth and fifth options will cause hypercalcaemia.

Standard therapy of choice is three times per week 1-alpha calcidol. Once the calcium approaches the normal range there is often an associated fall in parathyroid levels.

Cinacalcet may be used in patients with end-stage renal disease receiving maintenance haemodialysis, with frequent monitoring of parathormone and calcium.

Next question | Tag Question | Remove question

Rate this question

☆☆☆☆☆

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 1 hrs 43 mins 2 secs

Work Smart Session - MRCP Part 1

Question: 12 of 100

In which of the following patients is an ACE inhibitor contraindicated?

(Please select 1 option)

○	A 24-year-old woman with type 1 diabetes and microalbuminuria, who wants to start a family
○	A 28-year-old woman with reflux nephropathy and hypertension
○	A 34-year-old man with essential hypertension and a BMI of 32
◉	A 34-year-old woman with hypertension and a horseshoe kidney
○	A 62-year-old type 2 diabetes patient who has microalbuminuria and a stable creatinine of 210

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Shop
- Help

○	A 24-year-old woman with type 1 diabetes and microalbuminuria, who wants to start a family ← This is the correct answer
◉	A 28-year-old woman with reflux nephropathy and hypertension ✕ Incorrect answer selected
○	A 34-year-old man with essential hypertension and a BMI of 32
○	A 34-year-old woman with hypertension and a horseshoe kidney
○	A 62-year-old type 2 diabetes patient who has microalbuminuria and a stable creatinine of 210

ACE inhibitors are contraindicated in pregnancy. There is an increase in congenital cardiac and neurological abnormalities (New England Journal of Medicine 2006 354:2443-2451); and despite the fact this woman has microalbuminuria, use of an ACE inhibitor is not recommended.

In patients with elevated creatinine and microalbuminuria, use of an ACE inhibitor is still a reasonable option, as it has been proven to delay both further deterioration of creatinine and worsening albuminuria.

With respect to essential hypertension and a raised BMI, an ACE inhibitor may be appropriate; other options include a calcium antagonist.

Regarding beta-blockers and thiazides, evidence suggests they may increase insulin resistance and risk of diabetes, hence you may choose to avoid them here.

Other contraindications to ACE inhibition include

- Angio-oedema
- Breast feeding
- Significant renal artery stenosis.

Next question

Tag Question | Remove question

Question: 13 of 100

A 51-year-old male comes to the surgery complaining of nausea and fatigue. You have previously seen him with symptoms of sinusitis, and a saddle nose deformity.

Most recently he has begun to complain of shortness of breath and a chronic cough.

On examination he is hypertensive at 160/92 mmHg. There are bilateral inspiratory crackles on auscultation of the chest.

Investigations show

Haemoglobin	11.8 g/dl	(13.5-18)
White cell count	10.1 x 10^9/l	(4-10)
Platelets	182 x 10^9/l	(150-400)
Sodium	141 mmol/l	(134-143)
Potassium	5.5 mmol/l	(3.5-5)
Creatinine	230 µmol/l	(60-120)
ESR	72	(<10)
Urine	Blood++ Protein ++	

Which of the following is the most likely diagnosis?

(Please select 1 option)

- Goodpasture's syndrome
- IgA nephropathy
- Membranous nephropathy
- Minimal change disease
- Wegener's granulomatosis

Submit answer | Skip question | Tag Question | Remove question

Protein ++

Which of the following is the most likely diagnosis?

(Please select 1 option)

○	Goodpasture's syndrome
○	IgA nephropathy
○	Membranous nephropathy
○	Minimal change disease
◉	Wegener's granulomatosis ✓ Correct

Wegener's granulomatosis is a multi-system disorder characterised by necrotising granulomas of medium and small blood vessels. Patients have constitutional symptoms such as fever, lethargy and weight loss.

Organ specific involvement includes

- Eyes
- Upper airway
- Lung
- Renal
- Nervous system
- Skin
- Joints.

Men are affected slightly more often than women and typically present in the fourth or fifth decade. Patients often present with ocular or ENT symptoms for sometime before a diagnosis is made.

Autoimmune profile is likely to reveal a positive circulating anti-neutrophil cytoplasmic antibody (cANCA), and renal biopsy is the usual way to obtain a tissue diagnosis.

Treatment is with high dose steroids and cyclophosphamide, which has revolutionised this disease which is otherwise rapidly fatal.

Question: 14 of 100

A 7-year-old boy is brought to the surgery by his mother. He has become unwell with severe diarrhoea which is now mixed with blood.

History of note is a visit to a model farm a few days earlier. He is nauseous, has a severe headache, and feels very unwell.

On examination he is pyrexial 38.2°C, his BP is 142/88 mmHg. He has a soft, diffusely tender abdomen.

Investigations show

Haemoglobin	9.2 g/dl	(13.5-18)
White cell count	11.9 x 10^9/l	(4-10)
Platelets	76 x 10^9/l	(150-400)
Sodium	141 mmol/l	(134-143)
Potassium	4.9 mmol/l	(3.5-5)
Creatinine	192 µmol/l	(60-120)
Bilirubin	92 µmol/l	(<17)
Urine	Blood++ Protein ++	

Which of the following is the most likely diagnosis?

(Please select 1 option)

- *Brucella* infection
- *Campylobacter* infection
- *Escherichia coli* infection
- *Salmonella* infection
- *Shigella* infection

Submit answer | Skip question | Tag Question | Remove question

Question: 15 of 100

A 12-year-old boy presents to the surgery with peri-orbital and mild ankle oedema which has increased over the past few weeks.

Other history of note is a recent upper respiratory tract infection. He has been feeling increasingly tired and lethargic over the past few weeks.

On examination his BP is 138/72 mmHg. He has periorbital oedema and pitting ankle oedema.

Investigations show

Haemoglobin	12.4 g/dl	(13.5-18)
White cell count	7.8 x 10^9/l	(4-10)
Platelets	191 x 10^9/l	(150-400)
Sodium	141 mmol/l	(134-143)
Potassium	4.6 mmol/l	(3.5-5)
Creatinine	104 µmol/l	(60-120)
Serum albumin	28 g/l	(35-50)
Urine	Protein ++	

Which of the following is the most likely cause?

(Please select 1 option)

- IgA nephropathy
- Alport's syndrome
- Membranous nephropathy
- Minimal change nephropathy
- Post streptococcal glomerulonephritis

Question: 15 of 100

A 12-year-old boy presents to the surgery with peri-orbital and mild ankle oedema which has increased over the past few weeks.

Other history of note is a recent upper respiratory tract infection. He has been feeling increasingly tired and lethargic over the past few weeks.

On examination his BP is 138/72 mmHg. He has periorbital oedema and pitting ankle oedema.

Investigations show

Haemoglobin	12.4 g/dl	(13.5-18)
White cell count	7.8 x 10^9/l	(4-10)
Platelets	191 x 10^9/l	(150-400)
Sodium	141 mmol/l	(134-143)
Potassium	4.6 mmol/l	(3.5-5)
Creatinine	104 µmol/l	(60-120)
Serum albumin	28 g/l	(35-50)
Urine	Protein ++	

Which of the following is the most likely cause?

(Please select 1 option)

- IgA nephropathy
- Alport's syndrome
- Membranous nephropathy
- Minimal change nephropathy
- Post streptococcal glomerulonephritis

Sodium	141 mmol/l	(134-143)
Potassium	4.6 mmol/l	(3.5-5)
Creatinine	104 µmol/l	(60-120)
Serum albumin	28 g/l	(35-50)
Urine	Protein ++	

Which of the following is the most likely cause?

(Please select 1 option)

- ◉ IgA nephropathy ✕ Incorrect answer selected
- ○ Alport's syndrome
- ○ Membranous nephropathy
- ○ Minimal change nephropathy ← This is the correct answer
- ○ Post streptococcal glomerulonephritis

The history of periorbital oedema, normal blood pressure and creatinine, but proteinuria and low albumin is typical of minimal change disease.

The condition is much more common in this age range than membranous nephropathy.

The important point about making the diagnosis is that the condition responds to corticosteroid therapy in 90% or more of sufferers in childhood within two weeks, although treatment is usually continued for a period of eight weeks.

Next question

Remove Tag | Remove question

Rate this question

☆☆☆☆☆

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Question: 16 of 100

A 28-year-old man is referred to you by the practice nurse for hypertension management. She has seen him three times over the past four months and his BP is persistently elevated at around 155/92 mmHg.

Your partner has seen him previously for some non-specific right upper quadrant abdominal pain.

On examination of the abdomen you can feel bilateral enlarged kidneys, and a liver edge.

Investigations show

Haemoglobin	12.5 g/dl	(13.5-18)
White cell count	6.4 x 10^9/l	(4-10)
Platelets	182 x 10^9/l	(150-400)
Sodium	139 mmol/l	(134-143)
Potassium	4.8 mmol/l	(3.5-5)
Creatinine	182 µmol/l	(60-120)
Glucose	4.5 Mmol/l	(<6.0)
Urine	Blood ++ Protein -	

Which one of the following is most closely associated with his underlying condition?

(Please select 1 option)

- Aortic stenosis
- Coarctation of the aorta
- Diabetes mellitus
- Mitral valve prolapse
- Tricuspid stenosis

Potassium	4.8 mmol/l	(3.5-5)
Creatinine	182 µmol/l	(60-120)
Glucose	4.5 Mmol/l	(<6.0)
Urine	Blood ++ Protein -	

Which one of the following is most closely associated with his underlying condition?

(Please select 1 option)

◉	Aortic stenosis ✕ Incorrect answer selected
○	Coarctation of the aorta
○	Diabetes mellitus
○	Mitral valve prolapse ← This is the correct answer
○	Tricuspid stenosis

A young man presenting with renal failure, haematuria and liver and renal masses raises the suspicion of polycystic kidney disease.

Associated liver cysts are found in around 80% of individuals with polycystic kidney disease. Pancreatic cysts are rarer, and may in some cases be associated with recurrent pancreatitis.

Patients are at increased risk of renal stones, but the predominant increase is seen in urate stones, rather than other types.

Up to 25% of patients may have some degree of mitral valve prolapse.

MODY 5 is associated with hepatic and renal cysts and diabetes mellitus, but that is less likely to be the diagnosis here in the presence of a normal glucose.

Polycystic kidney disease carries an autosomal dominant pattern of inheritance, but may occur as a de novo mutation in 5%.

Next question

Tag Question | Remove question

Work Smart Session - MRCP Part 1

Question: 17 of 100

A 62-year-old man with a history of type 2 diabetes and renal failure comes to the emergency department. He currently uses continuous ambulatory peritoneal dialysis, and has noticed an increase in his insulin requirements over the past 24 hours, dull abdominal pain, and now has a cloudy bag.

On examination he is pyrexial 37.8°C and looks unwell, his blood pressure is 142/88 mmHg, with a pulse of 90. His abdomen is generally tender to palpation.

Haemoglobin	10.4 g/dl	(13.5-18)
White cell count	13.6 x 10^9/l	(4-10)
Platelets	190 x 10^9/l	(150-400)
Sodium	137 mmol/l	(134-143)
Potassium	5.3 mmol/l	(3.5-5)
Creatinine	342 µmol/l	(60-120)
CRP	88	(<10)
Peritoneal dialysis fluid	>100 white cells/cm^2	

Which of the following organisms is most likely to be responsible?

(Please select 1 option)

- *C. albicans*
- *S. aureus*
- *S. faecalis*
- *S. pyogenes*
- *S. viridians*

Submit answer | Skip question | Tag Question | Remove question

http://my.onexamination.com/Assessment/Que
Questions Set : REF55101

Haemoglobin	10.4 g/dl	(13.5-18)
White cell count	13.6 x 10^9/l	(4-10)
Platelets	190 x 10^9/l	(150-400)
Sodium	137 mmol/l	(134-143)
Potassium	5.3 mmol/l	(3.5-5)
Creatinine	342 µmol/l	(60-120)
CRP	88	(<10)
Peritoneal dialysis fluid	>100 white cells/cm^2	

Which of the following organisms is most likely to be responsible?

(Please select 1 option)

○	*C. albicans*
◉	*S. aureus* ✓ Correct
○	*S. faecalis*
○	*S. pyogenes*
○	*S. viridians*

Staphylococcus aureus, *Staphylococcus epidermidis*, *Pseudomonas aeruginosa*, and *Escherichia coli* are the commonest causes of peritonitis in peritoneal dialysis patients. Severe infections may be polymicrobial.

Treatment with intraperitoneal antibiotics is superior to intravenous antibiotics. Persistent or recurrent peritonitis should prompt catheter removal.

Next question

Tag Question | Remove question

Rate this question

☆☆☆☆☆

EN 3:47 PM 3/1/2011

commenced him on amlodipine 5 mg daily.

You understand on further questioning that his brother has haematuria and renal impairment and his father died of a stroke at the age of 42. On examination his blood pressure is 152/88 mmHg, he has bilateral ballotable kidneys.

Investigations show

Haemoglobin	13.4 g/dl	(13.5-18)
White cell count	6.0 x 10^9/l	(4-10)
Platelets	242 x 10^9/l	(150-400)
Sodium	140 mmol/l	(134-143)
Potassium	4.7 mmol/l	(3.5-5)
Creatinine	162 µ/l	(60-120)
Urine	Blood ++ Protein -	

Which of the following is the investigation most appropriate to elucidate the underlying diagnosis?

(Please select 1 option)

○	Contrast CT abdomen
○	Cystoscopy
○	Intravenous pyelogram (IVP)
○	Plain abdominal film
◉	Ultrasound abdomen ✓ Correct

The fact that his father and brother are both affected is suggestive of an autosomal dominant inherited disorder, probably autosomal dominant polycystic kidney disease (ADPKD).

Given that his father had a stroke at a young age, this raises the possibility of a berry aneurysm and subsequent subarachnoid haemorrhage.

A 30-year-old Caucasian man with HIV infection was found to have high blood pressure at 180/118 mmHg (high on several occasions). His father died of stroke at the age of 51.

Routine blood test showed:

Sodium	145 mmol/l	(135-145)
Potassium	3.4 mmol/l	(3.5-5.1)
Creatinine	99 mmol/l	(60-110)
Urea	4.9 mmol/l	(2.9-9.0)
Urinanalysis	No proteinuria	
Plasma aldosterone	815 pmol/l	(28-445)
Plasma renin	0.3 ng/ml/h	(0.7-5)
Renal ultrasound	Normal-sized kidneys	
CD4	769 cells/ml	
HIV RNA	4531 copies/ml	

He was not on any antiretroviral therapy.

What is the most likely cause of his high arterial blood pressure?

(Please select 1 option)

- ○ Adult polycystic kidney
- ○ Conn's syndrome
- ○ Familial essential hypertension
- ○ HIV associated nephropathy
- ○ Non-Hodgkin's lymphoma involving kidneys

(Please select 1 option)

○	Adult polycystic kidney
◉	Conn's syndrome ✓ Correct
○	Familial essential hypertension
○	HIV associated nephropathy
○	Non-Hodgkin's lymphoma involving kidneys

High aldosterone and low renin levels indicate primary hyperaldosteronism which accounts for up to 10% of all hypertensive patients. It is the most prevalent form of secondary hypertension.

Potassium level is often normal or the lower limit of normal and so hypokalaemia is not a prerequisite for diagnosis of Conn's syndrome.

Normal renal ultrasound makes adult polycystic kidney an unlikely cause of high blood pressure.

High aldosterone and low renin level is not seen in familial essential hypertension.

HIV associated nephropathy causes proteinuria.

Non-Hodgkin's lymphoma is often associated with low CD4 count.

Reference:
Hammer F, Stewart PM. Investigating hypertension in a young person. BMJ 2009; 338:885-6.

Next question

Tag Question | Remove question

Rate this question

☆☆☆☆☆

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Which of the following is most appropriate?

(Please select 1 option)

◉	Ultrasound renal tract ✓ Correct
○	CT KUB (Kidneys, Ureters and Bladder)
○	MRI kidneys
○	MR angiography of renal tract
○	Plain abdominal x ray

Acute imaging of the kidneys is intended primarily to exclude obstructive uropathy, which would be demonstrated on ultrasound imaging. Ultrasound imaging is a safe, non-invasive means to rapidly exclude a correctable cause of renal impairment. It is readily available in most hospitals and can be performed by a sonographer or radiologist.

A CT KUB is indicated when the USS (and clinical history) is suggestive of the presence of renal calculi, whether or not they are causing obstruction.

MR imaging of the kidneys can help determining the nature of a lesion seen on ultrasound imaging. It is expensive, time-consuming, and not available in all locations. Furthermore many patients with magnetic materials inserted eg. Pacemakers, defibrilators are precluded from entering the strong magnetic field. These factors preclude its use as a first-line approach to excluding acute obstruction of the kidney.

MR angiography is helpful to exclude renal artery stenosis. This will not confirm or refute the presence of post-renal obstruction.

A plain abdominal x-ray will occasionally demonstrate the presence of a radio-opaque renal calculi, but cannot confirm or refute the presence of post-renal obstruction. It should not be done routinely in all patients with acute renal impairment unless there is a strong clinical suspicion of renal calculi (in which case most patients will proceed to having a CT KUB examination).

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 12 mins 43 secs

Work Smart Session - MRCP Part 1

Question: 2 of 100

A 63-year-old woman is admitted to hospital with a three day history of diarrhoea and vomiting. Her family tell you she has been virtually unable to eat or drink, but has managed to take her tablets during that time. Her past medical history includes essential hypertension and ischaemic heart disease. Her current medication consists aspirin 75 mg daily, ramipril 5 mg daily, simvastatin 40 mg daily. Her admission bloods demonstrate: sodium 144, potassium 4.1, urea 10.8, creatinine 195.

Which of the following is most appropriate?

(Please select 1 option)

○	Give clopidogrel 300 mg stat
○	Withhold ramipril
○	Double dose of ramipril
○	Give loperamide
○	Withhold aspirin

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 2 hrs 28 mins 5 secs

Work Smart Session - MRCP Part 1

Question: 20 of 100

A 17-year-old woman underwent a renal transplant. She was concerned about the effects of long-term ciclosporin treatment.

Which one of the following is a common adverse effect of this drug?

(Please select 1 option)

- ○ Alopecia
- ○ Bone marrow depression
- ○ Hepatotoxicity
- ◉ Nephrotoxicity
- ○ Paraesthesia

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Time taken: 2 hrs 28 mins 52 secs

Work Smart Session - MRCP Part 1

Question: 20 of 100

A 17-year-old woman underwent a renal transplant. She was concerned about the effects of long-term ciclosporin treatment.

Which one of the following is a common adverse effect of this drug?

(Please select 1 option)

○	Alopecia
○	Bone marrow depression
○	Hepatotoxicity
◉	Nephrotoxicity ✓ Correct
○	Paraesthesia

Ciclosporin causes hypertrichosis rather than alopecia and the most frequent adverse side effect of this drug is nephrotoxicity.

Post renal transplant, the two most common causes of declining renal function are graft rejection and ciclosporin toxicity.

Hepatotoxicity and paraesthesia are less common side effects of the drug.

Next question

Tag Question | Remove question

Rate this question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 2 hrs 28 mins 52 secs

Work Smart Session - MRCP Part 1

Question: 21 of 100

A 16-year-old female presents with a three year history of recurrent colicky loin pain. One year ago she passed a renal calculus.

Twenty four hour urine collection showed normal levels of calcium, phosphate and urate, but elevated levels of arginine, cystine, lysine and ornithine.

Which one of the following features is characteristic of this condition?

(Please select 1 option)

○	Accumulation of cystine in collecting system
○	Autosomal dominant inheritance
◉	Cystine deposits within the cornea
○	Functional defects within the glomeruli
○	Radiolucent renal stone formation

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Question: 21 of 100

A 16-year-old female presents with a three year history of recurrent colicky loin pain. One year ago she passed a renal calculus.

Twenty four hour urine collection showed normal levels of calcium, phosphate and urate, but elevated levels of arginine, cystine, lysine and ornithine.

Which one of the following features is characteristic of this condition?

(Please select 1 option)

○	Accumulation of cystine in collecting system ← This is the correct answer
○	Autosomal dominant inheritance
○	Cystine deposits within the cornea
○	Functional defects within the glomeruli
◉	Radiolucent renal stone formation ✕ Incorrect answer selected

This condition is typical of cystinuria/nephropathic cystinosis, an autosomal recessive genetic defect in membrane transport for cystine, lysine, ornithine and arginine in epithelial cells.

The disease is characterised by recurrent nephrolithiasis.

Radiolucent stones are not specific for this condition and may be seen with uric acid stones.

Next question

Remove Tag | Remove question

Rate this question

☆☆☆☆☆

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 2 hrs 39 mins 7 secs

Work Smart Session - MRCP Part 1

Question: 22 of 100

A 65-year-old man presents with renal colic. The following day he passes a stone in his urine with analysis revealing that it is composed of uric acid.

Which one of the following is the most likely cause of this type of renal stone?

(Please select 1 option)

○	Allopurinol
○	Chronic renal failure
○	Primary hyperparathyroidism
○	Secondary polycythaemia
○	Thiazide diuretics

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

○	Chronic renal failure
○	Primary hyperparathyroidism
◉	Secondary polycythaemia ✕ Incorrect answer selected
○	Thiazide diuretics ← This is the correct answer

Uric acid stones occur in 5-25% of all cases of nephrolithiasis. They are associated with hyperuricaemia and hyperuricosuria.

Predisposing factors for uric acid stone formation are

- Dehydration
- High purine load (high protein diet)
- As a primary factor in idiopathic gout
- Associated with high cell turnover (for example, haematological malignancy).

Chronic renal failure is incorrect, as there is hyperuricaemia without hyperuricosuria.

Hyperparathyroidism is associated with calcium stones, not uric acid stones.

Primary polycythaemia would predispose to uric acid stone formation, whereas secondary polycythaemia does not.

Allopurinol is prescribed to treat gout and prevents uric acid formation, hence it reduces the frequency of uric acid stones.

The correct answer is thiazide diuretics. Thiazide diuretics cause hyperuricaemia and can predispose to hyperuricosuria and uric acid stone formation. Uric acid stones are also associated with underlying hypertension.

Thiazide diuretics are used to treat calcium stones as they increase the reabsorption of calcium from the proximal tubules, preventing hypercalciuria.

Next question

Remove Tag | Remove question

Rate this question

☆☆☆☆☆

Question: 23 of 100

A 52-year-old woman presents with left loin pain. Past history included hypertension and progressive cognitive decline.

On examination she was pyrexial, had livedo reticularis and a blood pressure of 180/100 mmHg. Examination of the abdomen revealed no masses but there was tenderness in the left flank.

Investigations revealed:

Haemoglobin	12.9 g/dl	(11.5-16.5)
White cell count	8.7 x 10^9/l	(4-11)
Platelet count	83 x 10^9/l	(150-400)
Serum creatinine	106 mol/l	(60-110)

Urine dipstick analysis:
Blood +++
Protein +

Which one of the following tests is most likely to be positive?

(Please select 1 option)

- Anti-cardiolipin antibody
- Anti-glomerular basement membrane antibody
- Anti-mitochondrial antibody
- Anti-neutrophil cytoplasmic antibody
- Anti-streptolysin O antibody

Submit answer | Skip question | Tag Question | Remove question

Serum creatinine	106 mol/l	(60-110)

Urine dipstick analysis:
Blood +++
Protein +

Which one of the following tests is most likely to be positive?

(Please select 1 option)

◉	Anti-cardiolipin antibody ✓ Correct
○	Anti-glomerular basement membrane antibody
○	Anti-mitochondrial antibody
○	Anti-neutrophil cytoplasmic antibody
○	Anti-streptolysin O antibody

This patient has features to suggest systemic lupus erythematosus (SLE) with antiphospholipid syndrome in this presentation, possibly due to renal vein thrombosis (flank pain with blood and protein in urine).

The diagnosis would be supported by the thrombocytopenia, history of hypertension and the livedo reticularis.

Wegener's with positive anti-neutrophil cytoplasmic antibody (ANCA) would be a less likely diagnosis.

Further reading:
Antiphospholipid syndrome Hughes Syndrome Foundation

Next question

Tag Question Remove question

Rate this question
☆☆☆☆☆

Time taken: 3 hrs 7 mins 1 secs

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Work Smart Session - MRCP Part 1

Question: 24 of 100

Which is the predominant site of effect of thiazide diuretics?

(Please select 1 option)

○	Cortical collecting duct
○	Early distal tubule
○	Late distal tubule
○	Proximal tubule
○	Thick ascending limb, Loop of Henle

Submit answer Skip question Tag Question Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Question: 24 of 100

Which is the predominant site of effect of thiazide diuretics?

(Please select 1 option)

○	Cortical collecting duct
◉	Early distal tubule ✓ Correct
○	Late distal tubule
○	Proximal tubule
○	Thick ascending limb, Loop of Henle

Thiazide diuretics act on the cortical diluting segment of the nephron, predominantly in the early distal tubule.

Loop diuretics mainly act on the thick ascending limb of the Loop of Henle.

Potassium sparing diuretics, for example amiloride, act on the distal nephron.

(For a simplistic review see ABC of heart failure.)

Next question

Tag Question Remove question

Rate this question

☆☆☆☆☆

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 3 hrs 8 mins 4 secs

Work Smart Session - MRCP Part 1

Question: 25 of 100

An 18-year-old female student attends the clinic as her father has just died with end-stage renal failure. He had been diagnosed with autosomal dominant polycystic kidney disease (ADPKD).

She wishes to know what investigations she requires.

Which of the following is an appropriate strategy in her management?

(Please select 1 option)

○	Geneticist referral
○	Glomerular filtration rate estimation
○	MRI brain
◉	Ultrasound of the renal tract
○	Urine dipstick

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

(Please select 1 option)

○	Geneticist referral ← This is the correct answer
○	Glomerular filtration rate estimation
○	MRI brain
◉	Ultrasound of the renal tract ✗ Incorrect answer selected
○	Urine dipstick

An ultrasound of the renal tract may not be appropriate at this patient's age, given that cysts may not become apparent until the age of 20.

Gross haematuria in ADPKD carries a poor prognosis however microscopic haematuria may be a complication.

Subarachnoid haemorrhage may be a cause of mortality in 9% of patients with ADPKD, though 8% of patients have an asymptomatic intracranial aneurysm; if the diagnosis is confirmed and there is a strong history of subarachnoid haemorrhage then an MRI would be indicated.

Genetic counselling is most appropriate in this context and genetic linkage analysis may be utilised.

Next question | Remove Tag | Remove question

Rate this question

☆☆☆☆☆

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 3 hrs 9 mins 10 secs

Work Smart Session - MRCP Part 1

Question: 26 of 100

A 34-year-old female presents with shortness of breath. She has been treated for asthma by her GP with an inhaled steroid, but the GP has documented an eosinophilia of 1.1 x 10^9/L (14%) (Normal <0.1 x 10^9/L). She has been referred to the clinic because her GP found her creatinine to be 347 µmol/l (60-110µmol/l).

Which of the following would support a diagnosis of Churg-Strauss syndrome?

(Please select 1 option)

- ○ Extravascular eosinophils on vascular biopsy
- ◉ Fixed pulmonary infiltrates on chest radiographs
- ○ Peak flow <150ml/minute
- ○ Peripheral alveolar filling infiltrate predominantly in the upper lobes on a chest radiograph
- ○ Peripheral "stocking" neuropathy

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

(Please select 1 option)

○	Extravascular eosinophils on vascular biopsy ← This is the correct answer
◉	Fixed pulmonary infiltrates on chest radiographs ✕ Incorrect answer selected
○	Peak flow <150ml/minute
○	Peripheral alveolar filling infiltrate predominantly in the upper lobes on a chest radiograph
○	Peripheral "stocking" neuropathy

- A diagnosis of Churg-Strauss syndrome requires four of the following features:
-
- asthma
- eosinophilia greater than 10%
- mononeuropathy or polyneuropathy
- paranasal sinus abnormality
- non-fixed pulmonary infiltrates visible on chest radiographs and
- blood vessels with extravascular eosinophils.
-
- Peripheral alveolar filling infiltrate predominantly in the upper lobes on a chest radiograph is typical of chronic eosinophilic pneumonia.
-
- A peripheral "stocking and glove" neuropathy is not typical of Churg-Strauss syndrome and is more common in Type 2 diabetes.

Next question | Tag Question | Remove question

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 3 hrs 10 mins 52 secs

Work Smart Session - MRCP Part 1

Question: 27 of 100

A 62-year-old man with type 2 diabetes for 10 years attends for his annual review.His home blood glucose levels are 7-10 pre-breakfast, he remains overweight despite following his diet and being regularly active. Unfortunately he still smokes 10 cigarettes a day. His medication includes metformin 850 mg TDS, gliclazide 160 mg BD, simvastatin 40 mg OD, aspirin 75 mg OD, ramipril 10 mg OD. On examination his blood pressure is 145/85 mmHg with a BMI of 31.2. He has background diabetic retinopathy, with a distal sensory neuropathy. Recent bloods include a creatinine of 154micromol/l, and an HbA1c of 8.4%.

What is the appropriate intervention?

(Please select 1 option)

- Add insulin glargine to current treatment
- Add Novorapid TDS and insulin glargine
- Add pioglitazone 30 mg/day
- Stop gliclazide and metformin and use insulin glargine
- Stop metformin and commence insulin glargine

Submit answer | Skip question | Tag Question | Remove question

A 62-year-old man with type 2 diabetes for 10 years attends for his annual review.His home blood glucose levels are 7-10 pre-breakfast, he remains overweight despite following his diet and being regularly active. Unfortunately he still smokes 10 cigarettes a day. His medication includes metformin 850 mg TDS, gliclazide 160 mg BD, simvastatin 40 mg OD, aspirin 75 mg OD, ramipril 10 mg OD. On examination his blood pressure is 145/85 mmHg with a BMI of 31.2. He has background diabetic retinopathy, with a distal sensory neuropathy. Recent bloods include a creatinine of 154micromol/l, and an HbA1c of 8.4%.

What is the appropriate intervention?

(Please select 1 option)

○	Add insulin glargine to current treatment
○	Add Novorapid TDS and insulin glargine
○	Add pioglitazone 30 mg/day
○	Stop gliclazide and metformin and use insulin glargine
◉	Stop metformin and commence insulin glargine ✓ Correct

This patient has diabetic nephropathy as evidenced by proteinuria, hypertension and elevated creatinine.Current practice recommends the discontinuation of metformin if there is evidence of a reduced glomerular filtration rate, evidenced by a creatinine of greater than 130 µmol/l or eGFR less than 60 ml/min/1.73m^2. Therefore metformin should be stopped; this will lead to inevitable decline in overall diabetic control, which will need insulin therapy, which can be used alongside the sulphonylurea gliclazide.The use of pioglitazone is relatively contraindicated given the renal impairment because of the risk of associated fluid retention.

Next question | Tag Question | Remove question

Rate this question

☆☆☆☆☆

Time taken: 3 hrs 23 mins 57 secs

Work Smart Session - MRCP Part 1

Question: 28 of 100

A 37-year-old woman underwent a kidney transplant which never functioned.

A biopsy revealed pathological features consistent with acute rejection associated with anti-HLA antibodies.

Which type of immunoglobulin is expected to account for this process?

(Please select 1 option)

○	Ig A
○	Ig D
○	Ig E
○	Ig G
○	Ig M

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

A 37-year-old woman underwent a kidney transplant which never functioned.

A biopsy revealed pathological features consistent with acute rejection associated with anti-HLA antibodies.

Which type of immunoglobulin is expected to account for this process?

(Please select 1 option)

○	Ig A
○	Ig D
○	Ig E
◉	Ig G ✓ Correct
○	Ig M

This acute rejection is recognised and due to anti-IgG antibodies to the human leukocyte antigen (HLA) incompatible tissues with primary activation of T cells.

The acute response is treated with immunosuppressants.

Next question

Tag Question Remove question

Rate this question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

A 35-year-old man presents with left loin pain and haematuria. He comments that he has had three episodes of similar symptoms in the past.

On examination, he is afebrile and has mild pallor.

Investigations show:

Sodium	140 mmol/L (137-144)
Potassium	3.0 mmol/L (3.5-4.9)
Chloride	115 mmol/L (95-107)
Bicarbonate	12 mmol/L (20-28)
Calcium	2.5 mmol/L (2.2-2.6)
Urea	19 mmol/L (2.5-7.5)
Urinalysis	pH 6.5, protein 1+, RBC 1+, White cell count 1+

What is the most likely diagnosis?

(Please select 1 option)

○	Bartter's syndrome
○	Conn's syndrome
○	Renal tubular acidosis type 1
○	Renal tubular acidosis type 2
○	Renal tubular acidosis type 4

Urinalysis	pH 6.5, protein 1+, RBC 1+, White cell count 1+

What is the most likely diagnosis?

(Please select 1 option)

○	Bartter's syndrome
◉	Conn's syndrome ✕ Incorrect answer selected
○	Renal tubular acidosis type 1 ← This is the correct answer
○	Renal tubular acidosis type 2
○	Renal tubular acidosis type 4

The patient has metabolic acidosis with failure appropriately to acidify the urine, pointing to a diagnosis of renal tubular acidosis (RTA).

Type 1 RTA is due to distal tubule defect to excrete hydrogen ions whereas type 2 RTA is associated with proximal tubule defect to reabsorb bicarbonate.

Type 1 is associated with nephrocalcinosis.

Both type 1 and 2 are associated with hypokalaemia whereas type 4 is characterised by hyperkalaemia.

Bartter's and Conn's syndromes are causes of hypokalaemia and metabolic alkalosis.

Next question

Remove Tag Remove question

Question: 2 of 100

A 63-year-old woman is admitted to hospital with a three day history of diarrhoea and vomiting. Her family tell you she has been virtually unable to eat or drink, but has managed to take her tablets during that time. Her past medical history includes essential hypertension and ischaemic heart disease. Her current medication consists aspirin 75 mg daily, ramipril 5 mg daily, simvastatin 40 mg daily. Her admission bloods demonstrate: sodium 144, potassium 4.1, urea 10.8, creatinine 195.

Which of the following is most appropriate?

(Please select 1 option)

○	Give clopidogrel 300 mg stat
◉	Withhold ramipril ✓ Correct
○	Double dose of ramipril
○	Give loperamide
○	Withhold aspirin

The history is entirely consistent with gastroenteritis, and as a result of the protracted vomiting the patient has become dehydrated. In this context an ACE inhibitor (ramipril) is dangerous and should be stopped.

Within the kidneys the afferent and efferent arterioles take blood to (afferent) and from (efferent) the glomerulus. ACE inhibitors work by decreasing the tone of the efferent arterioles, which in a euvolaemic patient can protect the kidney in hypertension, diabetes and other insults. However in a hypovolaemic patient (such as this patient) this can lead to catastrophic impairment of renal function.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Question: 3 of 100

A 22-year-old woman who is taking long term doxycycline for severe acne comes to the clinic complaining of chronic thirst and polyuria. She has to pass urine two to three times per night, which is highly unusual for her.

There is no significant past medical history, and her only medication is the oral contraceptive pill.

On examination her lying BP is 136/80 mmHg, with a postural drop of 15 mmHg. Her BMI is 29. There were no other significant findings on physical examination.

Investigations show

Haemoglobin	13.8 g/dl	(11.5-16.5)
White cells	6.3 x 10^9/l	(4-11)
Platelets	222 x 10^9/l	(150-400)
Sodium	141 mmol/l	(135-146)
Potassium	4.8 mmol/l	(3.5-5)
Creatinine	122 µmol/l	(79-118)
Urea	8.5 mmol/l	(2.5-6.7)

Which of the following is the most appropriate treatment?

(Please select 1 option)

- ○ Discontinue the doxycycline
- ○ Fluid restrict her
- ○ Increase her oral fluid intake
- ○ Intranasal vasopressin
- ○ Oral bendroflumethiazide

A 28-year-old female is referred with a three month history of tiredness and weakness.

On examination, pulse is 82 bpm and blood pressure is 128/72 mmHg. No specific abnormalities are evident on examination of the cardiovascular, respiratory, abdominal or neurological systems.

Investigations reveal:

Serum sodium	142 mmol/l	(137-144)
Serum potassium	3.0 mmol/l	(3.5-4.9)
Serum urea	4.2 mmol/l	(2.5-7.5)
Serum creatinine	82 µmol/l	(60-110)
Serum chloride	73 mmol/l	(95-107)
Plasma glucose	5.5 mmol/l	(3.0-6.0)
Urinary chloride	60 mmol/l	(20-350)

Which of the following is the likely diagnosis?

(Please select 1 option)

○	Bartter's syndrome
○	Conn's syndrome
○	Drug ingestion
○	Liddle's syndrome
○	Non-classical congenital adrenal hyperplasia (CAH)

Which of the following is the likely diagnosis?

(Please select 1 option)

○	Bartter's syndrome
○	Conn's syndrome
◉	Drug ingestion ✓ Correct
○	Liddle's syndrome
○	Non-classical congenital adrenal hyperplasia (CAH)

This young woman has hypokalaemia and hypochloraemia.

The normal blood pressure would exclude a diagnosis of Conn's, CAH, or Liddle's syndrome (apparent mineralocorticoid excess). Similarly, drug ingestion associated with hypokalaemia liquorice/carbenoxolone is associated with hypertension (and low urinary chloride less than 20 mmol/l).

Bartter's syndrome is a rare, recessive condition associated with weakness, lethargy and growth retardation and is found in youngsters. Hypokalaemic hypochloraemic alkalosis is seen in the condition but symptoms would be more apparent at a much younger age than this woman.

If Gitelman's syndrome were offered then that would be a better option.

Therefore the most likely diagnosis as the symptoms have arisen only over the last three months and no other features are apparent on examination, is diuretic abuse.

Further reading:
Postgrad Med J 2001;77:e4 BMJ

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 3 hrs 33 mins 19 secs

Work Smart Session - MRCP Part 1

Question: 31 of 100

A 32-year-old female is diagnosed with Goodpasture's syndrome.

Which of the following therapies used in conjunction with plasmapheresis and corticosteroids would be expected to improve prognosis associated with the condition?

(Please select 1 option)

- Azathioprine
- Cyclophosphamide
- Cyclosporin
- Mycophenolate mofetil
- Tacrolimus

Submit answer | Skip question | Remove question

Question: 31 of 100

A 32-year-old female is diagnosed with Goodpasture's syndrome.

Which of the following therapies used in conjunction with plasmapheresis and corticosteroids would be expected to improve prognosis associated with the condition?

(Please select 1 option)

○	Azathioprine
◉	Cyclophosphamide ✓ Correct
○	Cyclosporin
○	Mycophenolate mofetil
○	Tacrolimus

Studies reveal that without treatment mortality is as high as 90% in association with Goodpasture's.

However the prognosis is drastically improved with the removal of antigen through plasmapheresis, immunosuppression with corticosteroids and cyclophosphamide.

There are some studies revealing the potential of mycophenolate mofetil but the evidence is rather anecdotal.

Next question | Tag Question | Remove question

Rate this question

☆☆☆☆☆

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 3 hrs 34 mins 2 secs

Work Smart Session - MRCP Part 1

Question: 32 of 100

A 7-year-old boy is admitted with renal colic due to renal calculus.

His mother has a similar history of recurrent calculi.

What is the most likely explanation for recurrent renal calculi in both mother and child?

(Please select 1 option)

○	Cystinosis
○	Cystinuria
○	Hyperoxaluria
○	Idiopathic hypercalciuria
○	Urate uropathy

Submit answer | Skip question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Question: 32 of 100

A 7-year-old boy is admitted with renal colic due to renal calculus.

His mother has a similar history of recurrent calculi.

What is the most likely explanation for recurrent renal calculi in both mother and child?

(Please select 1 option)

○	Cystinosis
◉	Cystinuria ✕ Incorrect answer selected
○	Hyperoxaluria
○	Idiopathic hypercalciuria ← This is the correct answer
○	Urate uropathy

Idiopathic hypercalciuria has a familial or sporadic pattern. In the familial pattern an autosomal dominant inheritance is present.

The type of the disease is identical in affected members of the same family and the typical presentation is of recurrent urinary calculi.

Cystinuria, cystinosis, urate uropathy and hyperoxaluria are autosomal recessive conditions.

Next question

Remove question

Rate this question

☆☆☆☆☆

Time taken: 3 hrs 34 mins 58 secs

Work Smart Session - MRCP Part 1

Question: 33 of 100

A 30-year-old female presents with fevers and a three month history of malaise.

Results show:

Creatinine	250 µmol/L (60-110)
Complement C3	23 mg/dL (65-190)

What is the likely diagnosis?

(Please select 1 option)

- HIV nephropathy
- Infective endocarditis
- Membranous nephropathy
- Microscopic polyangiitis
- Minimal change nephropathy

Submit answer | Skip question | Tag Question | Remove question

Creatinine	250 µmol/L (60-110)
Complement C3	23 mg/dL (65-190)

What is the likely diagnosis?

(Please select 1 option)

○	HIV nephropathy
◉	Infective endocarditis ✓ Correct
○	Membranous nephropathy
○	Microscopic polyangiitis
○	Minimal change nephropathy

Hypocomplementaemia is associated with either vasculitides such as systemic lupus erythematosus and cryoglobulinaemia but is also associated with a non-vascultic process such as subacute bacterial endocarditis (SBE).

In this case with the three month history and fevers SBE is suggested.

In microscopic polyangiitis, which is classically small vessel, complement would be expected to be normal.

Next question

Tag Question Remove question

Rate this question

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 3 hrs 36 mins 57 secs

Work Smart Session - MRCP Part 1

Question: 34 of 100

A 32-year-old male with type 1 diabetes undergoes a 24 hour urine collection.

Which of the following urine albumin concentrations signify microalbuminuria?

(Please select 1 option)

○	10 mg/day
○	50 mg/day
○	500 mg/day
○	1 g/day
○	3.5 g/day

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Which of the following urine albumin concentrations signify microalbuminuria?

(Please select 1 option)

○	10 mg/day
◉	50 mg/day ✓ Correct
○	500 mg/day
○	1 g/day
○	3.5 g/day

Microalbuminuria is defined as a urine albumin excretion of between 30-300 mg per 24 hours.

A concentration above 300 mg/24 hours signifies albuminuria and a concentration above 3.5 g/24 hours signifies overt proteinuria.

Microalbuminuria is not just an indictor of early renal involvement but it also identifies increased cardiovascular risk with an approximate two- fold cardiovascular risk above the already increased risk in the diabetic population.

A useful surrogate of the total albumin excretion is the albumin: creatinine ratio. The urinary albumin:creatinine ratio is measured using the first morning urine sample where practicable.

Microalbuminuria is indicated where there is an albumin:creatinine ratio ≥2.5 mg/mmol (men) or 3.5 mg/mmol (women).

Proteinuria is indicated by a ratio of ≥30 mg/mmol.

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 3 hrs 45 mins 16 secs

Work Smart Session - MRCP Part 1

Question: 36 of 100

A 16-year-old girl developed pulmonary haemorrhage and acute renal failure requiring dialysis.

Investigations revealed:

Renal biopsy	Crescentic glomerulonephritis

Which one of the following antibodies is most likely to be found in the blood?

(Please select 1 option)

- Anticardiolipin
- Anticentromere
- Antimitochondrial
- Antimyeloperoxidase
- Antinuclear

Submit answer | Skip question | Tag Question | Remove question

Which one of the following antibodies is most likely to be found in the blood?

(Please select 1 option)

○	Anticardiolipin
○	Anticentromere
○	Antimitochondrial
◉	Antimyeloperoxidase ✓ Correct
○	Antinuclear

This patient manifests a pulmonary renal syndrome which is most commonly due to an anti-neutrophil cytoplasmic antibody test (ANCA) positive vasculitis and less commonly due to Goodpasture's syndrome (anti-glomerular basement membrane [GBM] antibodies).

ANCA antibodies are of two types:

1. C-ANCA which correlates with anti-proteinase 3 antibodies (PR3)
2. P-ANCA which correlates with anti-myeloperoxidase antibodies. P-ANCA/MPO antibodies are highly sensitive and specific for rapidly progressive glomerulonephritis and haemorrhagic alveolar capillaritis.

Anti-mitochondrial antibodies are found in primary biliary cirrhosis.

Anti-centromere antibodies are found in CREST/scleroderma syndrome.

ANA and anti-cardiolipin antibodies are found in systemic lupus erythematosus (SLE) which is not a cause of pulmonary renal syndrome.

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 3 hrs 49 mins 47 secs

Work Smart Session - MRCP Part 1

Question: 37 of 100

A 28-year-old man presented with hypertension.

On examination he had palpable kidneys and abdominal ultrasound shows bilaterally enlarged cystic kidneys.

Which one of the following conditions is most likely to be present in this patient?

(Please select 1 option)

- Mitral stenosis
- Nail dystrophy
- Polycythaemia
- Short stature
- Testicular atrophy

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

A 28-year-old man presented with hypertension.

On examination he had palpable kidneys and abdominal ultrasound shows bilaterally enlarged cystic kidneys.

Which one of the following conditions is most likely to be present in this patient?

(Please select 1 option)

○	Mitral stenosis
○	Nail dystrophy
◉	Polycythaemia ✓ Correct
○	Short stature
○	Testicular atrophy

The most likely diagnosis here is adult polycystic kidney disease, which is associated with valvular heart abnormalities, incompetence and aneurysms of the cerebral circulation.

However, it is also associated with excessive erythropoietin production and polycythaemia.

Next question

Tag Question | Remove question

Rate this question

© 2011 BMJ Publishing Group Ltd. All rights reserved. Terms and conditions Privacy policy

Work Smart Session - MRCP Part 1

Question: 38 of 100

A 17-year-old boy presented with a non-blanching rash over his legs, a swollen knee and painless frank haematuria.

Investigations revealed:

Serum creatinine	210 µmol/L (60-110)
Urine dipstick analysis: Blood	+++
Urine dipstick analysis: Protein	+
Urine culture	Negative
Ultrasound of the kidneys	Normal

Which glomerular abnormality is most likely to be present at renal biopsy?

(Please select 1 option)

- ○ Focal and segmental sclerosis
- ○ Foot process fusion
- ○ Linear deposition of IgG on the basement membrane
- ○ Mesangial deposition of IgA
- ○ Thickening of basement membranes

Urine culture	Negative
Ultrasound of the kidneys	Normal

Which glomerular abnormality is most likely to be present at renal biopsy?

(Please select 1 option)

○	Focal and segmental sclerosis
○	Foot process fusion
○	Linear deposition of IgG on the basement membrane
◉	Mesangial deposition of IgA ✓ Correct
○	Thickening of basement membranes

The likely diagnosis here is Henoch-Schonlein purpura (HSP).

HSP is an inflammatory disorder of unknown cause characterised by IgA-dominant immune complexes in smaller venules, capillaries and arterioles. It presents with purpura, arthritis (especially ankles and knees), abdominal pains, haematuria and proteinuria.

HSP is often associated with infectious agents such as group A *Streptococci* and *Mycoplasma*.

If there is progression to renal impairment then renal histopathology may include minimal change to severe glomerulonephritis that is indistinguishable from IgA nephropathy. However, mesangial Ig A deposits are the most typical features of HSP on renal biopsy.

Next question | Tag Question | Remove question

Rate this question

Time taken: 3 hrs 52 mins 57 secs

Work Smart Session - MRCP Part 1

Question: 39 of 100

A 70-year-old man was referred by his GP with difficulty in treating hypertension.

He had longstanding hypertension which had been well controlled over many years but recently he was found to have a blood pressure of 190/110 mmHg which proved resistant to additional treatment.

He was generally asymptomatic and complied with medication. Investigations showed normal U+Es.

Which one of the following is the most likely cause?

(Please select 1 option)

- ○ Chronic pyelonephritis
- ○ Conn's syndrome (primary hyperaldosteronism)
- ○ Phaeochromocytoma
- ○ Polycystic kidney disease
- ○ Renovascular disease

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

A 70-year-old man was referred by his GP with difficulty in treating hypertension.

He had longstanding hypertension which had been well controlled over many years but recently he was found to have a blood pressure of 190/110 mmHg which proved resistant to additional treatment.

He was generally asymptomatic and complied with medication. Investigations showed normal U+Es.

Which one of the following is the most likely cause?

(Please select 1 option)

○	Chronic pyelonephritis
○	Conn's syndrome (primary hyperaldosteronism)
○	Phaeochromocytoma
○	Polycystic kidney disease
◉	Renovascular disease ✓ Correct

Primary hyperaldosteronism (Conn's syndrome) typically has hypokalaemic alkalosis.

One should also suspect Conn's with patients resistant to conventional antihypertensive treatment and with the electrolytes in the direction of Conn's without necessarily being outside the normal range (plasma Na > 140 and K < 4).

However, in this patient's case he has longstanding hypertension but has deteriorated. Therefore the most likely cause is renovascular disease related to his hypertension.

Next question

Tag Question | Remove question

Which of the following is the most appropriate treatment?

(Please select 1 option)

◉	Discontinue the doxycycline ✓ Correct
○	Fluid restrict her
○	Increase her oral fluid intake
○	Intranasal vasopressin
○	Oral bendroflumethiazide

Tetracyclines are known to be a cause of nephrogenic diabetes insipidus, as are

- Lithium
- Certain anti-fungals
- Certain anti-viral agents.

Whilst increasing her oral intake may relieve some of her symptoms of thirst, discontinuing the doxycycline is the only way to resolve both her thirst and her polyuria.

High dose intranasal vasopressin may relieve her symptoms but the most appropriate treatment is discontinuation of the tetracycline antibiotic.

Next question

Tag Question | Remove question

Rate this question

☆☆☆☆☆

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

A 52-year-old man presents to the clinic having problems controlling his blood pressure, despite taking three anti-hypertensive agents, ramipril 10 mg, indapamide 2.5 mg, and amlodipine 5 mg.

Over the past few weeks he has been monitoring his BP at home and it is rarely below 155/90 mmHg.

On examination in the clinic his BP is 160/95 mmHg, his pulse is 85 and regular. He has a left carotid bruit. Respiratory and abdominal examinations are unremarkable.

Investigations show

Haemoglobin	12.0 g/dl	(13.5-17.7)
White cells	6.3 x 10^9/l	(4-11)
Platelets	200 x 10^9/l	(150-400)
Sodium	140 mmol/l	(135-146)
Potassium	4.8 mmol/l	(3.5-5)
Creatinine	182 µmol/l	(79-118)

Renal ultrasound scan showed significant size discrepancy, with the left kidney 2 cm smaller than the right.

Which of the following is the most appropriate next investigation?

(Please select 1 option)

- Contrast CT
- Duplex ultrasound scanning
- IVU
- Magnetic resonance angiogram
- Traditional angiography

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 3 hrs 55 mins 11 secs

Work Smart Session - MRCP Part 1

Question: 40 of 100

A 30-year-old woman becomes anuric 24 hours after a difficult laparoscopic cholecystectomy.

Investigations reveal:

Serum urea	9.2 mmol/l	(2.5-7.5)
Serum creatinine	120 micro mol/l	(60-110)

The blood pressure is 90/50 mmHg.

What is the next single most appropriate course of action in the management of the anuria?

(Please select 1 option)

- 1 L normal saline intravenously as fast as possible.
- Commence intravenous low-dose dopamine
- Give an 80 mg intravenous bolus of furosemide
- Give 500 ml intravenous plasma expander over 4 hours
- Urgent renal ultrasound

Submit answer | Skip question | Tag Question | Remove question

◉	1 L normal saline intravenously as fast as possible. ✓ Correct
○	Commence intravenous low-dose dopamine
○	Give an 80 mg intravenous bolus of furosemide
○	Give 500 ml intravenous plasma expander over 4 hours
○	Urgent renal ultrasound

This question is dealing with postoperative acute renal failure. This what you might find on the morning ward round and wonder why the problem was not picked up during the night.

Note that even when the glomerular filtration rate is zero, the serum creatinine tends not to rise faster than 200 micro mol/l per day - so the patient's creatinine of 120 micro mol/l may be the beginning of established renal failure.

Immediate management consists of restoring the circulation as quickly as possible; debate still continues whether it is better to use colloid or crystalloid.

In this case it would seem to be more appropriate to use 1 L of normal saline as the time scale for plasma expander is too long.

If urine output and renal function recover as soon as intravascular volume is restored, the diagnosis of pre-renal uraemia is made; if they do not then the diagnosis is acute tubular necrosis (ATN).

In a seemingly previously cardiovascularly-well 30-year-old with hypotension, giving 1 L over a short time will not precipitate any problems.

There is little evidence to suggest that loop diuretics and dopamine are effective in the treatment of ATN.

The next problem is to find out why the patient was hypotensive after surgery.....

Question: 41 of 100

A 30-year-old male presents with oedema and proteinuria.

On examination his blood pressure was 120/70 mmHg.

Investigations reveal:

Creatinine	88 µmol/L (60-110)
Albumin	25 g/L (37-49)
Urinalysis	No blood
Protein	++++
Urinary protein excretion	7g/24hr (<0.2)

- Ultrasound of renal tract normal right kidney, absent left kidney

Which is the most appropriate course of action for this patient?

(Please select 1 option)

○	Albumin transfusion
○	Angiotensin converting enzyme (ACE) inhibitor therapy
○	High protein diet
○	Renal biopsy
○	Trial of steroid therapy

http://my.onexamination.com/Assessment/Que
Questions Set : REF7559
passmedicine.com
passmedicine.com

○	Renal biopsy
◉	Trial of steroid therapy ✓ Correct

This patient has nephrotic syndrome, which is a combination of:

- Proteinuria (usually > 3g/24 hrs)
- Hypoalbuminaemia (<35g/L)
- Oedema
- Hyperlipidaemia.

The most appropriate course of action here would be to undergo a trial of steroid therapy.

Ideally a renal biopsy would be indicated to determine the cause of the nephrotic syndrome, however as this patient only has one kidney then this would be considered a relative contraindication for such a procedure.

A high protein diet / albumin transfusion would be of little to no benefit - and the latter would need to be salt poor.

ACE inhibitors reduce proteinuria and slow deterioration in glomerular filtration rate (GFR).

In this case given the patient's age he may well have minimal change glomerulonephritis (GN) (commonest in children), which is normally steroid responsive.

In the young adult histological diagnoses are in general: minimal change > mesangiocapillary > FSGS > lupus > membranous > diabetes.

In general steroids are tried first and then second line agents such as cyclosporin and cyclophosphamide are introduced if needed.

Next question
Tag Question
Remove question

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 3 hrs 58 mins 35 secs

Work Smart Session - MRCP Part 1

Question: 42 of 100

A 25-year-old female wishes to start a family but she is concerned as her 50-year-old mother had adult polycystic kidney disease.

Examination reveals no specific abnormalities.

Which is the most appropriate screening test for polycystic kidney disease in this woman?

(Please select 1 option)

○	Genetic linkage analysis
○	Intravenous urogram
○	Isotope renography
○	Renal ultrasound
○	Urinalysis

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

EN 3:55 PM 3/1/2011

(Please select 1 option)

◉	Genetic linkage analysis ✕ Incorrect answer selected
○	Intravenous urogram
○	Isotope renography
○	Renal ultrasound ← This is the correct answer
○	Urinalysis

The answer lies between renal ultrasound and genetic linkage analysis. Polycystic kidney disease is an autosomal dominant disorder. Mutations in at least three different genes can lead to autosomal dominant polycystic disease (APKD).

1. PKD-1 on chromosome 16: 85% of cases. Polycystin 1 is an integral membrane glycoprotein involved in cell/matrix interactions
2. PKD-2 on chromosome 4: 10% of cases. Polycystin 2 which may associate with polycystin 1 through a common signalling pathway
3. A third gene mutation is known but its exact chromosomal location is not.

Diagnosis is made by multiple bilateral renal cysts and a positive family history.

Genetic linkage studies: Can exclude or make the diagnosis in younger patients. Requires blood from at least two affected family members.

Ultrasonography:

- In PKD 1 families, age related diagnostic criteria are used: two cysts in under 30 years age group.
- At least two cysts in each kidney in 30-59 years. Four cysts in each kidney for over 60 years.

CT: More sensitive than USS and may aid in diagnosis in younger patients.

MR angiography: In patients with a family history of intracranial aneurysm - to screen for cerebral aneurysms.

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 3 hrs 59 mins 19 secs

Work Smart Session - MRCP Part 1

Question: 43 of 100

A 60-year-old male presents with typical renal colic and one day later passes a small stone.

However, the original x ray of the abdomen revealed no obvious calculi.

What is the most likely composition of his calculus?

(Please select 1 option)

- Calcium
- Cystine
- Oxalate
- Phosphate
- Uric acid

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

What is the most likely composition of his calculus?

(Please select 1 option)

○	Calcium
◉	Cystine ✗ Incorrect answer selected
○	Oxalate
○	Phosphate
○	Uric acid ← This is the correct answer

The main constituent will be uric acid.

Major causes of stone formation:

- Calcium stones (80%) - hypercalciuria (for example, primary hyperparathyroidism), hyperoxaluria (for example, XS intake, ileal disease and bypass)
- Uric acid stones (10%) - high purine intake, high cell turnover
- Cystine stones (2%) - cystinuria (AR defect in dibasic amino acid transporter)
- Infection stones (5%) - chronic infection with urea splitting organisms causes stones made of magnesium ammonium phosphate and calcium phosphate
- Other stones (3%) - include xanthine stones, rare renal chloride channel mutations can cause stone formation.

There appears to be a male predominance with a 2:1 ratio.

Calcium and infection stones are radio-opaque, cystine stones are weakly radio-opaque and urate stones are radiolucent.

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 4 hrs 33 secs

Work Smart Session - MRCP Part 1

Question: 44 of 100

A 45-year-old man presented to the nephrology clinic with severe generalised oedema.

Investigations showed:

Serum albumin	20 g/L (37-49)
24-hour urinary protein excretion	14.6 g (<0.2 g)
Renal biopsy	Normal on light microscopy, normal on immunoflorescence

There was no significant improvement in his symptoms or signs after three months treatment with prednisolone 60 mg OD.

What is the most likely diagnosis?

(Please select 1 option)

- ○ Focal segmental glomerulosclerosis
- ○ Membranous nephropathy
- ○ Minimal change disease
- ○ Myeloma
- ○ Renal vein thrombosis

◉	Minimal change disease ✓ Correct
○	Myeloma
○	Renal vein thrombosis

This patient has symptoms and signs of a nephrotic syndrome. A renal biopsy was normal on light microscopy and immunofluorescence.

Focal segmental glomerulosclerosis and membranous nephropathy are histological diagnoses. As this patient's renal biopsy was normal he cannot have these diagnoses.

Myeloma generally causes a cast nephropathy, but can also cause

- Fanconi syndrome
- Light chain amyloidosis
- Light chain deposition
- Infiltration of renal interstitium by plasma cells
- Calcium precipitation and
- Renal infection.

This may cause acute renal failure, chronic renal failure or nephrotic syndrome.

All the above lesions should be visible on light microscopy of the renal biopsy.

Renal vein thrombosis is an uncommon cause of the nephrotic syndrome. It is not normally associated with such heavy proteinuria and if it is, there are usually changes seen on microscopy.

The likely diagnosis is minimal change nephropathy. Although it is more common in children it does occur in adults and is then associated with poorer outcomes. As well as heavy proteinuria oval fat bodies may also be seen in the urine.

Time taken: 4 hrs 3 mins 19 secs

Work Smart Session - MRCP Part 1

Question: 45 of 100

A 45-year-old man with chronic renal failure presents to clinic complaining of increasing fatigue and weakness.

He receives three hours of haemodialysis, thrice weekly. His blood pressure is measured at 176/110 mmHg pre-dialysis and 166/95 mmHg post-dialysis.

Investigations pre-dialysis show:

Hb	9.5 g/d	(13.0-18.0)
Potassium	6.9 mmol/l	(3.5-4.9)
Creatinine	1567 µmol/l	(60-110)
Calcium	(corrected) 2.1 mmol/l	(2.2-2.6)

Which of the following options is most appropriate initial management for this patient?

(Please select 1 option)

- ○ Give alfacalcidol to correct hypocalcaemia
- ○ Increase the duration of each dialysis session
- ○ Reduce the potassium concentration in the dialysate
- ○ Start erythropoietin to increase haemoglobin level
- ○ Start ramipril to gain better control of his blood pressure

◉	Increase the duration of each dialysis session ✓ Correct
○	Reduce the potassium concentration in the dialysate
○	Start erythropoietin to increase haemoglobin level
○	Start ramipril to gain better control of his blood pressure

This patient has been poorly managed! Again the question is the issue here. What is the most appropriate management in this case?

Pre-dialysis blood pressure and blood investigations are a poor indication of dialysis adequacy. It would be more helpful in this question to have post-dialysis blood results, especially urea, which could give an idea of dialysis adequacy.

His post-dialysis blood pressure is too high. It should be controlled with antihypertensive medication if the patient is achieving his dry weight with fluid ultra filtration on haemodialysis.

His haemoglobin is lower than 11 g/dl, which is the minimum level a patient with end stage renal failure should have. Initially he should be treated with IV iron, and if the haemoglobin is still low, erythropoietin should be commenced.

Hyperkalaemia can cause lethargy and muscle weakness, but only if the levels are over 7 mmol/l. The above potassium level is probably expected pre-dialysis.

His corrected calcium is borderline low (aim for 2.2-2.6 mmol/l), but should not cause the above symptoms.

This patient has non-specific symptoms. He is hypertensive post-dialysis, and has a very high pre-dialysis serum creatinine. He requires further management of his haemoglobin, blood pressure and calcium levels.

None of the above would cause the non-specific deterioration seen in this patient, and therefore the most appropriate management strategy that would affect most things would be increasing the dialysis adequacy, by increasing the duration of each dialysis session.

Further reading:

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 4 hrs 5 mins 24 secs

Work Smart Session - MRCP Part 1

Question: 46 of 100

A 14-year-old old boy presents with a sore throat and macroscopic haematuria.

What would light microscopy of a kidney biopsy most likely show?

(Please select 1 option)

- Collapsed glomeruli
- Crescentic glomerulonephritis
- Mesangial hypercellularity
- Normal tissue
- Segmental sclerosis

Submit answer | Skip question | Tag Question | Remove question

- Community
- Shop
- Help

A 14-year-old old boy presents with a sore throat and macroscopic haematuria.

What would light microscopy of a kidney biopsy most likely show?

(Please select 1 option)

○	Collapsed glomeruli
○	Crescentic glomerulonephritis
◉	Mesangial hypercellularity ✓ Correct
○	Normal tissue
○	Segmental sclerosis

The most common cause of macroscopic haematuria in a child is IgA nephritis.

This usually develops one to two days after a sore throat. It is most common in the second and third decades of life and is three times more common in males.

The urine may be frankly bloody or may be the colour of cola. There are no clots in the urine and the haematuria is generally painless although some patients complain of mild loin pain.

It tends to settle spontaneously within five days although the episodes may be recurrent lasting for one to two years.

Renal biopsy will show mesangial IgA deposition on immunofluorescence and light microscopy will show mesangial hypercellularity and matrix expansion.

Next question | Tag Question | Remove question

Rate this question

Time taken: 4 hrs 6 mins 18 secs

Work Smart Session - MRCP Part 1

Question: 47 of 100

A 62-year-old man with a longstanding history of hypertension is seen in the outpatient clinic.

Investigations show:

Creatinine	280 µmol/L (60-110)

Urinalysis

Blood	++
Protein	1.8 g/L

- Ultrasound scan of kidneys left kidney 8.5 cm; right kidney 8.9 cm

What is the best investigation to diagnose the cause of his renal impairment?

(Please select 1 option)

- ○ Intravenous urogram (IVU)
- ○ Isotope renogram
- ○ Renal angiogram
- ○ Renal biopsy
- ○ Retrograde pyelogram

Protein	1.8 g/L

- Ultrasound scan of kidneys left kidney 8.5 cm; right kidney 8.9 cm

What is the best investigation to diagnose the cause of his renal impairment?

(Please select 1 option)

○	Intravenous urogram (IVU)
○	Isotope renogram
◉	Renal angiogram ✕ Incorrect answer selected
○	Renal biopsy ← This is the correct answer
○	Retrograde pyelogram

This patient has a long history of hypertension, therefore it should have been appropriately controlled in the clinic.

The patient now presents with bilaterally shrunken kidneys, renal impairment and evidence of a glomerulonephritis.

In the presence of mild to moderate hypertension, proteinuria indicates either underlying renal disease or renovascular disease.

As this patient has blood and protein in the urine, on the background of impaired renal function and shrunken kidneys, the best investigation would be to perform a renal biopsy (assuming the hypertension was controlled). This would differentiate between renovascular disease and glomerulonephritis, which may be reversible.

If this patient had the above clinical findings without blood and protein in the urine, then the investigation of choice would be a renal angiogram, to diagnose renovascular disease.

Time taken: 4 hrs 8 mins 43 secs

Work Smart Session - MRCP Part 1

Question: 48 of 100

A 16-year-old girl presented to the nephrology clinic with a four-day history of steadily increasing generalised oedema. There was no past history of note.

On examination she weighed 45kg. Her blood pressure was 90/55 mmHg.

Investigations revealed:

Serum creatinine	55 µmol/L (60-110)
Serum albumin	20 g/L (37-49)

- 24 hour urinary protein excretion 4.8g (<0.2g)
- Ultrasound scan of kidneys normal

If this patient is treated with prednisolone (1mg/kg for six weeks), what are the chances of her disease going into complete remission?

(Please select 1 option)

○	<20%
○	20 – 39%
○	40 – 59%
○	60 – 80%
○	>80%

If this patient is treated with prednisolone (1mg/kg for six weeks), what are the chances of her disease going into complete remission?

(Please select 1 option)

○	<20%
○	20 – 39% ← This is the correct answer
○	40 – 59%
◉	60 – 80% ✕ Incorrect answer selected
○	>80%

This girl has probably developed idiopathic glomerulonephritis, which accounts for 90% of all childhood cases of the nephrotic syndrome. The main cause is minimal change nephrotic syndrome.

The first line treatment for minimal change nephropathy is prednisolone for four to six weeks (60mg/m^2) reducing to 40mg/m^2 for a further four to six weeks.

With this treatment 93% of children will respond with complete loss of proteinuria within eight weeks.

However, once remission is induced, 66% of children will have at least one relapse (34% will have complete remission).

Between 40 and 55% of children affected, who initially respond to steroids, will develop multiple relapses when the steroids are reduced.

Early, frequent relapses (three or more in the first six months) signify a relapsing course which requires treatment with cyclophosphamide.

Next question | Remove Tag | Remove question

Time taken: 4 hrs 10 mins 22 secs

Work Smart Session - MRCP Part 1

Question: 49 of 100

A 70-year-old woman was referred with a six-week history of painless macroscopic haematuria.

Her only medications were IM sodium aurothiomalate and oral ibuprofen, which she took for rheumatoid arthritis.

Investigations:

Serum creatinine	92 mol/L (60-110)
Urine dipstick	Blood++++
Protein	+

- Abdominal plain x ray normal
- Ultrasound kidneys and renal tract normal

Which one of the following is the best initial investigation?

(Please select 1 option)

○	Cystoscopy
○	Intravenous urogram (IVU)
○	Renal biopsy
○	Stop ibuprofen
○	Stop sodium aurothiomalate

Protein	+

- Abdominal plain x ray normal
- Ultrasound kidneys and renal tract normal

Which one of the following is the best initial investigation?

(Please select 1 option)

◉	Cystoscopy ✓ Correct
○	Intravenous urogram (IVU)
○	Renal biopsy
○	Stop ibuprofen
○	Stop sodium aurothiomalate

This lady has macroscopic haematuria and a trace of protein in the urine. She is taking ibuprofen and IM sodium aurothiomalate (gold). Her renal function is normal, as is the plain abdominal x ray and USS renal tract.

Ibuprofen is a common cause of interstitial nephritis, and this could present with painless haematuria.

Sodium aurothiomalate commonly causes trace proteinuria, and if present on its own is unimportant, but it can also cause membranous glomerulonephritis, which this lady could have.

However. the most important thing to exclude would be a bladder tumour initially before embarking upon a renal biopsy. Therefore cystoscopy is the best initial investigation.

Next question

Tag Question | Remove question

A 62-year-old woman presents with severe nausea and lethargy a few days after beginning diclofenac and amoxicillin from her GP for pain and a urinary tract infection. She has no past history of note apart from hypertension for which she takes ramipril, and she believes she injured her back lifting a wardrobe.

On examination her BP is 159/92 mmHg, she has bilateral crackles on auscultation of the chest, her pulse is 89 and regular. Abdominal examination is unremarkable. She has a widespread erythematous rash.

Investigations show

Hb	11.9 g/dl	(13.5-18)
WCC	8.9 x 10^9/l Eosinophilia	(4-11)
PLT	203 x 10^9/l	(150-400)
Na	139 mmol/l	(135-146)
K	6.1 mmol/l	(3.5-5)
Cr	382 mmol/l	(79-118)
Urine protein	++	
Blood	-	
White cells	-	

Which of the following is the most likely diagnosis?

(Please select 1 option)

- Acute tubular necrosis
- Churg-Strauss syndrome
- Interstitial nephritis
- Membranous nephropathy
- Pyelonephritis

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 4 hrs 12 mins 42 secs

Work Smart Session - MRCP Part 1

Question: 50 of 100

Which of the following is least true regarding IgA nephropathy?

(Please select 1 option)

○	Commonly follows a sore throat
○	Is the most common glomerulonephritis in the world
○	Light chains may be found in the urine
○	May be associated with a rash and arthritis
○	Predominantly affects young men

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Time taken: 4 hrs 13 mins 9 secs

Work Smart Session - MRCP Part 1

Question: 50 of 100

Which of the following is least true regarding IgA nephropathy?

(Please select 1 option)

○	Commonly follows a sore throat
○	Is the most common glomerulonephritis in the world
◉	Light chains may be found in the urine ✓ Correct
○	May be associated with a rash and arthritis
○	Predominantly affects young men

IgA nephropathy (Berger's disease) is the most common glomerulonephritis worldwide and characteristically affects young males, presenting with frank haematuria after an episode of pharyngitis.

However it may also present with proteinuria, microscopic haematuria, renal failure or hypertension.

It is probably part of a spectrum of disease with Henoch-Schonlein purpura, which presents with arthritis, rash, abdominal pain and nephritis. In both there are mesangial IgA deposits in the kidney.

Next question | Tag Question | Remove question

Rate this question

☆☆☆☆☆

Time taken: 4 hrs 13 mins 9 secs

Work Smart Session - MRCP Part 1

Question: 51 of 100

A 16-year-old female presents with ankle swelling four days after having had a sore throat. On examination she had a blood pressure of 125/80 mmHg and ankle oedema. Investigations reveal:

Creatinine	90 µmol/l	(60-110)
Albumin	25 g/l	(37-49)
24 hour urinary protein	9 g	(<0.2)

What is the most likely diagnosis?

(Please select 1 option)

- Idiopathic membranous nephropathy
- IgA nephropathy
- Membranoproliferative glomerulonephritis
- Minimal change nephropathy
- Post-streptococcal glomerulonephritis

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

○	Idiopathic membranous nephropathy
○	IgA nephropathy ← This is the correct answer
○	Membranoproliferative glomerulonephritis
◉	Minimal change nephropathy ✕ Incorrect answer selected
○	Post-streptococcal glomerulonephritis

Idiopathic membranous nephropathy (option A) accounts for 2-5% of cases of nephritic syndrome in children, and 20-30% of cases in adults.

The immune mechanism that leads to the development of membranous nephropathy is unknown. Histologically, it is characterised by diffuse thickening of the glomerular basement membrane (GBM) on light microscopy. On immunofluorescence, the thickening is caused by immune deposits of IgG and C3, on the subepithelial surface of the GBM.

When not idiopathic, it is associated with

- AI diseases (SLE, rheumatoid arthritis, thyroid disease)
- drugs (gold, penicillamine, captopril)
- malignancy (bronchus, breast, stomach, colon, prostate)
- infections (hep B, syphilis, leprosy, filariasis)
- diabetes mellitus.

Membranoproliferative (or mesangiocapillary) glomerulonephritis (option C) can be classed into three types (I, II, and III) depending on which complement pathway is activated. It is associated with SLE, cryoglobulinaemia with or without hep C, chronic infections (SBE) or with neoplasms. It is not associated acutely with upper respiratory tract infections.

Minimal change nephropathy (option D) is the most common form of nephrotic syndrome in children. The histological findings on light

(SBE) or with neoplasms. It is not associated acutely with upper respiratory tract infections.

Minimal change nephropathy (option D) is the most common form of nephrotic syndrome in children. The histological findings on light microscopy are normal or small looking glomeruli. On electron microscopy there is effacement of the epithelial cell foot processes over the outer surface of the GBM. It tends to be steroid responsive in children, but over 60% of children will have further relapses. In adults, it is associated with Hodgkin's lymphoma, and other carcinomas.

Post streptococcal GN (option E), as the name implies, occurs 10-14 days after an acute infection. The typical case occurs following infection with group A Lancefield streptococci (β-haemolytic strep, *S. pyogenes*) either causing pharyngitis or skin infections. It is more common in the developing world. The histology shows diffuse proliferative GN, with infiltration by neutrophil polymorphs. The main treatment is eradication of the infection (10/7 course of penicillin) and symptomatic relief of the acute nephritis. The need for dialysis is uncommon, and complete recovery of renal function should occur.

The correct answer is IgA nephritis (option B). IgA nephritis is most common during the second and third decade of life. It commonly occurs within two days of an onset of an upper respiratory tract infection, or less commonly infection of other mucous membranes (e.g. GI, bladder, breast). It should be diagnosed by a renal biopsy, where IgA is seen deposited in the mesangium.

The treatment of IgA nephritis is variable. In a patient with haematuria only, the treatment is conservative. When there is nephrotic range proteinuria (>3 g/day - as in this case) an 8-12 week course of prednisolone should be prescribed. If the proteinuria is <3 g/day an ACE inhibitor can be used. In all patients, careful control of blood pressure should be achieved, by using ACE inhibitors in the first instance, and regular follow up of renal function and urinalysis.

30% of children will have a spontaneous remission within 10 years, but 25% will go on to develop ESRF within 20 years.

Next question

Tag Question

Remove question

Rate this question

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 4 hrs 18 mins 2 secs

Work Smart Session - MRCP Part 1

Question: 52 of 100

A 21-year-old female presents with joint pains and rash. On examination her blood pressure was 140/100 mmHg.

Investigations reveal:

Creatinine	90 µmol/l	(60-110)
Anti dsDNA antibodies	Strongly positive	(0-73)
24 hour urinary protein excretion	1.7 g	(<0.2)
Renal biopsy	Membranous nephropathy	

What is the most appropriate next treatment?

(Please select 1 option)

- A. ACE inhibitor for blood pressure control
- B. Cyclophosphamide
- C. NSAIDs for arthralgia
- D. Prednisolone for immunosuppression
- E. Warfarin anticoagulation

Submit answer | Skip question | Tag Question | Remove question

What is the most appropriate next treatment?

(Please select 1 option)

○	A. ACE inhibitor for blood pressure control ← This is the correct answer
○	B. Cyclophosphamide
○	C. NSAIDs for arthralgia
◉	D. Prednisolone for immunosuppression ✕ Incorrect answer selected
○	E. Warfarin anticoagulation

This patient has systemic lupus erythematosus with the disease affecting her kidneys.

The biopsy has shown pure membranous nephropathy, classifying the disease as class V(a) on the 1995 WHO classification of lupus nephritis. Class V(a and b) have a low rate of progression to renal failure.

There is no clear consensus on treatment, but most nephrologists would start treatment with prednisolone. Cyclophosphamide could be added in later as a steroid sparing agent.

Warfarin is not considered an appropriate treatment as if this lady exhibited any prothrombotic tendencies (on the background of antiphospholipid antibody disease) she should be started on aspirin.

Non-steroidal anti-inflammatory medication would treat her arthralgia but would have no effect on the prognosis of the disease.

As there is a low rate of progression of renal disease in this patient the blood pressure should be aggressively treated with an angiotensin-converting enzyme (ACE) inhibitor and this could assist in reducing the proteinuria.

Therefore, the correct answer should be A, but closely followed by answer D.

Work Smart Session - MRCP Part 1

Question: 53 of 100

A 25-year-old woman who is 20 weeks pregnant is diagnosed with pyelonephritis.

She had suffered recurrent urinary infections since childhood and her family history reveals that her mother had a history of hypertension and had been told she had a kidney problem.

Examination was normal and urea and creatinine were both normal.

What is the most likely diagnosis?

(Please select 1 option)

- A. Autosomal dominant polycystic kidney disease
- B. Bladder outlet obstruction
- C. Normal physiological urinary stasis of pregnancy
- D. Reflux nephropathy
- E. Renal stone disease

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

What is the most likely diagnosis?

(Please select 1 option)

◉	A. Autosomal dominant polycystic kidney disease ✕ Incorrect answer selected
○	B. Bladder outlet obstruction
○	C. Normal physiological urinary stasis of pregnancy
○	D. Reflux nephropathy ← This is the correct answer
○	E. Renal stone disease

This lady has had recurrent urinary tract infections since childhood and now presents with pyelonephritis. Pyelonephritis is an uncommon infection in pregnancy and requires aggressive treatment with antibiotics. It is associated with preterm labour in 4% and may lead to fetal distress.

The answer is not ADPKD (A) as symptoms do not tend to occur before the age of 40.

Bladder outlet obstruction (B) should not occur in pregnancy and would cause hydronephrosis and worsening renal function.

Answer C is incorrect as this should not cause pyelonephritis.

Renal stone disease (E) does predispose to developing urinary tract infections but is less likely than reflux nephropathy.

The correct answer is reflux nephropathy (D). This lady has a long history of urinary tract infections with probable underlying reflux scarring and this would predispose her to developing pyelonephritis in pregnancy.

Next question

Remove Tag | Remove question

Rate this question

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 4 hrs 21 mins 27 secs

Work Smart Session - MRCP Part 1

Question: 54 of 100

A 65-year-old female is referred with a long history of hypertension and episodic urinary tract infections. Dipstick analysis of the urine shows Blood +++ together with protein +++. Her urea is 20 mmol/L (2.5-7.5) and creatinine is 280 µmol/L (60-110).

An ultrasound of abdomen is requested and shows left and right kidneys of 9 cm in size (10-12) without evidence of obstruction.

Which one of the following is the best investigation to diagnose the cause of her renal failure?

(Please select 1 option)

- A. Isotope renography
- B. IV urography
- C. Renal angiography
- D. Renal biopsy
- E. Retrograde pyelography

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Help

Which one of the following is the best investigation to diagnose the cause of her renal failure?

(Please select 1 option)

○	A. Isotope renography
○	B. IV urography
○	C. Renal angiography
◉	D. Renal biopsy ✓ Correct
○	E. Retrograde pyelography

This patient has impaired renal function with hypertension and significant proteinuria and haematuria (? glomerulonephritis). The kidneys are smaller than expected with no evidence of obstruction.

Intravenous urography (B) is not the investigation of choice in a patient with impaired renal function.

Isotope renography (A) would provide information about the relative function of each kidney and would show areas of scarring due to renal stone disease, infection, or vascular disease. It would also exclude congenital malformations of the kidneys. Although useful it would not provide information on the cause of the haematuria and proteinuria.

Renal angiography (C) is the gold standard for assessing renovascular disease. It is an invasive procedure with potential complications. This investigation would not exclude causes of proteinuria and haematuria.

Retrograde pyelography (E) would be useful if there were any evidence of obstruction.

The best investigation is a renal biopsy. This would show any changes of glomerulonephritis along with renal scaring from longstanding hypertension or urinary tract infections.

Next question

Tag Question | Remove question

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 4 hrs 23 mins 41 secs

Work Smart Session - MRCP Part 1

Question: 55 of 100

A 30-year-old woman receives a cadaveric renal transplantation after having had renal failure, with a neuropathic bladder for which she performed intermittent self-catheterisation.

Six months after transplantation she presents with acute pain in the region of the transplanted kidney.

Which one of the following is the most likely reason for the pain?

(Please select 1 option)

- Acute retention of urine
- Allograft rejection
- Pyelonephritis
- Renal calculi
- Renal infarction

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

unlikely occurrence.

Due to the elapsed time between the transplant and this episode, allograft rejection can be discounted. This is because chronic rejection (more than three months post transplant) is a painless process, with difficult to control hypertension, proteinuria and slowly rising serum creatinine.

Accelerated rejection (one to five days post transplant) can present with fever, an acutely tender swollen graft, and rapidly rising serum creatinine.

Acute rejection (five days to three months) is clinically silent in the majority, but can present with a swollen, tender kidney.

Renal infarction can also be discounted. This can be a surgical complication of renal transplantation, but it presents early with a calyceal fistula and urinary leak.

Renal stones could cause acute pain in the region of a transplanted kidney, but would be less likely in this patient than acute retention of urine.

The answer in this case is acute pyelonephritis.

This patient is in the intermediate stage of the post-transplantation immunosuppression, when the patient is most immunocompromised (three to six months post-transplant).

She is at high risk of an acute episode of pyelonephritis in the transplanted kidney, due to the immunosuppression, the neuropathic bladder and self-catheterisation. This would present like an acute rejection episode, with a tender swollen graft, low-grade pyrexia, and deteriorating graft function.

This would be commonly associated with septicaemia in this patient, and requires parenteral antibiotics.

If this lady were to be managed as a transplant rejection, with high dose intravenous steroids, the result could be catastrophic.

- Help

Which one of the following is the most likely reason for the pain?

(Please select 1 option)

○	Acute retention of urine
◉	Allograft rejection ✕ Incorrect answer selected
○	Pyelonephritis ← This is the correct answer
○	Renal calculi
○	Renal infarction

Acute urinary retention would not cause pain overlying a transplanted kidney, and as this lady self-catheterises, it would be an unlikely occurrence.

Due to the elapsed time between the transplant and this episode, allograft rejection can be discounted. This is because chronic rejection (more than three months post transplant) is a painless process, with difficult to control hypertension, proteinuria and slowly rising serum creatinine.

Accelerated rejection (one to five days post transplant) can present with fever, an acutely tender swollen graft, and rapidly rising serum creatinine.

Acute rejection (five days to three months) is clinically silent in the majority, but can present with a swollen, tender kidney.

Renal infarction can also be discounted. This can be a surgical complication of renal transplantation, but it presents early with a calyceal fistula and urinary leak.

Renal stones could cause acute pain in the region of a transplanted kidney, but would be less likely in this patient than acute retention of urine.

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 4 hrs 25 mins 2 secs

Work Smart Session - MRCP Part 1

Question: 56 of 100

A 70-year-old man is admitted to hospital complaining of a twelve day history of loin pain, fevers and occasional rigors. On examination, his temperature is 37.9°C. The renal function is normal.

Urinalysis of a mid stream urine shows:

White cell count	>100/mm^3
Red cell count	>50/mm^3

No organisms seen, with no growth.

Which would be your first investigation of choice?

(Please select 1 option)

- CT abdomen and pelvis
- Intravenous urogram (IVU)
- Prostatic specific antigen (PSA) measurement
- Transthoracic echocardiogram
- Ultrasound scan renal tract

○	Intravenous urogram (IVU)
○	Prostatic specific antigen (PSA) measurement
○	Transthoracic echocardiogram
◉	Ultrasound scan renal tract ✓ Correct

Renal cell carcinomas may present in a variety of ways, with only a minority being diagnosed with the classical triad of:

- haematuria
- loin pain
- a palpable mass.

Relatively common presentations include:

- anaemia
- hypertension
- pyrexia of unknown origin
- fatigue
- increased plasma viscosity.

Less common presentations include:

- hypercalcaemia
- polycythaemia
- liver dysfunction
- enteropathy

- liver dysfunction
- enteropathy
- myopathy.

Urinalysis may show sterile pyuria, as here.

Other causes of sterile pyuria are:

- partially treated urinary tract infections (UTI)
- tuberculosis (TB) of the renal tract
- urethritis and sexually transmitted diseases
- acute glomerulo-nephritis
- tubulo-interstitial diseases
- adult polycystic kidney disease
- renal stones.

Ultrasound scan of the renal tract would be the first investigation of choice, as it is able to pick up 95% of renal cell carcinomas greater than 1 cm in diameter. It would also exclude infective or inflammatory collections within the renal tract.

If required a computerised tomography (CT) +/- guided biopsy could be obtained to prove the diagnosis.

An intravenous urogram (IVU) was considered the investigation of choice before the advent of ultrasound.

A chest x ray and bone scan would be required to complete the basic investigations.

Next question

Tag Question

Remove question

Rate this question

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 4 hrs 26 mins 59 secs

Work Smart Session - MRCP Part 1

Question: 57 of 100

A 42-year-old female with a recent diagnosis of systemic sclerosis, is referred to hospital with a complaint of headaches and blurred vision. She has a past medical history of asthma. On examination, her blood pressure is 230/120 mmHg and there is bilateral papilloedema.

Which of the following medications should be prescribed immediately?

(Please select 1 option)

○	IV furosemide
○	IV labetolol
○	IV sodium nitroprusside
○	Oral enalapril
○	Sublingual nimodipine

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

○	IV furosemide
○	IV labetolol
◉	IV sodium nitroprusside ✕ Incorrect answer selected
○	Oral enalapril ← This is the correct answer
○	Sublingual nimodipine

Systemic sclerosis is a systemic disorder characterised by skin thickening due to the deposition of collagen in the dermis. Adverse prognostic features are renal, cardiac or pulmonary involvement.

A major complication is the development of scleroderma renal crisis. This is characterised by the abrupt onset of severe hypertension, usually with retinopathy, together with rapid deterioration of renal function and heart failure. It develops in 8-15% of patients with diffuse systemic sclerosis especially associated with rapid progression of diffuse skin disease. It usually presents early, within three years of diagnosis. The pathogenic mechanisms leading to renal damage are not known.

The clinical presentation is typically with the symptoms of malignant hypertension

- Headaches
- Blurred vision
- Fits
- Heart failure.

Renal function is impaired and usually rapidly deteriorates. The hypertension is almost always severe with a diastolic BP over 100 mmHg in 90% of patients. There is hypertensive retinopathy in about 85% of patients with exudates and haemorrhages and if severe, papilloedema.

Scleroderma renal crisis is a medical emergency. The hypertension should be treated with an ACE inhibitor. The aim is to reduce the blood pressure gradually as an abrupt fall can lead to cerebral ischaemia or infarctions (as in any accelerated hypertension). Calcium

○	Oral enalapril ← This is the correct answer
○	Sublingual nimodipine

Systemic sclerosis is a systemic disorder characterised by skin thickening due to the deposition of collagen in the dermis. Adverse prognostic features are renal, cardiac or pulmonary involvement.

A major complication is the development of scleroderma renal crisis. This is characterised by the abrupt onset of severe hypertension, usually with retinopathy, together with rapid deterioration of renal function and heart failure. It develops in 8-15% of patients with diffuse systemic sclerosis especially associated with rapid progression of diffuse skin disease. It usually presents early, within three years of diagnosis. The pathogenic mechanisms leading to renal damage are not known.

The clinical presentation is typically with the symptoms of malignant hypertension

- Headaches
- Blurred vision
- Fits
- Heart failure.

Renal function is impaired and usually rapidly deteriorates. The hypertension is almost always severe with a diastolic BP over 100 mmHg in 90% of patients. There is hypertensive retinopathy in about 85% of patients with exudates and haemorrhages and if severe, papilloedema.

Scleroderma renal crisis is a medical emergency. The hypertension should be treated with an ACE inhibitor. The aim is to reduce the blood pressure gradually as an abrupt fall can lead to cerebral ischaemia or infarctions (as in any accelerated hypertension). Calcium channel blockers may be added to ACE inhibitors.

Deterioration in renal function can be rapid, with gross pulmonary oedema; therefore patients with scleroderma renal crisis should be managed in hospitals with facilities for dialysis.

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 4 hrs 28 mins 8 secs

Work Smart Session - MRCP Part 1

Question: 58 of 100

A 50-year-old female presents with acute chest pain and dyspnoea.

Examination reveals bilateral ankle oedema with 24 hour urine protein assessment showing 8g/d (<0.2).

Which is the most likely explanation for these findings?

(Please select 1 option)

○	Factor V Leiden
○	Reduced antithrombin III activity
○	Reduced concentration of von Willebrand's factor
○	Reduced factor VIII
○	Reduced fibrinogen concentration

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 4 hrs 29 mins 43 secs

Work Smart Session - MRCP Part 1

Question: 58 of 100

A 50-year-old female presents with acute chest pain and dyspnoea.

Examination reveals bilateral ankle oedema with 24 hour urine protein assessment showing 8g/d (<0.2).

Which is the most likely explanation for these findings?

(Please select 1 option)

○	Factor V Leiden
◉	Reduced antithrombin III activity ✓ Correct
○	Reduced concentration of von Willebrand's factor
○	Reduced factor VIII
○	Reduced fibrinogen concentration

This patient has developed nephrotic syndrome and appears to have had a thromboembolic event.

The suggestion is that she has had nephritic syndrome before developing the thromboembolism.

Deranged coagulation associated with nephrotic syndrome is a consequence of AT III deficiency, increased fibrinogen and increased factor VIIIc.

Next question | Tag Question | Remove question

Question: 59 of 100

You are called to the Emergency Department to assess a 21-year-old student who has presented with bloody diarrhoea.

The diarrhoea started two weeks previously and was associated with increasing nausea and malaise and mild swelling of the lower limbs. She was having difficulty passing urine. She had eaten steak from the local butcher at a friend's barbeque the day before developing diarrhoea.

On examination she was pale with evidence of petechiae over her legs. Her face appeared puffy. Blood pressure was 160/95 mmHg. She was apyrexial but had a tachycardia and crackles on inspiration at both lung bases. There was an old appendicectomy scar in the right iliac fossa.

Investigations showed:

Haemoglobin	8.5 g/dl	(11.5-16.5)
White cell count	13.2 x 10^9/l	(4-11)
Neutrophils	9.5 x 10^9/l	(1.5-7)
Platelets	35 x 10^9/l	(150-400)
PT	12 s	(11.5-15.5)
APTT	34 s	(30-40)
Fibrinogen	4 g/l	(1.8-5.4)
Serum sodium	139 mmol/l	(137-144)
Serum potassium	6.1 mmol/l	(3.5-4.9)
Serum urea	40 mmol/l	(2.5-7.5)
Serum creatinine	411 µmol/l	(60-110)

Platelets	35 x 10^9/l	(150-400)
PT	12 s	(11.5-15.5)
APTT	34 s	(30-40)
Fibrinogen	4 g/l	(1.8-5.4)
Serum sodium	139 mmol/l	(137-144)
Serum potassium	6.1 mmol/l	(3.5-4.9)
Serum urea	40 mmol/l	(2.5-7.5)
Serum creatinine	411 µmol/l	(60-110)
Serum albumin	27 g/l	(37-49)
Dipstick urine	Blood ++ Protein +	

What is the single most important next investigation to determine the diagnosis?

(Please select 1 option)

- ASO titres
- Renal tract ultrasound
- Stool culture
- Transthoracic echocardiogram
- Urine microscopy

Submit answer | Skip question | Tag Question | Remove question

http://my.onexamination.com/Assessment/Que
Questions Set : REF5318
passmedicine.com
passmedicine.com

○	Renal tract ultrasound
◉	Stool culture ✓ Correct
○	Transthoracic echocardiogram
○	Urine microscopy

This patient has haemolytic uraemic syndrome (HUS).

It typically presents with a triad of

- Acute renal failure (ARF)
- Microangiopathic haemolytic anaemia
- Thrombocytopaenia with normal clotting.

HUS is a complication of infection with verocytotoxin producing *Escherichia coli* usually of the serotype 0157:H7.

Toxins produced in the intestine enter the blood and bind to endothelial cells in target organs. Endothelial cell damage leads to platelet and fibrin deposition with resultant fragmentation of circulating red blood cells and microvascular occlusion.

The syndrome has also been reported after infections with coxsackie, echovirus and *Shigella*.

HUS is characterised by the sudden onset of haemolytic anaemia with fragmentation of red blood cells, thrombocytopaenia and acute renal failure after a prodromal illness of acute gastroenteritis often with bloody diarrhoea.

Clinical signs include increasing pallor, haematuria, oliguria and purpura. Jaundice is occasionally seen. Hypertension may be present.

Typical results show an anaemia, thrombocytopaenia, and often a neutrophilia. Blood film shows fragmented erythrocytes.

Urea and electrolytes are typical of acute renal failure. There is normal coagulation and fibrinogen.

Neurological complications include

- Stroke, seizure and coma occur in 25% of patients
- Rarely pancreatitis
- Pleural and pericardial effusions.

Approximately 5% of patients will develop end stage renal failure.

Long term renal sequelae range from proteinuria to chronic renal failure.

Therapy is supportive with

- correction of anaemia
- correction of uraemia by early dialysis
- strict fluid balance
- treatment of hypertension.

Major differential diagnosis is

1. Sepsis with DIC - presents with abnormalities of clotting parameters.
2. TTP - thrombotic thrombocytopaenic purpura presents with microangiopathic haemolytic anaemia, thrombocytopaenic purpura, neurologic abnormalities, fever, and renal disease.

Renal abnormalities tend to be more severe in HUS.

Although once considered variants of a single syndrome, recent evidence suggests that the pathogenesis of TTP and HUS is different. Patients with TTP lack a plasma protease that is responsible for the breakdown of von Willebrand factor (vWF) multimers and these accumulate in the plasma. The activity of this protease is normal in patients with HUS.

Until the test for vWF protease activity becomes available, differentiation between HUS and TTP is based on the presence of central

- correction of uraemia by early dialysis
- strict fluid balance
- treatment of hypertension.

Major differential diagnosis is

1. Sepsis with DIC - presents with abnormalities of clotting parameters.
2. TTP - thrombotic thrombocytopaenic purpura presents with microangiopathic haemolytic anaemia, thrombocytopaenic purpura, neurologic abnormalities, fever, and renal disease.

Renal abnormalities tend to be more severe in HUS.

Although once considered variants of a single syndrome, recent evidence suggests that the pathogenesis of TTP and HUS is different. Patients with TTP lack a plasma protease that is responsible for the breakdown of von Willebrand factor (vWF) multimers and these accumulate in the plasma. The activity of this protease is normal in patients with HUS.

Until the test for vWF protease activity becomes available, differentiation between HUS and TTP is based on the presence of central nervous system involvement in TTP and the more severe renal involvement in HUS.

In HUS 90% of patients are children and a history of prodromal diarrhoeal illness is more common.

The therapy of choice for TTP is plasma exchange with fresh frozen plasma.

Next question | Tag Question | Remove question

Rate this question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Cr	382 mmol/l	(79-118)
Urine protein	++	
Blood	-	
White cells	-	

Which of the following is the most likely diagnosis?

(Please select 1 option)

○	Acute tubular necrosis
◉	Churg-Strauss syndrome ✕ Incorrect answer selected
○	Interstitial nephritis ← This is the correct answer
○	Membranous nephropathy
○	Pyelonephritis

The rapid onset of renal failure, coupled with a rash and eosinophilia is highly suspicious of a diagnosis of interstitial nephritis as a result of exposure to non-steroidal or amoxicillin.

Whilst eosinophilia is not usually seen in interstitial nephritis as a result of NSAIDs, it is seen in penicillin induced interstitial nephritis.

CT scanning and ultrasound are the main imaging modalities, with IVU being rarely used now. Renal biopsy is definitive in cases where the diagnosis is in doubt.

Resolution of renal failure usually begins after the causative agent is discontinued.

Next question

Remove Tag | Remove question

Rate this question

☆☆☆☆☆

A 16-year-old boy presents with periorbital and peripheral oedema which has developed over the past few weeks. He had a previous episode some two years earlier but this responded over the course of a few weeks to a course of prednisolone.

On examination he has a BP of 141/80 mmHg, with pulse of 68. His chest is clear but he has bilateral pitting oedema.

Investigations show

Haemoglobin	12.9 g/dl	(13.5-8)
White cell count	6.1 x 10^9/l	(4-10)
Platelets	209 x 10^9/l	(150-400)
Sodium	139 mmol/l	(134-143)
Potassium	4.8 mmol/l	(3.5-5)
Creatinine	110 µmol/l	(60-120)
Albumin	24 g/l	(30-50)
Urine	Protein ++	

Which of the following represents the most appropriate management plan for him?

(Please select 1 option)

- Oral combination corticosteroids and cyclophosphamide
- Oral corticosteroids
- Oral cyclophosphamide
- Oral methotrexate
- Renal biopsy

Submit answer | Skip question | Tag Question | Remove question

Question: 60 of 100

A 60-year-old man presents with right foot drop, left foot and left hand numbness, fever, malaise, weight loss, polymyalgia and polyarthralgia of approximately one month duration.

On examination, he appears ill, with a temperature of 38.5°C and blood pressure of 180/100 mmHg.

Investigations reveal:

Haemoglobin	8.0 g/dL (13.0-18.0)
Erythrocyte sedimentation rate	100 mm/hr (0-20)
Serum creatinine	180 µmol/L (60-110)

- Urine analysis: Blood ++
- Urine microscopy: White cells and red cell casts

Which one of the following is the most likely diagnosis?

(Please select 1 option)

○	Antiphospholipid syndrome
○	Giant cell arteritis
○	Paraneoplastic syndrome
○	POEMS syndrome
○	Polyarteritis nodosa

Serum creatinine	180 µmol/L (60-110)

- Urine analysis: Blood ++
- Urine microscopy: White cells and red cell casts

Which one of the following is the most likely diagnosis?

(Please select 1 option)

○	Antiphospholipid syndrome
○	Giant cell arteritis
○	Paraneoplastic syndrome
○	POEMS syndrome
◉	Polyarteritis nodosa ✓ Correct

This patient has a mononeuritis multiplex, fever, hypertension, and nephritic renal involvement suggesting a diagnosis of PAN.

POEMS is a polyneuropathy, organomegaly, endocrinopathy and myeloma of which a few features are absent; and nephritic syndrome is not a feature.

Next question | Tag Question | Remove question

Rate this question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 4 hrs 37 mins 2 secs

Work Smart Session - MRCP Part 1

Question: 61 of 100

A 55-year-old man who has received haemodialysis for many years presents with deteriorating discomfort in both shoulders. Past medical history included bilateral carpal tunnel decompression.

His investigations reveal:

Haemoglobin	10 g/dl	(13.0-18.0)
ESR	30 mm/1st hr	(1-10)
C reactive protein	12 mg/l	(<10)
Urate	0.58 mmol/l	(<0.45)

What is the most likely diagnosis?

(Please select 1 option)

- ß2 microglobulin amyloidosis
- Gout
- Osteoarthritis
- Polymyalgia rheumatica
- Pseudogout

ESR	30 mm/1st hr	(1-10)
C reactive protein	12 mg/l	(<10)
Urate	0.58 mmol/l	(<0.45)

What is the most likely diagnosis?

(Please select 1 option)

- ◉ ß2 microglobulin amyloidosis ✓ Correct
- ○ Gout
- ○ Osteoarthritis
- ○ Polymyalgia rheumatica
- ○ Pseudogout

The features of shoulder pain associated with a past history of carpal tunnel syndrome in a patient receiving haemodialysis suggests a diagnosis of ß2 microglobulin amyloidosis.

Amyloid deposits composed of ß2 microglobulin as the major constituent protein are mainly localised in joints and periarticular bone and lead to destructive arthropathy which tends to develop five to ten years after the initiation of dialysis.

Death from amyloidosis of gut and heart may occur after 20 years of dialysis.

Next question | Tag Question | Remove question

Rate this question

☆☆☆☆☆

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 4 hrs 37 mins 40 secs

Work Smart Session - MRCP Part 1

Question: 62 of 100

A 23-year-old female presents at 16 weeks into her first pregnancy with a blood pressure of 144/96 mmHg. A 24 hour urine collection reveals a protein excretion of 0.7 g/d (<0.2)

What is the most likely explanation for these findings?

(Please select 1 option)

- Essential hypertension
- Gestational hypertension
- Normal changes of pregnancy
- Pre-eclampsia
- Secondary hypertension

Submit answer | Skip question | Tag Question | Remove question

Work Smart Session - MRCP Part 1

Question: 62 of 100

A 23-year-old female presents at 16 weeks into her first pregnancy with a blood pressure of 144/96 mmHg. A 24 hour urine collection reveals a protein excretion of 0.7 g/d (<0.2)

What is the most likely explanation for these findings?

(Please select 1 option)

◉	Essential hypertension ✗ Incorrect answer selected
○	Gestational hypertension
○	Normal changes of pregnancy
○	Pre-eclampsia
○	Secondary hypertension ← This is the correct answer

This pregnant woman has hypertension and proteinuria (as defined by a blood pressure above 140/90 mmHg and proteinuria above 0.3 g/d). It would not be regarded as normal to have this high a blood pressure or protein content of urine.

Pre-eclampsia is a disease occurring in the second half of pregnancy (after 20 weeks gestation), and conventionally, characterised by pregnancy-induced hypertension with proteinuria and often with oedema.

Gestational hypertension is defined as blood pressure elevation detected for the first time after midpregnancy, without proteinuria.

Essential hypertension is unlikely in this female as there is a suggestion of renal disease which makes secondary hypertension the likely option.

Next question

Remove Tag | Remove question

Question: 63 of 100

A 45-year-old lady presents with fatigue and lethargy, and has established end stage renal failure. She has been on haemodialysis for the past three years and receives dialysis for three hours three times a week at a regional haemodialysis centre.

At one of her regular visits for haemodialysis she is found to have the following observations and investigations.

Blood pressure	170/95	
Serum K^+	5.7 mmol/l	(3.5-4.9)
Serum corrected calcium	2.0 mmol/l	(2.2-2.6)
Hb	9.0 g/dl	(11.5-16.5)
Creatinine	1300 mol/l	(60-110)

Post-dialysis her blood pressure is recorded as 160/95 mmHg.

Which of the following is the best option for management of this lady's symptoms?

(Please select 1 option)

- ○ Increase dialysis hours
- ○ Treat anaemia with erythropoietin
- ○ Treat hyperkalaemia
- ○ Treat hypocalcaemia
- ○ Treat hypertension with ramipril

Which of the following is the best option for management of this lady's symptoms?

(Please select 1 option)

○	Increase dialysis hours
◉	Treat anaemia with erythropoietin ✓ Correct
○	Treat hyperkalaemia
○	Treat hypocalcaemia
○	Treat hypertension with ramipril

This person's main complaint is of fatigue. Treating her with erythropoietin would therefore be the most appropriate therapy particularly with her anaemia.

Increasing dialysis is unlikely to be acceptable to most patients and renal units though this is an option some patients would choose, especially those on 'home haemodialysis'.

Vascular disease is an important cause of death in dialysis patients and this lady may very well need additional treatment of blood pressure.

Further reading:
Managing anaemia in renal failure (pdf) The Pharmaceutical Journal 2004 273:603-605

Anaemia management in chronic kidney disease NICE

Revised European Best Practice Guidelines for the Management of Anaemia in Patients with Chronic Renal Failure (May 2004) Nephrology Dialysis Transplantation

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 4 hrs 42 mins 35 secs

Work Smart Session - MRCP Part 1

Question: 64 of 100

A 25-year-old female is admitted with acute dyspnoea and chest pain.

A diagnosis of pulmonary embolism is confirmed and her investigations reveal urine dipstick protein ++ but no blood, anti-double standed DNA antibodies of 200 U/mL (0 - 73), with a 24 hour urinary protein concentration of 5g (< 0.2).

Which one of the following diagnoses is most likely to be found on renal biopsy?

(Please select 1 option)

○	AA amyloid
○	Focal segmental glomerulonephritis
○	IgA nephropathy
○	Membranous nephropathy
○	Minimal change nephropathy

Submit answer | Skip question | Tag Question | Remove question

Question: 64 of 100

A 25-year-old female is admitted with acute dyspnoea and chest pain.

A diagnosis of pulmonary embolism is confirmed and her investigations reveal urine dipstick protein ++ but no blood, anti-double standed DNA antibodies of 200 U/mL (0 - 73), with a 24 hour urinary protein concentration of 5g (< 0.2).

Which one of the following diagnoses is most likely to be found on renal biopsy?

(Please select 1 option)

○	AA amyloid
○	Focal segmental glomerulonephritis
○	IgA nephropathy
◉	Membranous nephropathy ✓ Correct
○	Minimal change nephropathy

This young woman has thromboembolic disease, the nephrotic syndrome with positive anti-ds DNA antibodies suggests a diagnosis of systemic lupus erythematosus.

Nephrotic syndrome in the absence of hypertension, active urinary sediment, or significant hypocomplementaemia suggests membranous nephropathy.

The thromboembolic disease may arise due to nephrotic syndrome per se or from an associated antiphospholipid syndrome.

Next question | Tag Question | Remove question

Rate this question

Time taken: 4 hrs 45 mins 52 secs

Work Smart Session - MRCP Part 1

Question: 65 of 100

A 68-year-old male is referred by his general practitioner with deteriorating hypertension and renal function.

Investigations show:

Serum creatinine	250 mol/L (60-110)
Urinalysis	+ protein

Renal ultrasound scan:

- left kidney 9 cm long
- right kidney 7 cm, no obstruction (10-12 cm)

Which of the following would be the most appropriate investigation for this patient?

(Please select 1 option)

○	Intravenous renography
○	Isotope renography
○	MR angiography
○	Renal biopsy
○	Retrograde pyelography

Renal ultrasound scan:

- left kidney 9 cm long
- right kidney 7 cm, no obstruction (10-12 cm)

Which of the following would be the most appropriate investigation for this patient?

(Please select 1 option)

○	Intravenous renography
○	Isotope renography
◉	MR angiography ✓ Correct
○	Renal biopsy
○	Retrograde pyelography

The diagnosis is likely to be atherosclerotic renal artery stenosis (RAS) as suggested by the asymmetric reduction in renal size, with mild proteinuria quite common in the condition.

Investigations include captopril renography, magnetic resonance (MR) angiography which is virtually as good as renal arteriography.

None of the other investigations are appropriate for RAS.

Next question

Tag Question Remove question

Rate this question

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 4 hrs 46 mins 53 secs

Work Smart Session - MRCP Part 1

Question: 66 of 100

A 72-year-old male presented to his GP with depression after the death of his wife.

His notes also reveal that he has a two year history of urinary hesitancy and poor stream. His GP prescribed him some medication and the following day he developed acute urinary retention.

Which of the following drugs is most likely to have precipitated the urinary retention?

(Please select 1 option)

- Amitriptyline
- Diazepam
- Fluoxetine
- Venlafaxine
- Zopiclone

Submit answer | Skip question | Tag Question | Remove question

and the following day he developed acute urinary retention.

Which of the following drugs is most likely to have precipitated the urinary retention?

(Please select 1 option)

◉	Amitriptyline ✓ Correct
○	Diazepam
○	Fluoxetine
○	Venlafaxine
○	Zopiclone

Amitriptyline has anticholinergic effects, being associated with tachycardia, dry mouth and urinary retention.

These features are not typical of selective serotonin reuptake inhibitors (SSRIs) such as venlafaxine and fluoxetine, with urinary retention and dry mouth rarely reported.

Diazepam, a benzodiazepine does not have anticholinergic effects.

Zopiclone is a benzodiazepine-like agent whose side effects include drowsiness.

Next question | Tag Question | Remove question

Rate this question

☆☆☆☆☆

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 4 hrs 48 mins 9 secs

Work Smart Session - MRCP Part 1

Question: 67 of 100

Which of the following is a known risk factor for the development of chronic rejection of kidney transplantation?

(Please select 1 option)

○	Age
○	Anti-smooth muscle antibodies
○	Presence of anti-HLA antibodies
○	Smoking
○	Toxoplasma infection

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

○	Presence of anti-HLA antibodies ← This is the correct answer
◉	Smoking ✕ Incorrect answer selected
○	Toxoplasma infection

Chronic rejection is characterised by fibrosis of normal organ structures.

The pathogenesis of chronic rejection is not clear - some prefer the term "chronic allograft dysfunction" since both immunological (antigen-dependent and antigen-independent) and non-immunological factors have been identified.

Cell-mediated and humoral immune mechanisms have been implicated in this form of graft rejection.

It has also been suggested that rejection is a response to chronic ischaemia caused by injury to endothelial cells.

Proliferation of intimal smooth muscle is observed leading to vascular occlusion.

The fact that chronic rejection is rare in transplants between human leukocyte antigen (HLA)-identical siblings suggests that HLA-antigen dependent immunological factors are important.

Risk factors include:

- Number of previous acute rejection episodes
- Presence of anti-HLA antibodies
- Anti-endothelial antibodies
- Cytomegalovirus (CMV) infection
- Dyslipidaemia
- Hypertension
- Functional mass of the donor kidney and
- Delayed graft function (a clinical manifestation of ischaemia/reperfusion injury).

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 4 hrs 51 mins 9 secs

Work Smart Session - MRCP Part 1

Question: 68 of 100

Which one of the following cytokines is strongly implicated in renal scarring?

(Please select 1 option)

○	Interferon alpha
○	Interleukin-1
○	Granulocyte colony stimulating factor
○	Transforming growth factor-beta
○	Tumour necrosis factor alpha

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Time taken: 4 hrs 51 mins 43 secs

Work Smart Session - MRCP Part 1

Question: 68 of 100

Which one of the following cytokines is strongly implicated in renal scarring?

(Please select 1 option)

○	Interferon alpha
○	Interleukin-1
○	Granulocyte colony stimulating factor
○	Transforming growth factor-beta ← This is the correct answer
◉	Tumour necrosis factor alpha ✕ Incorrect answer selected

TGF-beta is a potent recruiter for fibroblasts which are implicated in renal scarring.

IFN-alpha is implicated more in lymphocyte response and IL-1/TNF-alpha in the acute phase response.

G-CSF is a stimulant of granulocyte cell line maturation.

Next question

Remove Tag Remove question

Rate this question

☆☆☆☆☆

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Time taken: 4 hrs 51 mins 43 secs

Work Smart Session - MRCP Part 1

Question: 69 of 100

A 45-year-old man on regular haemodialysis complained of weakness and exertional fatigue. On examination, his blood pressure was 170/105 mmHg (pre-dialysis) and 160/95 mmHg (post-dialysis).

Investigations pre-dialysis revealed:

Haemoglobin	9.0 g/dl	(13.0-18.0)
Serum potassium	6.9 mmol/l	(3.5-4.9)
Serum creatinine	1250 µmol/l	(60-110)
Serum corrected calcium	2.1 mmol/l	(2.2-2.6)

Which intervention is most likely to improve his symptoms?

(Please select 1 option)

- ○ Correct hypocalcaemia with alfacalcidol
- ○ Improve blood pressure control with ramipril
- ○ Increase haemoglobin with epoetin
- ○ Increase the length of each dialysis session
- ○ Lower the potassium in the dialysate

Submit answer | Skip question | Tag Question | Remove question

Serum corrected calcium	2.1 mmol/l	(2.2-2.6)

Which intervention is most likely to improve his symptoms?

(Please select 1 option)

○	Correct hypocalcaemia with alfacalcidol
○	Improve blood pressure control with ramipril
◉	Increase haemoglobin with epoetin ✓ Correct
○	Increase the length of each dialysis session
○	Lower the potassium in the dialysate

This is a tough question with many possible answers. But and importantly, this question asks: how to improve his symptoms? Changing the question around, such as how to improve blood pressure or how to improve prognosis alters the answer.

There are several deficiencies in the management of this patient with end stage renal failure. The symptoms described are more in keeping with his anaemia.

A mild hypocalcaemia and hyperkalaemia would not give rise to his symptoms. This also applies to his uncontrolled hypertension. His pre-dialysis creatinine implies he is under-dialysed but would not give rise to exertional fatigue.

Bearing in mind all the above the question specifically asks what intervention would improve his symptoms. In which case one would have to elect EPO irrespective of blood pressure, calcium, etc.

Next question

Tag Question | Remove question

Rate this question

White cell count	6.1 x 10^9/l	(4-10)
Platelets	209 x 10^9/l	(150-400)
Sodium	139 mmol/l	(134-143)
Potassium	4.8 mmol/l	(3.5-5)
Creatinine	110 µmol/l	(60-120)
Albumin	24 g/l	(30-50)
Urine	Protein ++	

Which of the following represents the most appropriate management plan for him?

(Please select 1 option)

- ○ Oral combination corticosteroids and cyclophosphamide
- ◉ Oral corticosteroids ✓ Correct
- ○ Oral cyclophosphamide
- ○ Oral methotrexate
- ○ Renal biopsy

The age of this patient and his previous response to corticosteroids is suggestive of an underlying diagnosis of minimal change nephropathy. As such, a further course of corticosteroids is the treatment of choice.

Given the inherent but low risks associated with renal biopsy, it is usually only attempted when three or more episodes of oedema have occurred.

Very few patients with minimal change disease actually progress to end stage renal disease, and only around 10% of children with the disease suffer from hypertension.

Next question

Tag Question | Remove question

Rate this question

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 1 hrs 26 mins 55 secs

Work Smart Session - MRCP Part 1

Question: 7 of 100

A 57-year-old woman who has been receiving haemodialysis for the past five years is found dead in bed by her husband. She had a long history of type 1 diabetes for over 20 years and in her later years suffered from neuropathy and retinopathy as well as chronic renal failure. Most recently she was under investigation for angina.

Which of the following is the most likely cause of death in this patient?

(Please select 1 option)

- Hyperkalaemia
- Hypoglycaemia
- Myocardial infarction
- Pulmonary embolus
- Stroke

Submit answer | Skip question | Tag Question | Remove question

Question: 70 of 100

A 45-year-old man had recurrent nephrolithiasis.

Renal function tests and serum calcium measurements were normal.

A 24 hour urine collection revealed:

Volume	3L
Calcium	15 mmol/24 hours (2.5-7.5)
Oxalate	200 mmol/24 hours (90-450)
Uric acid	3 mmol/24 hours (1.48-4.45)
Citrate	2mmol/24hours (0.3-3.4)

What is the most useful therapy to reduce stone formation?

(Please select 1 option)

- ○ Allopurinol
- ○ Dietary calcium restriction
- ○ Penicillamine
- ○ Potassium citrate
- ○ Thiazide diuretic

Uric acid	3 mmol/24 hours (1.48-4.43)
Citrate	2mmol/24hours (0.3-3.4)

What is the most useful therapy to reduce stone formation?

(Please select 1 option)

○	Allopurinol
○	Dietary calcium restriction
○	Penicillamine
○	Potassium citrate
◉	Thiazide diuretic ✓ Correct

This patient has hypercalciuria and thiazide diuretics can decrease urinary excretion of calcium and possibly oxalate.

Dietary calcium restriction will not limit calciuria, given the large amount of calcium that can be mobilised from bone.

The lack of hyperuricosuria and hypocitratraturia excludes the other treatments offered.

Next question

Tag Question | Remove question

Rate this question

☆☆☆☆☆

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 4 hrs 54 mins 30 secs

Work Smart Session - MRCP Part 1

Question: 71 of 100

A 30-year-old woman presented with hypertension (160/110 mmHg), elevated titres of antibodies to double-stranded DNA, and proteinuria (1g per 24 hours).

A renal biopsy demonstrated WHO class II lupus nephritis (mesangial disease).

What is the most appropriate single treatment for this patient?

(Please select 1 option)

- Antihypertensive medication
- High-dose corticosteroids
- Intravenous cyclophosphamide
- Oral cyclophosphamide
- Plasma exchange

Submit answer | Skip question | Tag Question | Remove question

- Shop
- Help

A renal biopsy demonstrated WHO class II lupus nephritis (mesangial disease).

What is the most appropriate single treatment for this patient?

(Please select 1 option)

○	Antihypertensive medication ← This is the correct answer
◉	High-dose corticosteroids ✕ Incorrect answer selected
○	Intravenous cyclophosphamide
○	Oral cyclophosphamide
○	Plasma exchange

There is good evidence that immunosuppression could alter outcome in the presence of proliferative glomerulonephritis but not in mesangial or membranous glomerulonephritis.

Therefore the best line of treatment would be a conservative approach to address risk factors for progression of renal impairment such as uncontrolled hypertension.

There is no good evidence to support plasma exchange as an effective treatment modality in lupus nephritis.

Next question

Remove Tag | Remove question

Rate this question

☆☆☆☆☆

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 4 hrs 55 mins 55 secs

Work Smart Session - MRCP Part 1

Question: 72 of 100

A 60-year-old man wishes to act as a kidney donor to his 37-year-old wife.

She has end stage renal failure from polycystic kidney disease and is maintained on peritoneal dialysis.

The couple have two teenage daughters, neither of whom have renal cysts on recent ultrasound scans.

Which one of the following statements is correct?

(Please select 1 option)

○	Living related donation from one of the daughters would be preferable to donation from the husband
○	Living unrelated donation is not recommended in cases of inherited renal disease
○	The age difference between husband and wife is a relative contraindication to transplantation
○	The husband should not be accepted for kidney donation until all siblings have been considered
○	The results of living unrelated kidney donation are sufficiently poor that organ donation should not proceed

Submit answer | Skip question | Tag Question | Remove question

- Help

The couple have two teenage daughters, neither of whom have renal cysts on recent ultrasound scans.

Which one of the following statements is correct?

(Please select 1 option)

○	Living related donation from one of the daughters would be preferable to donation from the husband
○	Living unrelated donation is not recommended in cases of inherited renal disease
◉	The age difference between husband and wife is a relative contraindication to transplantation ✕ Incorrect answer selected
○	The husband should not be accepted for kidney donation until all siblings have been considered ← This is the correct answer
○	The results of living unrelated kidney donation are sufficiently poor that organ donation should not proceed

Providing there is a sibling who is proven not to have polycystic kidney disease, living related donation should be considered as this would ensure a better match and better graft survival.

As teenagers polycystic kidney disease may not be manifest ultrasonographically in her daughters.

Living unrelated kidney donation does not produce bad results. In patients with polycystic kidney disease, or for other inherited diseases, a graft from an unrelated donor would not necessarily succumb to the same disease process.

Where there is a shortage of donors the age difference certainly would not be considered a relative contraindication to kidney donation.

Next question

Remove Tag Remove question

Rate this question

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 4 hrs 58 mins 2 secs

Work Smart Session - MRCP Part 1

Question: 73 of 100

A 25-year-old man developed bilateral loin pain and frank haematuria.

His symptoms had started 24 hours after developing a sore throat. His blood pressure was 138/88 mmHg. Urinalysis was positive for blood (4+) and protein (2+).

What is the most likely diagnosis?

(Please select 1 option)

○	IgA nephropathy
○	Microscopic polyangiitis
○	Nephrolithiasis
○	Post-streptococcal glomerulonephritis
○	Septicaemia

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

A 25-year-old man developed bilateral loin pain and frank haematuria.

His symptoms had started 24 hours after developing a sore throat. His blood pressure was 138/88 mmHg. Urinalysis was positive for blood (4+) and protein (2+).

What is the most likely diagnosis?

(Please select 1 option)

◉	IgA nephropathy ✓ Correct
○	Microscopic polyangiitis
○	Nephrolithiasis
○	Post-streptococcal glomerulonephritis
○	Septicaemia

The acute onset of the disease is suggestive of IgA nephropathy which characteristically occurs in young males in their 20s and 30s.

Haematuria occurs within 12-24 hours of pharyngitis, accompanied also by loin pain, muscle pain and fever. Prognosis is usually good especially in children. In adults, between 25-50% may develop end-stage renal failure. No specific treatment available.

Classically, the patient has streptococcal infection one to three weeks before the onset of acute nephritic syndrome (post-strep GN).

There is a long prodromal systemic illness lasting months or years in microscopic polyangiitis which differs from Wegener's granulomatosis in its absence of respiratory tract granulomatous inflammation.

Time taken: 4 hrs 58 mins 54 secs

Work Smart Session - MRCP Part 1

Question: 74 of 100

A 49-year-old woman has been an in-patient for the past 10 days for treatment of a bronchopneumonia. She has developed the onset of chills, fever, and skin rash over the past two days.

A peripheral blood film reveals eosinophilia. On urinalysis she has ++ proteinuria. There is no past history of renal disease. Her haemoglobin A_{1c} is normal.

These findings would most strongly suggest which of the following diagnoses?

(Please select 1 option)

○	Acute serum sickness
○	Acute tubular necrosis
○	Drug-induced interstitial nephritis
○	IgA nephropathy
◉	Post-streptococcal glomerulonephritis (GN)

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

onset of chills, fever, and skin rash over the past two days.

A peripheral blood film reveals eosinophilia. On urinalysis she has ++ proteinuria. There is no past history of renal disease. Her haemoglobin A_{1c} is normal.

These findings would most strongly suggest which of the following diagnoses?

(Please select 1 option)

○	Acute serum sickness
○	Acute tubular necrosis
○	Drug-induced interstitial nephritis ← This is the correct answer
○	IgA nephropathy
◉	Post-streptococcal glomerulonephritis (GN) ✕ Incorrect answer selected

The findings are typical of a drug-induced acute interstitial nephritis.

Post-streptoccocal GN appears weeks after the acute infection.

Berger's disease (IgA nephropathy) is characterised by haematuria and often follows a 'flu-like' illness.

Eosinophilia is not typical for serum sickness.

Next question

Remove Tag Remove question

Rate this question

☆☆☆☆☆

Question: 75 of 100

A 60-year-old man was diagnosed last year with adenocarcinoma of the lung and a 4 cm mass lesion was treated with a right lower lobectomy.

He now has an abdominal CT scan that reveals scattered hepatic mass lesions and hilar lymphadenopathy. For several weeks, he has had increasing malaise.

His results show

Urinalysis	Protein +++
24 hour urine protein	2.7 g/24hr
Serum urea	30 mmol/L (2.5-7.5)
Serum creatinine	450 µmol/L (60-110)

A renal biopsy shows focal deposition of IgG and C3 with a granular pattern.

What is the most likely diagnosis?

(Please select 1 option)

- ○ Goodpasture's syndrome
- ○ Membranous glomerulonephritis
- ○ Minimal change glomerulonephritis
- ○ Nodular glomerulosclerosis
- ○ Rapidly progressive glomerulonephritis

had increasing malaise.

His results show

Urinalysis	Protein +++
24 hour urine protein	2.7 g/24hr
Serum urea	30 mmol/L (2.5-7.5)
Serum creatinine	450 µmol/L (60-110)

A renal biopsy shows focal deposition of IgG and C3 with a granular pattern.

What is the most likely diagnosis?

(Please select 1 option)

○	Goodpasture's syndrome
○	Membranous glomerulonephritis ← This is the correct answer
○	Minimal change glomerulonephritis
○	Nodular glomerulosclerosis
◉	Rapidly progressive glomerulonephritis ✕ Incorrect answer selected

Most cases of membranous GN are idiopathic, but in some patients there is a history of an infection or a malignancy (usually lung) with antigenemia.

Next question

Remove Tag Remove question

Rate this question

Question: 76 of 100

A 15-year-old girl was seen by her family physician because of increasing lethargy. She had a recent history of the "flu".

Biochemistry tests show that she has renal impairement.

Serum sodium	140 mmol/L (137-144)
Serum potassium	4.2 mmol/L (3.5-4.9)
Serum urea	28 mmol/L (2.5-7.5)
Serum creatinine	280 µmol/L (60-110)

Her condition does not improve after several weeks on corticosteroid therapy, so a renal biopsy is performed. The biopsy demonstrates the presence of segmental sclerosis of 3 of 10 glomeruli identified in the biopsy specimen.

Immunofluorescence studies and electron microscopy do not reveal evidence for immune deposits.

What is the most appropriate advice to give regarding her condition?

(Please select 1 option)

- She has an underlying malignancy
- She may require a renal transplant in 10 years
- She will improve if she loses weight
- She will likely develop a restrictive lung disease
- She will probably improve with additional corticosteroid therapy

Serum potassium	4.2 mmol/L (3.5-4.9)
Serum urea	28 mmol/L (2.5-7.5)
Serum creatinine	280 µmol/L (60-110)

Her condition does not improve after several weeks on corticosteroid therapy, so a renal biopsy is performed. The biopsy demonstrates the presence of segmental sclerosis of 3 of 10 glomeruli identified in the biopsy specimen.

Immunofluorescence studies and electron microscopy do not reveal evidence for immune deposits.

What is the most appropriate advice to give regarding her condition?

(Please select 1 option)

○	She has an underlying malignancy
◉	She may require a renal transplant in 10 years ✓ Correct
○	She will improve if she loses weight
○	She will likely develop a restrictive lung disease
○	She will probably improve with additional corticosteroid therapy

The findings point to focal segmental glomerulosclerosis (FSGS) which leads to chronic renal failure in half of cases.

The lack of resolution with corticosteroid therapy and the progression to chronic renal failure is what sets FSGS apart from minimal change disease.

Next question

Tag Question | Remove question

Rate this question

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 5 hrs 6 mins 17 secs

Work Smart Session - MRCP Part 1

Question: 77 of 100

A 66-year-old man has developed chronic renal failure with a serum urea of 60 mmol/l (2.5-7.5) and creatinine of 650 mol/l (60-110).

Auscultation of the chest reveals a friction rub over the cardiac apex.

Which of the following types of pericarditis is he likely to have?

(Please select 1 option)

- Constrictive
- Fibrinous
- Haemorrhagic
- Purulent
- Serous

Submit answer | Skip question | Tag Question | Remove question

Time taken: 5 hrs 6 mins 57 secs

Work Smart Session - MRCP Part 1

Question: 77 of 100

A 66-year-old man has developed chronic renal failure with a serum urea of 60 mmol/l (2.5-7.5) and creatinine of 650 mol/l (60-110).

Auscultation of the chest reveals a friction rub over the cardiac apex.

Which of the following types of pericarditis is he likely to have?

(Please select 1 option)

○	Constrictive
◉	Fibrinous ✓ Correct
○	Haemorrhagic
○	Purulent
○	Serous

The uraemia leads to exudation of fibrin onto the epicardial and pericardial surfaces.

Haemorrhagic pericarditis is more typical of tuberculosis or metastatic tumour.

Serous pericarditis is more typical of collagen vascular diseases.

Next question

Tag Question | Remove question

Rate this question

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 5 hrs 6 mins 57 secs

Work Smart Session - MRCP Part 1

Question: 78 of 100

Which one of the following statements regarding renal function is correct?

(Please select 1 option)

○	A ten minute period of hyperventilation will normally be expected to lead to an increased rate of bicarbonate excretion in urine
○	Sodium reabsorption in the tubules is mainly controlled by aldosterone
○	The daily solute excretion will lie between 75 and 300 mosmol
○	The permeability of the proximal nephron to water increases in the presence of vasopressin
○	The rate of ammonium excretion in urine is inversely related to the rate of urinary hydrogen ion excretion

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Shop
- Help

(Please select 1 option)

○	A ten minute period of hyperventilation will normally be expected to lead to an increased rate of bicarbonate excretion in urine ← This is the correct answer
○	Sodium reabsorption in the tubules is mainly controlled by aldosterone
◉	The daily solute excretion will lie between 75 and 300 mosmol ✕ Incorrect answer selected
○	The permeability of the proximal nephron to water increases in the presence of vasopressin
○	The rate of ammonium excretion in urine is inversely related to the rate of urinary hydrogen ion excretion

Arginine vasopressin (AVP) acts on the collecting ducts increasing permeability to water.

The total solute excretion is approximately 700 mosmol/d.

Sodium reabsorption is mostly through active transport in the loop of Henle with only a modest reabsorption facilitated by aldosterone.

A ten minute period of hyperventilation would cause a respiratory alkalosis leading to an increased secretion of bicarbonate and retention of hydrogen ions.

The rate of ammonium excretion is proportional to the rate of hydrogen ion excretion.

Next question

Remove Tag Remove question

Rate this question

☆☆☆☆☆

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 5 hrs 9 mins

Work Smart Session - MRCP Part 1

Question: 79 of 100

Which one of the following statements is correct?

(Please select 1 option)

○	Adult polycystic renal disease is inherited as an autosomal recessive trait
○	Alport's syndrome affects females more severely than males
○	Medullary sponge kidney is typically not inherited but is a congenital condition.
○	Nephrogenic diabetes insipidus (DI) is inherited as an autosomal dominant trait
○	Reflux nephropathy is inherited as an autosomal recessive trait

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Time taken: 5 hrs 10 mins 18 secs

Work Smart Session - MRCP Part 1

Question: 79 of 100

Which one of the following statements is correct?

(Please select 1 option)

○	Adult polycystic renal disease is inherited as an autosomal recessive trait
○	Alport's syndrome affects females more severely than males
◉	Medullary sponge kidney is typically not inherited but is a congenital condition. ✓ Correct
○	Nephrogenic diabetes insipidus (DI) is inherited as an autosomal dominant trait
○	Reflux nephropathy is inherited as an autosomal recessive trait

Polycystic kidney disease (PKD) is usually autosomal dominant although the infantile form is autosomal recessive.

Nephrogenic DI is usually X-linked.

Features of Alport's syndrome (hereditary nephritis, haematuria, progressive renal failure and high-frequency nerve deafness) are usually more marked in in males.

Neither reflux nephropathy nor medullary sponge kidneys are hereditary conditions.

Next question

Tag Question | Remove question

Rate this question

☆☆☆☆☆

A 57-year-old woman who has been receiving haemodialysis for the past five years is found dead in bed by her husband. She had a long history of type 1 diabetes for over 20 years and in her later years suffered from neuropathy and retinopathy as well as chronic renal failure. Most recently she was under investigation for angina.

Which of the following is the most likely cause of death in this patient?

(Please select 1 option)

○	Hyperkalaemia
○	Hypoglycaemia
◉	Myocardial infarction ✓ Correct
○	Pulmonary embolus
○	Stroke

Patients who undergo long term haemodialysis suffer from increasing arterial calcification, which is associated with both increased risk of myocardial infarction and stroke, but the greatest absolute increase is in MI rates.

Interestingly, trials of high dose statins have proved disappointing in the dialysis population, suggesting that calcification drives much of the increased risk.

Whilst both hypoglycaemia and hyperkalaemia are alternative possibilities as causes of death, myocardial infarction is more likely than both to have been responsible.

A 34-year-old man presents with worsening shortness of breath, wheeze, lethargy and nausea. He has a history of asthma which has been managed by one of your partners with salbutamol and a twice daily combination of a long acting beta-2 agonist and an inhaled steroid inhaler.

On examination his BP is 150/92 mmHg, his pulse is 80 and regular. He has extensive wheeze throughout both lung fields.

Investigations show

Haemoglobin	11.8 g/dl	(13.5-18)
White cell count	10.1 x 10^9/l (Eosinophils 30%)	(4-10)
Platelets	190 x 10^9/l	(150-400)
Sodium	140 mmol/l	(134-143)
Potassium	4.9 mmol/l	(3.5-5)
Creatinine	189 µmol/l	(60-120)
ESR	62	(<10)
Urine	Blood++ Protein ++	

Which of the following is the most likely diagnosis?

(Please select 1 option)

- Alport's syndrome
- Churg-Strauss syndrome
- IgA nephropathy
- Post-streptococcal glomerulonephritis
- Wegener's granulomatosis

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 5 hrs 10 mins 18 secs

Work Smart Session - MRCP Part 1

Question: 80 of 100

Which of the following statements regarding idiopathic membranous nephropathy is correct?

(Please select 1 option)

○	Immune complex deposits are typically seen in the glomerular mesangium.
○	It characteristically presents in the first decade of life.
○	Males are twice as commonly affected as females.
○	Progression to end-stage renal failure is rapid.
○	The nephritic syndrome is a characteristic presentation.

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Work Smart Session - MRCP Part 1

Question: 80 of 100

Which of the following statements regarding idiopathic membranous nephropathy is correct?

(Please select 1 option)

○	Immune complex deposits are typically seen in the glomerular mesangium.
○	It characteristically presents in the first decade of life.
◉	Males are twice as commonly affected as females. ✓ Correct
○	Progression to end-stage renal failure is rapid.
○	The nephritic syndrome is a characteristic presentation.

Membranous nephropathy is characterised by thickened basement membranes and monotonous granular deposits of IgG and C3 distributed in the epimembranous space of virtually all glomerular capillaries.

The mesangium may be involved at a later stage of the disease and is more typical of secondary disease.

It is typically seen in the over 40 age group with a male predominance of 2 to 1 and is associated with a variable prognosis with 25% developing endstage renal failure (ESRF) over 10 years and 25% going into remission. There is a higher rate of remission for the idiopathic form.

The majority of patients manifest with a pure nephrotic syndrome.

A nephritic presentation is rare.

Next question | Tag Question | Remove question

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 5 hrs 11 mins 41 secs

Work Smart Session - MRCP Part 1

Question: 81 of 100

Which of the following is a feature of cystinuria?

(Please select 1 option)

- Accumulation of cystine in the kidney
- A useful response to acidification of urine
- Autosomal dominant inheritance
- Excessive urinary arginine excretion
- Radiolucent urinary calculi

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Which of the following is a feature of cystinuria?

(Please select 1 option)

◉	Accumulation of cystine in the kidney ✗ Incorrect answer selected
○	A useful response to acidification of urine
○	Autosomal dominant inheritance
○	Excessive urinary arginine excretion ← This is the correct answer
○	Radiolucent urinary calculi

Cystinuria is the commonest inborn error of amino acid transport.

Amino acids excreted in urine are cystine, ornithine, arginine and lysine (mnemonic - COAL).

The renal stones are radio-opaque due to the presence of sulphur.

It is inherited as an autosomal recessive condition.

Management includes alkalinisation along with high fluid intake (>4 L/day); d-penicillamine may also be used.

It is cystinosis that leads to accumulation of cystine in the kidney.

Next question

Remove Tag Remove question

Rate this question

☆☆☆☆☆

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 5 hrs 12 mins 32 secs

Work Smart Session - MRCP Part 1

Question: 82 of 100

In chronic untreated renal failure which of the following findings is characteristic?

(Please select 1 option)

○	Hypercalcaemia
○	Hypercalcinuria
○	Hyperosmolar dehydration
○	Hypokalaemia
○	Metabolic alkalosis

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

○	Hypercalcaemia
○	Hypercalcinuria ← This is the correct answer
○	Hyperosmolar dehydration
○	Hypokalaemia
◉	Metabolic alkalosis ✕ Incorrect answer selected

Major pathophysiological abnormalities of chronic renal failure:

- Accumulation of nitrogenous waste products
- Acidosis: bicarbonate wasting, decreased ammonia secretion, decreased acid excretion
- Sodium wasting: solute diuresis, tubular damage
- Sodium retention: nephrotic syndrome, CCF, anuria, excess sodium intake
- Urinary concentrating defect: nephron loss, solute diuresis
- Hyperkalaemia: decreased glomerular filtration rate (GFR), acidosis, hyperaldosteronism
- Renal osteodystrophy: decreased intestinal calcium absorption, impaired 12-dihydroxy vitamin D production, secondary hyperparathyroidism
- Growth retardation: protein calorie deficiency, renal osteodystrophy, acidosis, anaemia
- Anaemia: decreased erythropoeitin production, low grade haemolysis, inadequate intake
- Bleeding tendency: thrombocytopenia, decreased platelet function
- Infection: defective granulocyte function
- Neurology: uraemia, aluminium toxicity results in fatigue, poor concentration, headache, memory loss, slurred speech, muscle weakness and cramps, seizures and coma
- GI ulceration: gastric acid hypersecretion

Major pathophysiological abnormalities of chronic renal failure:

- Accumulation of nitrogenous waste products
- Acidosis: bicarbonate wasting, decreased ammonia secretion, decreased acid excretion
- Sodium wasting: solute diuresis, tubular damage
- Sodium retention: nephrotic syndrome, CCF, anuria, excess sodium intake
- Urinary concentrating defect: nephron loss, solute diuresis
- Hyperkalaemia: decreased glomerular filtration rate (GFR), acidosis, hyperaldosteronism
- Renal osteodystrophy: decreased intestinal calcium absorption, impaired 12-dihydroxy vitamin D production, secondary hyperparathyroidism
- Growth retardation: protein calorie deficiency, renal osteodystrophy, acidosis, anaemia
- Anaemia: decreased erythropoeitin production, low grade haemolysis, inadequate intake
- Bleeding tendency: thrombocytopenia, decreased platelet function
- Infection: defective granulocyte function
- Neurology: uraemia, aluminium toxicity results in fatigue, poor concentration, headache, memory loss, slurred speech, muscle weakness and cramps, seizures and coma
- GI ulceration: gastric acid hypersecretion
- Hypertension: sodium and water overload, hyperammonaemia
- Hypertriglyceridaemia: decreased plasma lipoprotein lipase activity
- Pericarditis and cardiomyopathy: cause unknown
- Glucose intolerance: tissue insulin resistance.

Copyright © 2002 Dr Colin Melville

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 5 hrs 14 mins 7 secs

Work Smart Session - MRCP Part 1

Question: 83 of 100

Which of the following is characteristic of Bartter's syndrome?

(Please select 1 option)

○	Diarrhoea
○	Hyperkalaemia
○	Metabolic acidosis
○	Secondary hyperaldosteronism
○	Reduced renal concentrating ability

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

(Please select 1 option)

○	Diarrhoea
○	Hyperkalaemia
○	Metabolic acidosis
◉	Secondary hyperaldosteronism ✓ Correct
○	Reduced renal concentrating ability

Bartter's syndrome is a rare form of renal potassium wasting characterised by hypokalaemia, normotension, and elevated renin and aldosterone levels.

It is occasionally autosomal recessive.

There is hyperplasia of the juxtaglomerular apparatus in most cases.

It is postulated that the primary defect is in chloride reabsorption in the ascending limb, resulting in sodium chloride excessively presented to the distal tubule, with sodium reabsorption in exchange for potassium, resulting in urinary sodium wasting.

There is secondary stimulation of prostaglandin synthesis, which activates the renin angiotensin aldosterone system which exacerbates the renal potassium wasting.

Younger children typically present with

- growth failure
- muscle weakness
- constipation
- polyuria
- dehydration

There is secondary stimulation of prostaglandin synthesis, which activates the renin angiotensin aldosterone system which exacerbates the renal potassium wasting.

Younger children typically present with

- growth failure
- muscle weakness
- constipation
- polyuria
- dehydration.

Older children typically present with

The potassium is <2.5 mmol/l, there is metabolic alkalosis, and hyperammonaemia with hyperaldosteronism.

There are high levels of urinary potassium and chloride.

The high urinary chloride level is helpful in distinguishing it from similar presentations which have low urinary chloride levels, such as

- liquorice, laxative, or diuretic use
- persistent vomiting or diarrhoea
- pyelonephritis
- diabetes insipidus.

Oral potassium and indomethacin may be used.

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 5 hrs 16 mins 36 secs

Work Smart Session - MRCP Part 1

Question: 84 of 100

Which of the following is associated with hyperuricaemia?

(Please select 1 option)

○	Can be reduced with low dose aspirin therapy
○	Can be treated with uricosuric drugs even in renal failure
○	In primary gout is inherited in an autosomal dominant manner
○	Is usually due to an excess purine consumption
○	Occurs in association with acute lymphoblastic leukaemia

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Community
- Shop
- Help

Which of the following is associated with hyperuricaemia?

(Please select 1 option)

○	Can be reduced with low dose aspirin therapy
○	Can be treated with uricosuric drugs even in renal failure
○	In primary gout is inherited in an autosomal dominant manner
○	Is usually due to an excess purine consumption
◉	Occurs in association with acute lymphoblastic leukaemia ✓ Correct

Hyperuricaemia may be due to increased purine intake, urate production or reduced urate clearance, and is most commonly due to the latter.

Therefore it can occur in association with enhanced cell destruction, particularly leukaemias.

Primary gout has no obvious mode of inheritance, but familial juvenile gouty nephropathy is an autosomal dominantly inherited disorder.

Low dose aspirin may exacerbate gout but high dose aspirin is uricosuric.

Many of the uricosuric drugs may be detrimental in renal failure and may not be effective.

Next question | Tag Question | Remove question

Rate this question

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 5 hrs 17 mins 14 secs

Work Smart Session - MRCP Part 1

Question: 85 of 100

Which of the following is true concerning a 68-year-old male with type 2 diabetes diagnosed with type IV renal tubal acidosis (RTA)?

(Please select 1 option)

○	Aminoaciduria would be expected
○	Fludrocortisone treatment is effective
○	Increased glomerular filtration rate (GFR) is expected
○	Increased urinary bicarbonate would be expected
○	Normal renal handling of K^+ and H^+

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Time taken: 5 hrs 17 mins 53 secs

Work Smart Session - MRCP Part 1

Question: 85 of 100

Which of the following is true concerning a 68-year-old male with type 2 diabetes diagnosed with type IV renal tubal acidosis (RTA)?

(Please select 1 option)

◉	Aminoaciduria would be expected ✕ Incorrect answer selected
○	Fludrocortisone treatment is effective ← This is the correct answer
○	Increased glomerular filtration rate (GFR) is expected
○	Increased urinary bicarbonate would be expected
○	Normal renal handling of K^+ and H^+

H^+ secretion, sodium reabsorption and ammonia production diminishes.

RTA 4 is, in effect, hyporeninaemic hypoaldosteronism or failure of aldosterone action, and thus helped treated with mineralocorticoids. It is usually seen in chronic renal disease and hence low GFR and particularly.

Aminoaciduria and increased urine bicarbonate are features of RTA types 1 and 2.

Next question

Remove Tag Remove question

Rate this question

☆☆☆☆☆

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 5 hrs 17 mins 53 secs

Work Smart Session - MRCP Part 1

Question: 86 of 100

Which of the following concerning the pH of urine is correct?

(Please select 1 option)

- a. Is a useful indicator of the acid/base balance of the blood
- b. Rises on a vegetarian diet
- c. Is determined by the concentration of ammonium
- d. Is lower than 5.5 in renal tubular acidosis (RTA)
- e. Would be above 7.0 after prolonged and severe vomiting

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Time taken: 5 hrs 18 mins 22 secs

Work Smart Session - MRCP Part 1

Question: 86 of 100

Which of the following concerning the pH of urine is correct?

(Please select 1 option)

○	a. Is a useful indicator of the acid/base balance of the blood
◉	b. Rises on a vegetarian diet ✓ Correct
○	c. Is determined by the concentration of ammonium
○	d. Is lower than 5.5 in renal tubular acidosis (RTA)
○	e. Would be above 7.0 after prolonged and severe vomiting

c. Excretion of ammonium occurs when an acid urine is produced but the pH of urine is of course determined by the concentration of H+ ions.

d. Unable to lower the pH to less than 5.5 in RTA.

e. This would be expected in an attempt to compensate for the loss of acid; however when there is extracellular fluid depletion the retention of sodium takes priority.

Instead of bicarbonate being excreted it is reabsorbed in the proximal and distal nephron and this perpetuates the metabolic alkalosis until the fluid balance is restored with intravenous (IV) fluids.

Next question

Tag Question | Remove question

Rate this question

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 5 hrs 18 mins 22 secs

Work Smart Session - MRCP Part 1

Question: 87 of 100

Which of the following concerning renal blood flow is true?

(Please select 1 option)

○	Can be measured using the Fick principle
○	Is decreased in response to hypoxia
○	Is 40% of the cardiac output at rest
○	Is higher in the medulla than the cortex
○	Is increased when renal nerves are stimulated

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Time taken: 5 hrs 18 mins 58 secs

Work Smart Session - MRCP Part 1

Question: 87 of 100

Which of the following concerning renal blood flow is true?

(Please select 1 option)

○	Can be measured using the Fick principle ← This is the correct answer
○	Is decreased in response to hypoxia
○	Is 40% of the cardiac output at rest
○	Is higher in the medulla than the cortex
◉	Is increased when renal nerves are stimulated ✕ Incorrect answer selected

Renal blood flow (RBF) is approximately 25% of cardiac output.

The 'Fick principle' can be used to estimate RBF through clearance.

RBF is higher in the cortex than medulla as one might expect with the increasing glomeruli in this region.

Sympathetic stimuli produce vasoconstriction and RBF should be increased in response to hypoxia.

Next question

Remove Tag | Remove question

Rate this question

☆☆☆☆☆

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 5 hrs 18 mins 58 secs

Work Smart Session - MRCP Part 1

Question: 88 of 100

Which one of the following is true concerning antidiuretic hormone (ADH)?

(Please select 1 option)

○	Carbamazepine potentiates its release
○	Ethanol potentiates its release
○	It circulates in the blood bound to neurohypophysin
○	It is a cyclic octapeptide
○	It is synthesised in the posterior pituitary

Submit answer | Skip question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Time taken: 5 hrs 20 mins 13 secs

Work Smart Session - MRCP Part 1

Question: 88 of 100

Which one of the following is true concerning antidiuretic hormone (ADH)?

(Please select 1 option)

◉	Carbamazepine potentiates its release ✓ Correct
○	Ethanol potentiates its release
○	It circulates in the blood bound to neurohypophysin
○	It is a cyclic octapeptide
○	It is synthesised in the posterior pituitary

ADH is a nonapeptide manufactured in the paraventricular and supra-optic nuclei of the hypothalamus and released from the posterior pituitary.

It acts on the collecting ducts improving water permeability and hence water retention.

Carbamazepine as well as other agents such as thiazides and selective serotin reuptake inhibitors (SSRIs) may potentiate its release.

Ethanol usually inhibits release.

http://acbrown.com/kidney/Lectures/RnWatr/RnWatrAntiTrmn.htm

Next question

Remove Tag | Remove question

Rate this question

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 5 hrs 20 mins 13 secs

Work Smart Session - MRCP Part 1

Question: 89 of 100

Which of the following is a feature of pseudohypoparathyroidism?

(Please select 1 option)

○	Increased urinary phosphate and cAMP with PTH infusion
○	Low serum calcium and high serum phosphate
○	Low serum calcium and low serum phosphate
○	Low serum PTH
○	Shortened second and third metacarpals

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Time taken: 5 hrs 20 mins 42 secs

Work Smart Session - MRCP Part 1

Question: 89 of 100

Which of the following is a feature of pseudohypoparathyroidism?

(Please select 1 option)

○	Increased urinary phosphate and cAMP with PTH infusion
◉	Low serum calcium and high serum phosphate ✓ Correct
○	Low serum calcium and low serum phosphate
○	Low serum PTH
○	Shortened second and third metacarpals

The biochemistry shows a hypocalcaemia with hyperphosphataemia being usual but elevated parathyroid hormone (PTH) due to resistance to PTH.

This is due to mutation of the PTH receptor with abnormality of the Gsalpha subunit with reduced cyclic adenosine monophosphate (cAMP) production following a PTH infusion.

There are associated phenotypic signs including short stature, low IQ and shortened fourth and fifth metacarpals.

Next question | Tag Question | Remove question

Rate this question

Potassium	4.9 mmol/l	(3.5-5)
Creatinine	189 µmol/l	(60-120)
ESR	62	(<10)
Urine	Blood++ Protein ++	

Which of the following is the most likely diagnosis?

(Please select 1 option)

○	Alport's syndrome
◉	Churg-Strauss syndrome ✓ Correct
○	IgA nephropathy
○	Post-streptococcal glomerulonephritis
○	Wegener's granulomatosis

The history of rapidly worsening symptoms of asthma, accompanied by hypertension, raised creatinine and blood and proteinuria are features of Churg-Strauss.

Churg-Strauss is a small and medium sized artery vasculitis. p-ANCA is positive in 70% of patients.

High dose steroids with the addition of cyclophosphamide or azathioprine are standard therapy for the condition.

With treatment the one year survival rate for Churg-Strauss is 90%; 62% at five years.

Next question

Tag Question | Remove question

Question: 9 of 100

A 14-year-old boy is referred by the practice nurse for follow up with you. He was brought by his mother to see the practice nurse because of progressive hearing loss.

Examination and basic investigations revealed nothing of note, apart from haematuria detected on routine urine testing. Apparently he has an 18-year-old brother who also suffers from deafness and has mild renal impairment.

Investigations show

Haemoglobin	13.0 g/dl	(13.5-18)
White cell count	7.1 x 10^9/l	(4-10)
Platelets	199 x 10^9/l	(150-400)
Sodium	140 mmol/l	(134-143)
Potassium	4.7 mmol/l	(3.5-5)
Creatinine	110 µmol/l	(60-120)
ESR	8	(<10)
Urine	Blood +	

Which of the following is the most likely diagnosis?

(Please select 1 option)

- ○ Alport's syndrome
- ○ Autosomal dominant polycystic kidney disease
- ○ IgA nephropathy
- ○ Membranous nephropathy
- ○ Minimal change disease

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 5 hrs 20 mins 42 secs

Work Smart Session - MRCP Part 1

Question: 90 of 100

Which of the following features would be expected in acute tubular necrosis?

(Please select 1 option)

○	Creatinine clearance would be expected to be normal one year after the initial insult
○	Heavy proteinuria on urinalysis
○	Red cell casts on urinalysis
○	Urine plasma osmolality ratio is more than 1:1
○	Urine sodium concentration greater than 30 mmol/l

Submit answer | Skip question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Time taken: 5 hrs 22 mins 16 secs

Work Smart Session - MRCP Part 1

Question: 90 of 100

Which of the following features would be expected in acute tubular necrosis?

(Please select 1 option)

○	Creatinine clearance would be expected to be normal one year after the initial insult
○	Heavy proteinuria on urinalysis
○	Red cell casts on urinalysis
○	Urine plasma osmolality ratio is more than 1:1
◉	Urine sodium concentration greater than 30 mmol/l ✓ Correct

Red cell casts suggest nephritis and normalisation of the creatinine clearance occurs in only 40% of cases one year later.

Proteinuria, usually mild, is common with granular casts found on urinalysis.

The urine sodium concentration is typically above 30 mmol/l and osmolality ratio <1:1.

Further reading:
Acute Tubular Necrosis eMedicine

Next question

Remove Tag | Remove question

Rate this question
☆☆☆☆☆

Time taken: 5 hrs 22 mins 16 secs

Work Smart Session - MRCP Part 1

Question: 91 of 100

A 70-year-old female is admitted 12 hours after taking an overdose of aspirin.

Investigations revealed:

Serum sodium	138 mmol/l	(137-144)
Serum potassium	5.9 mmol/l	(3.5-4.9)
Serum bicarbonate	14 mmol/l	(20-28)
Serum urea	18.1 mmol/l	(2.5-7.5)
Serum creatinine	238 mol/l	(60-110)
Serum salicylate	1120 mg/l	(8)

What is the most appropriate treatment of this patient?

(Please select 1 option)

- ○ Haemodialysis
- ○ Haemofiltration
- ○ Intravenous sodium bicarbonate
- ○ Peritoneal dialysis
- ○ Urine alkalinisation

Serum urea	18.1 mmol/l	(2.5-7.5)
Serum creatinine	238 mol/l	(60-110)
Serum salicylate	1120 mg/l	(8)

What is the most appropriate treatment of this patient?

(Please select 1 option)

- ◉ Haemodialysis ✓ Correct
- ○ Haemofiltration
- ○ Intravenous sodium bicarbonate
- ○ Peritoneal dialysis
- ○ Urine alkalinisation

This patient is at major risk of aspirin toxicity as reflected by the excessive aspirin concentration and appears to have developed acute renal failure - she is acidotic with an elevated potassium.

Bicarbonate is recommended as a supportive therapy but in this patient, haemodialysis is the treatment of choice. The latter is advised when the plasma-salicylate concentration is greater than 700 mg/litre (5.1 mmol/litre) or in the presence of severe metabolic acidosis as recommended within the BNF poisons section.

There is nothing wrong with haemofiltration it just removes the toxin more slowly.

Read more (very detailed) about haemofiltration vs. haemodialysis in poisoning (pdf).

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 5 hrs 23 mins 41 secs

Work Smart Session - MRCP Part 1

Question: 92 of 100

The following are complications of nephrotic syndrome with the exception of:

(Please select 1 option)

- Accelerated hypertension
- Acute renal failure
- Hypocalcaemia
- Pneumococcal infection
- Venous thrombosis

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Time taken: 5 hrs 24 mins 7 secs

Work Smart Session - MRCP Part 1

Question: 92 of 100

The following are complications of nephrotic syndrome with the exception of:

(Please select 1 option)

○	Accelerated hypertension ← This is the correct answer
○	Acute renal failure
◉	Hypocalcaemia ✕ Incorrect answer selected
○	Pneumococcal infection
○	Venous thrombosis

Complications also include hyperlipidaemia, protein malnutrition and loss of binding proteins in urine.

Nephrotic syndrome is likely to be associated with hypocalcaemia (vitamin D binding protein and vitamin D lost in nephrotic urine) and hypovolaemia (low blood pressure).

Next question

Remove Tag Remove question

Rate this question

☆☆☆☆☆

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 5 hrs 24 mins 7 secs

Work Smart Session - MRCP Part 1

Question: 93 of 100

Which of the following is least likely with the HLA complex?

(Please select 1 option)

○	CD4 T cells recognise antigen when co-presented with MHC class II
○	CD8 T cells recognise antigen when co-presented with major histocompatibility complex (MHC) class I
○	HLA matching is more important in kidney transplantation than liver transplantation
○	Multiple sclerosis is associated with HLA DR2
○	Polymorphisms occur in class I, but not class II, MHC genes

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Community
- Shop
- Help

Which of the following is least likely with the HLA complex?

(Please select 1 option)

○	CD4 T cells recognise antigen when co-presented with MHC class II
○	CD8 T cells recognise antigen when co-presented with major histocompatibility complex (MHC) class I
○	HLA matching is more important in kidney transplantation than liver transplantation
○	Multiple sclerosis is associated with HLA DR2
◉	Polymorphisms occur in class I, but not class II, MHC genes ✓ Correct

Polymorphisms occur in both class I and II genes.

Cytotoxic T cells express the molecule CD8 on the cell surface and only recognise antigen when presented by the T cell receptor (TCR) in conjunction with class I MHC.

T helper cells express CD4 on the cell surface and only recognise antigen when presented by TCR and class II MHC.

T helper cells are divided into Th1 and Th2 depending on function and cytokines released:

- Th1 cells secrete IL-2 and interferon-gamma and are involved in stimulating a cytotoxic immune response
- Th2 cells secrete IL-4, IL-5, IL-10 and stimulate a humoral (antibody) response by B cells.

Liver allografts are less immunogenic than kidney grafts.

Next question | Tag Question | Remove question

Rate this question

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 5 hrs 25 mins 10 secs

Work Smart Session - MRCP Part 1

Question: 94 of 100

Which of the following is correct in asymptomatic chronic renal failure (CRF)?

(Please select 1 option)

○	Decrease in blood pressure accompanied by increase in extracellular fluid
○	Increase serum [alkaline phosphotase] mainly due to liver isoenzyme
○	Serum ionised [calcium] is normal
○	Serum [phosphate] characteristically increased before GFR falls to 30 ml/min
○	There is increase in tubular excretion of urate

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Community
- Shop
- Help

Which of the following is correct in asymptomatic chronic renal failure (CRF)?

(Please select 1 option)

○	Decrease in blood pressure accompanied by increase in extracellular fluid
○	Increase serum [alkaline phosphotase] mainly due to liver isoenzyme
○	Serum ionised [calcium] is normal ← This is the correct answer
◉	Serum [phosphate] characteristically increased before GFR falls to 30 ml/min ✕ Incorrect answer selected
○	There is increase in tubular excretion of urate

Urate retention is common feature in CRF.

Total serum [calcium] is reduced or at lower limits of normal but ionised [calcium] is normal unless steps are taken to treat acidosis actively, for example, with sodium bicarbonate.

Plasma phosphate and chloride are almost always raised.

Hyperphosphataemia occurs when glomerular filtration rate [GFR] falls less than 30 ml/min.

Increased bone alkaline phosphotase reflects osteodystrophy.

Hypertension is due largely to salt and water retention, and also overactivity of renin angiotensin systems.

Next question

Remove Tag | Remove question

Rate this question

☆☆☆☆☆

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 5 hrs 26 mins 18 secs

Work Smart Session - MRCP Part 1

Question: 95 of 100

Which of the following is true concerning metastatic calcification in chronic renal failure (CRF)?

(Please select 1 option)

- Characteristically caused by calcium oxalate deposition
- Decreased by vitamin D
- Increased prevalence with time on haemodialysis
- Rapidly reversed in all sites after parathyroidectomy
- Unaffected by time on CAPD

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Which of the following is true concerning metastatic calcification in chronic renal failure (CRF)?

(Please select 1 option)

◉	Characteristically caused by calcium oxalate deposition ✗ Incorrect answer selected
○	Decreased by vitamin D
○	Increased prevalence with time on haemodialysis ← This is the correct answer
○	Rapidly reversed in all sites after parathyroidectomy
○	Unaffected by time on CAPD

CRF is associated with

- Low serum calcium
- Hyperphosphataemia
- Increased parathyroid hormone (PTH)
- Reduced intestinal calcium absorption and
- Raised alkaline phosphatase.

Parathyroidectomy improves extraskeletal calcification, but vascular calcification improves less than periarticular calcification.

Metastatic calcification is due mainly to calcium phosphate deposition, although CRF managed with dialysis is the commonest cause of secondary oxalosis (acute arthritis of small joints with digital calcific deposits). Prolonged treatment with vitamin D (hence hypercalcaemia and hyperphosphataemia) increases extraskeletal calcification.

Next question

Remove Tag | Remove question

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 5 hrs 27 mins 25 secs

Work Smart Session - MRCP Part 1

Question: 96 of 100

A 63-year-old male recently admitted with sepsis is noted to have a urine output of approximetely 20 mls per hour.

The oliguria is more likely to be due to prerenal failure than intrinsic renal failure if which of the folllowing is correct?

(Please select 1 option)

○	A blood pressure of 150/90 and good tissue perfusion.
○	A urine free of red blood cells or casts
○	A urine:plasma urea ratio <3
○	Urine osmolality <350 mOsm/l
○	Urinary sodium >10mmol/l

Submit answer | Skip question | Tag Question | Remove question

- Shop
- Help

(Please select 1 option)

○	A blood pressure of 150/90 and good tissue perfusion.
○	A urine free of red blood cells or casts ← This is the correct answer
○	A urine:plasma urea ratio <3
○	Urine osmolality <350 mOsm/l
◉	Urinary sodium >10mmol/l ✕ Incorrect answer selected

Oliguria is defined as < 400 ml urine/day.

Red cell casts present in

- Acute glomerulonephritis
- Renal vasculitis
- Accelerated hypertension and
- Interstitial nephritis.

Pre-renal failure is renal dysfunction due to hypoperfusion (urinary sodium <20, urine osmolality >500, urine/plasma ratio >8, and urine/plasma creatinine >40).

Acute tubular necrosis is acute renal failure due to circulatory compromise and/or nephrotoxins (urinary sodium >40, urine osmolality <350, urine/plasma ratio <3, and urine/plasma creatinine <20).

Next question | Remove Tag | Remove question

Rate this question

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 5 hrs 30 mins 25 secs

Work Smart Session - MRCP Part 1

Question: 97 of 100

Are the following true concerning anti-neutrophilic cytoplasmic autoantibodies?

(Please select 1 option)

○	ANCA positive glomerulonephritis characteristically causes nephrotic syndrome
○	Cause neutropenia in SLE
○	Increased in systemic lupus erythematosus (SLE)
○	Positive only in Wegener's syndrome associated with renal disease
○	Present in inflammatory bowel disease

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Time taken: 5 hrs 37 mins 12 secs

Work Smart Session - MRCP Part 1

Question: 97 of 100

Are the following true concerning anti-neutrophilic cytoplasmic autoantibodies?

(Please select 1 option)

○	ANCA positive glomerulonephritis characteristically causes nephrotic syndrome
○	Cause neutropenia in SLE
○	Increased in systemic lupus erythematosus (SLE)
○	Positive only in Wegener's syndrome associated with renal disease
◉	Present in inflammatory bowel disease ✓ Correct

Eighty five percent of untreated subjects with Wegener's will have circulating anti-neutrophil cytoplasmic antibody (cANCA) and those with limited disease are less likely to have positive serology.

Perinuclear anti-neutrophil cytoplasmic antibody (pANCA) is present in approximately 70% with ulcerative colitis and less than 20% of Crohn's patients.

Neither p nor c-ANCA is typical of SLE.

Initial renal damage causes proteinuria (focal proliferative glomerulonephritis) but renal function can deteriorate rapidly with development of acute focal necrotising glomerulonephritis.

Next question | Tag Question | Remove question

Rate this question

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 5 hrs 37 mins 12 secs

Work Smart Session - MRCP Part 1

Question: 98 of 100

A patient with end stage renal disease is receiving haemodialysis and erythropoietin.

Which of the following does erythropoietin therapy cause?

(Please select 1 option)

○	Benign intracranial hypertension
○	Hypotension
○	Myositis
○	Osteoporosis
○	Seizures

Submit answer | Skip question | Tag Question | Remove question

○	Osteoporosis
◉	Seizures ✓ Correct

Hypertension is a frequent problem associated with erythropoietin and may induce seizures.

A particular symptom is the onset of sudden stabbing migraine-like headache and should raise awareness to the possibility of hypertensive crisis.

Other adverse effects of treatment with erythropoietin include:

- hyperkalaemia in uraemic patients

- increased packed cell volume (PCV) (especially with misuse by normal individuals)

- thrombocythaemia

- shunt thrombosis

- induction of iron deficiency

- skin rashes

- urticaria and

- flu-like illness.

Next question

Tag Question | Remove question

Rate this question

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 5 hrs 40 mins 11 secs

Work Smart Session - MRCP Part 1

Question: 99 of 100

In which of the following circumstances would the treatment of anaemia with erythropoetin still be expected to be effective?

(Please select 1 option)

- Aluminium toxicity
- Folate deficiency
- Hyperkalaemia
- Infection
- Iron deficiency

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

In which of the following circumstances would the treatment of anaemia with erythropoetin still be expected to be effective?

(Please select 1 option)

◉	Aluminium toxicity ✗ Incorrect answer selected
○	Folate deficiency
○	Hyperkalaemia ← This is the correct answer
○	Infection
○	Iron deficiency

Epoetin (recombinant human erythropeitin) is used

- In chronic renal failure
- To shorten the period of anaemia in those receiving platinum-based chemotherapy and
- Prevention of anaemia in premature babies with low birth weight.

Its efficacy may be impaired in certain circumstances particularly with iron deficiency but also with aluminium toxicity, folate deficiency and infection. In the latter the switch to the acute phase proteins impairs its function.

Its efficacy is unimpaired in hyperkalaemia.

Next question

Remove Tag Remove question

Rate this question

☆☆☆☆☆

Creatinine	110 µmol/l	(60-120)
ESR	8	(<10)
Urine	Blood +	

Which of the following is the most likely diagnosis?

(Please select 1 option)

◉	Alport's syndrome ✓ Correct
○	Autosomal dominant polycystic kidney disease
○	IgA nephropathy
○	Membranous nephropathy
○	Minimal change disease

Alport's syndrome comprises

- Sensorineural hearing loss
- Progressive renal failure
- Haematuria
- Ocular abnormalities including cataract formation.

The condition is often associated with an X linked dominant inheritance pattern and hence males are more severely affected.

Prevalence is around 1 in 5000, and the condition occurs because of type 4 collagen mutations. Deafness usually occurs before the onset of renal failure, which is related itself to progressive nephritis.

Rigorous control of hypertension may delay the onset of end stage renal failure, which is seen in 90% of patients with Alport's by the age of 40 years.

Next question | Tag Question | Remove question

Rate this question

Time taken:

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Work Smart Session - MRCP Part 1

Question: 1 of 100

A 75-year-old woman presents with a two month history of episodic loss of vision in her right eye. Her electrocardiogram was normal and carotid ultrasound reveal a 50% stenosis of the right internal carotid artery.

What is the most appropriate treatment for this patient?

(Please select 1 option)

○	Aspirin
○	Carotid endarterectomy
○	Dipyridamole
○	Prednisolone
○	Warfarin

Submit answer | Skip question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 20 mins 46 secs

Work Smart Session - MRCP Part 1

Question: 10 of 100

A 36-year-old female presents with a six month history of having problems sleeping at night. She has been woken on numerous occasions by her legs which are irritable and feel that they are being tugged. She needs to keep moving them. This urge lasts for variable periods and she finds little relief from rubbing the legs. No abnormalities are noted on examination of her legs.

Which of the following is the most appropriate treatment for this patient?

(Please select 1 option)

- Amitriptyline
- Gabapentin
- Psychiatric referral
- Ropinirole
- Venlafaxine

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 5 hrs 33 mins 4 secs

Work Smart Session - MRCP Part 1

Question: 100 of 100

A 24-year-old female presents with vague frontal headaches and visual disturbance.

She has a past history of acne for which she is receiving treatment. Examination reveals her to be obese with a blood pressure of 110/70 mmHg. There is absence of the central retinal vein pulsation on fundoscopic examination.

Which of the following drugs account for these findings?

(Please select 1 option)

○	Ampicillin
○	Dianette
○	Erythromycin
○	Isotretinoin
○	Topical tetracycline

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Question: 100 of 100

A 24-year-old female presents with vague frontal headaches and visual disturbance.

She has a past history of acne for which she is receiving treatment. Examination reveals her to be obese with a blood pressure of 110/70 mmHg. There is absence of the central retinal vein pulsation on fundoscopic examination.

Which of the following drugs account for these findings?

(Please select 1 option)

○	Ampicillin
○	Dianette ← This is the correct answer
○	Erythromycin
◉	Isotretinoin ✕ Incorrect answer selected
○	Topical tetracycline

Dianette, like any oral contraceptive, may be associated with benign intracranial hypertension (BIH).

Topical tetracycline is not associated with BIH.

Rarely BIH has been associated with isotretinoin but usually in combination with a tetracycline.

Finish

Remove Tag | Remove question

Rate this question

- Help

Which of the following is the most appropriate treatment for this patient?

(Please select 1 option)

○	Amitriptyline
○	Gabapentin
○	Psychiatric referral
◉	Ropinirole ✓ Correct
○	Venlafaxine

This patient has features of restless legs syndrome (RLS). Typically there is an uncomfortable sensation in the legs and a feeling of needing to move them.

The exact aetiology is unknown. Although no specific tests exist for the diagnosis it is based on the International Restless Legs Syndrome Study Group four basic criteria for diagnosing RLS:

(1) a desire to move the limbs, often associated with paresthesias or dysesthesias

(2) symptoms that are worse or present only during rest and are partially or temporarily relieved by activity

(3) motor restlessness, and

(4) nocturnal worsening of symptoms.

Treatment depends on the severity of the problem and the most appropriate treatment here would be ropinirole, which is the only agent licensed for this purpose.

Next question

Tag Question | Remove question

Time taken: 21 mins 37 secs

Work Smart Session - MRCP Part 1

Question: 11 of 100

A 55-year-old man presents with neck pain.

One week previously he had attended for a sigmoidoscopy and was given intravenous sedation during this procedure. One day prior to admission his neck and shoulders had become stiff.

On examination, the temperature was 38.0°C, blood pressure was 100/60 mmHg and heart rate 100 bpm.

There were absent biceps jerks and weakness of trapezius, deltoid and triceps bilaterally. The cranial nerves and lower limbs were normal.

There was a soft systolic murmur, and the chest was clear.

Which examination is likely to confirm the diagnosis?

(Please select 1 option)

○	Cervical spine X-ray
○	CT head
○	Echocardiography
○	Lumbar puncture
○	MRI neck

Submit answer | Skip question | Tag Question | Remove question

Which examination is likely to confirm the diagnosis?

(Please select 1 option)

○	Cervical spine X-ray
○	CT head
◉	Echocardiography ✕ Incorrect answer selected
○	Lumbar puncture
○	MRI neck ← This is the correct answer

The features suggest a paraspinal abscess affecting C4-C6 given the neurological findings.

The investigation of the patient should include all of the above tests.

Paraspinal abscess is often associated with infection in an intravenous (IV) line, which may or may not be apparent as cellulites.

Neurological signs, once apparent, should lead to rapid investigation as once they are present recovery of strength may be slow, or not at all.

A magnetic resonance imaging (MRI) of the neck should delineate the anatomy of the abscess, which will not be seen on a computerised tomography (CT) scan of the head.

However, given that these lesions are usually due to seeding of *Staphylococcus aureus*, endocarditis is a possibility.

Cerebral spinal fluid (CSF) should show an elevated protein with raised white cells, and a low/normal glucose.

Next question

Remove Tag | Remove question

Time taken: 25 mins 42 secs

Work Smart Session - MRCP Part 1

Question: 12 of 100

A 59-year-old female pub landlady presents with acute, severe lumbar back pain.

There is no history of orthopaedic problems and until this event, she had been in perfect health.

The patient complains of parasthesiae in the lower limbs, and on further questioning has not voided urine since the onset of the pain.

Neurological examination reveals weakness (3/5 of both lower limbs, loss of sensation in L4, L5 and S1. Vibration sensation and joint position sensation is preserved. Reflexes in the ankles and knees are absent, and the plantar response is equivocal.

The blood pressure is 158/68 mmHg, heart rate 95 bpm, temperature 36.9°C and ECG shows normal sinus rhythm with no ischaemic changes.

The remainder of the examination is normal.

Which of the following should be undertaken next for this patient?

(Please select 1 option)

○	CT head
○	Duplex scan of aorta
○	MRI spinal cord
○	Rectal examination
○	USS abdomen

○	Duplex scan of aorta
◉	MRI spinal cord ✕ Incorrect answer selected
○	Rectal examination ← This is the correct answer
○	USS abdomen

The diagnosis here is spinal stroke otherwise known as spinal artery thrombosis.

The acute presentation of the symptoms is suggestive of a vascular event.

The easiest and safest way to make the diagnosis is magnetic resonance imaging (MRI) of the spinal cord. However, loss of rectal tone is extremely supportive of the diagnosis.

Bladder dysfunction is also suggested by the lack of urine.

Guillan-Barre and acute inflammatory demyelinating polyneuropathy (AIDP) are important differentials here, but do not usually cause sphincter dysfunction. The sensory loss is more suggestive of a peripheral neuropathy, in that there is distal sensory loss and no sensory level.

Spinal cord compression is also an important differential and the so-called 'surgical causes', for example, epidural abscess, spinal tumour, and granuloma.

The fact that this patient is apyrexial is thus significant.

A rectal examination is an important discriminator in the clinical findings and should be undertaken prior to MRI.

A computerised tomography (CT) scan of the head may be undertaken out of hours, prior to an MRI, as lumbar puncture and cerebrospinal fluid (CSF) examination are vital examinations in the work up of this patient.

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 28 mins 5 secs

Work Smart Session - MRCP Part 1

Question: 13 of 100

A 40-year-old male presents to casualty with weakness and parasthesiae of the right arm and leg. The symptoms developed 12 hours after the onset of a piercing left sided headache. There is no neck stiffness, but there is a pain in the left side of the neck and occiput. Kernig's sign is negative. The patient is afebrile, and blood results are normal.

What is the investigation of choice?

(Please select 1 option)

- Contrast arteriography
- CT head
- Duplex scanning of the neck vessels
- Lumbar puncture
- MRI brain

Submit answer | Skip question | Remove Tag | Remove question

occiput. Kernig's sign is negative. The patient is afebrile, and blood results are normal.

- Shop
- Help

What is the investigation of choice?

(Please select 1 option)

○	Contrast arteriography ← This is the correct answer
◉	CT head ✕ Incorrect answer selected
○	Duplex scanning of the neck vessels
○	Lumbar puncture
○	MRI brain

Ischaemic neurological features (transient or completed strokes) are found in 30-80% of presenting patients presenting with carotid artery dissection. Pulsatile tinnitus is common, as well as syncope and amaurosis fugax. Headache is commonly ipsilateral to the side of the carotid dissection, and recurrence of the headache suggests extension or recurrence of the dissection. The most accurate study and the current gold standard for diagnosis of carotid artery dissection, contrast arteriography should be strongly considered if neurological findings are incompatible with the findings of CT head, there is mono or hemiparesis with normal mental state, signs or history of major cervical trauma with abnormal neurology, or basilar skull fracture in a patient with altered mental status. In the absence of arteriography, Duplex scanning or MRI with MRA may be considered the next best tests. Limitations of duplex scanning include difficulties of scanning the distal internal carotid artery, detecting emboli, and evaluating intracranial arteries. The combination of MRI and MRA is more reliable in detecting dissection than either modality alone. Lumbar puncture results may be misleading, as xanthochromia may occur when a haematoma propagates. This rare finding may lead to a diagnosis of subarachnoid hemorrhage and failure to perform further carotid workup.

Next question

Remove Tag | Remove question

Rate this question

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 37 mins 20 secs

Work Smart Session - MRCP Part 1

Question: 14 of 100

A 78-year-old male is brought to the Emergency Department and has a witnessed seizure in the resuscitation room.

His blood glucose is recorded as 1.0 mmol/l. He does not have diabetes, and has no other significant past medical history.

He is given 50 ml of 50% dextrose and he slowly recovers over the next one hour. A serum cortisol concentration later returns as 800 nmol/l (120-600).

Which of the following would be the most relevant investigation for this man?

(Please select 1 option)

- Chest x ray
- CT head scan
- Electrocardiogram
- Prolonged 72 hour fast
- Short synacthen test

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

800 nmol/l (120-600).

Which of the following would be the most relevant investigation for this man?

(Please select 1 option)

○	Chest x ray
○	CT head scan
○	Electrocardiogram
◉	Prolonged 72 hour fast ✓ Correct
○	Short synacthen test

The historical and biochemical evidence here suggests a diagnosis of spontaneous hypoglycaemia, and the most likely cause would be an insulinoma. However, one would wish to exclude possible drug administration and although not mentioned here, a sulphonylurea screen should be undertaken.

He has presented with symptomatic hypoglycaemia, is not diabetic and therefore should not have received insulin or a sulphonylurea.

There is nothing to suggest alcohol or drug misuse. Similarly, there is nothing to suggest sepsis.

However, to prove a diagnosis of spontaneous hypoglycaemia, a prolonged fast is required and should he develop hypoglycaemia, measurement of insulin and C-peptide will be needed to confirm the diagnosis.

The appropriate cortisol response during his hypoglycaemic episode (cortisol 800) excludes hypoadrenalism.

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 39 mins 14 secs

Work Smart Session - MRCP Part 1

Question: 15 of 100

A 74-year-old retired newsagent presents with left-sided weakness. The weakness had developed slowly over the preceding six hours.

On examination he has a left hemiparesis and left facial weakness. His blood pressure is 180/100 mmHg and a heart rate 90 bpm regular. The patient's wife tells you that he has been choking on fluids since the weakness developed.

What should be your first action out of the following options?

(Please select 1 option)

- CT head
- IV streptokinase
- NG tube placement
- Nifedipine 10 mg stat
- Test his swallow with a glass of water

Submit answer | Skip question | Tag Question | Remove question

- Help

regular. The patient's wife tells you that he has been choking on fluids since the weakness developed.

What should be your first action out of the following options?

(Please select 1 option)

○	CT head
○	IV streptokinase
○	NG tube placement
○	Nifedipine 10 mg stat
◉	Test his swallow with a glass of water ✓ Correct

National stroke guidelines suggest that the risk of aspiration after acute cerebrovascular accident (CVA) should be assessed immediately on admission. If the patient spluttered, aspirated, coughed or choked on fluid that you administered then you should make him nil by mouth and perhaps place an nasogastric (NG) tube until review by the nutritionists/SALT team.

If you were considering this gentleman for thrombolysis then a CT would need to be carried out urgently (or an MRI!).

Thrombolysis of strokes is a developing service and is not common practice as yet but it is useful to consider this option in an acute CVA which presents early (that is, less than three hours). It is likely that we will be thrombolysing selected patients in the near future.

Hypertension post-CVA serves a protective function and anti-hypertensives should usually be avoided in the first week.

Next question | Tag Question | Remove question

Rate this question

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 45 mins 43 secs

Work Smart Session - MRCP Part 1

Question: 16 of 100

A 65-year-old male presents with bilateral leg pain.

There is no relevant past medical history, and no excess alcohol use. Both knee reflexes are reduced.

Fasting glucose is 6.5 mmol/L.

Which is the next investigation most likely to confirm the diagnosis?

(Please select 1 option)

○	B12 and folate
○	Chest x ray
○	CSF examination
◉	MRI spine
○	Oral glucose tolerance test

Submit answer | Skip question | Tag Question | Remove question

Question: 16 of 100

A 65-year-old male presents with bilateral leg pain.

There is no relevant past medical history, and no excess alcohol use. Both knee reflexes are reduced.

Fasting glucose is 6.5 mmol/L.

Which is the next investigation most likely to confirm the diagnosis?

(Please select 1 option)

○	B12 and folate
○	Chest x ray
○	CSF examination
○	MRI spine
◉	Oral glucose tolerance test ✓ Correct

The suggestion of bilateral leg pain, weakness and reduced knee reflexes with an impaired fasting glucose concentration suggests a diagnosis of diabetic amyotrophy. This is confirmed with a formal OGTT.

Diabetic amyotrophy is not uncommonly a presenting feature of diabetes in the elderly. The features are of an asymmetrical but bilateral quadriceps wasting and weakness with diminished reflexes.

Next question

Tag Question | Remove question

Rate this question

☆☆☆☆☆

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 47 mins 45 secs

Work Smart Session - MRCP Part 1

Question: 17 of 100

A 69-year-old male presents with sudden onset weakness of his legs associated with urinary retention. Five years previously he was diagnosed with sigmoid colonic carcinoma which was surgically resected.

Examination revealed a flaccid paraparesis of the legs with absent tendon reflexes and plantar responses. Pinprick and temperature sensations were absent to T12 level, but there was a relative sparing of light touch and joint position sensation.

What is the most likely diagnosis?

(Please select 1 option)

- Anterior spinal artery occlusion
- Intramedullary spinal cord metastasis
- Spinal cord compression due to vertebral metastasis
- T11/12 central disc prolapse
- Transverse myelitis

Submit answer | Skip question | Tag Question | Remove question

diagnosed with sigmoid colonic carcinoma which was surgically resected.

Examination revealed a flaccid paraparesis of the legs with absent tendon reflexes and plantar responses. Pinprick and temperature sensations were absent to T12 level, but there was a relative sparing of light touch and joint position sensation.

What is the most likely diagnosis?

(Please select 1 option)

◉	Anterior spinal artery occlusion ✓ Correct
○	Intramedullary spinal cord metastasis
○	Spinal cord compression due to vertebral metastasis
○	T11/12 central disc prolapse
○	Transverse myelitis

The lesion is involving the anterior two thirds of the spinal cord which spares light touch, vibration and position sense, but causes loss of pain and temperature sensation distally.

The diagnostic possibilities therefore include anterior spinal artery occlusion, which is rare, and intramedullary spinal cord metastasis.

The condition has developed quite suddenly, which is the key and supports a vascular event.

Intramedullary spinal cord lesions are also rare, and vertebral metastasis causing cord compression occurs more commonly; however the clinical signs suggest sparing of the dorsal columns.

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 50 mins 33 secs

Work Smart Session - MRCP Part 1

Question: 18 of 100

A 55-year-old male is admitted with vomiting.

He has a long history of alcohol abuse, appears slightly jaundiced and is dishevelled and unkempt. He was started on an intravenous glucose infusion and diazepam and he symptomatically improved.

One day later he becomes confused, develops vomiting, diplopia and is unable to stand.

What is the most likely diagnosis?

(Please select 1 option)

- Benzodiazepine intoxication
- Delirium tremens
- Hepatic encephalopathy
- Subdural haematoma
- Vitamin B deficiency

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

A 55-year-old male is admitted with vomiting.

He has a long history of alcohol abuse, appears slightly jaundiced and is dishevelled and unkempt. He was started on an intravenous glucose infusion and diazepam and he symptomatically improved.

One day later he becomes confused, develops vomiting, diplopia and is unable to stand.

What is the most likely diagnosis?

(Please select 1 option)

○	Benzodiazepine intoxication
○	Delirium tremens
○	Hepatic encephalopathy
◉	Subdural haematoma ✕ Incorrect answer selected
○	Vitamin B deficiency ← This is the correct answer

This patient is manifesting signs of Wernicke's encephalopathy with confusion, oculomotor signs and ataxia affecting gait and stance. Wernicke's encephalopathy is a medical emergency, requiring urgent intravenous thiamine.

The episode has been precipitated by intravenous dextrose administration which has exhausted his vitamin B reserves, hence B vitamins must be administered to all alcoholic patients requiring dextrose.

Next question | Tag Question | Remove question

Rate this question

☆☆☆☆☆

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 53 mins 30 secs

Work Smart Session - MRCP Part 1

Question: 19 of 100

An 85-year-old woman with diabetes mellitus presented with sudden onset of wild flinging movements of the left arm which disappeared during sleep.

What is the most likely explanation?

(Please select 1 option)

- Contralateral subthalamic nucleus infarction
- Focal motor seizures
- Hypoglycaemia
- Ipsilateral caudate nucleus infarction
- Ipsilateral cerebellar infarction

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 55 mins 54 secs

Work Smart Session - MRCP Part 1

Question: 19 of 100

An 85-year-old woman with diabetes mellitus presented with sudden onset of wild flinging movements of the left arm which disappeared during sleep.

What is the most likely explanation?

(Please select 1 option)

◉	Contralateral subthalamic nucleus infarction ✓ Correct
○	Focal motor seizures
○	Hypoglycaemia
○	Ipsilateral caudate nucleus infarction
○	Ipsilateral cerebellar infarction

This is hemiballismus, and in a diabetic patient is likely to be due to a vascular event in the contralateral subthalamic nucleus.

Next question | Tag Question | Remove question

Rate this question

☆☆☆☆☆

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Work Smart Session - MRCP Part 1

Question: 1 of 100

A 75-year-old woman presents with a two month history of episodic loss of vision in her right eye. Her electrocardiogram was normal and carotid ultrasound reveal a 50% stenosis of the right internal carotid artery.

What is the most appropriate treatment for this patient?

(Please select 1 option)

◉	Aspirin ✓ Correct
○	Carotid endarterectomy
○	Dipyridamole
○	Prednisolone
○	Warfarin

The patient experienced transient ischaemic attacks (TIAs) of the form of amaurosis fugax due to carotid artery stenosis.

Carotid endarterectomy is only indicated if the stenosis is 70-99%.

Aspirin is the treatment of choice and good control of all vascular risk factors.

Warfarin is not indicated unless the patient is in atrial fibrillation (AF).

Next question

Remove Tag | Remove question

Rate this question

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 3 mins 18 secs

Work Smart Session - MRCP Part 1

Question: 2 of 100

A 60-year-old male is referred with episodes of severe vertigo which may last up to four hours and are associated with vomiting and pain in the right ear.

On examination during an attack he is noted to have right horizontal nystagmus together with mild right-sided sensorineural deafness.

Which one of the following is the most likely diagnosis?

(Please select 1 option)

- Acoustic neuroma
- Benign positional vertigo
- Labyrinthitis
- Ménière's disease
- Vertebrobasilar ischaemic attacks

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 55 mins 54 secs

Work Smart Session - MRCP Part 1

Question: 20 of 100

Which one of the following statements is correct?

(Please select 1 option)

- The abducens nerve supplies the lacrimal gland
- The facial nerve supplies the parotid salivary gland
- The oculomotor nerve supplies the dilator pupillae muscle
- The trochlear nerve supplies the superior rectus muscle
- The vagus nerve supplies the palatal muscles

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Question: 20 of 100

Which one of the following statements is correct?

(Please select 1 option)

○	The abducens nerve supplies the lacrimal gland
○	The facial nerve supplies the parotid salivary gland
○	The oculomotor nerve supplies the dilator pupillae muscle
○	The trochlear nerve supplies the superior rectus muscle
◉	The vagus nerve supplies the palatal muscles ✓ Correct

The lacrimal gland is supplied by the facial nerve.

The glossopharyngeal nerve supplies the parotid salivary gland controlling salivary secretions.

The oculomotor nerve carries parasympathetic efferents to the sphincter pupillae muscle.

The optic nerve carries sympathetic postganglionic fibres to the dilator pupillae muscle.

The trochlear nerve supplies the superior oblique muscle.

The occulomotor nerve innervates the superior rectus.

Next question

Tag Question | Remove question

Rate this question

☆☆☆☆☆

Time taken: 1 hrs 3 mins 47 secs

Work Smart Session - MRCP Part 1

Question: 21 of 100

Hearing losses of a mild degree or worse (>25dB) are present in around 10% of the population. As the population ages, the percentage of people with hearing loss also increases.

Which of the following age-percentage loss combinations is not correct for the general population?

(Please select 1 option)

○	At birth approximately 0.3% affected
○	Aged 50-59: approximately 10% affected
○	Aged 60-69: approximately 25% affected
○	Aged 70-79: approximately 50% affected
◉	Aged 80-89: approximately 50% affected ✓ Correct

Percentage of the population with a significant hearing loss increases with each decade of life.

For the 80-89-year-old age group, around 70-80% of them will have a degree of hearing loss >25dB.

Next question

Tag Question | Remove question

Rate this question

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 1 hrs 3 mins 47 secs

Work Smart Session - MRCP Part 1

Question: 22 of 100

A 30-year-old male presents with a week history of right arm weakness. Originally the problem began with severe pain in the neck which radiated into the right shoulder, which was followed by weakness.

Examination revealed winging of the right scapula with weakness of right shoulder abduction and elbow extension. There was some sensory loss over the lateral aspect of the right shoulder and right triceps reflex was absent.

What is the most likely diagnosis?

(Please select 1 option)

- C7 entrapment radiculopathy
- Central C5/6 disc prolapse
- Neuralgic amyotrophy
- Suprascapular nerve entrapment
- Traction of lateral cord of brachial plexus

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

which radiated into the right shoulder, which was followed by weakness.

Examination revealed winging of the right scapula with weakness of right shoulder abduction and elbow extension. There was some sensory loss over the lateral aspect of the right shoulder and right triceps reflex was absent.

What is the most likely diagnosis?

(Please select 1 option)

○	C7 entrapment radiculopathy
◉	Central C5/6 disc prolapse ✕ Incorrect answer selected
○	Neuralgic amyotrophy ← This is the correct answer
○	Suprascapular nerve entrapment
○	Traction of lateral cord of brachial plexus

Neuralgic amyotrophy is a brachial plexopathy (usually upper brachial plexus) usually preceded by an infective picture.

It usually presents with severe pain for days to weeks followed by weakness and sensory loss over the corresponding territory of the brachial plexus (more commonly C5-7).

It is a self-limiting condition but recovery may be slow (years).

Next question

Remove Tag Remove question

Rate this question

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 1 hrs 9 mins 26 secs

Work Smart Session - MRCP Part 1

Question: 23 of 100

A 55-year-old woman with multiple sclerosis is treated for severe hip adductor muscle spasticity and two days later develops double vision.

Which one of the following treatments is she likely to have been given?

(Please select 1 option)

- ○ Botulinum toxin
- ○ Dantrolene
- ○ Intrathecal baclofen
- ○ Oral baclofen
- ○ Tizanidine

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Question: 23 of 100

A 55-year-old woman with multiple sclerosis is treated for severe hip adductor muscle spasticity and two days later develops double vision.

Which one of the following treatments is she likely to have been given?

(Please select 1 option)

○	Botulinum toxin ← This is the correct answer
◉	Dantrolene ✕ Incorrect answer selected
○	Intrathecal baclofen
○	Oral baclofen
○	Tizanidine

Botulinum toxin is the treatment of choice for focal dystonia (such as torticollis, and hemi-facial spasm) and focal dystonia.

The primary action of the toxin is to block acetylcholine release at the neuromuscular junction and so to produce muscle weakness.

Occasionally systemic absorption of the toxin can affect distal muscles causing symptoms such as diplopia and dysphagia.

Next question

Remove Tag Remove question

Rate this question

☆☆☆☆☆

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 1 hrs 10 mins 21 secs

Work Smart Session - MRCP Part 1

Question: 24 of 100

A 28-year-old female, three days post-partum, develops severe headache associated with seizures.

During her pregnancy her blood pressure had been mildly elevated in the third trimester.

On examination, she had a GCS of 15 but was slightly confused and drowsy. Her temperature was 37.5ºC, she had mild nuchal rigidity but neurological examination was otherwise normal.

What is the most likely diagnosis?

(Please select 1 option)

- ○ Bacterial meningitis
- ○ Cortical vein thrombosis
- ○ Eclampsia
- ○ Intracerebral haemorrhage
- ○ Subarachnoid haemorrhage

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

During her pregnancy her blood pressure had been mildly elevated in the third trimester.

On examination, she had a GCS of 15 but was slightly confused and drowsy. Her temperature was 37.5ºC, she had mild nuchal rigidity but neurological examination was otherwise normal.

What is the most likely diagnosis?

(Please select 1 option)

○	Bacterial meningitis
◉	Cortical vein thrombosis ✓ Correct
○	Eclampsia
○	Intracerebral haemorrhage
○	Subarachnoid haemorrhage

Post-partum period is a risk factor of cortical vein and sinus thrombosis.

It typically presents with headache, seizures and focal neurological deficit two to three weeks postpartum (but is also seen earlier).

Other clinical presentations include a benign intercranial hypertension (BIH) type of picture (papilloedema, visual disturbances and headaches) or a subacute encephalopathic picture. Thrombophilia screen should be performed.

Eclampsia typically improves following delivery. The seizures can occur prepartum, intrapartum, or postpartum.

If the seizure occurs postpartum, it usually occurs within the first 24 hours after delivery.

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 1 hrs 11 mins 59 secs

Work Smart Session - MRCP Part 1

Question: 25 of 100

A 35-year-old woman is referred with right eye pain that has deteriorated over the last week.

On examination she had a mild ptosis of the right eye and was aware of diplopia with vertical image separation on looking upwards. She also had weakness of elevation of the right eye.

What is the most likely diagnosis?

(Please select 1 option)

- Cavernous sinus thrombosis
- Graves' ophthalmopathy
- Myasthenia gravis
- Posterior communicating artery aneurysm
- Sphenoid sinusitis

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

A 35-year-old woman is referred with right eye pain that has deteriorated over the last week.

On examination she had a mild ptosis of the right eye and was aware of diplopia with vertical image separation on looking upwards. She also had weakness of elevation of the right eye.

What is the most likely diagnosis?

(Please select 1 option)

○	Cavernous sinus thrombosis
○	Graves' ophthalmopathy
○	Myasthenia gravis
◉	Posterior communicating artery aneurysm ✓ Correct
○	Sphenoid sinusitis

The signs are consistent with a partial third nerve palsy associated with periorbital pain.

In a young person a posterior communicating artery aneurysm needs to be excluded.

With cavernous sinus thrombosis one should expect some other signs such as periorbital swelling, proptosis, and conjuctival injection.

With Graves' eye disease one should expect proptosis and lid retraction.

Myasthenia gravis does not present with pain.

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 1 hrs 13 mins 26 secs

Work Smart Session - MRCP Part 1

Question: 26 of 100

A 54-year-old male presents with progressive pins and needles and numbness in both feet which have deteriorated over the last six months.

He has a 10 year history of type 2 diabetes mellitus and had cervical spondylosis for which he underwent surgery eight years ago. He also confessed to drinking approximately 40 units of alcohol weekly.

On examination he had a mild bilateral weakness of foot dorsiflexion, both ankle reflexes were absent and plantar responses were flexor. There was absent sensation to light touch to mid-shin level with loss of joint position sensation in the toes and absent vibration sensation below the hips. He had a marked sensory ataxia and pseudoathetosis of upper limbs. He had no evidence of a retinopathy and urinalysis was normal.

What is the most likely diagnosis?

(Please select 1 option)

○	Alcohol-induced neuropathy
○	Central lumbar disc prolapse
○	Cervical cord compression
○	Diabetic peripheral neuropathy
○	Vitamin B_{12} deficiency

He has a 10 year history of type 2 diabetes mellitus and had cervical spondylosis for which he underwent surgery eight years ago. He also confessed to drinking approximately 40 units of alcohol weekly.

On examination he had a mild bilateral weakness of foot dorsiflexion, both ankle reflexes were absent and plantar responses were flexor. There was absent sensation to light touch to mid-shin level with loss of joint position sensation in the toes and absent vibration sensation below the hips. He had a marked sensory ataxia and pseudoathetosis of upper limbs. He had no evidence of a retinopathy and urinalysis was normal.

What is the most likely diagnosis?

(Please select 1 option)

○	Alcohol-induced neuropathy
○	Central lumbar disc prolapse
○	Cervical cord compression
○	Diabetic peripheral neuropathy
◉	Vitamin B_{12} deficiency ✓ Correct

Diabetic peripheral neuropathy usually goes in parallel with retinopathy and nephropathy.

It is also slowly progressive and affects mainly spinothalamic pathway.

Alcohol induced peripheral neuropathy is also slowly progressive and affects mainly spinothalamic pathway.

Vitamin B_{12} deficiency usually causes a more rapidly progressive neuropathy with dorsal column involvement (joint position and vibration involvement with sensory ataxia and pseudoathetosis of upper limbs).

Next question

Tag Question | Remove question

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 1 hrs 21 mins

Work Smart Session - MRCP Part 1

Question: 27 of 100

A 69-year-old man is admitted with pain and numbness in his right foot following a right hip replacement.

In his past medical history he had been treated for lower backache by his GP.

On examination there was weakness of all movements at the right ankle, with absent right ankle jerk, and sensory impairment on the lateral aspect and sole of the foot.

Where is the most likely site of the lesion?

(Please select 1 option)

○	Femoral nerve
○	Lumbosacral plexus
○	Obturator nerve
○	Sciatic nerve
◉	S1 spinal root

Submit answer | Skip question | Tag Question | Remove question

Question: 27 of 100

A 69-year-old man is admitted with pain and numbness in his right foot following a right hip replacement.

In his past medical history he had been treated for lower backache by his GP.

On examination there was weakness of all movements at the right ankle, with absent right ankle jerk, and sensory impairment on the lateral aspect and sole of the foot.

Where is the most likely site of the lesion?

(Please select 1 option)

○	Femoral nerve
○	Lumbosacral plexus
○	Obturator nerve
○	Sciatic nerve ← This is the correct answer
◉	S1 spinal root ✕ Incorrect answer selected

Sciatic nerve palsy is a known complication of a total hip replacement (as femoral nerve palsy).

It causes global weakness of the ankle due to the involvement of both of its branches: tibial nerve (plantaflexion and inversion) and common peroneal nerve (dorsiflexion and eversion).

The left ankle jerk is absent due to tibial nerve involvement.

Next question | Tag Question | Remove question

Rate this question

Time taken: 1 hrs 33 mins 12 secs

Work Smart Session - MRCP Part 1

Question: 28 of 100

A 45-year-old man presented with a three day history of headache and increasing confusion.

On examination he was febrile with marked neck stiffness.

Investigations revealed:

Cerebrospinal fluid analysis (normal ranges are shown in brackets):

White cell count	600/ml (<5)
White cell differential	>90% Neutrophils
Gram stain	Gram-negative diplococci

Which one of the following antibiotics, given intravenously, is the most appropriate treatment?

(Please select 1 option)

- ○ Ampicillin
- ○ Benzylpenicillin
- ○ Cefuroxime
- ○ Ciprofloxacin
- ○ Gentamicin

http://my.onexamination.com/Assessment/Que
Questions Set : REF6301
Hotmail - dr.zahir2009@hotm...

○	Ampicillin
◉	Benzylpenicillin ✓ Correct
○	Cefuroxime
○	Ciprofloxacin
○	Gentamicin

This is clearly a case of meningococcal meningitis. The commonest causes of bacterial meningitis in adults are:

- *Neisseria meningitidis* (Gram negative diplococci)
- *Streptococcus pneumoniae* (Gram positive diplococci).

Treatment of bacterial meningitis

On the basis of Gram stain results:

- Gram stain unavailable or no stainable organisms: Cefotaxime ± ampicillin
- Gram-positive cocci: Cefotaxime + vancomycin
- Gram-positive bacilli: Ampicillin + gentamicin
- Gram-negative cocci: Benzyl penicillin (Penicillin G)
- Gram-negative bacilli: Cefotaxime + gentamicin

On the basis of CSF culture:

- *Streptococcus pneumoniae*
  - If penicillin MIC <0.06 µgrams/mL: Benzyl penicillin (Penicillin G) or cefotaxime
  - If penicillin MIC >0.1 µgrams/ml (that is, penicillin-resistant pneumococcus): Cefotaxime (+ vancomycin if susceptibility to

http://my.onexamination.com/Assessment/Que
Questions Set : REF6301
Hotmail - dr.zahir2009@hotm...

Treatment of bacterial meningitis

On the basis of Gram stain results:

- Gram stain unavailable or no stainable organisms: Cefotaxime ± ampicillin
- Gram-positive cocci: Cefotaxime + vancomycin
- Gram-positive bacilli: Ampicillin + gentamicin
- Gram-negative cocci: Benzyl penicillin (Penicillin G)
- Gram-negative bacilli: Cefotaxime + gentamicin

On the basis of CSF culture:

- *Streptococcus pneumoniae*
  - If penicillin MIC <0.06 µgrams/mL: Benzyl penicillin (Penicillin G) or cefotaxime
  - If penicillin MIC >0.1 µgrams/ml (that is, penicillin-resistant pneumococcus): Cefotaxime (+ vancomycin if susceptibility to broad-spectrum cephalosporins reduced)
- *Neisseria meningitidis*: Benzyl penicillin (Penicillin G)
- *Haemophilus influenzae*: Cefotaxime
- *Listeria monocytogenes*: Ampicillin + gentamicin
- Group B streptococcus: Benzyl penicillin (Penicillin G).

Next question
Tag Question
Remove question

Rate this question

Time taken: 1 hrs 34 mins 51 secs

Work Smart Session - MRCP Part 1

Question: 29 of 100

A 59-year-old woman presents with polysymptomatology. On examination she has prominent fasciculations.

From which of the following conditions is she unlikely to suffer?

(Please select 1 option)

- Cervical spondylosis
- Motor neurone disease
- Multiple sclerosis
- Spinal muscular atrophy
- Thyrotoxicosis

Submit answer | Skip question | Tag Question | Remove question

A 59-year-old woman presents with polysymptomatology. On examination she has prominent fasciculations.

From which of the following conditions is she unlikely to suffer?

(Please select 1 option)

○	Cervical spondylosis
○	Motor neurone disease
◉	Multiple sclerosis ✓ Correct
○	Spinal muscular atrophy
○	Thyrotoxicosis

Fasciculations suggest lower motor neurone disease. Fasciculations may be seen in otherwise normal individuals with no muscular weakness/atrophy. If pronounced and combined with muscle atrophy they usually signify motor neurone disease (MND).

They may also be seen in diseases that involve

- Spinal cord grey matter
- Lesions of anterior roots
- Peripheral neuropathies.

They may also be seen with severe metabolic disturbance, dehydration, thyrotoxicosis, but not in demyelinating disease of the central nervous system.

Next question

Tag Question | Remove question

Rate this question

☆☆☆☆☆

(Please select 1 option)

○	Acoustic neuroma
○	Benign positional vertigo
◉	Labyrinthitis ✕ Incorrect answer selected
○	Ménière's disease ← This is the correct answer
○	Vertebrobasilar ischaemic attacks

This is a typical history of Ménière's disease.

The attacks are paroxysmal, lasting hours and consist of

- Vertigo
- Vomiting
- Pressure within the ear
- Deafness.

After many attacks the patient may develop irreversible sensorineural deafness (of low frequency).

Prochlorperazine or cinnarizine usually helps vomiting, and restriction of salt and fluid may hasten resolution. Occasionally diuretics may be used but there is little evidence for efficacy.

Further reading:
Ménière's disease Patient UK
Medical treatment, Ménière's disease GP Notebook

Next question

Remove Tag | Remove question

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 11 mins 25 secs

Work Smart Session - MRCP Part 1

Question: 3 of 100

A 34-year-old male presents with back pain and weakness.

Which of the following would support a diagnosis of prolapsed intervertebral disc?

(Please select 1 option)

○	Bilateral symmetrical nerve involvement
○	Loss of sensation over the left outer upper thigh
○	No evidence of nerve compression
◉	Pain which is unremitting in character
○	Pain which is worse on resting

Submit answer | Skip question | Tag Question | Remove question

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 1 hrs 35 mins 51 secs

Work Smart Session - MRCP Part 1

Question: 30 of 100

A 29-year-old female presents with acute right-sided weakness.

She has one child aged four years and had two spontaneous abortions in the past. After the birth of her child she developed a DVT and required three months' anticoagulation with warfarin.

Examination revealed a right hemiparesis. A CT head scan showed a left middle cerebral artery territory infarct.

What is the most likely finding on echocardiography?

(Please select 1 option)

- Atrial septal defect
- Bicuspid aortic valve
- Left atrial myxoma
- Normal appearances
- Ventricular septal defect

Submit answer | Skip question | Tag Question | Remove question

A 29-year-old female presents with acute right-sided weakness.

She has one child aged four years and had two spontaneous abortions in the past. After the birth of her child she developed a DVT and required three months' anticoagulation with warfarin.

Examination revealed a right hemiparesis. A CT head scan showed a left middle cerebral artery territory infarct.

What is the most likely finding on echocardiography?

(Please select 1 option)

○	Atrial septal defect
○	Bicuspid aortic valve
○	Left atrial myxoma
◉	Normal appearances ✓ Correct
○	Ventricular septal defect

This patient has a prothrombotic tendency suggestive of the lupus anticoagulant with recurrent abortions, previous deep vein thrombosis (DVT) and now she has developed a left hemiparesis.

This has occurred off warfarin and it is highly unlikely to be due to any right to left transference of clot.

It is more likely to be due to spontaneous infarct related to the thrombophilia and her heart is likely to be normal.

Next question

Tag Question | Remove question

Rate this question

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 1 hrs 39 mins 39 secs

Work Smart Session - MRCP Part 1

Question: 31 of 100

A 40-year-old man suffers an intracerebral infarction.

Which of the following features in this patient would not be considered as a risk factor for his stroke?

(Please select 1 option)

- Blood pressure 156/72 mmHg
- Marijuana use
- Mitral valve prolapse
- Plasma cholesterol of 6.5 mmol/l
- Smoker of 5 cigarettes per day

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Question: 31 of 100

A 40-year-old man suffers an intracerebral infarction.

Which of the following features in this patient would not be considered as a risk factor for his stroke?

(Please select 1 option)

○	Blood pressure 156/72 mmHg
◉	Marijuana use ✓ Correct
○	Mitral valve prolapse
○	Plasma cholesterol of 6.5 mmol/l
○	Smoker of 5 cigarettes per day

Like ischaemic heart disease/myocardial infarction (IHD/MI), epidemiological studies show an increased risk of stroke associated with hypercholesterolaemia. Other risk factors for stroke include isolated systolic hypertension in particular.

A previous history of deep vein thrombosis (DVT) may suggest a coagulation disorder.

Cocaine is associated with an increased risk of intracerebral infarction; marijuana is associated with increased susceptibility to schizophrenic episodes, particularly in the younger age group.

Next question | Tag Question | Remove question

Rate this question

☆☆☆☆☆

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 1 hrs 40 mins 43 secs

Work Smart Session - MRCP Part 1

Question: 32 of 100

A 30-year-old woman complains of daily frontal headaches for the preceding year. They occur at various times of the day and are worse with stress.

On examination, the left pupil is 2 mm larger than the right. It is reactive to accommodation but not to light.

Which of the following features would be inconsistent with the diagnosis?

(Please select 1 option)

○	Absent biceps jerk
○	Exaggerated response to dilute pilocarpine drops instilled in the left eye
○	Fine hand tremor
○	Ptosis
○	Resolution of anisocoria with time

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

A 30-year-old woman complains of daily frontal headaches for the preceding year. They occur at various times of the day and are worse with stress.

On examination, the left pupil is 2 mm larger than the right. It is reactive to accommodation but not to light.

Which of the following features would be inconsistent with the diagnosis?

(Please select 1 option)

○	Absent biceps jerk
◉	Exaggerated response to dilute pilocarpine drops instilled in the left eye ✕ Incorrect answer selected
○	Fine hand tremor
○	Ptosis ← This is the correct answer
○	Resolution of anisocoria with time

This patient has an Adie pupil which happens to coexist with tension headache.

An absent biceps jerk would be consistent with Holmes-Adie syndrome.

The characteristic abnormality in this condition is degeneration of parasympathetic nerves in the cilliary ganglion which leads to denervation of the pupil and hence hypersensitvity to dilute pilocarpine drops. The affected pupil is usually larger than the other but may constrict with time.

The cause of the associated arreflexia is unknown. A fine hand tremor may accompany anxiety states associated with tension headache but ptosis requires an organic explanation.

Next question

Remove Tag | Remove question

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 1 hrs 45 mins 57 secs

Work Smart Session - MRCP Part 1

Question: 33 of 100

Which of the following statements regarding phenylketonuria is correct?

(Please select 1 option)

○	Inheritance is X linked recessive
○	Is classically due to deficiency of tyrosine hydroxylase
○	Mental retardation does not occur if the patient adheres to a phenylalanine free diet
○	Serum tyrosine levels are typically low
○	Urinary phenylalanine metabolites are typically high

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Help

○	Is classically due to deficiency of tyrosine hydroxylase
○	Mental retardation does not occur if the patient adheres to a phenylalanine free diet
○	Serum tyrosine levels are typically low
◉	Urinary phenylalanine metabolites are typically high ✓ Correct

Phenylketonuria (PKU) is the result of hyperphenylalaninaemia. It is autosomal recessive, with a prevalence of 1:10-20,000 live births.

Phenylalanine is an essential amino acid. Dietary phenylalanine is not utilised for protein synthesis, but is normally degraded via the tyrosine pathway. Failure of this results in other metabolites that cause brain damage.

Deficiency of phenylalanine hydroxylase (chromosome 12) or of the cofactor tetrahydrobiopterin (genes on chromosome 10 and 4) causes accumulation of phenylalanine in body fluids. The affected infant is usually normal at birth, and although blood phenylalanine levels may rise as early as four hours after birth, mental retardation develops gradually, and may not be apparent for a few months.

About 25% of infants have seizures, but over 50% have an abnormal EEG.

Microcephaly, prominent maxilla, growth retardation and wide-spaced teeth are found in untreated children.

Even with dietary treatment some degree of cognitive impairment is seen, and can vary from gross impairment or changes detected on cognitive tests.

Cerebral white matter changes are seen in older patients and may reflect a combination of late diagnosis and dietary indiscretion.

Diagnosis of classic PKU requires raised Phe levels, normal plasma tyrosine levels, increased urinary Phe metabolites and normal cofactor (tetrahydrobiopterin) concentrations.

Time taken: 1 hrs 48 mins 20 secs

Work Smart Session - MRCP Part 1

Question: 34 of 100

A 40-year-old civil servant attends the clinic stating that she has difficulty swallowing.

She gives a two month history of difficulty with solids which has progressed to difficulty tolerating liquids in the previous two weeks. She has noticed some weakness in her right arm which has affected her ability to lift certain objects like the kettle. Previously, she has enjoyed good health with no hearing loss or facial weakness. She describes no visual symptoms.

On examination, she has an absent gag reflex on the right, with reduced palatal movements. There is weakness on rotating the head to the left with flattening and weakness of elevation of the right shoulder. Eye movements, visual acuity, hearing and tongue movements are all normal.

Where is the likely site of the lesion?

(Please select 1 option)

○	Left cerebello-pontine angle
○	Left jugular foramen
○	Right cerebello-pontine angle
○	Right jugular foramen
○	Right pons

Submit answer | Skip question | Tag Question | Remove question

movements are all normal.

Where is the likely site of the lesion?

(Please select 1 option)

○	Left cerebello-pontine angle
○	Left jugular foramen
○	Right cerebello-pontine angle
◉	Right jugular foramen ✓ Correct
○	Right pons

The clinical scenario is that of a right sided pathology affecting the IX, X and XI cranial nerves.

This produces the palatal weakness and the swallowing difficulties (IX/X), while the shoulder and sternocleidomastoid weakness are due to accessory nerve (XI) involvement.

The absence of hearing loss or facial weakness makes a cerebello-pontine angle lesion unlikely.

A lesion outside the skull may also involve the XII nerve (tongue).

The most likely site, therefore is the jugular foramen.

Next question

Tag Question Remove question

Rate this question

☆☆☆☆☆

A 60-year-old woman attends the casualty department with a six week history of lethargy, neck pain, weakness in the upper limbs and gait disturbance. She describes occasional episodes of electrical sensation shooting down her spine on flexing her neck.

She has a long history of lower back pain, primary generalised osteoarthritis, and vitiligo. She takes voltarol regularly. She neither smokes nor drinks.

She is of Pakistani origin and has been in this country for the past six years. There is no history of recent foreign travel.

On examination she is afebrile. General examination is unremarkable except for vitiligo. Examination of the cranial nerves is normal. There is no wasting of the limbs but there are a few fasciculations in brachioradialis and biceps on the right. Tone is mildly increased. Apart from mild weakness of elbow, wrist and finger flexion and extension, more marked on the right, power is normal. There is inversion of the right supinator reflex, and triceps, knee and ankle jerks are brisk bilaterally. Right plantar is extensor, the left flexor. Sensation and coordination are within normal limits. Gait is mildly spastic.

Investigations show:

Hb	11.3 g/L (11.5-16.5)
WCC	7 x 10^9/L (4-11 x10^9)
Platelets	130 x 10^9/L (150-400 x10^9)
Coagulation screen	Normal
ESR	27 mm/h (0-30mm/1st hour)
CRP	17 mg/L (<10)
Sodium	137 mmol/l (137-144)
Potassium	4.2 mmol/l (3.5-4.9)
Urea	5.7 mmol/l (2.5-7.5)
Creatinine	87 umol/l (60-110)

CRP	17 mg/L (<10)
Sodium	137 mmol/l (137-144)
Potassium	4.2 mmol/l (3.5-4.9)
Urea	5.7 mmol/l (2.5-7.5)
Creatinine	87 µmol/l (60-110)
Protein	83 g/L (61-76)
Albumin	33 g/L (37-49)
Calcium	2.23 mmol/l (2.2-2.6)
Phosphate	1.2 mmol/l (0.8-1.4)
LFTs	Normal
CXR:	Normal
x Ray cervical spine:	Extensive osteophytes. Normal alignment.

What is the most likely diagnosis?

(Please select 1 option)

- ○ Degenerative cervical spondyloarthropathy
- ○ Motor neurone disease
- ○ Multiple myeloma
- ○ Polymyalgia rheumatica
- ○ Syringomyelia

LFTs	Normal
CXR:	Normal
x Ray cervical spine:	Extensive osteophytes. Normal alignment.

What is the most likely diagnosis?

(Please select 1 option)

○	Degenerative cervical spondyloarthropathy ← This is the correct answer
◉	Motor neurone disease ✕ Incorrect answer selected
○	Multiple myeloma
○	Polymyalgia rheumatica
○	Syringomyelia

The inverted supinator jerk localises the lesion to C 5/6.

Cervical spondylosis is associated with pain in the neck that may radiate down the arms or back. Sphincter disturbance is uncommon.

Multiple myeloma is associated with a high erythrocyte sedimentation rate, renal impairment, hypercalcaemia and raised globulin.

Syringomyelia would involve sensory modalities.

Motor neurone disease is a possibility, although it would be unusual for MND to localise this specifically to the C spine.

Next question

Remove Tag

Remove question

Rate this question

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 2 hrs 39 mins 9 secs

Work Smart Session - MRCP Part 1

Question: 36 of 100

A 55-year-old Caucasian man presented to hospital with fever, intermittent rigors, and worsening fatigue. He had returned from a business trip to West Africa six months previously.

What is the most likely diagnosis?

(Please select 1 option)

○	Brucellosis
○	Leishmaniasis
○	*Plasmodium falciparum* malaria
○	*Plasmodium ovale* malaria
○	Typhoid fever

Submit answer | Skip question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

(Please select 1 option)

○	Brucellosis
○	Leishmaniasis
○	*Plasmodium falciparum* malaria
◉	*Plasmodium ovale* malaria ✓ Correct
○	Typhoid fever

The Duffy blood group on the red blood cells acts as a receptor for *P. vivax*. West Africans lack the Duffy blood group and therefore *P. ovale* replaces *P. vivax* in this region.

Both *P. vivax* and *P. ovale* have a liver hypnozoite stage which can cause repeated relapses.

P. falciparum typically presents within the first three months of return.

Visceral leishmaniasis is not endemic in West Africa.

Brucellosis is a zoonosis transmitted through contaminated and untreated milk and by direct contact with infected animals. The incubation period of brucellosis is usually one to three weeks, but sometimes may be several months. It may have either a sudden or insidious onset and is accompanied by continued, intermittent, or irregular fever.

Typhoid fever presents within one to three weeks from return from an endemic area.

Next question

Remove Tag | Remove question

Rate this question

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 2 hrs 40 mins 52 secs

Work Smart Session - MRCP Part 1

Question: 37 of 100

A 30-year-old female was commenced on carbamazepine for partial complex seizures and was also advised to discontinue her moderate alcohol consumption.

Therapeutic concentrations of carbamazepine were achieved within four days with a dose of 200 mg daily but the dose needed to be increased to 400 mg daily within two weeks to achieve a therapeutic plasma concentration.

Which one of the following is likely to account for this observation?

(Please select 1 option)

○	Auto-induction of carbamazepine metabolism
○	Auto-inhibition of carbamazepine metabolism
◉	Cessation of alcohol intake
○	Concomitant prescription of the oral contraceptive pill
○	Reduced bioavailablity of carbamazepine

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Question: 37 of 100

A 30-year-old female was commenced on carbamazepine for partial complex seizures and was also advised to discontinue her moderate alcohol consumption.

Therapeutic concentrations of carbamazepine were achieved within four days with a dose of 200 mg daily but the dose needed to be increased to 400 mg daily within two weeks to achieve a therapeutic plasma concentration.

Which one of the following is likely to account for this observation?

(Please select 1 option)

○	Auto-induction of carbamazepine metabolism ← This is the correct answer
○	Auto-inhibition of carbamazepine metabolism
◉	Cessation of alcohol intake ✕ Incorrect answer selected
○	Concomitant prescription of the oral contraceptive pill
○	Reduced bioavailablity of carbamazepine

Alcohol is a liver enzyme inducer therefore stopping the alcohol should increase the activity of the carbamazepine not reduce its activity.

It is well recognised that carbamazepine is a P450 enzyme inducer but it is less well appreciated that it causes auto-induction and so would require increase in dose to maintain the same therapeutic concentration.

Next question

Remove Tag | Remove question

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 2 hrs 45 mins 30 secs

Work Smart Session - MRCP Part 1

Question: 38 of 100

A 50-year-old man presented with paraesthesia in the ring and little fingers of his right hand.

On examination there was wasting of the hypothenar eminence of his right hand.

Which one of the following movements would you expect to be weak in this patient?

(Please select 1 option)

○	Abduction of the thumb
○	Adduction of the thumb
○	Extension of the little finger
○	Flexion of the index finger
○	Opposition of the thumb

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

A 50-year-old man presented with paraesthesia in the ring and little fingers of his right hand.

On examination there was wasting of the hypothenar eminence of his right hand.

Which one of the following movements would you expect to be weak in this patient?

(Please select 1 option)

○	Abduction of the thumb
◉	Adduction of the thumb ✓ Correct
○	Extension of the little finger
○	Flexion of the index finger
○	Opposition of the thumb

The clinical features suggest an ulnar neuropathy.

Abduction and opposition of the thumb and flexion of the index finger are via the median nerve.

Extension of the little finger is via the radial nerve.

Next question

Tag Question | Remove question

Rate this question

☆☆☆☆☆

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 2 hrs 55 mins 12 secs

Work Smart Session - MRCP Part 1

Question: 39 of 100

A 55-year-old man presents with a resting tremor of his right arm and a diagnosis of idiopathic Parkinson's disease is made.

Which one of the following drugs is most likely to help his tremor?

(Please select 1 option)

- Amantadine
- Benzhexol
- Cabergoline
- Co-careldopa
- Selegiline

Submit answer | Skip question | Tag Question | Remove question

Time taken: 2 hrs 57 mins 19 secs

Work Smart Session - MRCP Part 1

Question: 39 of 100

A 55-year-old man presents with a resting tremor of his right arm and a diagnosis of idiopathic Parkinson's disease is made.

Which one of the following drugs is most likely to help his tremor?

(Please select 1 option)

○	Amantadine
◉	Benzhexol ✓ Correct
○	Cabergoline
○	Co-careldopa
○	Selegiline

Anticholinergic treatment (for example, benzhexol) is the treatment of choice of tremor predominantly Parkinson's disease.

L-dopa and dopamine agonists are the treatment of choice for bradykinesia and rigidity.

Next question

Tag Question | Remove question

Rate this question

☆☆☆☆☆

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

A 34-year-old male presents with back pain and weakness.

Which of the following would support a diagnosis of prolapsed intervertebral disc?

(Please select 1 option)

○	Bilateral symmetrical nerve involvement
○	Loss of sensation over the left outer upper thigh ← This is the correct answer
○	No evidence of nerve compression
◉	Pain which is unremitting in character ✕ Incorrect answer selected
○	Pain which is worse on resting

Prolapsed intervertebral disc is associated with pain and neurological loss in one nerve root.

Frequently roots of the sciatic nerve are affected.

Compression of more than one root suggests an alternative diagnosis.

Pain at rest would suggest an alternative diagnosis such as infection, tumour or metabolic disease, as would unremitting pain.

Next question

Remove Tag Remove question

Rate this question

☆☆☆☆☆

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 12 mins 51 secs

Work Smart Session - MRCP Part 1

Question: 4 of 100

A 26-year-old female is admitted to ICU with severe asthma.

She is ventilated for one week, and receives IV co-amoxiclav/clarithromycin, magnesium, prednisolone, sedatives and muscle relaxants.

She improves gradually but two days after stopping muscle relaxants she still is unable to be weaned from ventilatory support.

On examination, she is alert but has flaccid weakness of all limbs.

Which of the following is the likely diagnosis?

(Please select 1 option)

○	Critical illness polyneuropathy
○	Guillain-Barré syndrome
○	Hypermagnesaemia
○	Prolonged neuromuscular blockade
○	Steroid induced myopathy

Submit answer | Skip question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Time taken: 2 hrs 57 mins 19 secs

Work Smart Session - MRCP Part 1

Question: 40 of 100

A 39-year-old painter presents with a burning pain in both feet, which has deteriorated over the last six months.

He drinks 60 units of alcohol weekly and has a family history of pernicious anaemia.

On examination he has impairment of all modalities of sensation in both feet but particularly pain and temperature and absent ankle jerks.

What is the most likely diagnosis?

(Please select 1 option)

○	Alcoholic peripheral neuropathy
○	Chronic inflammatory demyelinating polyradiculopathy
○	Hereditary sensory neuropathy
○	Lead neuropathy
○	Vitamin B12 deficiency

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Shop
- Help

He drinks 60 units of alcohol weekly and has a family history of pernicious anaemia.

On examination he has impairment of all modalities of sensation in both feet but particularly pain and temperature and absent ankle jerks.

What is the most likely diagnosis?

(Please select 1 option)

◉	Alcoholic peripheral neuropathy ✓ Correct
○	Chronic inflammatory demyelinating polyradiculopathy
○	Hereditary sensory neuropathy
○	Lead neuropathy
○	Vitamin B12 deficiency

Alcohol abuse and diabetes are the commonest causes of peripheral neuropathy in the United Kingdom.

Vitamin B12 deficiency causes neuropathy that affects only the dorsal column (joint position, light touch and vibration).

Lead neuropathy is purely motor affecting mainly the upper limbs.

Chronic inflammatory demyelinating polyradiculopathy causes manly motor impairment (distal and proximal).

Next question | Tag Question | Remove question

Rate this question

☆☆☆☆☆

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 2 hrs 59 mins 44 secs

Work Smart Session - MRCP Part 1

Question: 41 of 100

A 35-year-old woman presents with pains in the right arm.

On examination she has wasting and weakness of the intrinsic muscles of the right hand, absent tendon reflexes in the right arm and impaired pinprick sensation in the right hand and forearm.

What is the most likely diagnosis?

(Please select 1 option)

- Combined median and ulnar nerve lesions
- Lower trunk brachial plexus lesion
- Neuralgic amyotrophy
- Syringomyelia
- Thoracic outlet syndrome

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

A 35-year-old woman presents with pains in the right arm.

On examination she has wasting and weakness of the intrinsic muscles of the right hand, absent tendon reflexes in the right arm and impaired pinprick sensation in the right hand and forearm.

What is the most likely diagnosis?

(Please select 1 option)

○	Combined median and ulnar nerve lesions
○	Lower trunk brachial plexus lesion
○	Neuralgic amyotrophy
◉	Syringomyelia ✓ Correct
○	Thoracic outlet syndrome

Median and ulnar nerve lesions would not cause absent reflexes in the arm.

Lower trunk brachial plexus (C8/T1) would not cause absent reflexes in the arm.

Neuralgic amyotrophy affects the upper plexus (C5-6) and therefore does not cause wasting of small muscles of hand.

Thoracic outlet syndrome will not cause absent reflexes.

Syringomyelia typically causes loss of reflexes, spinothalamic sensory loss, and weakness. It can be asymmetrical initially.

Next question

Tag Question Remove question

Rate this question

☆☆☆☆☆☆

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 3 hrs 1 mins 20 secs

Work Smart Session - MRCP Part 1

Question: 42 of 100

A 30-year-old female presents with weight gain, some hair loss and a tremor six months after commencing single drug treatment.

Which one of the following drugs is most likely to be responsible for her symptoms?

(Please select 1 option)

○	Carbamazepine
○	Lamotrigine
○	Phenytoin
○	Sodium valproate
◉	Topiramate

Submit answer | Skip question | Tag Question | Remove question

○	Lamotrigine
○	Phenytoin
◉	Sodium valproate ✓ Correct
○	Topiramate

Sodium valproate is associated with

- weight gain
- tremor
- hair loss
- teratogenicity
- polycystic ovary disease.

Lamotrigine is associated with skin rash (and Stevens-Johnson syndrome in severe cases).

Topiramate is associated with

- renal stones
- weight loss
- cognitive impairment
- tingling in extremities.

Phenytoin is associated with

- peripheral neuropathy
- cerebellum syndrome
- acne
- hirsutism
- gingival hypertrophy
- hypocalcaemia.

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 3 hrs 2 mins 38 secs

Work Smart Session - MRCP Part 1

Question: 43 of 100

A 30-year-old man complains of fairly rapid worsening of his central vision. His acuity is normal on pinhole testing.

Which of the following would not account for his symptoms?

(Please select 1 option)

- Diabetes mellitus
- Eye drops
- Eyelid swelling
- Lens subluxation
- Open angle glaucoma

Submit answer | Skip question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Which of the following would not account for his symptoms?

(Please select 1 option)

○	Diabetes mellitus
○	Eye drops
◉	Eyelid swelling ✗ Incorrect answer selected
○	Lens subluxation
○	Open angle glaucoma ← This is the correct answer

The defect in this patient's vision is corrected by viewing through a pinhole, which means that the problem is refractive and must therefore be localised to the cornea or the lens.

Causes of rapid changes in refractive error include:

- Senile cataract (increasingly myopic)
- Diabetes mellitus (high glucose raises refractive index of lens, hence myopic)
- Keratoconus (conical cornea, may occur rapidly in adolescence or early adulthood and causes myopia and astigmatism)
- Subluxation of the lens
- Eye drops (miotics produce myopia, mydriatics lead to hypermetropia) and
- Eyelid swelling.

Open angle glaucoma is associated with damage to the ganglion cells of the retina and therefore any visual deficit that is produced by it will not correct with a pinhole.

Next question

Remove Tag | Remove question

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 3 hrs 4 mins 25 secs

Work Smart Session - MRCP Part 1

Question: 44 of 100

Which of the following statements regarding CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) is correct?

(Please select 1 option)

- ○ It is associated with an abnormality of the X chromosome
- ○ It may present with migraine
- ◉ Computerised tomography (CT) of the brain is diagnostic
- ○ Death usually occurs in infancy
- ○ The thalami are usually spared

Submit answer | Skip question | Tag Question | Remove question

- Shop
- Help

(Please select 1 option)

○	It is associated with an abnormality of the X chromosome
◉	It may present with migraine ✓ Correct
○	Computerised tomography (CT) of the brain is diagnostic
○	Death usually occurs in infancy
○	The thalami are usually spared

CADASIL is a diffuse disease of small arteries, predominantly in the brain.

- It starts during mid adulthood and is characterised by:
-
- recurrent ischaemic events (transient or permanent)
- attacks of migraine with aura
- severe mood disorders
- sub-cortical dementia and
- a wide spread leukoencephalopathy on magnetic resonance imaging (MRI).
-
- CT brain is not diagnostic. Characteristic MRI changes include T2 .weighted hyperintensity of the periventricular white matter.
-
- A family history is almost always present, as it is an autosomal dominant condition, located to chromosome 19.
-
- Infarcts are subcortical, and the thalami and basal ganglia are usually involved.

Time taken: 3 hrs 5 mins 35 secs

Work Smart Session - MRCP Part 1

Question: 45 of 100

A 28-year-old shop worker is referred with a three month history of recurrent episodes of disorientation and confusion.

Her boyfriend has found her wandering around the house on several occasions, apparently with no idea of where she is or how she got there. Her mood has been very low, with frequent emotional outbursts, and she has considered leaving her job because of problems with working the computer and managing customer's queries. Her boyfriend feels her condition is significantly worsening.

Physical examination is normal, apart from recurrent, asymetrical, jerks in all four limbs.

Which of the following investigations is likely to be most useful in reaching a diagnosis?

(Please select 1 option)

○	Chest x ray
○	CT head
○	EEG
○	Liver function tests
○	Visual evoked potentials

Submit answer | Skip question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Which of the following investigations is likely to be most useful in reaching a diagnosis?

(Please select 1 option)

○	Chest x ray
○	CT head
◉	EEG ✓ Correct
○	Liver function tests
○	Visual evoked potentials

This kind of rapid cognitive decline in a young person with myoclonus is strongly suggestive of Creutzfeldt-Jakob disease (CJD). This may be new variant (in which the electroencephalogram [EEG] may be abnormal though is often normal) or sporadic in which case characteristic EEG abnormalities may be expected.

The EEG in sporadic CJD may show significant abnormalities involving deep brain areas such as the thalami. Initially the changes are diffuse, and non-specific, developing into stereotyped high voltage components on a slow background. High voltage sharp waves may be synchronous with myoclonic jerks.

Tonsillar biopsy for 14-3-3 protein marker has a diagnostic sensitivity of around 80% for prion proteins.

Other investigations to exclude other causes of rapid cognitive decline, would include magnetic resonance imaging (MRI) and lumbar puncture.

Computed tomography (CT) may show non-specific changes with atrophy out of keeping with the patient's age.

Diagnosis is confirmed with biopsy.

Next question

Remove Tag | Remove question

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 3 hrs 7 mins 16 secs

Work Smart Session - MRCP Part 1

Question: 46 of 100

A 49-year-old man is diagnosed with small cell lung cancer.

Despite a normal brain MRI he develops progressive truncal ataxia.

Which of the following would be most useful in the diagnosis of his condition?

(Please select 1 option)

○	Anti-Purkinje cell antibody levels
○	Lumbar puncture
○	Serum calcium
○	Serum sodium
○	Visual evoked potentials

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Help

Which of the following would be most useful in the diagnosis of his condition?

(Please select 1 option)

◉	Anti-Purkinje cell antibody levels ✓ Correct
○	Lumbar puncture
○	Serum calcium
○	Serum sodium
○	Visual evoked potentials

Paraneoplastic syndromes are a result of antibody generation from or against malignant cells attacking normal tissue.

Examples include antineuronal antibodies (anti-Hu, anti-Yo, anti-Ri) directed against the Purkinje cells of the cerebellum leading to the cerebellar syndrome described above.

The Lambert-Eaton myasthenic syndrome (LEMS) is a pre-synaptic disorder of auto-antibody IgG directed against the pre-synaptic calcium channel leading to impaired acetylcholine release. Clinically, patients present with muscle weakness that improves with exercise.

Symptomatic hyponatraemia due to syndrome of inappropriate antidiuretic hormone secretion (SIADH) is treated with demeclocycline which induces nephrogenic diabetes insipidus leading to excretion of excess water.

Both non-small cell and small cell lung cancers are associated with paraneoplastic syndromes, although they are more common with the latter due to its neuroendocrine cell origin.

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 3 hrs 8 mins 5 secs

Work Smart Session - MRCP Part 1

Question: 47 of 100

A 39-year-old woman is found to have absent ankle jerks and gait disturbance.

Which of the following investigations is not indicated?

(Please select 1 option)

- ANA
- B_{12} levels
- Cholestanol levels
- Ferritin
- VDRL

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Help

○	ANA
○	B_{12} levels
○	Cholestanol levels
◉	Ferritin ✓ Correct
○	VDRL

Absent ankle jerks may occur in conditions associated with neuropathy (B_{12} deficiency, SLE, cerebrotendinous xanthomatosis) and dorsal root disease (tabes dorsalis).

Gait disturbance may occur for a variety of reasons:

- Sensory ataxia in B_{12} deficiency and tabes dorsalis
- Pyramidal signs in B_{12} deficiency and SLE
- Cerebellar ataxia in cerebrotendinous xanthomatosis.

Cerebrotendinous xanthomatosis is an inherited condition, associated with accumulation of cholesterol in tissues including brain, peripheral nerve and tendons which produces a clinical picture of

- early onset dementia
- gait ataxia
- loss of vibration sense
- cataracts
- large tendon xanthomata.

It is eminently treatable by the oral administration of chenodeoxycholic acid.

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 3 hrs 9 mins 25 secs

Work Smart Session - MRCP Part 1

Question: 48 of 100

A male teacher who is 31-years-old attends clinic with his partner who tells you that he has memory problems. The only other symptom is intermittent diarrhoea over the preceding four months.

He has limited vertical eye movements and exhibits rhythmic simultaneous eye and mouth movements.

Which pathogen is most likely to be the cause of his symptoms?

(Please select 1 option)

○	*Clostridium botulinum*
○	HIV
○	Prion protein
○	*Salmonella enteritidis*
○	*Tropheryma whippleii*

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

○	HIV
◉	Prion protein ✗ Incorrect answer selected
○	*Salmonella enteritidis*
○	*Tropheryma whippleii* ← This is the correct answer

This is a tough question.

The suggestion here is that the patient has Whipple's disease, due to intestinal infection with *Tropheryma whipplei*.

Non-neurological manifestations of Whipple's disease are more common and include chronic diarrhoea, malabsorption with steatorrhoea and associated abdominal distension and tenderness.

Neurological manifestations involve a chronic progressive impairment of higher mental function in association with seizures, myoclonus ataxia and oculomasticatory myorhythmia found uniquely in Whipple's.

The diagnosis is made by duodenal or jejunal biopsy and demonstrating the bacilli within the mucosa on PAS staining.

Characteristically, there is accumulation of glycoprotein and fat filled (PAS +ve) macrophage within the lamina propria.

Botulism does not produce this clinical picture.

An AIDS related dementia is possible, but abnormal facial movements would be unusual.

Creutzfeldt-Jakob disease (CJD) could also produce this picture, although myoclonus is usually more of a feature and cognitive impairment is more generalised and acute.

Salmonella enteritidis usually causes only an acute diarrhoeal illness, but may lead to bacteraemia and chronic long-term carriage and excretion.

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 3 hrs 10 mins 36 secs

Work Smart Session - MRCP Part 1

Question: 49 of 100

An 18-year-old male is diagnosed with Becker's muscular dystrophy.

Which of the following statements concerning the genetics of the condition is correct?

(Please select 1 option)

○	His brothers will all be affected
○	His daughters will have a 50% chance of being carriers
○	His daughters' sons will have a 50% chance of having the disease
○	His sons will be carriers of the condition
○	His sons' children will have a 50% chance of having the disease

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Question: 49 of 100

An 18-year-old male is diagnosed with Becker's muscular dystrophy.

Which of the following statements concerning the genetics of the condition is correct?

(Please select 1 option)

○	His brothers will all be affected
○	His daughters will have a 50% chance of being carriers
◉	His daughters' sons will have a 50% chance of having the disease ✓ Correct
○	His sons will be carriers of the condition
○	His sons' children will have a 50% chance of having the disease

Becker's muscular dystrophy is an X-linked condition and so 50% of males will be affected in a family.

His sons will get the X chromosome from his wife and so will not be carriers but all his daughters will be carriers.

However, his daughters' sons will consequently have a 50% chance of inheriting the disease as all his daughters are carriers and there is a one in two chance (50:50) of passing the gene onto their sons.

On the other hand his sons who are not affected do not pass on the condition.

Next question | Tag Question | Remove question

Rate this question

☆☆☆☆☆

relaxants.

She improves gradually but two days after stopping muscle relaxants she still is unable to be weaned from ventilatory support.

On examination, she is alert but has flaccid weakness of all limbs.

Which of the following is the likely diagnosis?

(Please select 1 option)

○	Critical illness polyneuropathy
○	Guillain-Barré syndrome
○	Hypermagnesaemia
◉	Prolonged neuromuscular blockade ✓ Correct
○	Steroid induced myopathy

The history suggests prolonged neuromuscular junction (NMJ) blockade which may be exacerbated by both corticosteroids and magnesium.

This condition was originally described with suxamethonium due to hereditary reductions in plasma cholinesterase activity. However, drugs and electrolyte abnormalities may exacerbate this.

Next question

Remove Tag Remove question

Rate this question

☆☆☆☆☆

Time taken: 14 mins 2 secs

Work Smart Session - MRCP Part 1

Question: 5 of 100

A 40-year-old female presents with fatigue.

She has a six month history of secondary amenorrhoea and galactorrhoea.

Examination shows an obese lady with a BMI of 36 kg/m^2. Neurological examination is normal. A prolactin is measured at 3124 mU/L (normal <550mU/L) and thyroid function tests reveal a free T4 of 7.5 nmol/l and a TSH of 120 mU/l . A CT scan shows a bulky pituitary gland.

Which of the following is the likely diagnosis?

(Please select 1 option)

○	Cushing's syndrome
○	Hypothyroidism
○	Macroprolactinoma
○	Microprolactinoma
○	Type 2 diabetes

Submit answer | Skip question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 3 hrs 13 mins 18 secs

Work Smart Session - MRCP Part 1

Question: 50 of 100

A 43-year-old man presented with diplopia of six weeks duration. On examination he had normal corrected visual acuity in each eye, restriction of adduction of the right eye and nystagmus in the left eye on left lateral gaze.

What is the most likely diagnosis?

(Please select 1 option)

- ○ Brainstem demyelination
- ○ Graves' ophthalmopathy
- ○ Internal carotid artery aneurysm
- ○ Lateral medullary syndrome
- ○ Steele-Richardson syndrome

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Question: 50 of 100

A 43-year-old man presented with diplopia of six weeks duration. On examination he had normal corrected visual acuity in each eye, restriction of adduction of the right eye and nystagmus in the left eye on left lateral gaze.

What is the most likely diagnosis?

(Please select 1 option)

○	Brainstem demyelination ← This is the correct answer
○	Graves' ophthalmopathy
○	Internal carotid artery aneurysm
○	Lateral medullary syndrome
◉	Steele-Richardson syndrome ✕ Incorrect answer selected

The features are suggestive of internuclear ophthalmoplegia which is due to a lesion at the medial longitudinal fasciculus and in this male the most likely explanation is multiple sclerosis (MS).

Other causes include brainstem infarction, syphilis and Lyme disease.

Next question

Remove Tag Remove question

Rate this question

☆☆☆☆☆

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 3 hrs 16 mins 58 secs

Work Smart Session - MRCP Part 1

Question: 51 of 100

Which vertebral level and corresponding structure is correct?

(Please select 1 option)

○	C4 and bifurcation of the carotid artery
○	T2 and manubriosternal joint
○	T8 and aortic opening in the diaphragm
○	T10 and opening for vena cava in diaphragm
○	T12 and oesophageal opening in the diaphragm

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Time taken: 3 hrs 19 mins 5 secs

Work Smart Session - MRCP Part 1

Question: 51 of 100

Which vertebral level and corresponding structure is correct?

(Please select 1 option)

◉	C4 and bifurcation of the carotid artery ✓ Correct
○	T2 and manubriosternal joint
○	T8 and aortic opening in the diaphragm
○	T10 and opening for vena cava in diaphragm
○	T12 and oesophageal opening in the diaphragm

The carotid artery bifurcates at C4.

The manubriosternsal joint (angle of Louis) lies at the level of the T4/5 intervertebral disk.

The caval opening in the diaphragm lies at T8.

The oesoghageal opening of the diaphragm lies at T10.

The aortic opening is at T12.

Next question

Tag Question | Remove question

Rate this question

☆☆☆☆☆

Question: 52 of 100

An 18-year-old woman sustains severe head injuries in a road traffic accident.

The following day her investigations show:

Sodium	160 mmol/l	(137-144)
Potassium	3.7 mmol/l	(3.5-4.9)
Chloride	120 mmol/l	(95-107)
Urea	3.0 mmol/l	(2.5-7.5)
Creatinine	90 µmol/l	(60- 110)

Which one of the following statements is correct?

(Please select 1 option)

- Rapid rehydration with 5% dextrose is indicated
- She has the syndrome of inappropriate antidiuretic hormone secretion (SIADH)
- She should be treated with sodium restriction
- She will have a hypercholraemic acidosis
- Urine osmolality will be low

Submit answer | Skip question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Chloride	120 mmol/l	(95-107)
Urea	3.0 mmol/l	(2.5-7.5)
Creatinine	90 µmol/l	(60- 110)

Which one of the following statements is correct?

(Please select 1 option)

○	Rapid rehydration with 5% dextrose is indicated
○	She has the syndrome of inappropriate antidiuretic hormone secretion (SIADH)
◉	She should be treated with sodium restriction ✕ Incorrect answer selected
○	She will have a hypercholraemic acidosis
○	Urine osmolality will be low ← This is the correct answer

There is a marked hypernatraemia with elevated chloride but normal potassium and urea in a patient with severe head injuries.

The likely cause of this presentation is diabetes insipidus. Urine osmolality is therefore likely to be low.

You cannot say that she has a hyperchloraemic acidosis as you do not have her bicarbonate concentration but if you assume that the anion gap would be normal, that is 10-12, then this would suggest that the bicarbonate is elevated, suggesting either a metabolic alkalosis or respiratory acidosis with compensation.

Although restoration of normal volaemia and osmolality is required, giving 5% dextrose may exacerbate any cerebral oedema and so correction should be gradual.

Next question

Remove Tag | Remove question

Rate this question

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 3 hrs 33 mins 9 secs

Work Smart Session - MRCP Part 1

Question: 53 of 100

An 80-year-old male presented with acute right-sided weakness.

Examination revealed minimal right facial weakness, impaired elevation of the right shoulder, with relatively preserved right hand strength. There was global weakness in the right leg which appeared to be maximal in the foot.

Which of the following arteries is most likely to have been affected?

(Please select 1 option)

- Anterior cerebral artery
- Lenticulostriate artery
- Middle cerebral artery
- Posterior cerebral artery
- Posterior communicating artery

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

○	Anterior cerebral artery ← This is the correct answer
○	Lenticulostriate artery
◉	Middle cerebral artery ✕ Incorrect answer selected
○	Posterior cerebral artery
○	Posterior communicating artery

It's a tricky question and it is purposely so.

The wording of the description could be due to middle or anterior artery circulation stroke but the challenge is to choose which is the more likely.

The case as described is the classic presentation of an anterior cerebral artery stroke as originally described in the literature. (Critchley M. The anterior cerebral artery and its syndromes. Brain 1930; 53:120-165.)

Unilateral occlusion (distal to ant. comm. origin) of **anterior cerebral artery** produces contralateral sensorimotor deficits mainly involving the lower extremity with relative sparing of face and hands (think of the humunculus).

The lateral lenticulostriate artery is a branch of the middle cerebral artery. Occlusion causes damage to the internal capsule resulting in contralateral hemiparesis and sensory deficit. Speech may be affected (medial temporal lobe) as well as visual function (Meyer's loop: optic radiations affected).

Middle cerebral artery: Occlusion at the stem (proximal segment) results in:

- Contralateral hemiplegia affecting face, arm, and leg (lesser)
- Homonymous hemianopia - ipsilateral head/eye deviation
- If on left: global aphasia

Posterior cerebral artery: A variety of neurological syndromes including:

- Pure hemisensory loss
- Visual field loss- a variety
- Visual agnosia
- Disorders of reading (alexia, dyslexia) and more ...

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 3 hrs 34 mins 9 secs

Work Smart Session - MRCP Part 1

Question: 54 of 100

A 60-year-old woman presented with a small right pupil, right ptosis and impaired sweating over the ipsilateral forehead. Sweating on the rest of the face was unaffected.

Where is the most likely site of this lesion?

(Please select 1 option)

- Cervical spinal cord
- Common carotid artery
- Hypothalamus
- Internal carotid artery
- Lateral medulla

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 3 hrs 39 mins 14 secs

Work Smart Session - MRCP Part 1

Question: 54 of 100

A 60-year-old woman presented with a small right pupil, right ptosis and impaired sweating over the ipsilateral forehead. Sweating on the rest of the face was unaffected.

Where is the most likely site of this lesion?

(Please select 1 option)

○	Cervical spinal cord
○	Common carotid artery
○	Hypothalamus
◉	Internal carotid artery ✓ Correct
○	Lateral medulla

Because the sympathetic plexus accompanying the internal carotid artery innervates sweat glands only to the medial forehead, facial anhydrosis does not occur significantly with postganglionic Horner syndrome.

Next question | Tag Question | Remove question

Rate this question

☆☆☆☆☆

Time taken: 3 hrs 39 mins 14 secs

Work Smart Session - MRCP Part 1

Question: 55 of 100

A 56-year-old woman presents with problematical tremor which has deteriorated over the last three months and she notes that it is exacerbated by changes in position.

She has a past history of asthma for which she is taking inhaled salbutamol and one year ago she underwent liver transplantation for primary biliary cirrhosis for which she takes cyclosporin.

On examination she seems quite well but has a noticeable coarse tremor of her outstretched hands. There are no other abnormalities noticeable on neurological examination.

How should this patient be managed?

(Please select 1 option)

○	Add benzhexol
○	L-Dopa
○	Propranolol
◉	Reduce dose cyclosporin
○	Reduce dose salbutamol

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Help

primary biliary cirrhosis for which she takes cyclosporin.

On examination she seems quite well but has a noticeable coarse tremor of her outstretched hands. There are no other abnormalities noticeable on neurological examination.

How should this patient be managed?

(Please select 1 option)

○	Add benzhexol
○	L-Dopa
○	Propranolol
◉	Reduce dose cyclosporin ✓ Correct
○	Reduce dose salbutamol

Cyclosporin is well known to cause coarse tremor. In the first instance the dose should be reduced. Usually the neurological side effects of cyclosporin are dose dependent.

The tremor with salbutamol tends not to be coarse as described in this case, being approximately 10-12 Hz.

Next question | Tag Question | Remove question

Rate this question

☆☆☆☆☆

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Question: 56 of 100

A 56-year-old female presented to her GP with pain in the left side of her neck radiating down the lateral aspect of her arm and forearm.

She had also noticed some weakness of her left shoulder and struggled to elevate her arm. She had a longstanding history of rheumatoid arthritis, treated with steroids and penicillamine. She was a non-smoker and did not drink any alcohol.

On examination there was some wasting over the left deltoid and evidence of fasciculations. Neck movements appeared full except that lateral movement exacerbated the left arm pain.

On examination of the upper limb, tone appeared reduced at the elbow and wrist and the biceps jerk was only present on re-enforcement. The left supinator jerk was inverted and the triceps jerk appeared brisk. There was some weakness of left shoulder abduction, elbow flexion and supination, but finger movements and elbow extension were intact. There was a sensory deficit over the lateral aspect of the left upper arm and forearm. The right arm appeared normal.

On examination of he lower limb, tone was increased, but power appeared normal. All reflexes were brisk and both plantar responses were extensor.

Investigations showed:

Haemoglobin	11.4 g/dl	(13.0 18.0 g/dL)
White cell count	3.4 x 10^9/L	(4 11 x 10^9/L)
Platelets	245 x 10^9/L	(150 400 x 10^9/L)
ESR (Westergren)	45 mm/1st hour	(0 15 mm/1st hour)
Serum sodium	145 mmol/L	(137 144 mmol/L)
Serum potassium	3.2 mmol/L	(3.5 4.9 mmol/L)
Serum urea	6.7 mmol/L	(2.5 7.5 mmol/L)
Serum creatinine	135 umol/L	(60 110 umol/L)
Serum creatine kinase	178 U/L	(24 170 U/L)
Fasting plasma glucose	8.7 mmol/L	(3 6 mmol/L)

What is the most likely diagnosis?

normal.

On examination of he lower limb, tone was increased, but power appeared normal. All reflexes were brisk and both plantar responses were extensor.

Investigations showed:

Haemoglobin	11.4 g/dl	(13.0 18.0 g/dL)
White cell count	3.4 x 10^9/L	(4 11 x 10^9/L)
Platelets	245 x 10^9/L	(150 400 x 10^9/L)
ESR (Westergren)	45 mm/1st hour	(0 15 mm/1st hour)
Serum sodium	145 mmol/L	(137 144 mmol/L)
Serum potassium	3.2 mmol/L	(3.5 4.9 mmol/L)
Serum urea	6.7 mmol/L	(2.5 7.5 mmol/L)
Serum creatinine	135 umol/L	(60 110 umol/L)
Serum creatine kinase	178 U/L	(24 170 U/L)
Fasting plasma glucose	8.7 mmol/L	(3 6 mmol/L)

What is the most likely diagnosis?

(Please select 1 option)

- Cervical myelopathy
- Circumflex neuropathy
- Inclusion body myositis
- Motor neurone disease
- Steroid-induced myopathy

Submit answer | Skip question | Tag Question | Remove question

Serum creatinine	135 umol/L	(60 110 umol/L)
Serum creatine kinase	178 U/L	(24 170 U/L)
Fasting plasma glucose	8.7 mmol/L	(3 6 mmol/L)

What is the most likely diagnosis?

(Please select 1 option)

○	Cervical myelopathy ← This is the correct answer
○	Circumflex neuropathy
◉	Inclusion body myositis ✕ Incorrect answer selected
○	Motor neurone disease
○	Steroid-induced myopathy

This patient has a cervical myelopathy, most likely as a result of her rheumatoid arthritis.

The likely level is C5/C6 given that there is weakness of the deltoid, biceps and supinator and the supinator jerk is inverted.

She also has long tract signs in her legs with hypertonia and hyper-reflexia.

A circumflex neuropathy would account for the weakness and fasciculations of the deltoid, but would not explain the upper motor neurone signs in the legs, or weakness of the biceps and supinator.

Inclusion body myositis, an inflammatory myopathy, would present with bilateral often-asymmetrical weakness, which has a tendency to affect distal musculature. The tendon reflexes would be normal and the creatine kinase would be normal or mildly elevated.

Motor neurone disease presents with upper and lower motor signs in absence of sensory disturbance.

A steroid induced myopathy would cause proximal weakness and wasting with normal reflexes and sensation.

Next question

Remove Tag | Remove question

EN 9:54 PM 3/5/2011

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 3 hrs 49 mins 9 secs

Work Smart Session - MRCP Part 1

Question: 57 of 100

An 80-year-old woman has a three month history of progressive numbness and unsteadiness of her gait.

On examination, there is a mild spastic paraparesis, with brisk knee reflexes, ankle reflexes are present with reinforcement, extensor plantars, sensory loss in the legs with a sensory level at T10, impaired joint position sense in the toes, and loss of vibration sense below the iliac crests.

Investigations were as follows:-

Haemoglobin	12.2 g/dL (12-16)
MCV	95 fL (80-96)

What is the most likely diagnosis?

(Please select 1 option)

- Anterior spinal artery occlusion
- Dorsal meningioma
- Multiple sclerosis
- Subacute combined degeneration of the cord
- Tabes dorsalis

Submit answer | Skip question | Remove Tag | Remove question

Investigations were as follows:-

Haemoglobin	12.2 g/dL (12-16)
MCV	95 fL (80-96)

What is the most likely diagnosis?

(Please select 1 option)

○	Anterior spinal artery occlusion
◉	Dorsal meningioma ✓ Correct
○	Multiple sclerosis
○	Subacute combined degeneration of the cord
○	Tabes dorsalis

The presence of a sensory loss at T10 indicates a thoracic myelopathy.

Subacute combined degeneration of the cord is unlikely as the haemoglobin concentration and mean corpuscular volume (MCV) are normal.

Anterior spinal artery occlusion is unlikely as the history is progessive and chronic.

Next question

Remove Tag Remove question

Rate this question

☆☆☆☆☆

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 3 hrs 53 mins 2 secs

Work Smart Session - MRCP Part 1

Question: 58 of 100

A 73-year-old man presents with an abrupt onset of double vision and left leg weakness.

Examination shows weakness of abduction of the right eye and right-sided facial weakness affecting upper and lower parts of the face. He also has a left hemiparesis.

Where is the lesion?

(Please select 1 option)

- Left frontal lobe
- Left lateral medulla
- Right corpus striatum
- Right midbrain
- Right pons

Submit answer | Skip question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

A 73-year-old man presents with an abrupt onset of double vision and left leg weakness.

Examination shows weakness of abduction of the right eye and right-sided facial weakness affecting upper and lower parts of the face. He also has a left hemiparesis.

Where is the lesion?

(Please select 1 option)

○	Left frontal lobe
○	Left lateral medulla
○	Right corpus striatum
○	Right midbrain
◉	Right pons ✓ Correct

The abducens nucleus is next to the facial nucleus in pons.

They commonly co-exist in a pontine cerebrovascular accident (CVA).

Hemiparesis is also a common feature of pontine lesion.

Next question | Tag Question | Remove question

Rate this question

☆☆☆☆☆

Question: 59 of 100

A 92-year-old man was admitted in a confused state. He has a history of immobility due to severe lower back pain. He had been losing weight for three months and had complaints of weakness, urinary frequency, thirst, poor urinary stream and constipation.

Lumbar spine x rays show severe osteopenia and collapse of the body of the vertebra at L3. Investigations show:

Haemoglobin	9.6 g/dl	(13.0-18.0)
Sodium	144 mmol/l	(137-144)
Potassium	3.9 mmol/l	(3.5-4.9)
Urea	10.4 mmol/l	(2.5-7.5)
Creatinine	120 mol/l	(60-110)
Glucose	8 mmol/l	(3.0-6.0)
Dipstick urine	Blood ++, protein +	

What is the most important immediate investigation?

(Please select 1 option)

- ○ Chest x ray
- ○ Monosodium urate (MSU)
- ○ Prostate specific antigen
- ○ Serum calcium
- ○ Serum protein electrophoresis

Lumbar spine x rays show severe osteopenia and collapse of the body of the vertebra at L3. Investigations show:

Haemoglobin	9.6 g/dl	(13.0-18.0)
Sodium	144 mmol/l	(137-144)
Potassium	3.9 mmol/l	(3.5-4.9)
Urea	10.4 mmol/l	(2.5-7.5)
Creatinine	120 mol/l	(60-110)
Glucose	8 mmol/l	(3.0-6.0)
Dipstick urine	Blood ++, protein +	

What is the most important immediate investigation?

(Please select 1 option)

○	Chest x ray
○	Monosodium urate (MSU)
○	Prostate specific antigen
○	Serum calcium ← This is the correct answer
◉	Serum protein electrophoresis ✕ Incorrect answer selected

The likely underlying diagnosis is myeloma. The symptoms of constipation, weakness and thirst indicate hypercalcemia.

Serum calcium should be the **immediate** investigation.

pituitary gland.

Which of the following is the likely diagnosis?

(Please select 1 option)

○	Cushing's syndrome
○	Hypothyroidism ← This is the correct answer
◉	Macroprolactinoma ✕ Incorrect answer selected
○	Microprolactinoma
○	Type 2 diabetes

Hypothyroidism is not an uncommon cause of hyperprolactinaemia and should be part of the work up of all patients with an elevated prolactin.

The clinical scenario here would be consistent with a diagnosis of hypothyroidism.

Macroprolactin may masquerade as hyperprolactinaemia and most laboratories now carry out this assay if requested in patients with hyperprolactinaemia. Cabergoline or bromocriptine should only be commenced if a macroprolactinoma is confirmed.

A bulky pituitary gland on CT scan is not a significant finding and an MRI of the pituitary is required to delineate the anatomy of the pituitary gland.

Bitemporal hemianopia would be a feature of a macroprolactinoma impinging on the optic chiasm.

Next question

Remove Tag | Remove question

EN 4:21 PM 3/1/2011

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 16 mins 3 secs

Work Smart Session - MRCP Part 1

Question: 6 of 100

A 30-year-old lady who suffers from migraine complains that taking the recommended dose of paracetamol during an attack fails to relieve her headache. She has no other significant past medical history. She is a smoker of 15 cigarettes per day and also drinks alcohol 16 units per week.

Which of the following factors most likely explains the lack of efficacy of paracetamol in this lady?

(Please select 1 option)

- Bacterial overgrowth
- Delayed gastric emptying
- First pass metabolism
- p450 enzyme induction
- p450 enzyme inhibition

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 4 hrs 8 mins 24 secs

Work Smart Session - MRCP Part 1

Question: 61 of 100

A 45-year-old man has a history of progressive weakness for five weeks. He had particular difficulty getting out of the bath.

On examination there was severe truncal and proximal limb weakness, without wasting or fasciculation.

Tendon reflexes, plantar responses and sensation were all normal.

The vital capacity was 1.8L.

What is the most likely diagnosis?

(Please select 1 option)

○	Cervical myelitis
○	Guillain-Barre syndrome
○	Polio
○	Polymyositis
○	Syringobulbia

Submit answer | Skip question | Tag Question | Remove question

A 45-year-old man has a history of progressive weakness for five weeks. He had particular difficulty getting out of the bath.

On examination there was severe truncal and proximal limb weakness, without wasting or fasciculation.

Tendon reflexes, plantar responses and sensation were all normal.

The vital capacity was 1.8L.

What is the most likely diagnosis?

(Please select 1 option)

○	Cervical myelitis
◉	Guillain-Barre syndrome ✕ Incorrect answer selected
○	Polio
○	Polymyositis ← This is the correct answer
○	Syringobulbia

The presentation of myopathy is characterised by proximal weakness with normal reflexes and sensation and the absence of fasciculations.

Polymyositis is the commonest cause of inflammatory muscle disease in people under 50-years-old (inclusion body myositis is the commonest in those over 50-years-old).

Next question

Remove Tag Remove question

Rate this question

☆☆☆☆☆

Time taken: 4 hrs 10 mins 57 secs

Work Smart Session - MRCP Part 1

Question: 62 of 100

A 72-year-old woman has a five year history of worsening mental functioning with trouble remembering things. She has no problems with movement.

She is noted on an MRI scan of the brain to have symmetrically increased size of the lateral ventricles along with cerebral cortical atrophy in a mainly frontal and parietal distribution.

A lumbar puncture reveals a normal opening pressure, and analysis of the clear, colorless cerebrospinal fluid reveals glucose and protein which are in normal ranges.

Cell count on the CSF shows 3 WBCs (all lymphocytes) and 1 RBC.

A fundoscopic examination is normal.

Which of the following findings is most likely associated with her underlying disease process?

(Please select 1 option)

○	Increased numbers of Lewy bodies
○	Loss of Betz cells
○	Loss of gamma aminobutyric acid (GABA)
○	Perivascular mononuclear inflammation
○	Presence of the e4 allele of apolipoprotein E

Submit answer | Skip question | Remove Tag | Remove question

She is noted on an MRI scan of the brain to have symmetrically increased size of the lateral ventricles along with cerebral cortical atrophy in a mainly frontal and parietal distribution.

A lumbar puncture reveals a normal opening pressure, and analysis of the clear, colorless cerebrospinal fluid reveals glucose and protein which are in normal ranges.

Cell count on the CSF shows 3 WBCs (all lymphocytes) and 1 RBC.

A fundoscopic examination is normal.

Which of the following findings is most likely associated with her underlying disease process?

(Please select 1 option)

○	Increased numbers of Lewy bodies
○	Loss of Betz cells
○	Loss of gamma aminobutyric acid (GABA)
◉	Perivascular mononuclear inflammation ✕ Incorrect answer selected
○	Presence of the e4 allele of apolipoprotein E ← This is the correct answer

She has findings characteristic for Alzheimer's disease.

Loss of GABA is seen in Parkinson's disease.

Perivascular mononuclear inflammation is seen in multiple sclerosis.

Loss of Betz cells is seen in motor neurone disease.

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 4 hrs 13 mins 25 secs

Work Smart Session - MRCP Part 1

Question: 63 of 100

Which of the following is correct regarding herpes simplex encephalitis?

(Please select 1 option)

○	Is associated with a polymorphonuclear pleocytosis in the CSF
○	Produces a diffuse, evenly distributed inflammation of cerebral tissues
○	Produces a typical EEG pattern with lateralised periodic discharges at 2 Hz
○	Should be treated with acyclovir as soon as the diagnosis is confirmed by urgent CSF viral antibody titres
○	Shows a peak incidence in the autumn

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

http://my.onexamination.com/Assessment/Que
Questions Set : REF4335
File Edit View Favorites Tools Help

Time taken: 4 hrs 14 mins 9 secs

Work Smart Session - MRCP Part 1

Question: 63 of 100

Which of the following is correct regarding herpes simplex encephalitis?

(Please select 1 option)

○	Is associated with a polymorphonuclear pleocytosis in the CSF
○	Produces a diffuse, evenly distributed inflammation of cerebral tissues
◉	Produces a typical EEG pattern with lateralised periodic discharges at 2 Hz ✓ Correct
○	Should be treated with acyclovir as soon as the diagnosis is confirmed by urgent CSF viral antibody titres
○	Shows a peak incidence in the autumn

This EEG pattern is seen but is not diagnostic.

Winter is the peak incidence.

A lymphocytosis is characteristic in the cerebrospinal fluid (CSF).

Temporal lobe location is typical not diffuse.

Immediate treatment is required on clinical suspicion - do not wait!

Next question

Tag Question Remove question

Rate this question

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 4 hrs 14 mins 9 secs

Work Smart Session - MRCP Part 1

Question: 64 of 100

A 48-year-old female patient develops an acute, severe and isolated right C6 radiculopathy affecting both the motor and sensory roots.

She is examined in an EMG clinic three weeks after the onset of symptoms.

Which of the following statements is true?

(Please select 1 option)

○	Absent sensory nerve potentials would be expected on examination of the thumb and index finger on the right.
○	A repeat examination 12 months later is likely to reveal rapidly recruited low amplitude short duration motor units in the clinically involved muscle on EMG.
○	Fibrillation potentials would be expected in the right extensor carpi ulnaris and extensor pollicis brevis.
○	Triceps tendon jerk is likely to be depressed or absent.
○	Voluntary motor unit activity may be absent in the right biceps.

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Time taken: 4 hrs 17 mins 22 secs

Work Smart Session - MRCP Part 1

Question: 64 of 100

A 48-year-old female patient develops an acute, severe and isolated right C6 radiculopathy affecting both the motor and sensory roots.

She is examined in an EMG clinic three weeks after the onset of symptoms.

Which of the following statements is true?

(Please select 1 option)

○	Absent sensory nerve potentials would be expected on examination of the thumb and index finger on the right. ← This is the correct answer
○	A repeat examination 12 months later is likely to reveal rapidly recruited low amplitude short duration motor units in the clinically involved muscle on EMG.
○	Fibrillation potentials would be expected in the right extensor carpi ulnaris and extensor pollicis brevis.
◉	Triceps tendon jerk is likely to be depressed or absent. ✕ Incorrect answer selected
○	Voluntary motor unit activity may be absent in the right biceps.

A difficult question. Thumb and index finger are within the C6 dermatome.

Extensor pollicis brevis and extensor carpi ulnaris are supplied by C7/8. Fibres from C7/8 are also responsible for the triceps reflex.

A pattern of rapidly recruited low amplitude short duration motor units on the electromyogram (EMG) would be considered to represent myopathic changes rather than de-innervation.

Next question | Tag Question | Remove question

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 4 hrs 17 mins 22 secs

Work Smart Session - MRCP Part 1

Question: 65 of 100

Which of the following statements regarding hiccup is true?

(Please select 1 option)

○	Is caused by a tonic relaxation of the diaphragm.
○	Is commonly caused by local irritation to the vagus nerve.
○	Can reliably be treated with theophylline.
○	May be caused by a foreign body in the nose.
○	May be caused by a posterior fossa tumour.

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Community
- Shop
- Help

Which of the following statements regarding hiccup is true?

(Please select 1 option)

○	Is caused by a tonic relaxation of the diaphragm.
○	Is commonly caused by local irritation to the vagus nerve.
○	Can reliably be treated with theophylline.
○	May be caused by a foreign body in the nose.
◉	May be caused by a posterior fossa tumour. ✓ Correct

Hiccup is caused by frequent or rhythmic clonic contraction of the diaphragm. When prolonged, other causes should be considered including:

- CNS disease: Posterior fossa tumour, brain injury, encephalitis
- Phrenic nerve or diaphragm irritation: Tumour, pleurisy, pneumonia, intrathoracic adenopathy, pericarditis, gastro-oesophageal reflux, oesophagitis
- Systemic causes: Alcohol intoxication, uraemia
- Other: Foreign body or insect in the ear. In infants it may be associated with apnoea or hyperventilation.

Folk remedies include aerophagia, breath holding, pharyngeal stimulation, distraction. Haloperidol, metaclopramide and several anaesthetic agents are also said to work.

Copyright © 2002 Dr Colin Melville

Next question | Tag Question | Remove question

Rate this question

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 4 hrs 17 mins 59 secs

Work Smart Session - MRCP Part 1

Question: 66 of 100

Which of the following is true regarding sensory neural hearing loss?

(Please select 1 option)

○	Approximately 1 per 1000 children will have greater than 40db hearing loss.
○	The incidence is half as high in babies admitted to neonatal intensive care units compared with the normal population.
○	The risk is increased in children who have had post-natal rubella.
○	The risk is increased in Down syndrome.
○	The risk is increased in Werdnig-Hoffman syndrome.

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

(Please select 1 option)

○	Approximately 1 per 1000 children will have greater than 40db hearing loss. ← This is the correct answer
○	The incidence is half as high in babies admitted to neonatal intensive care units compared with the normal population.
○	The risk is increased in children who have had post-natal rubella.
◉	The risk is increased in Down syndrome. ✕ Incorrect answer selected
○	The risk is increased in Werdnig-Hoffman syndrome.

Sensory neural hearing loss is caused by lesions in the cochlea or the auditory nerve or central connections. It may be unilateral or bilateral. Language acquisition and secondary educational difficulties follow, with social isolation, and an increased risk of mental health problems. The approximate incidence is 1 per 1000 children.

Risk factors include:

- Neonatal intensive-care unit (NICU) admission: low birth weight, less than 32 weeks gestation, prolonged ventilation, prolonged jaundice, ototoxic drugs, hypoxic ischaemic encephalopathy, neonatal meningitis
- Congenital infection (rubella, cytomegalovirus [CMV])
- Dysmorphic syndromes (affecting head and neck)
- Family history of a close relative needing a hearing aid below the age of 5 years
- Infections: acute bacterial or TB meningitis, mumps (latter usually unilateral).

If all risk factors are considered, only around 50% of cases could be identified by testing between 5 and 10% of all babies.

Conductive hearing loss is related to middle ear pathology. This is commoner in Down syndrome, cleft palate, Turner's syndrome, and facial malformation syndromes.

Werdnig-Hoffman is associated with normal hearing.

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 4 hrs 18 mins 55 secs

Work Smart Session - MRCP Part 1

Question: 67 of 100

Which of the following is a form of generalised seizure?

(Please select 1 option)

- Automatisms
- Aversive seizures
- Benign rolandic epilepsy
- Epilepsia partialis continua
- Lennox-Gastaut syndrome

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

(Please select 1 option)

○	Automatisms
○	Aversive seizures
◉	Benign rolandic epilepsy ✕ Incorrect answer selected
○	Epilepsia partialis continua
○	Lennox-Gastaut syndrome ← This is the correct answer

Seizures may be classified as:

a) Partial

- Simple partial (consciousness retained), motor, sensory, autonomic, psychic
- Complex partial (consciousness impaired):
- Simple partial followed by impaired consciousness, or consciousness impaired at onset
- Partial seizures with secondary generalisation

b) Generalised seizures

- Absences (typical or atypical)
- Generalised tonic clonic
- Tonic
- Clonic
- Myoclonic
- Atonic
- Infantile spasms

- Simple partial (consciousness retained), motor, sensory, autonomic, psychic
- Complex partial (consciousness impaired):
- Simple partial followed by impaired consciousness, or consciousness impaired at onset
- Partial seizures with secondary generalisation

b) Generalised seizures

- Absences (typical or atypical)
- Generalised tonic clonic
- Tonic
- Clonic
- Myoclonic
- Atonic
- Infantile spasms

c) Unclassified aversive seizures are a form of simple partial seizure, consisting of head turning and conjugate eye movements.

Rasmussen's encephalitis is a subacute inflammatory encephalitis, and is one cause of epilepsia partialis continua.

Complex partial seizures often contain automatisms which may be elementary (including lip smacking, chewing, swallowing or salivation), or automatic behaviour (semi-purposive unco-ordinated or unplanned gestures including picking and pulling at clothing).

Rolandic epilepsy is a benign partial epilepsy associated with centro-temporal spikes. There is an excellent prognosis.

Further reading:
Lennox-Gastaut syndrome GP Notebook

© 2002 Dr Colin Melville

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 4 hrs 19 mins 29 secs

Work Smart Session - MRCP Part 1

Question: 68 of 100

Which of the following forms of encephalitis is caused by a neuroimmunological response?

(Please select 1 option)

- ○ Cytomegalovirus
- ○ Enteral viruses
- ○ Herpes simplex
- ○ HIV infection
- ○ Measles

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Which of the following forms of encephalitis is caused by a neuroimmunological response?

(Please select 1 option)

○	Cytomegalovirus
○	Enteral viruses
○	Herpes simplex
○	HIV infection
◉	Measles ✓ Correct

Encephalitis may be caused by:

- Direct invasion by a neurotoxic virus (encephalitis)
- Post-infectious encephalopathy: delayed brain swelling because of an immunological response to the antigen
- Slow virus infection, for example, human immunodeficiency virus [HIV] or subacute sclerosing panencephalitis [SSPE].

Direct infection is most commonly caused by enteral viruses, herpes simplex virus (HSV) 1 and 2, varicella, cytomegalovirus (CMV), and Epstein-Barr virus (EBV).

It is also occasionally caused by respiratory viruses, human herpes virus 6 (HHV6), rubella or mumps.

A post-infectious illness may also be caused by measles or varicella zoster (cerebellar ataxia).

Copyright © 2002 Dr Colin Melville

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 4 hrs 24 mins 59 secs

Work Smart Session - MRCP Part 1

Question: 69 of 100

A young teenager presents with fever and headache. He has received oral amoxicillin for three days.

Which of the following cerebrospinal fluid (CSF) findings would virtually exclude a partially treated bacterial meningitis?

(Please select 1 option)

○	A CSF glucose of 45% of blood glucose
○	A negative CSF culture
○	A negative gram stain
○	A negative Kernig's Sign
○	A white cell count of 3

Submit answer | Skip question | Remove Tag | Remove question

- Community
- Shop
- Help

A young teenager presents with fever and headache. He has received oral amoxicillin for three days.

Which of the following cerebrospinal fluid (CSF) findings would virtually exclude a partially treated bacterial meningitis?

(Please select 1 option)

○	A CSF glucose of 45% of blood glucose
○	A negative CSF culture
○	A negative gram stain
○	A negative Kernig's Sign
◉	A white cell count of 3 ✓ Correct

The assessment of children with suspected bacterial meningitis who have already received antibiotic therapy from their GP is a common diagnostic problem.

Partial treatment may reduce the incidence of positive CSF gram stains to < than 60%, and it also reduces the ability to grow the bacteria, particularly meningococcus.

CSF glucose, protein, neutrophils and bacterial antigen testing or polymerase chain reaction (PCR) should be completely unaffected. A normal white cell count would make the diagnosis very unlikely.

Copyright © 2002 Dr Colin Melville

Next question

Remove Tag | Remove question

Rate this question

☆☆☆☆☆

A 30-year-old lady who suffers from migraine complains that taking the recommended dose of paracetamol during an attack fails to relieve her headache. She has no other significant past medical history. She is a smoker of 15 cigarettes per day and also drinks alcohol 16 units per week.

Which of the following factors most likely explains the lack of efficacy of paracetamol in this lady?

(Please select 1 option)

○	Bacterial overgrowth
◉	Delayed gastric emptying ✓ Correct
○	First pass metabolism
○	p450 enzyme induction
○	p450 enzyme inhibition

"When salicylate absorption from effervescent aspirin tablets was studied during migraine, the rate of absorption was found to be reduced relative to that found in non-migrainous volunteers and in the same patients when headache-free. There is evidence that this reduced rate of absorption is caused by gastrointestinal stasis and reduced rate of gastric emptying. Patients in whom aspirin absorption was delayed were more likely to take longer to respond and to require additional treatment." Clin Pharmacokinet. 1978 Jul-Aug;3(4):313-8. Metoclopramide may be useful in accelerating gastric emptying.

The same has also been shown with paracetamol absorption. Br J Clin Pharmacol. 1984 Dec;18(6):867-71

Next question | Tag Question | Remove question

Rate this question

☆☆☆☆☆

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 16 mins 54 secs

Work Smart Session - MRCP Part 1

Question: 7 of 100

A 36-year-old police officer presents with a three day history of slurred speech. She also complains of double vision and a sensation of breathlessness.

The oxygen saturations are 99% on air. Neurological examination reveals normal power, reflexes and plantar responses.

Which of the following would improve symptoms in this presentation?

(Please select 1 option)

- G-CSF
- Edrophonium
- Non-steroidal anti-inflammatory drugs
- Physiotherapy
- Plasmapheresis

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 4 hrs 26 mins 18 secs

Work Smart Session - MRCP Part 1

Question: 70 of 100

Which of the following clinical manifestations suggests Guillain-Barré (GB) syndrome?

(Please select 1 option)

○	Asymmetrical involvement of distal muscles
○	Brisk tendon reflexes
○	Bulbar involvement in about 50% of cases
○	Normal cerebrospinal fluid (CSF) protein
○	Weakness beginning in the arms

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

◉	Asymmetrical involvement of distal muscles ✕ Incorrect answer selected
○	Brisk tendon reflexes
○	Bulbar involvement in about 50% of cases ← This is the correct answer
○	Normal cerebrospinal fluid (CSF) protein
○	Weakness beginning in the arms

GB is a post-infectious polyneuropathy causing demyelination in mainly motor but also sensory nerves.

It usually follows a non-specific viral infection. Campylobacter and mycoplasma are recognised causes.

Weakness begins in the legs and progressively ascends to involve the trunk, upper limbs and finally the bulbar muscles (Landry's ascending paralysis).

Asymmetry is present in only 9% of patients, with symmetrical involvement being typical. Usually there is painless progression over days or weeks, but in cases of abrupt onset, there may be tenderness or muscle pain.

Bulbar involvement occurs in 50%, with a risk of aspiration and respiratory insufficiency can be problematic.

In the Miller Fisher syndrome there is external ophthalmoplegia, ataxia and areflexia.

In 20% of cases there is urinary incontinence or retention.

Clinical symptoms usually improve within two to three weeks, though a chronic relapsing form is recognised.

CSF protein is elevated to more than twice the upper limit of normal, with normal glucose and no pleocytosis. Bacterial cultures are negative and viral cultures rarely isolate anything.

The dissociation between a high CSF protein and a lack of cellular response in a person with an acute or subacute polyneuropathy is diagnostic of Guillain-Barre Syndrome.

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 4 hrs 27 mins 21 secs

Work Smart Session - MRCP Part 1

Question: 71 of 100

A 35-year-old female presents with headaches. Examination reveals papilloedema.

Which of the following would make the diagnosis of benign intracranial hypertension (BIH) unlikely?

(Please select 1 option)

- Absence of retinal venous pulsations
- Bilateral upgoing plantar responses
- Normal ventricles on CT or MRI scan
- Reduced visual acuity
- Sixth cranial nerve palsy

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Work Smart Session - MRCP Part 1

Question: 71 of 100

A 35-year-old female presents with headaches. Examination reveals papilloedema.

Which of the following would make the diagnosis of benign intracranial hypertension (BIH) unlikely?

(Please select 1 option)

○	Absence of retinal venous pulsations
◉	Bilateral upgoing plantar responses ✓ Correct
○	Normal ventricles on CT or MRI scan
○	Reduced visual acuity
○	Sixth cranial nerve palsy

BIH is typically associated with papilloedema, reduced venous pulsation and normal appearances of the magnetic resonance imaging (MRI).

A VIth nerve palsy is a recognised association.

Reflexes are preserved and plantars are flexor.

Extensor plantars suggest a alternative diagnosis.

Next question

Tag Question | Remove question

Rate this question

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 4 hrs 42 mins 11 secs

Work Smart Session - MRCP Part 1

Question: 72 of 100

A 54-year-old female is admitted with progressive weakness following a trivial flu-like illness.

Which of the following would exclude Guillain-Barre Syndrome (GBS) as the diagnosis?

(Please select 1 option)

○	Autonomic dysfunction
○	Elevated protein on CSF examination
○	Evidence of muscle wasting
○	Ophthalmoplegia
○	Sensory level below T1

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

A 54 year old female is admitted with progressive weakness following a trivial flu like illness.

Which of the following would exclude Guillain-Barre Syndrome (GBS) as the diagnosis?

(Please select 1 option)

○	Autonomic dysfunction
○	Elevated protein on CSF examination
○	Evidence of muscle wasting
○	Ophthalmoplegia
◉	Sensory level below T1 ✓ Correct

GBS is a post-infectious acute polyneuritis typified by elevated cerebral spinal fluid (CSF) protein with few cells and often normal glucose.

There is a profound weakness associated with areflexia and peripheral sensory neuropathy.

Ophthalmoplegia is associated in particular with the Miller-Fisher variant.

However, a sensory level is NOT a feature and would suggest cervical myelopathy.

Muscle wasting is typical with prolonged illness.

Autonomic disease may also feature.

Next question

Tag Question | Remove question

Rate this question

☆☆☆☆☆

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 4 hrs 48 mins 11 secs

Work Smart Session - MRCP Part 1

Question: 73 of 100

Which of the following is a true of myasthenia gravis (MG)?

(Please select 1 option)

○	There is a strong association with anti-noradrenergic receptor antibodies
○	Neurotransmitter released at the motor end plate is greatly reduced
○	Repetitive stimulation of a motor nerve produces a reduction in the amplitude of the 5th response compared with the 1st in 98% of cases(electrodecremental test)
○	Electrical recordings of single motor unit activity commonly reveal variation in the latency of the various mucle fibre responses(jitter)
○	Subjective improvement in muscle strength following edrophonium is diagnostic of the condition

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Question: 73 of 100

Which of the following is a true of myasthenia gravis (MG)?

(Please select 1 option)

○	There is a strong association with anti-noradrenergic receptor antibodies
○	Neurotransmitter released at the motor end plate is greatly reduced
○	Repetitive stimulation of a motor nerve produces a reduction in the amplitude of the 5th response compared with the 1st in 98% of cases(electrodecremental test)
○	Electrical recordings of single motor unit activity commonly reveal variation in the latency of the various mucle fibre responses(jitter) ← This is the correct answer
◉	Subjective improvement in muscle strength following edrophonium is diagnostic of the condition ✕ Incorrect answer selected

Anti-acetylcholine receptor antibodies are typically found resulting in reduced ACh receptor numbers but sufficient neurotransmitter is released.

An increase in decrement on stimulation at 3Hz is detectable in some patients.

Jitter is the most sensitive emg index in MG but is not specific of the condition. The nerve conductions and electromyogram (EMG) studies are usually normal in myasthenia gravis, but the repetitive stimulation of a nerve may demonstrate decrements of the muscle action potential (far less than 98%).

Although improved muscle strength after edrophonium is seen, it is not diagnostic but depends more on the clinical presentation and presence of AChR ab.

Next question

Remove Tag | Remove question

Rate this question

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 4 hrs 59 mins 47 secs

Work Smart Session - MRCP Part 1

Question: 74 of 100

Which of the following is a recognised cause of a phrenic nerve palsy?

(Please select 1 option)

- Aortic aneurysm
- Dermoid
- Ganglioneuroma
- Pericardial cyst
- Sarcoidosis

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Time taken: 5 hrs 15 secs

Work Smart Session - MRCP Part 1

Question: 74 of 100

Which of the following is a recognised cause of a phrenic nerve palsy?

(Please select 1 option)

○	Aortic aneurysm ← This is the correct answer
○	Dermoid
○	Ganglioneuroma
◉	Pericardial cyst ✕ Incorrect answer selected
○	Sarcoidosis

The diaphragm is innervated by the phrenic nerve (C3,4,5).

Palsy is a recognised complication of thoracic surgery, infection, Guillain-Barre or invasion by an adjacent tumour.

It may also be stretched by an aortic aneurysm.

Next question

Remove Tag | Remove question

Rate this question

☆☆☆☆☆

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 5 hrs 15 secs

Work Smart Session - MRCP Part 1

Question: 75 of 100

In which of the following is mental retardation an expected finding?

(Please select 1 option)

- Alkaptonuria
- Cystinuria
- Glycogen storage disease
- Lactose intolerance
- Maple syrup urine disease

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 5 hrs 36 secs

Work Smart Session - MRCP Part 1

Question: 75 of 100

In which of the following is mental retardation an expected finding?

(Please select 1 option)

○	Alkaptonuria
○	Cystinuria
○	Glycogen storage disease
○	Lactose intolerance
◉	Maple syrup urine disease ✓ Correct

MENTAL RETARDATION. Fragile X syndrome-commonest male cause. Hypoxia at birth, intraventricular haemorrhage, rhesus disease, Congenital infections -toxoplasmosis, CMV, rubella, herpes), hypoglycaemia, meningitis, hypothyroidism (cretinism, tuberous sclerosis, Down's, Tay-Sach's, Cornelia De Lange, (Hartnup - biochemical, treatable with diet). -homocystinuria, phenylketonuria -maple syrup urine disease, tryptophanuria -galactosaemia

Next question Tag Question Remove question

Rate this question

☆☆☆☆☆

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 5 hrs 36 secs

Work Smart Session - MRCP Part 1

Question: 76 of 100

Which of the following is a characteristic feature of transient global amnesia?

(Please select 1 option)

○	Abnormal behaviour
○	Apraxia
○	Confabulation
○	Loss of personal identity
○	Normal perception

Submit answer | Skip question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Which of the following is a characteristic feature of transient global amnesia?

(Please select 1 option)

○	Abnormal behaviour
○	Apraxia
○	Confabulation
○	Loss of personal identity
◉	Normal perception ✓ Correct

Transient global amnesia (TGA) is a syndrome in which a previously well person suddenly becomes confused and amnesic.

The person appears bewildered and repeatedly asks questions about present and recent events, for example, "Where am I?"

TGA is characterised by the brain's sudden inability to form new memory traces (antrograde amnesia) plus retrograde memory loss for events of the preceding days, weeks or in some cases years.

During the attack, which affects both verbal and nonverbal memory, the patient is bewildered and anxious.

Self identification is preserved.

Behaviour is otherwise normal and appropriate.

'Characteristic' means that absence of the symptom would make you doubt the diagnosis. The presence of any of the other suggested options would suggest an alternative diagnosis.

Next question

Remove Tag Remove question

Rate this question

☆☆☆☆☆

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 5 hrs 1 mins 26 secs

Work Smart Session - MRCP Part 1

Question: 77 of 100

A 21-year-old man recovered from the immediate effects of a head injury sustained in a motor cycle accident three months previously.

Which one of the following is the most likely delayed consequence of severe traumatic brain injury?

(Please select 1 option)

○	Episodic hypersomnia
○	Multiple obsessional symptoms
○	Outbursts of aggressive behaviour
○	Pathological jealousy
○	Persistent anxiety

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Question: 77 of 100

A 21-year-old man recovered from the immediate effects of a head injury sustained in a motor cycle accident three months previously.

Which one of the following is the most likely delayed consequence of severe traumatic brain injury?

(Please select 1 option)

○	Episodic hypersomnia
○	Multiple obsessional symptoms
◉	Outbursts of aggressive behaviour ✕ Incorrect answer selected
○	Pathological jealousy
○	Persistent anxiety ← This is the correct answer

The condition is post-concussion syndrome and although many of the symptoms given may be seen the commonest one (headache) has been left out!

"The most common symptoms are headache and neck discomfort; changes in memory, concentration, and attention; dizziness; irritability, depression or anxiety; and sleep disturbance, among other symptoms."

There is

- A disturbance of thought
- A poor concentration span and
- Subjects are easily distracted.

Anxiety would seem the most common and therefore the most likely answer.

Next question

Remove Tag | Remove question

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 5 hrs 3 mins 50 secs

Work Smart Session - MRCP Part 1

Question: 78 of 100

Which of the following is least likely to cause choreiform movements?

(Please select 1 option)

○	Polyarteritis nodosa
○	Polycythaemia rubra vera
○	Rheumatic fever
○	Systemic lupus erythematosus
○	Thyrotoxicosis

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 5 hrs 4 mins 30 secs

Work Smart Session - MRCP Part 1

Question: 78 of 100

Which of the following is least likely to cause choreiform movements?

(Please select 1 option)

◉	Polyarteritis nodosa ✓ Correct
○	Polycythaemia rubra vera
○	Rheumatic fever
○	Systemic lupus erythematosus
○	Thyrotoxicosis

PAN affects medium sized arteries and usually involves peripheral nerves, bowel and rarely lungs.

Other causes of chorea are Huntington's chorea, rheumatic fever and senile chorea.

Next question

Tag Question Remove question

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 5 hrs 4 mins 30 secs

Work Smart Session - MRCP Part 1

Question: 79 of 100

Which of the following features are not compatible with the diagnosis of motor neurone disease (MND)?

(Please select 1 option)

○	Dementia
○	Dysphagia
○	Muscle cramps
○	Neck weakness
○	Optic atrophy

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Time taken: 5 hrs 5 mins 32 secs

Work Smart Session - MRCP Part 1

Question: 79 of 100

Which of the following features are not compatible with the diagnosis of motor neurone disease (MND)?

(Please select 1 option)

○	Dementia
○	Dysphagia
○	Muscle cramps
○	Neck weakness
◉	Optic atrophy ✓ Correct

10% of patients with MND have dementia (frontotemporal).

Optic atrophy is not a feature of MND.

Other features not compatible with the diagnosis are sensory impairment and bladder dysfunction.

Next question

Tag Question | Remove question

Rate this question

☆☆☆☆☆

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Community
- Shop
- Help

A 36-year-old police officer presents with a three day history of slurred speech. She also complains of double vision and a sensation of breathlessness.

The oxygen saturations are 99% on air. Neurological examination reveals normal power, reflexes and plantar responses.

Which of the following would improve symptoms in this presentation?

(Please select 1 option)

○	G-CSF
◉	Edrophonium ✓ Correct
○	Non-steroidal anti-inflammatory drugs
○	Physiotherapy
○	Plasmapheresis

This lady has symptoms suggesting myasthenia gravis.

Her breathlessness is probably secondary to anxiety about the symptoms and associated hyperventilation.

Edrophonium (Tensilon) is sometimes used in the diagnosis of myasthenia gravis and would be expected temporarily to improve symtpoms.

Next question

Tag Question | Remove question

Rate this question

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 18 mins 23 secs

Work Smart Session - MRCP Part 1

Question: 8 of 100

A 50-year-old man has drunk six units of alcohol a day for most of his adult life.

He has worsening symptoms of difficulty walking, headaches and urinary incontinence for the past ten months.

Of the following which is the most likely diagnosis?

(Please select 1 option)

○	Encephalopathy
○	Meningovascular syphilis
○	Normal pressure hydrocephalus
○	Syringomyelia
○	Wernicke-Korsakoff syndrome

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 5 hrs 5 mins 32 secs

Work Smart Session - MRCP Part 1

Question: 80 of 100

A 60-year-old woman presents with a 24 hours history of headache and vomiting. She has been on steroids for temporal arteritis for the last three years.

Examination demonstrates pyrexia, neck stiffness, photophobia, dysarthria, nystagmus and ataxia. CSF shows neutrophilic pleocytosis, low glucose, elevated protein.

What is the most likely diagnosis?

(Please select 1 option)

○	Carcinomatosis meningitis
○	Cryptococcal meningitis
○	Listeria meningitis
○	Meningococcal meningitis
○	Tuberculus meningitis

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

A 60-year-old woman presents with a 24 hours history of headache and vomiting. She has been on steroids for temporal arteritis for the last three years.

Examination demonstrates pyrexia, neck stiffness, photophobia, dysarthria, nystagmus and ataxia. CSF shows neutrophilic pleocytosis, low glucose, elevated protein.

What is the most likely diagnosis?

(Please select 1 option)

○	Carcinomatosis meningitis
○	Cryptococcal meningitis
◉	Listeria meningitis ✓ Correct
○	Meningococcal meningitis
○	Tuberculus meningitis

Risk factors for listeria meningitis include older age and immunosuppresion.

It is typically associated with brain stem signs.

Cerebrospinal fluid shows

- Neutrophilic pleocytosis
- Low glucose and
- High protein.

Next question

Tag Question | Remove question

Rate this question

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 5 hrs 7 mins 48 secs

Work Smart Session - MRCP Part 1

Question: 81 of 100

Which of the following investigations best supports a diagnosis of new variant CJD?

(Please select 1 option)

○	CSF analysis
○	CT brain
○	EMG
○	MRI brain
○	VEPs

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 5 hrs 8 mins 18 secs

Work Smart Session - MRCP Part 1

Question: 81 of 100

Which of the following investigations best supports a diagnosis of new variant CJD?

(Please select 1 option)

○	CSF analysis
○	CT brain
○	EMG
◉	MRI brain ✓ Correct
○	VEPs

MRI brain typically shows bilateral posterior thalamic high signal abnormalities in a patient with new variant Creutzfeldt-Jakob disease (CJD).

Cerebrospinal fluid (CSF) analysis only shows non-specific changes.

EMG and CT brain are normal.

Sporadic CJD (and not new variant CJD) is associated with specific EEG changes.

Next question

Tag Question Remove question

Rate this question

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 5 hrs 8 mins 18 secs

Work Smart Session - MRCP Part 1

Question: 82 of 100

For which of the following could a right carotid artery stenosis not account?

(Please select 1 option)

- Contralateral hemiplegia
- Contralateral hemisensory loss
- Drop attacks
- Dysphasia
- Right amaurosis fugax

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Work Smart Session - MRCP Part 1

Question: 82 of 100

For which of the following could a right carotid artery stenosis not account?

(Please select 1 option)

○	Contralateral hemiplegia
○	Contralateral hemisensory loss
○	Drop attacks ← This is the correct answer
◉	Dysphasia ✕ Incorrect answer selected
○	Right amaurosis fugax

Carotid artery disease causes

- Contralateral hemiplegia
- Hemisensory loss
- Homonymous hemianopia
- Dysphasia (right)
- Hemineglect (left).

Drop attacks are due to vertebrobasilar insufficiency.

Next question

Tag Question | Remove question

Rate this question

☆☆☆☆☆

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 5 hrs 9 mins 35 secs

Work Smart Session - MRCP Part 1

Question: 83 of 100

A 75-year-old woman presents with acute monocular visual loss.

Fundoscopy reveals a swollen pale optic disc in the affected eye.

What is the mose likely diagnosis?

(Please select 1 option)

- Central retinal vein occlusion.
- Closed angle glaucoma.
- Giant cell arteritis.
- Optic neuritis.
- Raised intracranial pressure.

Submit answer | Skip question | Tag Question | Remove question

Time taken: 5 hrs 10 mins 51 secs

Work Smart Session - MRCP Part 1

Question: 83 of 100

A 75-year-old woman presents with acute monocular visual loss.

Fundoscopy reveals a swollen pale optic disc in the affected eye.

What is the mose likely diagnosis?

(Please select 1 option)

◉	Central retinal vein occlusion. ✕ Incorrect answer selected
○	Closed angle glaucoma.
○	Giant cell arteritis. ← This is the correct answer
○	Optic neuritis.
○	Raised intracranial pressure.

The presence of a swollen optic disc suggests ischaemic optic neuropathy.

In elderly people giant cell arteritis is a common presentation of acute monocular visual loss.

Optic neuritis is very rare in people over the age of 50.

You will expect bilateral swollen optic discs in raised intracranial pressure.

In central retinal vein occlusion you will expect diffuse retinal haemorrhages.

Next question

Remove Tag | Remove question

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 5 hrs 10 mins 51 secs

Work Smart Session - MRCP Part 1

Question: 84 of 100

A 36-year-old man has a three month history of pain in his feet and lower legs. He was diagnosed as having diabetes at age 14 and treated with insulin. He is a cannabis smoker and drinks 30 units of alcohol per week.

On examination he has impaired pain and temperature sensation in feet and lower legs, normal joint position and vibration sense. His reflexes are normal.

What is the diagnosis?

(Please select 1 option)

○	Alcoholic polyneuropathy.
○	Chronic inflammatory demyelinating polyneuropathy (CIDP)
○	Diabetic polyneuropathy.
○	Syringomyelia.
○	Vitamin B12 deficiency.

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Question: 84 of 100

A 36-year-old man has a three month history of pain in his feet and lower legs. He was diagnosed as having diabetes at age 14 and treated with insulin. He is a cannabis smoker and drinks 30 units of alcohol per week.

On examination he has impaired pain and temperature sensation in feet and lower legs, normal joint position and vibration sense. His reflexes are normal.

What is the diagnosis?

(Please select 1 option)

◉	Alcoholic polyneuropathy. ✕ Incorrect answer selected
○	Chronic inflammatory demyelinating polyneuropathy (CIDP)
○	Diabetic polyneuropathy. ← This is the correct answer
○	Syringomyelia.
○	Vitamin B12 deficiency.

The history suggests small fibre painful peripheral sensory neuropathy. The comonest cause is diabetes.

Vitamin B12 deficiency causes impairment of joint position and vibration. Chronic inflammatory demyelinating polyneuropathy (CIDP) causes a large fibre peripheral neuropathy with areflexia.

In syringomyelia you have impaired pain and temperature only in the upper limbs.

Typically with alcoholic polyneuropathy all fibre types are affected and it is seen with a higher alcohol consumption than 30 units.

Next question

Remove Tag | Remove question

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 5 hrs 13 mins 17 secs

Work Smart Session - MRCP Part 1

Question: 85 of 100

The anticonvulsant Levetiracetam

(Please select 1 option)

○	Acts via the gamma-aminobutyric acid (GABA) receptor
○	Is associated with increased plasma concentrations of sodium valproate
○	Is associated with induction of hepatic cytochrome p450 enzymes
○	Is used as monotherapy for the treatment of generalised convulsions
○	Is well absorbed via the oral route

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 5 hrs 14 mins 57 secs

Work Smart Session - MRCP Part 1

Question: 85 of 100

The anticonvulsant Levetiracetam

(Please select 1 option)

○	Acts via the gamma-aminobutyric acid (GABA) receptor
○	Is associated with increased plasma concentrations of sodium valproate
○	Is associated with induction of hepatic cytochrome p450 enzymes
○	Is used as monotherapy for the treatment of generalised convulsions
◉	Is well absorbed via the oral route ✓ Correct

Levetiracetam (Keppra) is an adjunctive treatment for partial seizures with or without secondary generalisation. Its mechanism of action is unknown.

It is rapidly absorbed orally, it does not effect hepatic enzymes but dose reduction is required in renal failure.

The drug appears to be well tolerated with few side effects.

Next question

Tag Question Remove question

Rate this question

☆☆☆☆☆

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 5 hrs 14 mins 57 secs

Work Smart Session - MRCP Part 1

Question: 86 of 100

A 65-year-old man has a monotonous, slurred speech. He has an expressionless face and a festinant gait.

There is also impairment of vertical gaze.

What is the most likely underlying aetiology?

(Please select 1 option)

○	Cerebrovascular disease
○	Idiopathic
○	Shy-Drager syndrome
○	Steele-Richardson-Olszewski syndrome
○	Wilson's disease

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Shop
- Help

What is the most likely underlying aetiology?

(Please select 1 option)

○	Cerebrovascular disease
○	Idiopathic
◉	Shy-Drager syndrome ✕ Incorrect answer selected
○	Steele-Richardson-Olszewski syndrome ← This is the correct answer
○	Wilson's disease

Parkinson's disease is a triad of

- Bradykinesia
- Tremor and
- Rigidity.

Speech may be slurred and without accents or emphasis. Impairment of vertical gaze suggests the diagnosis of Steele-Richardson-Olszewski syndrome or supranuclear gaze palsy, which also cause pyramidal signs, dementia or frontal lobe syndrome.

Response to L-dopa is poor and median survival is about seven years.

Shy-Drager syndrome is associated with autonomic dysfunction and postural hypotension.

Wilson's disease presents in children and young adults with cirrhosis and parkinsonism, which later leads to dementia, dysphagia and immobility.

Next question

Remove Tag | Remove question

Rate this question

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 5 hrs 16 mins 24 secs

Work Smart Session - MRCP Part 1

Question: 87 of 100

Are the following true concerning baclofen?

(Please select 1 option)

○	Acts directly on skeletal muscle
○	Causes hallucinations when withdrawn
○	Causes rhabdomyolysis
○	Reduces Ca^{2+} release from sarcoplasmic reticulum
○	Reduces cerebral but not spinal spasticity

Submit answer | Skip question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Work Smart Session - MRCP Part 1

Question: 87 of 100

Are the following true concerning baclofen?

(Please select 1 option)

○	Acts directly on skeletal muscle
○	Causes hallucinations when withdrawn ← This is the correct answer
◉	Causes rhabdomyolysis ✕ Incorrect answer selected
○	Reduces Ca^{2+} release from sarcoplasmic reticulum
○	Reduces cerebral but not spinal spasticity

The primary site of action is the spinal cord by depressing monosynaptic and polysynaptic transmission. It can hyperpolarise cells by increasing K^{+} conductance and inhibit Ca^{2+} channels in others.

Rhabdomyolysis is caused by

- Clofibrate
- Aminocaproic acid
- HMG-CoA reductase inhibitors
- Neuroleptics (neuroleptic malignant syndrome).

Avoid abrupt withdrawal as it can cause serious side-effects including autonomic dysreflexia.

Next question | Remove Tag | Remove question

Rate this question

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 5 hrs 17 mins 30 secs

Work Smart Session - MRCP Part 1

Question: 88 of 100

A 25-year-old female presents with a two day history of diplopia and unsteadiness.

Two weeks ago she suffered an upper respiratory tract infection.

On examination there is complete ophthalmoplegia, areflexia and gait ataxia.

Which of the following blood tests is the most likely to confirm the underlying diagnosis?

(Please select 1 option)

- Acetylcholine receptors antibodies
- Anti GM1 antibodies
- Anti GQib antibodies
- Anti Hu antibodies
- Anti purkinje cell antibodies

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

○	Acetylcholine receptors antibodies
◉	Anti GM1 antibodies ✕ Incorrect answer selected
○	Anti GQib antibodies ← This is the correct answer
○	Anti Hu antibodies
○	Anti purkinje cell antibodies

The most likely diagnosis is Miller Fisher syndrome (variant of Guillain-Barre syndrome). It consists of complete or partial ophthalmoplegia, areflexia and ataxia. It usually follows antecedent infections. Serum IgG antibody to the ganglioside GQib is present in more than 95% of patients. It is highly specific for the syndrome.

Elevated levels of antibodies to the glycolipid ganglioside-monosialic acid (GM1 antibodies) have been shown in some instances to be associated with certain neurological disorders:

- Lower motor neuron syndromes
- Amyotrophic lateral sclerosis
- Multiple sclerosis
- Other multifocal neuropathies and
- Systemic lupus erythematosus (SLE) with central nervous system involvement.

Neuronal nuclear (Hu) antibodies (NNA) are found in a number of paraneoplastic syndromes, including

- Subacute sensory neuronopathy
- Paraneoplastic encephalomyelitis and
- Paraneoplastic cerebellar degeneration

and are associated with small cell lung carcinoma.

Purkinje cell cytoplasmic antibodies are useful for identifying individuals with subacute cerebellar degeneration or peripheral neuropathy due to a remote (autoimmune) effect of gynecologic or breast carcinoma.

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 5 hrs 19 mins 38 secs

Work Smart Session - MRCP Part 1

Question: 89 of 100

A 65-year-old man presents with four months history of swallowing difficulties (worse with liquids than solids).

He also complains of nasal regurgitation, coughing and choking episodes during meals and slight dysarthria. He lost one stone over the last eight weeks.

Which of the following investigations is the most appropriate for this case?

(Please select 1 option)

- Acetyl choline receptors antibodies
- Barium swallow
- CXR
- Gastroscopy
- Tumour markers

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Question: 89 of 100

A 65-year-old man presents with four months history of swallowing difficulties (worse with liquids than solids).

He also complains of nasal regurgitation, coughing and choking episodes during meals and slight dysarthria. He lost one stone over the last eight weeks.

Which of the following investigations is the most appropriate for this case?

(Please select 1 option)

◉	Acetyl choline receptors antibodies ✓ Correct
○	Barium swallow
○	CXR
○	Gastroscopy
○	Tumour markers

Nasal regurgitation, coughing and choking episodes during meals, dysphagia that is worse with liquids than solids and dysarthria indicate neurogenic dysphagia.

Important causes at this age include myasthenia gravis and motor neuron disease.

Mechanical dysphagia (for example, oesophageal and gastric carcinoma, oesophageal stricture, etc) causes dysphagia that is worse with solids than liquids.

Nasal regurgitation and dysarthria are not accompanying features of mechanical dysphagia.

Next question

Tag Question | Remove question

Rate this question

A 50-year-old man has drunk six units of alcohol a day for most of his adult life.

He has worsening symptoms of difficulty walking, headaches and urinary incontinence for the past ten months.

Of the following which is the most likely diagnosis?

(Please select 1 option)

○	Encephalopathy
○	Meningovascular syphilis
◉	Normal pressure hydrocephalus ✕ Incorrect answer selected
○	Syringomyelia ← This is the correct answer
○	Wernicke-Korsakoff syndrome

There is no suggestion of memory loss so normal pressure hydrocephalus and Wernicke-Korsakoff syndrome are less likely.

Encephalopathy is more likely to be associated with symptoms of drowsiness.

Although meningovascular syphilis can present in many different forms it is rather rare.

Syringomyelia is associated with headaches, motor and bladder symptoms and is the likely diagnosis.

In this scenario, the alcohol is a distractor.

Next question

Remove Tag Remove question

Rate this question

☆☆☆☆☆

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 19 mins 47 secs

Work Smart Session - MRCP Part 1

Question: 9 of 100

A 62-year-old male presents with weakness of the right hand. You note global wasting of the small hand muscles, there is also sensory loss over the medial border of the forearm around the elbow.

Which nerve root is damaged?

(Please select 1 option)

- C5
- C6
- C7
- C8
- T1

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 5 hrs 21 mins 32 secs

Work Smart Session - MRCP Part 1

Question: 90 of 100

A 68-year-old man presents with progressive visual impairment. On examination there is an incongruous homonymous hemianopia.

The most likely anatomical site of the neurological lesion is at:

(Please select 1 option)

○	chiasma
○	occipital lobe
○	optic nerve
○	optic radiation
○	optic tract

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Question: 90 of 100

A 68-year-old man presents with progressive visual impairment. On examination there is an incongruous homonymous hemianopia.

The most likely anatomical site of the neurological lesion is at:

(Please select 1 option)

○	chiasma
○	occipital lobe
○	optic nerve
○	optic radiation
◉	optic tract ✓ Correct

Optic neuropathy causes:

- a central scotoma
- an optic tract lesion
- an incongruous homonymous haemianopia
- a chiasmal lesion
- a bitemporal haemianopia
- an optic radiation and occipital lobe lesion
- a congruous homonymous hemianopia.

More on field defects

Next question

Tag Question | Remove question

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 5 hrs 22 mins 21 secs

Work Smart Session - MRCP Part 1

Question: 91 of 100

A 50-year-old man presented with 18 months history of parasthesia of his feet and hands.

On examination there is numbness of glove and stocking distribution with generalised hyporeflexia. Nerve conduction studies revealed demyelinative sensory polyneuropathy.

Which of the following conditions is the most likely diagnosis?

(Please select 1 option)

- Alcohol abuse
- Chronic inflammatory demyelinating polyneuropathy
- Diabetes
- Vasculitis
- Vitamin B_{12} deficiency

Submit answer | Skip question | Tag Question | Remove question

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 5 hrs 22 mins 21 secs

Work Smart Session - MRCP Part 1

Question: 91 of 100

A 50-year-old man presented with 18 months history of parasthesia of his feet and hands.

On examination there is numbness of glove and stocking distribution with generalised hyporeflexia. Nerve conduction studies revealed demyelinative sensory polyneuropathy.

Which of the following conditions is the most likely diagnosis?

(Please select 1 option)

- Alcohol abuse
- Chronic inflammatory demyelinating polyneuropathy
- Diabetes
- Vasculitis
- Vitamin B_{12} deficiency

Submit answer | Skip question | Tag Question | Remove question

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 5 hrs 23 mins 22 secs

Work Smart Session - MRCP Part 1

Question: 92 of 100

A 45-year-old man presents with an insidious onset of binocular horizontal diplopia and left sided facial pain.

On examination he has a left abducens nerve palsy and numbness over the maxillary division of the left trigeminal nerve.

Of the following which is the most likely anatomical site of his neurological lesion?

(Please select 1 option)

- Cavernous sinus
- Cerebellopontine angle
- Midbrain
- Petrous apex
- Superior orbital fissure

Submit answer | Skip question | Tag Question | Remove question

- Shop
- Help

Of the following which is the most likely anatomical site of his neurological lesion?

(Please select 1 option)

○	Cavernous sinus
○	Cerebellopontine angle
○	Midbrain
◉	Petrous apex ✓ Correct
○	Superior orbital fissure

In the pre-antibiotic era an abducens nerve palsy with ipsilateral pain and numbness was due to petrous osteitis (Gradenigo syndrome) but is now more likely the result of a meningioma or nasopharyngeal carcinoma of the petrous apex.

The cavernous sinus syndrome consists of variable involvement of

- Oculomotor
- Trochlear
- Abducens
- Trigeminal (ophthalmic and maxillary division) and
- Oculo-sympathetic nerves.

The superior orbital fissure syndrome is similar to the cavernous sinus syndrome except for the presence of proptosis.

Next question | Tag Question | Remove question

Rate this question

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 5 hrs 26 mins 39 secs

Work Smart Session - MRCP Part 1

Question: 93 of 100

A female patient aged 30 has a five year history of difficulty getting upstairs and out of a low chair and mild upper limb weakness but no pain. There is no family history.

She presented with severe type 2 respiratory failure. EMG showed evidence of myopathy.

Which is the most likely diagnosis?

(Please select 1 option)

○	Acid maltase deficiency
○	Inclusion body myositis
○	Lambert-Eaton myasthenic syndrome
○	Miller-Fisher syndrome
○	Polymyositis

Submit answer | Skip question | Tag Question | Remove question

Question: 93 of 100

A female patient aged 30 has a five year history of difficulty getting upstairs and out of a low chair and mild upper limb weakness but no pain. There is no family history.

She presented with severe type 2 respiratory failure. EMG showed evidence of myopathy.

Which is the most likely diagnosis?

(Please select 1 option)

○	Acid maltase deficiency ← This is the correct answer
○	Inclusion body myositis
○	Lambert-Eaton myasthenic syndrome
○	Miller-Fisher syndrome
◉	Polymyositis ✕ Incorrect answer selected

Acid maltase deficiency typically presents with insidious onset of proximal myopathy and early respiratory muscle weakness.

Respiratory failure in inflammatory myopathies (polymyositis, dermatomyositis, inclusion body myositis) and limb girdle muscular dystrophy are rare. Muscle biopsy shows vacuolation in muscle fibres.

Miller-Fisher syndrome, a variant of Guillain-Barré syndrome, is characterised by ophthalmoplegia, ataxia and areflexia.

Lambert-Eaton myasthenic syndrome, often a paraneoplastic phenomenon, is associated with hyporeflexia which returns after exercise, autonomic symptoms and fatiguability.

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 5 hrs 28 mins 3 secs

Work Smart Session - MRCP Part 1

Question: 94 of 100

A 60-year-old man awakens with painless loss of vision of his left eye.

Three years earlier he had suffered a similar episode involving the right eye. Visual loss in that eye has been stationary. He does not complain of any systemic symptoms.

What is the most likely diagnosis?

(Please select 1 option)

○	Acute angle-closure glaucoma
○	Arteritic ischaemic optic neuropathy
○	Compressive optic neuropathy
○	Nonarteritic ischaemic optic neuropathy
○	Optic neuritis

Submit answer | Skip question | Tag Question | Remove question

A 60-year-old man awakens with painless loss of vision of his left eye.

Three years earlier he had suffered a similar episode involving the right eye. Visual loss in that eye has been stationary. He does not complain of any systemic symptoms.

What is the most likely diagnosis?

(Please select 1 option)

◉	Acute angle-closure glaucoma ✕ Incorrect answer selected
○	Arteritic ischaemic optic neuropathy
○	Compressive optic neuropathy
○	Nonarteritic ischaemic optic neuropathy ← This is the correct answer
○	Optic neuritis

Sudden onset of painless monocular visual loss in patients aged 50 or more is commonly due to ischaemic optic neuropathy.

Commonly the symptoms are first noticed upon awakening in the morning. The fellow eye may suffer a similar event within 5 years.

There are no systemic features (weight loss, lethargy, malaise, jaw claudication, scalp tenderness) to suggest arteritic ischaemic optic neuropathy (giant cell arteritis). In giant cell arteritis, the fellow eye is usually affected within four weeks.

Optic neuritis is unlikely in a man of this age who had painless loss of vision.

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 5 hrs 29 mins 37 secs

Work Smart Session - MRCP Part 1

Question: 95 of 100

A broad-based ataxic gait occurs characteristically with:

(Please select 1 option)

○	Basal ganglia lesion
○	Cerebellar vermis lesion
○	Phenytoin toxicity
○	Proximal myopathy
○	Right-sided cerebral infarction

Submit answer | Skip question | Tag Question | Remove question

Time taken: 5 hrs 30 mins 31 secs

Work Smart Session - MRCP Part 1

Question: 95 of 100

A broad-based ataxic gait occurs characteristically with:

(Please select 1 option)

○	Basal ganglia lesion
○	Cerebellar vermis lesion
◉	Phenytoin toxicity ✓ Correct
○	Proximal myopathy
○	Right-sided cerebral infarction

Broad based gait is associated with cerebellar syndrome. However, lesions of cerebellar vermis cause truncal ataxia and tendency to fall backwards.

Basal ganglia disease causes extrapyramidal signs with Parkinsonism (festinant gait, marche à petits pas).

Proximal myopathy causes a waddling gait.

Right-sided cerebral infarction is associated with a hemiplegic gait.

Next question

Tag Question

Remove question

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 5 hrs 30 mins 31 secs

Work Smart Session - MRCP Part 1

Question: 96 of 100

Causes of dilated pupils include:

(Please select 1 option)

○	Argyll Robertson pupil
○	Ethylene glycol poisoning
○	Myotonic dystrophy
○	Organophosphate poisoning
○	Pontine haemorrhage

Submit answer | Skip question | Tag Question | Remove question

(Please select 1 option)

○	Argyll Robertson pupil
◉	Ethylene glycol poisoning ✓ Correct
○	Myotonic dystrophy
○	Organophosphate poisoning
○	Pontine haemorrhage

Causes of dilated pupils include:

- Holmes-Adie (myotonic) pupil

- third nerve palsy

- drugs and poisons (atropine, cobalt [CO], ethylene glycol).

Causes of small pupils include:

- Horner's syndrome

- old age

- pontine haemorrhage

- Argyll Robertson pupil

- drugs and poisons (opiates, organophosphates).

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 5 hrs 30 mins 54 secs

Work Smart Session - MRCP Part 1

Question: 97 of 100

A 25-year-old woman presents with a severe migraine.

Which of the following is not a recognised feature of migraine?

(Please select 1 option)

○	Bilateral fortification spectra
○	External ophthalmoplegia
○	Precipitation by oral contraceptives
○	Some symptoms improved by tricyclic antidepressants
○	Third nerve palsy

Submit answer | Skip question | Tag Question | Remove question

Time taken: 5 hrs 31 mins 48 secs

Work Smart Session - MRCP Part 1

Question: 97 of 100

A 25-year-old woman presents with a severe migraine.

Which of the following is not a recognised feature of migraine?

(Please select 1 option)

◉	Bilateral fortification spectra ✕ Incorrect answer selected
○	External ophthalmoplegia ← This is the correct answer
○	Precipitation by oral contraceptives
○	Some symptoms improved by tricyclic antidepressants
○	Third nerve palsy

Fortification spectra (jagged lines resembling battlements) and teichopsia (flashes) are common. Tricyclics can be useful for nausea.

Third nerve palsy is seen in ophthalmoplegic migraine.

Chronic progressive external ophthalmoplegia usually develops in childhood and is associated with ptosis, fatigue and limitation to eye- movements in all directions.

The disorder is in the cytochromes.

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 5 hrs 31 mins 48 secs

Work Smart Session - MRCP Part 1

Question: 98 of 100

Which of the following will not be affected by a lesion of the facial nerve in the internal auditory meatus?

(Please select 1 option)

○	Blinking
○	Hearing
○	Lacrimation
○	Sweating over the cheek
○	Taste

Submit answer | Skip question | Tag Question | Remove question

Time taken: 5 hrs 32 mins 23 secs

Work Smart Session - MRCP Part 1

Question: 98 of 100

Which of the following will not be affected by a lesion of the facial nerve in the internal auditory meatus?

(Please select 1 option)

○	Blinking
○	Hearing
○	Lacrimation
○	Sweating over the cheek ← This is the correct answer
◉	Taste ✕ Incorrect answer selected

The extent of dysfunction depends on the level of injury.

If it is proximal to geniculate ganglion, for example, internal auditory meatus, taste is lost in the anterior 2/3 of tongue. Also secretion from submandibular, sublingual and lacrimal glands is impaired.

Hyperacusis is due to paralysis of stapedius. Orbicularis oculi is affected causing inability to blink/close eyelids.

Sensation over face is supplied by the trigeminal nerve, and sweat glands are controlled by sympathetic nervous system, for example, anhydriosis in Horner's syndrome.

Next question

Tag Question Remove question

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 5 hrs 32 mins 23 secs

Work Smart Session - MRCP Part 1

Question: 99 of 100

The incidence of Down syndrome in children born to women aged less than 30 years is approximately which of the following?

(Please select 1 option)

○	1:500
○	1:1000
○	1:5000
○	1:10000
○	1:15000

Submit answer | Skip question | Remove Tag | Remove question

Time taken: 5 hrs 33 mins 4 secs

Work Smart Session - MRCP Part 1

Question: 99 of 100

The incidence of Down syndrome in children born to women aged less than 30 years is approximately which of the following?

(Please select 1 option)

○	1:500
○	1:1000 ← This is the correct answer
◉	1:5000 ✕ Incorrect answer selected
○	1:10000
○	1:15000

The incidence is roughly 1 in 1200 births for woman less than 30 and this incidence can rise to 1 in 60 by the age of 42.

Maternal age also affects the incidence of hydrocephalus, anencephaly and other chromosomal disorders.

Next question

Remove Tag Remove question

Rate this question

☆☆☆☆☆

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Question: 9 of 100

A 62-year-old male presents with weakness of the right hand. You note global wasting of the small hand muscles, there is also sensory loss over the medial border of the forearm around the elbow.

Which nerve root is damaged?

(Please select 1 option)

○	C5
○	C6
○	C7
○	C8
◉	T1 ✓ Correct

This patient has Klumpke's paralysis due to damage to the T1 nerve root. This root eventually supplies the median and ulnar nerves.

The ulnar nerve supplies all of the intrinsic hand muscles except for those of the thenar eminence and the first and second lumbricals which are innervated by the median nerve.

Next question

Tag Question | Remove question

Rate this question

☆☆☆☆☆

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken:

Question: 1 of 47

A 72-year-old man with a history of type 2 diabetes mellitus and multiple transient ischaemic attacks (TIAs) comes to the hospital complaining of visual field loss. He says this happened suddenly and he woke up with problems with his vision the morning before coming to the emergency department.

Medication includes clopidogrel, ramipril, atorvastatin, and metformin.

On examination his BP is 165/100 mmHg, his pulse is 76 and regular. Visual field examination reveals a right homonymous upper quadrantanopia.

Where is the most likely site for the underlying lesion?

(Please select 1 option)

○	Left occipital lobe
○	Left temporal lobe
○	Optic chiasm
○	Right optic nerve
○	Right temporal lobe

Submit answer | Skip question | Tag Question | Remove question

Work Smart Session - MRCP Part 1

Time taken: 21 mins 57 secs

Question: 10 of 47

A 37-year-old homosexual male presented to the medical take with an acute onset of reduced vision in his left eye.

Fundoscopy of the left eye revealed an extensive 'brushfire-like' lesion in the major superior temporal arcade with a large patch of white fluffy lesion mixed with extensive retinal haemorrhages.

What is the most likely diagnosis?

(Please select 1 option)

○	CMV retinitis
○	Ocular histoplasmosis
○	Syphilitic choroiditis
○	Syphilitic neuroretinitis
○	Tuberculous periphlebitis

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

A 37-year-old homosexual male presented to the medical take with an acute onset of reduced vision in his left eye.

Fundoscopy of the left eye revealed an extensive 'brushfire-like' lesion in the major superior temporal arcade with a large patch of white fluffy lesion mixed with extensive retinal haemorrhages.

What is the most likely diagnosis?

(Please select 1 option)

◉	CMV retinitis ✓ Correct
○	Ocular histoplasmosis
○	Syphilitic choroiditis
○	Syphilitic neuroretinitis
○	Tuberculous periphlebitis

This is a classic example of *Cytomegalovirus* (CMV) retinitis secondary to human immunodeficiency virus (HIV), as is suggestive of the information given in this scenario.

Ocular histoplasmosis and syphilitic choroiditis would give a fundus picture of multiple whitish lesions.

Syphilitic neuroretinitis would normally give a picture of a macular star exudation.

Tuberculous periphlebitis is the next closest answer, but does not fit the description of 'brushfire-like' lesion in that it gives a picture of perivenous sheathing and minimal retinal haemorrhages.

Next question | Tag Question | Remove question

Work Smart Session - MRCP Part 1

Time taken: 26 mins 32 secs

Question: 11 of 47

Which one of the following diseases is most likely to be associated with scleritis?

(Please select 1 option)

○	Ankylosing spondylitis
○	Crohn's disease
○	Rheumatoid arthritis
○	SLE
○	Ulcerative colitis

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 27 mins

Question: 11 of 47

Which one of the following diseases is most likely to be associated with scleritis?

(Please select 1 option)

○	Ankylosing spondylitis
○	Crohn's disease
◉	Rheumatoid arthritis ✓ Correct
○	SLE
○	Ulcerative colitis

Rheumatoid arthritis is associated with scleritis, whereas the other choices are more associated with anterior uveitis.

Next question

Tag Question

Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 27 mins

Question: 12 of 47

A 23-year-old man with an otherwise insignificant past medical history, presented with a sharp painful left eye over the last one day.

Ocular examination revealed a left mildly red eye with mild reduction of visual acuity.

There were no ocular discharges to note.

What is the most likely diagnosis?

(Please select 1 option)

- Episcleritis
- Herpetic keratitis
- Iritis
- Posterior uveitis
- Scleritis

Submit answer | Skip question | Tag Question | Remove question

A 23-year-old man with an otherwise insignificant past medical history, presented with a sharp painful left eye over the last one day.

Ocular examination revealed a left mildly red eye with mild reduction of visual acuity.

There were no ocular discharges to note.

What is the most likely diagnosis?

(Please select 1 option)

○	Episcleritis
○	Herpetic keratitis ← This is the correct answer
◉	Iritis ✕ Incorrect answer selected
○	Posterior uveitis
○	Scleritis

Any of the above given diagnoses can occur in a young man, but the history is that of a sharp painful eye, as opposed to a dull achy eye.

Any sharp ocular pain is more suggestive of corneal/ocular surface pathologies, and hence herpetic keratitis is the best answer.

Next question

Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 28 mins 16 secs

Question: 13 of 47

A 65-year-old hypermetropic lady was seen in an acute unselected medical take.

She presented with a three hour history of dull pain, lacrimation, photophobia and reduced vision in the right eye.

She had no significant past medical history.

Ocular examination revealed a painful red eye with an oval shaped pupil.

What is the most likely diagnosis?

(Please select 1 option)

- Acute angle closure glaucoma
- Episcleritis
- Iritis
- Keratoconjunctivitis
- Scleritis

Submit answer | Skip question | Tag Question | Remove question

A 65-year-old hypermetropic lady was seen in an acute unselected medical take.

She presented with a three hour history of dull pain, lacrimation, photophobia and reduced vision in the right eye.

She had no significant past medical history.

Ocular examination revealed a painful red eye with an oval shaped pupil.

What is the most likely diagnosis?

(Please select 1 option)

◉	Acute angle closure glaucoma ✓ Correct
○	Episcleritis
○	Iritis
○	Keratoconjunctivitis
○	Scleritis

Red eye of an acute painful dull nature, with photophobia and reduced vision in a hypermetropic person is highly indicative of acute angle closure glaucoma.

The pupil in this condition is usually mid-dilated oval shaped.

The oval shape is due to the iris sphincter ischaemia from the high intraocular pressure.

Work Smart Session - MRCP Part 1

Time taken: 30 mins 49 secs

Question: 14 of 47

A 45-year-old asthmatic man presented with bilateral blurry vision of gradual onset over the last two months.

On examination he was found to have bilateral posterior subcapsular cataract, more so in the right than the left.

His other past medical history was that he had galactosaemia when he was still a baby, but this has since been treated. He is on bronchodilator inhalers and steroid inhalers to control his asthma. His oral medication includes amiodarone, aspirin and simvastatin.

What is the most likely cause of his cataracts?

(Please select 1 option)

○	Amiodarone
○	Galactosaemia
○	Inhaled bronchodilators
○	Inhaled steroids
○	Simvastatin

Submit answer | Skip question | Tag Question | Remove question

On examination he was found to have bilateral posterior subcapsular cataract, more so in the right than the left.

His other past medical history was that he had galactosaemia when he was still a baby, but this has since been treated. He is on bronchodilator inhalers and steroid inhalers to control his asthma. His oral medication includes amiodarone, aspirin and simvastatin.

What is the most likely cause of his cataracts?

(Please select 1 option)

◉	Amiodarone ✕ Incorrect answer selected
○	Galactosaemia
○	Inhaled bronchodilators
○	Inhaled steroids ← This is the correct answer
○	Simvastatin

Inhaled steroids can cause cataracts.

Amiodarone causes vortex keratopathy.

Galactosaemia also does cause cataracts, but if the galactosaemia is treated, the cataract is reversible.

Inhaled bronchodilators and simvastatin are not known to cause cataracts.

Next question

Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 32 mins 53 secs

Question: 15 of 47

A 42-year-old lady presented with a two week history of noticing both her eyes were skewed towards the temporal side. She denied ocular pain and headaches. Her visual acuity was 6/6 on the Snellen chart in both eyes.

She was not able to adduct both eyes, but up and down gaze was fine. She had two previous episodes of optic neuritis in the right eye. The last episode happened four months ago.

Her walking was normal, and her deep tendon reflexes were present. She also had just recovered from gastroenteritis three weeks ago.

What is the most likely condition that the patient had presented with?

(Please select 1 option)

- Chronic progressive external ophthalmoplegia
- Internuclear ophthalmoplegia
- Miller Fisher syndrome
- Ocular myasthenia
- Parinaud's syndrome

Submit answer | Skip question | Tag Question | Remove question

side. She denied ocular pain and headaches. Her visual acuity was 6/6 on the Snellen chart in both eyes.

She was not able to adduct both eyes, but up and down gaze was fine. She had two previous episodes of optic neuritis in the right eye. The last episode happened four months ago.

Her walking was normal, and her deep tendon reflexes were present. She also had just recovered from gastroenteritis three weeks ago.

What is the most likely condition that the patient had presented with?

(Please select 1 option)

○	Chronic progressive external ophthalmoplegia
◉	Internuclear ophthalmoplegia ✓ Correct
○	Miller Fisher syndrome
○	Ocular myasthenia
○	Parinaud's syndrome

This is a case of walled eye bilateral internuclear ophthalmoplegia (WEBINO).

The history suggests a demyelinating process, and failure of ocular adduction in such cases should prompt the diagnosis of internuclear ophthalmoplegia.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 35 mins 7 secs

Question: 16 of 47

A 75-year-old man developed a gradual problem of not being able to look down over the last eight months. Then about two months ago, he was also not able to look up. He denied any diplopia, ocular pain or headaches.

There was no evidence of convergence retraction nystagmus, proptosis or ptosis.

What is the most likely diagnosis?

(Please select 1 option)

- Chronic progressive external ophthalmoplegia
- Ocular myasthenia
- Ocular myositis
- Parinaud's syndrome
- Thyroid eye disease

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Question: 16 of 47

A 75-year-old man developed a gradual problem of not being able to look down over the last eight months. Then about two months ago, he was also not able to look up. He denied any diplopia, ocular pain or headaches.

There was no evidence of convergence retraction nystagmus, proptosis or ptosis.

What is the most likely diagnosis?

(Please select 1 option)

◉	Chronic progressive external ophthalmoplegia ✓ Correct
○	Ocular myasthenia
○	Ocular myositis
○	Parinaud's syndrome
○	Thyroid eye disease

The history itself suggests a chronic progressive limitation of eye movements without any diplopia, proptosis or ptosis. Therefore, the most likely diagnosis is chronic progressive external ophthalmoplegia.

Ocular myasthenia usually presents with diplopia and ptosis.

Parinaud's syndrome usually manifests as up gaze palsy with convergence retraction nystagmus.

Next question | Tag Question | Remove question

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 37 mins 6 secs

Question: 17 of 47

A 24-year-old lady with a body mass index (BMI) of 36 and on the combined oral contraceptive pill presented with a one month history of increasing vertex headaches, worse in the mornings and worse on coughing and sneezing. She also complained of blurry vision in both eyes.

Fundoscopy revealed bilateral extensive papilloedema with a lot of flame shaped haemorrhages around and on the optic discs.

Which one of the following is the best long term management of this patient?

(Please select 1 option)

○	Changing the combined oral contraceptive pill to an oestrogen based one
○	Commence on aspirin
○	Perform lumbar puncture
○	Reduce weight
○	Start oral acetazolamide

Submit answer | Skip question | Tag Question | Remove question

also complained of blurry vision in both eyes.

Fundoscopy revealed bilateral extensive papilloedema with a lot of flame shaped haemorrhages around and on the optic discs.

Which one of the following is the best long term management of this patient?

(Please select 1 option)

○	Changing the combined oral contraceptive pill to an oestrogen based one
○	Commence on aspirin
○	Perform lumbar puncture
◉	Reduce weight ✓ Correct
○	Start oral acetazolamide

This patient has idiopathic intracranial hypertension. The best long term management is weight reduction, which can improve her symptoms.

Changing the combined oral contraceptive pill to a more oestrogen based one can worsen the symptoms.

Lumbar puncture and acetazolamide can help improve the symptoms, but should not be considered as long term management.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 39 mins 20 secs

Question: 18 of 47

A 26-year-old tall, thin, lady with a known cardiac valvulopathy, was reported to have skin laxity and folds on the back of the neck and her underarms.

Fundoscopy revealed bilateral angioid streaks with optic disc drusens.

What is the most likely diagnosis?

(Please select 1 option)

○	Ehlers-Danlos syndrome
○	Marfan's syndrome
○	Menkes syndrome
○	Osteogenesis imperfecta
○	Pseudoxanthoma elasticum

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Question: 18 of 47

A 26-year-old tall, thin, lady with a known cardiac valvulopathy, was reported to have skin laxity and folds on the back of the neck and her underarms.

Fundoscopy revealed bilateral angioid streaks with optic disc drusens.

What is the most likely diagnosis?

(Please select 1 option)

◉	Ehlers-Danlos syndrome ✗ Incorrect answer selected
○	Marfan's syndrome
○	Menkes syndrome
○	Osteogenesis imperfecta
○	Pseudoxanthoma elasticum ← This is the correct answer

Pseudoxanthoma elasticum with angioid streaks is also known as Grönblad-Strandberg syndrome.

Ehlers-Danlos and Marfan's syndrome are not associated with laxity and folds of skin on the back of the neck.

Menkes syndrome and osteogenesis imperfecta are not associated with angioid streaks.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 40 mins 22 secs

Question: 19 of 47

A 34-year-old man, who has just recovered from gastroenteritis following a recent trip to Turkey, suddenly developed progressive gait ataxia and restriction of eye movements in all directions of gaze.

There was no nystagmus.

What is the most likely diagnosis?

(Please select 1 option)

- Acute cerebellar degeneration
- Millard-Gubler syndrome
- Miller-Fisher syndrome
- Parinaud's syndrome
- Subacute combined degeneration of the spinal cord

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

What is the most likely diagnosis?

(Please select 1 option)

○	Acute cerebellar degeneration
○	Millard-Gubler syndrome
◉	Miller-Fisher syndrome ✓ Correct
○	Parinaud's syndrome
○	Subacute combined degeneration of the spinal cord

Miller-Fisher syndrome is a variant/spectrum of Guillain-Barré syndrome (GBS).

GBS is associated with *Campylobacter jejuni* infection, which can trigger this syndrome.

Miller-Fisher is classically described as a triad of

- External ophthalmoplegia
- Ataxia
- Areflexia

so the above history would be most in keeping with Miller-Fisher syndrome.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Medication includes clopidogrel, ramipril, atorvastatin, and metformin.

On examination his BP is 165/100 mmHg, his pulse is 76 and regular. Visual field examination reveals a right homonymous upper quadrantanopia.

Where is the most likely site for the underlying lesion?

(Please select 1 option)

○	Left occipital lobe
◉	Left temporal lobe ✓ Correct
○	Optic chiasm
○	Right optic nerve
○	Right temporal lobe

Temporal lobe lesions result in a bilateral homonymous hemianopia.

Occipital lobe lesions result in cortical blindness.

The most likely cause in this case is a thromboembolic event affecting the left temporal lobe. Given he has suffered multiple TIAs he should be considered for a work up including echocardiogram and carotid USS.

Anti-platelet management if tolerated should be with aspirin and dipyridamole as per the ESPS2 trial.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 3 mins 51 secs

Question: 2 of 47

A 29-year-old woman comes to the clinic because she is concerned that her left pupil is abnormally large. Her boyfriend noticed it and suggested she should see the doctor.

She has no past medical history of note, apart from an episode of shingles a few months earlier, and takes the oral contraceptive pill as her only medication. On further questioning she admits to unprotected sexual intercourse on two to three occasions over the past three to four years.

On examination her left pupil is clearly larger than the right. It hardly reacts to light at all, but does accommodate to near vision. You notice that re-dilatation is very slow however. Her BP is normal at 132/72 mmHg, and general physical examination is unremarkable.

How best can you confirm the diagnosis?

(Please select 1 option)

○	Chest x ray
○	Lumbar puncture
○	MRI brain
○	Reaction to weak miotic eye drops
◉	Syphilis serology

Submit answer | Skip question | Tag Question | Remove question

Work Smart Session - MRCP Part 1

Time taken: 42 mins 2 secs

Question: 20 of 47

A 61-year-old emmetropic female nurse presented with a three day history of missing steps when walking down the stairs as she was seeing double of each of the steps. She reported no such problems when walking up the stairs.

She admitted to bumping her head moderately hard when trying to get out of her car four days ago. She denied any deterioration of her visual acuity.

No horizontal diplopia was elicited.

What is the most likely cause of her problems?

(Please select 1 option)

○	Right inferior oblique palsy
○	Right inferior rectus palsy
○	Right superior oblique palsy
○	Right superior rectus palsy
○	This patient needs glasses for distance

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

A 61-year-old emmetropic female nurse presented with a three day history of missing steps when walking down the stairs as she was seeing double of each of the steps. She reported no such problems when walking up the stairs.

She admitted to bumping her head moderately hard when trying to get out of her car four days ago. She denied any deterioration of her visual acuity.

No horizontal diplopia was elicited.

What is the most likely cause of her problems?

(Please select 1 option)

○	Right inferior oblique palsy
○	Right inferior rectus palsy
◉	Right superior oblique palsy ✓ Correct
○	Right superior rectus palsy
○	This patient needs glasses for distance

This patient essentially suffered from vertical diplopia following bumping her head moderately hard.

The fourth cranial nerve can be affected in such a situation resulting in superior oblique palsy.

Next question

Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 42 mins 9 secs

Question: 21 of 47

A 28-year-old Lebanese lady developed left branch retinal artery occlusion (BRAO) one week after an uneventful elective caesarean section. She also developed some mouth and vulval ulcers two weeks post-partum.

Visual acuity in the affected left eye was counting fingers.

Full blood picture, U&Es and coagulation screen were all within normal limits. CRP was 28. Anti-nuclear antibody, ANA titre was 1:20.

What is the most likely cause of her left BRAO?

(Please select 1 option)

○	Amniotic fluid embolus
○	Behçet's disease
○	Fat embolus
○	Reiter's syndrome
○	SLE

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Full blood picture, U&Es and coagulation screen were all within normal limits. CRP was 28. Anti-nuclear antibody, ANA titre was 1:20.

What is the most likely cause of her left BRAO?

(Please select 1 option)

○	Amniotic fluid embolus
◉	Behçet's disease ✓ Correct
○	Fat embolus
○	Reiter's syndrome
○	SLE

Behçet's disease is an inflammatory condition of blood vessels of unknown aetiology. It is more common in people from the eastern Mediterranean and the Middle East.

The vasculitic process can affect many parts of the body, including the eye, which can lead to retinal artery occlusion among other things.

Mouth and genital ulcers with an inflammatory condition in a person from the Mediterranean region should make one think of Behçet's disease as the diagnosis.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 43 mins 45 secs

Question: 22 of 47

A 77-year-old male presents with sudden loss of vision in his right eye, associated with a relative afferent pupillary defect. He has poorly controlled systemic hypertension and raised cholesterol.

What is the most likely aetiology of his presentation?

(Please select 1 option)

- Cataract
- Chronic open angle glaucoma
- Macular degeneration
- Retinal vascular occlusion
- Retinitis pigmentosa

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 45 mins 1 secs

Question: 22 of 47

A 77-year-old male presents with sudden loss of vision in his right eye, associated with a relative afferent pupillary defect. He has poorly controlled systemic hypertension and raised cholesterol.

What is the most likely aetiology of his presentation?

(Please select 1 option)

○	Cataract
○	Chronic open angle glaucoma
○	Macular degeneration
○	Retinal vascular occlusion ← This is the correct answer
◉	Retinitis pigmentosa ✕ Incorrect answer selected

The history of acute loss of vision affecting one eye suggests an acute vascular occlusion, especially given the associated vascular risks.

The others cause a more chronic visual loss.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 45 mins 1 secs

Question: 23 of 47

A 24-year-old law student attends with visual loss affecting the right eye. She reports a constant headache for the last three months, and absence of menses for six months.

On examination her visual acuity in the right eye is 6/24, with slight constriction of the temporal field in that eye but she has no other neurological deficit. She is afebrile and haemodynamically stable.

What is the diagnosis?

(Please select 1 option)

○	Glaucoma
○	Migraine
○	Multiple sclerosis
○	Pituitary tumour
○	Pregnancy

Submit answer | Skip question | Tag Question | Remove question

she has no other neurological deficit. She is afebrile and haemodynamically stable.

What is the diagnosis?

(Please select 1 option)

○	Glaucoma
○	Migraine
○	Multiple sclerosis
◉	Pituitary tumour ✓ Correct
○	Pregnancy

This patient has a pituitary lesion; the history of headache and amenorrhoea suggests a prolactinoma or non-functioning tumour. This has been complicated by involvement of the visual pathway which has precipitated her visual loss.

She needs urgent assessment of her pituitary function and imaging of the pituitary gland by MRI scanning. One of the most important investigations to perform would be a serum prolactin.

The amenorrhoea would argue against this being retrobulbar neuritis associated with multiple sclerosis (MS), and similarly the peripheral visual field constriction would be unusual as a central scotoma and fluctuating visual loss would be more typical.

Next question

Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 46 mins 56 secs

Question: 24 of 47

A 60-year-old man presents with an acute red eye.

Of the following conditions which is the most likely cause?

(Please select 1 option)

- Closed angle glaucoma
- Optic neuritis
- Retinal vein occlusion
- Retinal detachment
- Vitreous haemorrhage

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

(Please select 1 option)

◉	Closed angle glaucoma ✓ Correct
○	Optic neuritis
○	Retinal vein occlusion
○	Retinal detachment
○	Vitreous haemorrhage

Of those listed the most likely to present with an acute red eye would be glaucoma.

Other causes of acute red eye include

- Anterior uveitis
- Corneal ulcers
- Conjunctivitis
- Scleritis
- Episcleritis
- Subconjunctival haemorrhage.

Optic neuritis presents with a particular type of central visual loss - a central scotoma.

Retinal vein occlusion, retinal detachment and vitreous haemorrhage would present as visual loss or disturbance.

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 47 mins 56 secs

Question: 25 of 47

A 26-year-old man presented with a 24 hour history of blurred vision in the left eye and mild left frontal headache. He had a ten year history of diabetes mellitus.

Examination of the left eye revealed a central scotoma.

What is the most likely diagnosis?

(Please select 1 option)

- Central retinal artery occlusion
- Diabetic retinopathy
- Migraine
- Optic neuritis
- Pituitary tumour

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

A 26-year-old man presented with a 24 hour history of blurred vision in the left eye and mild left frontal headache. He had a ten year history of diabetes mellitus.

Examination of the left eye revealed a central scotoma.

What is the most likely diagnosis?

(Please select 1 option)

○	Central retinal artery occlusion
○	Diabetic retinopathy
○	Migraine
◉	Optic neuritis ✓ Correct
○	Pituitary tumour

Occlusion of the central retinal artery or one of its branches which supplies the macular region will result in almost immediate diminution or loss of visual acuity in the involved eye and is usually without pain.

In a young diabetic the aetiology is usually an embolus of the central retinal artery or one of its branches. However there is pain associated with this visual loss, namely headache.

Diabetes is a cause of optic neuritis which is usually associated with headache.

Retinopathy, per se, would not lead to an acute central scotoma unless there was acute bleeding from neovascularisation.

Next question

Tag Qu

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 51 mins 20 secs

Question: 26 of 47

A 35-year-old woman is referred with right eye pain that has deteriorated over the last week.

On examination she had a mild ptosis of the right eye and was aware of diplopia with vertical image separation on looking upwards. She also had weakness of elevation of the right eye.

What is the most likely diagnosis?

(Please select 1 option)

- Cavernous sinus thrombosis
- Graves' ophthalmopathy
- Myasthenia gravis
- Posterior communicating artery aneurysm
- Sphenoid sinusitis

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

On examination she had a mild ptosis of the right eye and was aware of diplopia with vertical image separation on looking upwards. She also had weakness of elevation of the right eye.

What is the most likely diagnosis?

(Please select 1 option)

○	Cavernous sinus thrombosis
○	Graves' ophthalmopathy
○	Myasthenia gravis
◉	Posterior communicating artery aneurysm ✓ Correct
○	Sphenoid sinusitis

The signs are consistent with a partial third nerve palsy associated with periorbital pain.

In a young person a posterior communicating artery aneurysm needs to be excluded.

With cavernous sinus thrombosis one should expect some other signs such as periorbital swelling, proptosis, and conjuctival injection.

With Graves' eye disease one should expect proptosis and lid retraction.

Myasthenia gravis does not present with pain.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 54 mins 35 secs

Question: 27 of 47

A 18-year-old male presents with blurring of vision in his right eye.
Examination reveals visual acuity in the right eye of 6/18 and in the left eye 6/6.

Visual fields to confrontation reveal a right temporal visual field defect and partial loss of superior part of the temporal field of the left eye.

Where is the most likely position of the lesion responsible for this defect?

(Please select 1 option)

○	Occipital lobe
○	Optic chiasm
○	Optic nerve
○	Optic tract
○	Temporal lobe

Submit answer | Skip question | Tag Question | Remove question

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

A 18-year-old male presents with blurring of vision in his right eye.
Examination reveals visual acuity in the right eye of 6/18 and in the left eye 6/6.

Visual fields to confrontation reveal a right temporal visual field defect and partial loss of superior part of the temporal field of the left eye.

Where is the most likely position of the lesion responsible for this defect?

(Please select 1 option)

○	Occipital lobe
◉	Optic chiasm ✓ Correct
○	Optic nerve
○	Optic tract
○	Temporal lobe

The most likely localisation of the lesion is around the optic chiasm spreading up the right optic nerve. The signs indicate a bitemporal visual field defect with involvement of the right optic nerve (decreased visual acuity).

Occipital lobe lesion causes a congruous homonymous hemianopia whereas an optic tract lesion causes an incongruous homonymous hemianopia. Temporal lobe lesion causes an upper homonymous quantranopia.

Visual fields See also references.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 57 mins 3 secs

Question: 28 of 47

A 30-year-old man complains of fairly rapid worsening of his central vision. His acuity is normal on pinhole testing.

Which of the following would not account for his symptoms?

(Please select 1 option)

○	Diabetes mellitus
○	Eye drops
○	Eyelid swelling
○	Lens subluxation
○	Open angle glaucoma

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

○	Diabetes mellitus
○	Eye drops
○	Eyelid swelling
◉	Lens subluxation ✕ Incorrect answer selected
○	Open angle glaucoma ← This is the correct answer

The defect in this patient's vision is corrected by viewing through a pinhole, which means that the problem is refractive and must therefore be localised to the cornea or the lens.

Causes of rapid changes in refractive error include:

- Senile cataract (increasingly myopic)
- Diabetes mellitus (high glucose raises refractive index of lens, hence myopic)
- Keratoconus (conical cornea, may occur rapidly in adolescence or early adulthood and causes myopia and astigmatism)
- Subluxation of the lens
- Eye drops (miotics produce myopia, mydriatics lead to hypermetropia) and
- Eyelid swelling.

Open angle glaucoma is associated with damage to the ganglion cells of the retina and therefore any visual deficit that is produced by it will not correct with a pinhole.

Next question

Remove Tag Remove question

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 59 mins 18 secs

Question: 29 of 47

A 70-year-old female who has a history of chronic anxiety presents with a three day history of severe left temporal headache radiating from the eye to the scalp. She had also experienced discomfort during eating.

Which one of the following drugs should be given to this patient while awaiting the results of diagnostic tests?

(Please select 1 option)

- Acyclovir
- Carbamazepine
- Diclofenac
- Prednisolone
- Sumatriptan

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Question: 29 of 47

A 70-year-old female who has a history of chronic anxiety presents with a three day history of severe left temporal headache radiating from the eye to the scalp. She had also experienced discomfort during eating.

Which one of the following drugs should be given to this patient while awaiting the results of diagnostic tests?

(Please select 1 option)

○	Acyclovir
○	Carbamazepine
○	Diclofenac
◉	Prednisolone ✓ Correct
○	Sumatriptan

The history suggests temporal arteritis irrespective of the history of anxiety and in view of the sight-threatening nature of the disease, the patient should be commenced on steroids.

Although the differential diagnosis is also trigeminal neuralgia, steroids should be used here whilst awaiting diagnostic investigations as temporal arteritis may be sight-threatening if left untreated.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

physical examination is unremarkable.

How best can you confirm the diagnosis?

(Please select 1 option)

○	Chest x ray
○	Lumbar puncture
○	MRI brain
○	Reaction to weak miotic eye drops ← This is the correct answer
◉	Syphilis serology ✕ Incorrect answer selected

This history is typical of an Adie's tonic pupil, which is characteristically seen in young women, and may occur after an episode of zoster infection.

At the beginning of the condition the pupil is large, but over time becomes small and poorly reactive. Slit lamp examination may reveal small worm like contractions of the iris, but the usual diagnostic test is to use weak pilocarpine eye drops, which induce vigorous pupil contraction on the affected side, but only weak contraction of the pupil on the unaffected side.

In adults it tends to be a benign condition and is simply observed, however infants are usually referred because of an association with familial dystonias.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 6 mins

Question: 3 of 47

A 47-year-old man, who is currently being treated with quadruple therapy for pulmonary tuberculosis comes to the emergency department complaining of a sudden deterioration in the visual acuity in his left eye and loss of colour vision.

Which of the following anti-tuberculous agents is most likely to have been responsible?

(Please select 1 option)

○	Ethambutol
○	Isoniazid
○	Pyrazinamide
○	Rifampicin
○	Streptomycin

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 8 secs

Question: 30 of 47

A 35-year-old woman with type 1 diabetes mellitus presents for annual assessment.

Which one of the following features on fundoscopy would require urgent referral to an ophthalmologist?

(Please select 1 option)

○	Asteroid bodies
○	Hard exudates in the macular region
○	Intraretinal microvascular abnormalities
○	Scattered microaneurysms
◉	Soft exudates

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 51 secs

Show

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Question: 30 of 47

A 35-year-old woman with type 1 diabetes mellitus presents for annual assessment.

Which one of the following features on fundoscopy would require urgent referral to an ophthalmologist?

(Please select 1 option)

○	Asteroid bodies
○	Hard exudates in the macular region ← This is the correct answer
○	Intraretinal microvascular abnormalities
○	Scattered microaneurysms
◉	Soft exudates ✕ Incorrect answer selected

Scattered microaneurysms signify background DRn.

Intraretinal microvascular abnormalities (IRMAs) and soft exudates signify pre-proliferative retinopathy.

According to the NIeH, urgent referral to an ophthalmologist (seen within one week) is required if there is proliferative retinopathy or there is evidence of clinically significant macular oedema (hard exudates at the fovea).

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 51 secs

Question: 31 of 47

A 60-year-old male who was previously fit and well presented with a six week history of blurring of vision.

His investigation revealed a fasting plasma glucose of 12.9 mmol/L (3.0 - 6.0).

What is the most likely cause of his blurred vision?

(Please select 1 option)

○	Cataract
○	Maculopathy
○	Osmotic changes in the lens
○	Proliferative diabetic retinopathy
○	Retinal vein thrombosis

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 2 mins 43 secs

Question: 31 of 47

A 60-year-old male who was previously fit and well presented with a six week history of blurring of vision.

His investigation revealed a fasting plasma glucose of 12.9 mmol/L (3.0 - 6.0).

What is the most likely cause of his blurred vision?

(Please select 1 option)

○	Cataract
○	Maculopathy
◉	Osmotic changes in the lens ✓ Correct
○	Proliferative diabetic retinopathy
○	Retinal vein thrombosis

Without being given too much here, this patient is a newly diagnosed diabetic as we are told he was previously fit and well.

Therefore the most probable explanation for his blurred vision is osmotic change.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 2 mins 43 secs

Question: 32 of 47

A 17-year-old male with learning difficulties is brought for review by his worried parents after he described acute blurring of vision in his right eye.

Examination reveals ectopia lentis.

What is the most likely diagnosis?

(Please select 1 option)

○	Ehlers-Danlos syndrome
◉	Homocystinuria
○	Maple syrup urine disease
○	Marfan's syndrome
○	Metachromatic leukodystrophy

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Shop

◉	Homocystinuria ✓ Correct
○	Maple syrup urine disease
○	Marfan's syndrome
○	Metachromatic leukodystrophy

- Ectopia lentis/ subluxation of the lens is associated with:
-
- Ehlers-Danlos syndrome
- Marfan's syndrome
- Weil-Marchesani syndrome (short stature, skeletal abnormalities and ectopia lentis)
- Refsum's disease.
-
- In this case homocystinuria is likely due to the associated mental retardation.
-
- Patients typically have fair skin with coarse hair, osteoporosis, mental retardation (nearly 50%), seizure disorder, marfanoid habitus, and and increased thromboembolic risk.
-
- Metachromatic leukodystrophy is a lysosomal storage disorder characterised by lipid (sulfatide) accumulation in the central nervous system and associated with psychomotor retardation in infants with optic atrophy and blindness.

Next question | Tag Question | Remove question

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 4 mins 20 secs

Question: 33 of 47

A 23-year-old man presents with visual loss in his right eye and this is diagnosed as optic neuritis.

Which one of the following statements would be seen in an afferent pupillary defect?

(Please select 1 option)

- Accommodation response is unaffected
- Hypersensitive response to pilocarpine in the affected eye
- Irregular pupil of the affected eye
- Pupil of affected eye larger than the unaffected eye
- Pupil of affected eye smaller than the unaffected eye

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 5 mins 56 secs

Question: 33 of 47

A 23-year-old man presents with visual loss in his right eye and this is diagnosed as optic neuritis.

Which one of the following statements would be seen in an afferent pupillary defect?

(Please select 1 option)

○	Accommodation response is unaffected ← This is the correct answer
◉	Hypersensitive response to pilocarpine in the affected eye ✕ Incorrect answer selected
○	Irregular pupil of the affected eye
○	Pupil of affected eye larger than the unaffected eye
○	Pupil of affected eye smaller than the unaffected eye

Optic neuropathy **does not** cause any abnormalities of the shape or size of the pupil.

However the light reaction is diminished.

Accommodation is normal.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 5 mins 56 secs

Question: 34 of 47

A 72-year-old male presented with a quadrantic hemianopia.

Which of the following conditions is most likely to cause such a presentation?

(Please select 1 option)

- A lesion of the occipital cortex
- A lesion of the optic chiasma
- Bilateral diabetic retinopathy
- Chloroquine poisoning
- Tobacco amblyopia

Submit answer | Skip question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 6 mins 59 secs

Question: 34 of 47

A 72-year-old male presented with a quadrantic hemianopia.

Which of the following conditions is most likely to cause such a presentation?

(Please select 1 option)

○	A lesion of the occipital cortex ← This is the correct answer
◉	A lesion of the optic chiasma ✕ Incorrect answer selected
○	Bilateral diabetic retinopathy
○	Chloroquine poisoning
○	Tobacco amblyopia

A lesion of the optic chiasm would cause a bitemporal hemianopia.

Diabetic retinopathy may cause an 'apparent quadrantic hemianopia' because the distribution of the retinal changes may just correspond to quadrantic hemianopia - but this is not the most likely.

Tobacco amblyopia causes symmetric central or centrocaecal scotomas.

Chloroquine poisoning causes symmetric bilateral scotomas.

Next question

Remove Tag | Remove question

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 6 mins 59 secs

Question: 35 of 47

Regarding retinoblastoma which of the following statements is correct?

(Please select 1 option)

○	Bilateral involvement is found in 70% of cases.
○	The predisposition may be inherited as an autosomal recessive condition.
○	There is an increased risk of autoimmune disease.
○	They have often metastasised by the time of diagnosis.
○	They usually present with leukocoria.

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Regarding retinoblastoma which of the following statements is correct?

(Please select 1 option)

◉	Bilateral involvement is found in 70% of cases. ✕ Incorrect answer selected
○	The predisposition may be inherited as an autosomal recessive condition.
○	There is an increased risk of autoimmune disease.
○	They have often metastasised by the time of diagnosis.
○	They usually present with leukocoria. ← This is the correct answer

The incidence is 1 in 16,000 live births.

Genetic predisposition occurs in 20% of patients with unilateral disease, and 30% of patients with bilateral disease.

The gene has been localised to 13q and the inherited form is associated with an increased risk of malignancy such as osteosarcoma and pineal tumours. It may be inherited as autosomal dominant.

The commonest presentation is leukocoria (yellowish white pupil reflex), and there may be diminished or absent vision or strabismus.

Late symptoms are pupil irregularity, hyphema, pain, proptosis, and signs of raised intracranial pressure.

The tumours have rarely metastasised before they are detected.

Copyright © 2002 Dr Colin Melville

Next question | Remove Tag | Remove question

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 7 mins 35 secs

Question: 36 of 47

Which of the following concerning diabetic retinopathy is correct?

(Please select 1 option)

○	Improved glycaemic control is more effective than hypertensive control in reducing progression of disease.
○	Is unusual in patients with type 2 diabetes
○	Normal visual acuity is seen in proliferative retinopathy.
○	Progression may be reduced with statin therapy
○	Soft exudates are a feature of background retinopathy.

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 8 mins 4 secs

Question: 36 of 47

Which of the following concerning diabetic retinopathy is correct?

(Please select 1 option)

○	Improved glycaemic control is more effective than hypertensive control in reducing progression of disease.
○	Is unusual in patients with type 2 diabetes
◉	Normal visual acuity is seen in proliferative retinopathy. ✓ Correct
○	Progression may be reduced with statin therapy
○	Soft exudates are a feature of background retinopathy.

Diabetic retinopathy occurs in both type 1 and 2 DM and may be a presenting feature in type 2 as the condition may have existed for many years prior to diagnosis.

Progression may be slowed with improved glycaemic and hypertensive control but the latter has been shown to be more effective at reducing progression (UKPDS).

There are no data at present to suggest that statin therapy reduces disease progression.

Soft exudates are a feature of pre-proliferative Rn and despite quite marked new vessel disease the visual acuity may be normal.

Next question | Tag Question | Remove question

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 8 mins 4 secs

Question: 37 of 47

A 72-year-old male presents with diplopia.

Which one of the following features would suggest a third nerve palsy?

(Please select 1 option)

○	Enophthalmos
○	Constricted pupil
○	Convergent strabismus
○	Increased lacrimation
○	Unreactive pupil to light

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Question: 37 of 47

A 72-year-old male presents with diplopia.

Which one of the following features would suggest a third nerve palsy?

(Please select 1 option)

○	Enophthalmos
○	Constricted pupil
○	Convergent strabismus
○	Increased lacrimation
◉	Unreactive pupil to light ✓ Correct

In a third nerve palsy, there is typically ptosis with a dilated unreactive pupil and the eyeball is displaced downwards and outwards.

Enophthalmos is seen in Horner's syndrome. There would be a dilated not constricted pupil and a divergent squint, with the affected eye deviated 'down and out'.

Increased lacrimation may be seen in VIIth palsy.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 9 mins 8 secs

Question: 38 of 47

Which one of the following diagnoses is associated with acute iritis?

(Please select 1 option)

- Keratoconus
- Lyme disease
- Osteogenesis imperfecta
- Psoriatic arthropathy
- Refsum's disease

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Which one of the following diagnoses is associated with acute iritis?

(Please select 1 option)

○	Keratoconus
◉	Lyme disease ✕ Incorrect answer selected
○	Osteogenesis imperfecta
○	Psoriatic arthropathy ← This is the correct answer
○	Refsum's disease

Iritis is associated with conditions such as Reiter's, Behcet's, psoriatic arthropathy (about 20%) and inflammatory bowel disease.

A chronic iritis is rarely described in association with Lyme disease.

Osteogenesis imperfecta is associated with blue sclera.

Keratoconus, meaning "cone shaped," describes a condition in which the cornea (the clear front window of the eye) becomes thin and protrudes. This abnormal shape can cause serious distortion of visual images. It is not associated with iritis.

Refsum's disease is associated with retinitis pigmentosa.

Next question

Remove Tag Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 9 mins 58 secs

Question: 39 of 47

A 16-year-old girl presented with a three week history of headache and horizontal diplopia on far right lateral gaze. On two separate occasions she noted dimmed vision whilst bending forwards. Over the last year she had gained 12 kilograms in weight.

On examination, her weight was 95 kg, and height 162 cms.

Neurological examination revealed bilateral papilloedema and a partial right sixth cranial nerve palsy.

What is the most likely diagnosis?

(Please select 1 option)

○	Benign intracranial hypertension (BIH).
○	Multiple sclerosis.
○	Pituitary tumour
○	Superior sagittal vein thrombosis.
○	Thyroid eye disease.

Submit answer | Skip question | Tag Question | Remove question

- Shop

What is the most likely diagnosis?

(Please select 1 option)

◉	Benign intracranial hypertension (BIH). ✓ Correct
○	Multiple sclerosis.
○	Pituitary tumour
○	Superior sagittal vein thrombosis.
○	Thyroid eye disease.

This patient is markedly obese with a BMI of 36 and the history suggestive of BIH.

Vision may be affected with enlargement of the blind spot and the visual obscuration with movements that provoke a rise in intracranial pressure (ICP) (for example, bending) is typical of BIH.

Dysthyroid eye disease would not present like this and is more commonly associated with hyperthyroidism.

The papilloedema would argue against multiple sclerosis (MS).

A bitemporal hemianopia or a visual field defect would be expected with a pituitary tumour.

Venous sinus thrombosis is a possibility but would be expected to produce deteriorating symptoms.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Which of the following anti-tuberculous agents is most likely to have been responsible?

(Please select 1 option)

◉	Ethambutol ✓ Correct
○	Isoniazid
○	Pyrazinamide
○	Rifampicin
○	Streptomycin

The answer is ethambutol, which is associated with

- Retrobulbar neuritis
- Generalised cutaneous reactions
- Hepatitis
- Peripheral neuropathy.

The retrobulbar neuritis seen with ethambutol may be unilateral or bilateral; as such unilateral symptoms do not preclude the diagnosis.

- Isoniazid is associated with peripheral neuropathy, skin rash and hepatitis
- Pyrazinamide with arthralgia and hepatitis and
- Streptomycin with vestibular and auditory nerve damage.

Work Smart Session - MRCP Part 1

Time taken: 6 mins 45 secs

Question: 4 of 47

A 24-year-old lady presented with anisocoria, with the right pupil larger than the left, both in a brightly lit room and in a dim lit room. Her mother noticed this only five days ago.

The anisocoria was less marked in the dim lit room. Deep tendon reflexes were present and brisk throughout.

She occasionally noted horizontal diplopia with a right sided headache. There was no ptosis. Visual acuity was 6/6 on the Snellen chart in both eyes.

Which one of the following statements is most accurate?

(Please select 1 option)

○	The diagnosis is Holmes-Adie's syndrome
○	The diagnosis of a brain tumour needs to be excluded urgently
○	The diagnosis of a posterior communicating artery aneurysm needs to be excluded urgently
○	The pathological (diseased) pupil is actually the left pupil, diagnosis being Argyll Robertson pupil
○	When doing a swinging light test of the pupils, a right relative afferent papillary defect is to be expected

Submit answer | Skip question | Tag Question | Remove question

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 11 mins 58 secs

Question: 40 of 47

A patient presents with deteriorating vision.

On examination, fundoscopy reveals retinitis pigmentosa.

Which of the following conditions would be unlikely to be responsible for this presentation?

(Please select 1 option)

○	Abetalipoproteinaemia
○	Friedreich's ataxia
○	Kearns-Sayre syndrome
○	Laurence-Moon-Biedl syndrome
○	Refsum's disease

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

A patient presents with deteriorating vision.

On examination, fundoscopy reveals retinitis pigmentosa.

Which of the following conditions would be unlikely to be responsible for this presentation?

(Please select 1 option)

○	Abetalipoproteinaemia
○	Friedreich's ataxia ← This is the correct answer
○	Kearns-Sayre syndrome
◉	Laurence-Moon-Biedl syndrome ✕ Incorrect answer selected
○	Refsum's disease

Causes of pigmentary retinopathy include Usher's syndrome and mitochondrial myopathy.

Abetalipoproteinaemia is autosomal recessive and is associated with:

- Hypocholesterolaemia syndrome resembling Friedreich's ataxia
- Abnormally shaped red blood cells (RBC) (acanthocytes)
- Steatorrhoea and
- Fatty liver.

Friedreich's is associated with optic atrophy.

Next question

Remove Tag | Remove question

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 12 mins 47 secs

Question: 41 of 47

A 22-year-old female presents with a month history of episodic, brief visual loss affecting the right eye.

Over the last one year she had gained a considerable amount of weight. Examination reveals a BMI of 35, with bilateral optic disc swelling, worse on the right and small retinal haemorrhages on the right.

What is the most likely diagnosis?

(Please select 1 option)

- ○ Benign intracranial hypertension (BIH)
- ○ Craniopharyngioma
- ○ Graves' ophthalmopathy
- ○ Optic neuritis
- ○ Sagittal sinus thrombosis

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 13 mins 37 secs

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Question: 41 of 47

A 22-year-old female presents with a month history of episodic, brief visual loss affecting the right eye.

Over the last one year she had gained a considerable amount of weight. Examination reveals a BMI of 35, with bilateral optic disc swelling, worse on the right and small retinal haemorrhages on the right.

What is the most likely diagnosis?

(Please select 1 option)

◉	Benign intracranial hypertension (BIH) ✓ Correct
○	Craniopharyngioma
○	Graves' ophthalmopathy
○	Optic neuritis
○	Sagittal sinus thrombosis

This is a classic description of BIH.

Drugs such as tetracyclines, the oral contraceptive or pregnancy may be contributory.

Next question

Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 13 mins 37 secs

Question: 42 of 47

A 30-year-old female presents to the eye clinic with an acute history of pain and blurring in the right eye.

Examination reveals a visual acuity of 6/36 in the right eye but 6/6 in the left eye, a central scotoma in the right eye, with a right swollen optic disc.

What is the most likely diagnosis?

(Please select 1 option)

- Cavernous sinus thrombosis
- Compression of the optic nerve
- Glaucoma
- Optic neuritis
- Retinal vein occlusion

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 14 mins 49 secs

Question: 42 of 47

A 30-year-old female presents to the eye clinic with an acute history of pain and blurring in the right eye.

Examination reveals a visual acuity of 6/36 in the right eye but 6/6 in the left eye, a central scotoma in the right eye, with a right swollen optic disc.

What is the most likely diagnosis?

(Please select 1 option)

○	Cavernous sinus thrombosis
○	Compression of the optic nerve
○	Glaucoma
◉	Optic neuritis ✓ Correct
○	Retinal vein occlusion

The acute presentation with central scotoma, reduced visual acuity and a swollen optic disc in a young female suggests a diagnosis of multiple sclerosis with a retrobulbar neuritis.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 14 mins 49 secs

Question: 43 of 47

A 50-year-old man with a history of diabetis mellitus and hypertension attends an ophthalmic clinic for regular assessment.

On fundoscopy he is diagnosed to have preproliferative diabetic retinopathy.

Which of the following is characteristic of preproliferative diabetic retinopathy?

(Please select 1 option)

○	Hard exudates
○	Macular oedema
○	Microaneurysms
○	New vessels at the disc
○	Venous beading

Submit answer | Skip question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

A 50-year-old man with a history of diabetis mellitus and hypertension attends an ophthalmic clinic for regular assessment.

On fundoscopy he is diagnosed to have preproliferative diabetic retinopathy.

Which of the following is characteristic of preproliferative diabetic retinopathy?

(Please select 1 option)

○	Hard exudates
○	Macular oedema
○	Microaneurysms
○	New vessels at the disc
◉	Venous beading ✓ Correct

Microaneurysms and hard exudates are features of background diabetic retinopathy.

Macular oedema is associated with microaneurysms and hard exudates and is due to fluid leakage but is not necessarily a feature pre-proliferative or proliferative retinopathy although it may still require laser photocoagulation.

Venous beading, loops and soft exudates (cotton wool spots) are characteristic of the ischaemia associated with preproliferative diabetic retinopathy.

New vessels suggest proliferative retinopathy.

Next question

Remove Tag | Remove question

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 15 mins 38 secs

Question: 44 of 47

Which of the following may be associated with optic atrophy (OA)?

(Please select 1 option)

○	Anti-acetylcholinesterase antibodies
○	Intense iron deposition on liver biopsy
○	Low plasma caeruloplasmin
○	Red ragged fibres on muscle biopsy
○	XXY karyotype

Submit answer | Skip question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 16 mins 57 secs

Question: 44 of 47

Which of the following may be associated with optic atrophy (OA)?

(Please select 1 option)

○	Anti-acetylcholinesterase antibodies
○	Intense iron deposition on liver biopsy
○	Low plasma caeruloplasmin
◉	Red ragged fibres on muscle biopsy ✓ Correct
○	XXY karyotype

Red ragged fibres found in mitochondrial myopathy are found in Kearns-Sayre syndrome; mitochondrial myopathy, lactic acidosis and stroke-like episodes (MELAS); and Leber's optic atrophy.

Wilson's disease is associated with KF rings; and myotonic dystrophy rather than myasthenia gravis is associated with OA.

OA is not associated with Klinefelter's disease.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd. All rights reserved. Terms and conditions Privacy policy

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 16 mins 57 secs

Question: 45 of 47

Causes of dilated pupils include:

(Please select 1 option)

- Argyll Robertson pupil
- Ethylene glycol poisoning
- Myotonic dystrophy
- Organophosphate poisoning
- Pontine haemorrhage

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

○	Argyll Robertson pupil
◉	Ethylene glycol poisoning ✓ Correct
○	Myotonic dystrophy
○	Organophosphate poisoning
○	Pontine haemorrhage

Causes of dilated pupils include:

- Holmes-Adie (myotonic) pupil

- third nerve palsy

- drugs and poisons (atropine, cobalt [CO], ethylene glycol).

Causes of small pupils include:

- Horner's syndrome

- old age

- pontine haemorrhage

- Argyll Robertson pupil

- drugs and poisons (opiates, organophosphates).

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 17 mins 43 secs

Question: 46 of 47

Causes of a small pupil include:

(Please select 1 option)

- Carbon monoxide poisoning
- Ethylene glycol poisoning
- Holmes-Adie pupil
- Pontine haemorrhage
- Third nerve palsy

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

○	Ethylene glycol poisoning
○	Holmes-Adie pupil
◉	Pontine haemorrhage ✓ Correct
○	Third nerve palsy

Causes of small pupils include:

- Horner's syndrome

- old age

- pontine haemorrhage

- Argyll Robertson pupil

- drugs and poisons (opiates, organophosphates).

Causes of dilated pupils include:

- Holmes-Adie (myotonic) pupil

- third nerve palsy

- drugs and poisons (atropine, cobalt [CO], ethylene glycol).

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd. All rights reserved. Terms and conditions. Privacy policy.

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 18 mins 4 secs

Question: 47 of 47

Which of the following conditions is associated with a pathognomonic retinal change?

(Please select 1 option)

○	Infective endocarditis
○	Polycythaemia rubra vera
○	Sickle cell anaemia
○	Toxoplasmosis
◉	Wilson's disease

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 1 hrs 19 mins 51 secs

Question: 47 of 47

Which of the following conditions is associated with a pathognomonic retinal change?

(Please select 1 option)

○	Infective endocarditis
○	Polycythaemia rubra vera
○	Sickle cell anaemia ← This is the correct answer
○	Toxoplasmosis
◉	Wilson's disease ✕ Incorrect answer selected

Sickle cell disease (SCD) is associated with the 'black sunburst' - a chorioretinal scar, which is one of the commoner retinal manifestations of SCD and pathognomonic.

Roth spots, seen in infective endocarditis, are also seen in leukaemia.

Choroidoretinitis in toxoplasmosis may also be seen with other disorders.

The Kayser-Fleischer (KF) rings of Wilson's disease are found on the iris.

Finish | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

A 24-year-old lady presented with anisocoria, with the right pupil larger than the left, both in a brightly lit room and in a dim lit room. Her mother noticed this only five days ago.

The anisocoria was less marked in the dim lit room. Deep tendon reflexes were present and brisk throughout.

She occasionally noted horizontal diplopia with a right sided headache. There was no ptosis. Visual acuity was 6/6 on the Snellen chart in both eyes.

Which one of the following statements is most accurate?

(Please select 1 option)

○	The diagnosis is Holmes-Adie's syndrome
○	The diagnosis of a brain tumour needs to be excluded urgently
○	The diagnosis of a posterior communicating artery aneurysm needs to be excluded urgently ← This is the correct answer
◉	The pathological (diseased) pupil is actually the left pupil, diagnosis being Argyll Robertson pupil ✕ Incorrect answer selected
○	When doing a swinging light test of the pupils, a right relative afferent papillary defect is to be expected

The history of anisocoria, with headaches and diplopia should ring alarm bells, in that a life-threatening posterior communicating artery aneurysm/berry aneurysm needs to be excluded urgently.

Anisocoria being an efferent problem will not give a relative afferent papillary defect.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 10 mins 18 secs

Question: 5 of 47

An 18-year-old man was found to have multiple small pigmented lesions in the peripheral retina of both eyes.

These lesions resembled bear tracks. However, his visual acuity was 6/6 on the Snellen chart in both eyes. His father also had similar lesions.

Which one of the following would be the best next step in managing this man's condition?

(Please select 1 option)

- Referral to cardiology
- Referral to endocrinology
- Referral to gastroenterology
- Referral to infectious disease specialist
- Referral to ophthalmology

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Question: 5 of 47

An 18-year-old man was found to have multiple small pigmented lesions in the peripheral retina of both eyes.

These lesions resembled bear tracks. However, his visual acuity was 6/6 on the Snellen chart in both eyes. His father also had similar lesions.

Which one of the following would be the best next step in managing this man's condition?

(Please select 1 option)

○	Referral to cardiology
○	Referral to endocrinology
○	Referral to gastroenterology ← This is the correct answer
○	Referral to infectious disease specialist
◉	Referral to ophthalmology ✕ Incorrect answer selected

This description of the lesion is that of congenital hypertrophy of retinal pigment epithelium (CHRPE), which is associated with autosomal dominantly inherited familial adenomatous polyposis (FAP).

A referral to gastroenterology is the best next step.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 13 mins 42 secs

Question: 6 of 47

A 47-year-old man, otherwise fit and healthy, complained of a one week history of not being able to see objects placed at the centre of his visual fields, even with both eyes opened.

An objective visual fields test revealed an incongruous binasal hemianopia.

What is the most likely diagnosis?

(Please select 1 option)

○	Carotid-cavernous sinus fistula
◉	Craniopharyngioma
○	External carotid artery dissection
○	Internal carotid artery displacement
○	Pituitary tumour

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 16 mins 12 secs

Question: 6 of 47

A 47-year-old man, otherwise fit and healthy, complained of a one week history of not being able to see objects placed at the centre of his visual fields, even with both eyes opened.

An objective visual fields test revealed an incongruous binasal hemianopia.

What is the most likely diagnosis?

(Please select 1 option)

○	Carotid-cavernous sinus fistula
◉	Craniopharyngioma ✕ Incorrect answer selected
○	External carotid artery dissection
○	Internal carotid artery displacement ← This is the correct answer
○	Pituitary tumour

Bilateral internal carotid artery displacement can cause binasal incongruous hemianopia if the optic nerves are compressed.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 16 mins 12 secs

Question: 7 of 47

A 45-year-old lady with rheumatoid arthritis attended a routine appointment at the rheumatology clinic, and was complaining of a two day history of right red eye with dull pain.

She denied any photophobia and there was no ocular discharge noted.

What is the most likely diagnosis?

(Please select 1 option)

○	Acute angle closure glaucoma
○	Conjunctivitis
○	Inflammation caused by corneal melt
◉	Scleritis
○	Scleromalacia perforans

Submit answer | Skip question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Question: 7 of 47

A 45-year-old lady with rheumatoid arthritis attended a routine appointment at the rheumatology clinic, and was complaining of a two day history of right red eye with dull pain.

She denied any photophobia and there was no ocular discharge noted.

What is the most likely diagnosis?

(Please select 1 option)

○	Acute angle closure glaucoma
○	Conjunctivitis
○	Inflammation caused by corneal melt
◉	Scleritis ✓ Correct
○	Scleromalacia perforans

Rheumatoid arthritis is associated with both scleritis and episcleritis. Scleritis may cause severe pain and results in diffuse or nodular injection. Episcleritis results in ocular irritation with nodules.

In the absence of photophobia and discharge, scleritis would be the best answer.

Next question | Tag Question | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

Work Smart Session - MRCP Part 1

Time taken: 17 mins 14 secs

Question: 8 of 47

A 25-year-old man presented with night blindness and gradual deterioration of his peripheral visual fields bilaterally.

Ocular examination revealed bony spiculed lesions in the peripheral retina of both eyes with attenuated retinal blood vessels.

His only other past medical history is that of a first degree heart block.

Which one of the following statements is most correct?

(Please select 1 option)

○	There is a one in two chance of him passing this disease on to his offspring
○	There is a one in four chance of him passing this disease on to his offspring
○	There is a one in 10 chance of him passing this disease on to his offspring
○	There is a 100% chance of him passing this disease on to his offspring
○	There is no chance of him passing this disease on to his offspring

Submit answer | Skip question | Tag Question | Remove question

vessels.

His only other past medical history is that of a first degree heart block.

Which one of the following statements is most correct?

(Please select 1 option)

◉	There is a one in two chance of him passing this disease on to his offspring ✗ Incorrect answer selected
○	There is a one in four chance of him passing this disease on to his offspring
○	There is a one in 10 chance of him passing this disease on to his offspring
○	There is a 100% chance of him passing this disease on to his offspring
○	There is no chance of him passing this disease on to his offspring ← This is the correct answer

The diagnosis is Kearns-Sayre syndrome.

This is a mitochondrial inherited disease, and as such is only passed on by mothers to offspring.

It is a slowly progressive neuromuscular disorder associated with progressive external ophthalmoplegia and heart conduction defect.

Ocular manifestations include ptosis and peripheral retinal bony spiculed appearances.

Next question | Remove Tag | Remove question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

Work Smart Session - MRCP Part 1

Time taken: 19 mins 51 secs

Question: 9 of 47

A 75-year-old man, known to have ischaemic heart disease, with a previous history of alcohol abuse, presented with a one week history of deterioration of central vision in the right eye.

He denied any ocular pain or headache. An objective visual fields test was done and he was found to have a right central scotoma.

What is the most likely diagnosis?

(Please select 1 option)

○	Alcohol toxic amblyopia
○	Macular degeneration
○	Ocular ischaemic syndrome
○	Vitamin A deficiency
○	Vitamin B_{12} deficiency

Submit answer | Skip question | Tag Question | Remove question

- Dashboard
- Questions
- Scores
- Community
- Help
- Shop

A 75-year-old man, known to have ischaemic heart disease, with a previous history of alcohol abuse, presented with a one week history of deterioration of central vision in the right eye.

He denied any ocular pain or headache. An objective visual fields test was done and he was found to have a right central scotoma.

What is the most likely diagnosis?

(Please select 1 option)

○	Alcohol toxic amblyopia
○	Macular degeneration ← This is the correct answer
○	Ocular ischaemic syndrome
○	Vitamin A deficiency
◉	Vitamin B_{12} deficiency ✕ Incorrect answer selected

This history is most in keeping with macular degeneration.

The relatively short history is more suggestive of wet age-related macular degeneration, which is actually a systemic problem, of which ischaemic heart disease is a risk factor.

Toxic amblyopia will more often give a centro-caecal scotoma.

Central scotoma here indicates that only the macula region is involved.

Next question

Remove Tag | Remove question

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken:

MRCP Part 1 - January 2011

Question: 1 of 2

Deficiency of which of the following components of the complement system predisposes to infection with *Neisseria meningitidis*?

(Please select 1 option)

○	C1q
○	C1r
○	C1s
○	C3
○	C4

Submit answer | Skip question | Remove Tag

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A

- Dashboard
- Questions
- Scores
- Community
- Shop
- Help

Time taken: 1 mins 57 secs

MRCP Part 1 - January 2011

Question: 2 of 2

Which of the following may be responsible for an acute relapse of systemic lupus erythematosus (SLE) in a 38-year-old female?

(Please select 1 option)

- ○ Hydralazine therapy
- ○ Pregnancy
- ○ Progesterone only contraceptive pill
- ○ Salmeterol therapy
- ○ Winter holiday in Lapland

Submit answer | Skip question | Tag Question

© 2011 BMJ Publishing Group Ltd . All rights reserved . Terms and conditions . Privacy policy . A A A